EXPERT OPINION

Alprostadil infusion in patients with dry age related macular degeneration: a randomized controlled clinical trial

Albert J Augustin[†], Curt Diehm, Frank Grieger & Juergen Bentz
[†]*Direktor der Augenklinik, Klinikum Karlsruhe, Moltkestrasse, Karlsruhe, Germany*

Background: Age-related macular degeneration is the leading cause of blindness among elderly individuals in industrialized countries. New drugs and advanced concepts for the treatment of dry AMD (dAMD) are needed. A new approach is the application of intravenous infusions of prostaglandin E1.
Objective: The aim of this study was to assess efficacy and safety of intravenous alprostadil infusion in patients with dAMD.
Methods: This was a prospective, randomized, multi-center study. Patients were treated with intravenous infusion of either 60 μg alprostadil or placebo over 3 weeks. Main efficacy outcomes were mean differences in best corrected visual acuity (BCVA) from baseline assessed in early treatment diabetic retinopathy study (ETDRS) lines immediately, 3 months and 6 months after treatment.
Results: In the full analysis set (FAS) a mean difference of 0.89 ± 0.537 ETDRS lines according to analysis of variance-covariance (ANCOVA) resulted in the alprostadil group (n = 16) and a mean difference of -0.05 ± 0.578 in the placebo group (n = 17) 3 months after end of treatment. Thus, effectiveness of alprostadil infusion was numerically superior to placebo treatment by a mean of 0.94 lines after 3 months (1.51 lines after 6 months). These findings were more pronounced in the per protocol set (PPS). Safety results were in line with the good safety profile of alprostadil.
Conclusion: A numerical treatment effect in favor of alprostadil was visible, which lasted until the end of follow up. These results provide further evidence that alprostadil probably has a therapeutic effect in the treatment of dAMD and justify further clinical studies.

Keywords: age related macular degeneration, alprostadil, prostaglandin E1, therapy, visual acuity

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1. Introduction

Age-related macular degeneration (AMD) affects approximately 30 - 50 million people worldwide and is the leading cause of blindness among elderly individuals in western industrialized countries [1-4]. There are two forms of AMD: dry AMD (dAMD) which accounts for about 80% of all cases of AMD and neovascular AMD (nAMD). Early stage AMD is characterized by soft drusen, that is the formation of protein and lipid deposits between retina and choroid, and pigment abnormalities (hyper- or hypo-pigmentation). Early stages can progress to late stages of AMD at any time: geographic atrophy (GA; late stage of dAMD) or nAMD, which is indicated by the formation of new vessels. Severe vision loss due to AMD is mainly attributable to these advanced forms. It is estimated that due to demographic

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changes, in 2020 the vision threatening advanced forms will increase by > 50% [5]. Thus, the development of new powerful therapies is a matter of public and economic concern.

While there are several therapeutic approaches for nAMD, there are no established guidelines for dAMD treatment so far. Although vitamin supplementation can slow the progression of dAMD to advanced forms, uncritical administration is not advisable due to a number of possible adverse reactions [6,7]. Thus, new drugs and advanced concepts for the treatment of dAMD are urgently needed. One possible approach is the application of rheopheresis, which uses double filtration plasmapheresis to deplete serum from high molecular weight proteins. However, clinical trials on the use of rheopheresis in dAMD showed contradictory results and did not achieve the desired success so far [8,9].

Another approach is the application of intravenous infusions of prostaglandin E_1 (PGE_1) known pharmaceutically as alprostadil. An established use of alprostadil is the therapy of peripheral arterial occlusive disease (PAOD) [10,11]. Alprostadil is well-tolerated and characterized by multifarious pharmacological effects: While vasodilation and the inhibition of platelet function have long been regarded as the most important effects of PGE_1, it has been shown that the compound exhibits further effects, such as antioxidant effects, inhibition of pro-inflammatory cytokine release, inhibition of adhesion molecule expression, interactions with mediators of vascular function, inhibition of production and release of growth factors and gene regulation at the level of transcription [12,13].

Although their relevance in dAMD is yet not completely understood, vasodilation might be one important effect. Although study results, whether systemic hypertension (SHTN) is a strong risk factor for AMD and choroidal neovascularization (CNV) or not, are still incongruent [14-20], there is growing evidence that decreases in choroidal blood flow parameters may be involved in the development of AMD [21-25]. It is known for a long time that patients with dAMD show a reduction in choroidal blood flow and volume in comparison to age-matched patients without AMD [22]. Recent studies report an association between decreased choroidal circulatory parameters and risk factors for AMD development, suggesting that decreases in choroidal circulatory parameters may be involved in the development of AMD and pointing to a potential role of ischemia in the development of CNV [23-25].

Moreover, AMD is a multi-causal disease and even if its etiology is still not completely understood, it has been shown that excessive activation of inflammatory and immunological cascade with subsequent induction of damage participate in the mechanisms which originate the drusen [26]. Also, the complement cascade has been identified as a key factor in the pathogenesis of AMD [27]. At this point the multifarious pharmacological effects of alprostadil might be of some importance: The anti-ischemic effects of alprostadil are complex and clearly not limited to a direct vasodilator action. In addition, it also inhibits monocyte and neutrophil function, suggesting that alprostadil will also have anti-inflammatory effects. Moreover, inhibition of expression of adhesion molecules (E-selectin, ICAM-1 and VCAM-1), release of inflammatory cytokines (TNFα, MCP-1), matrix components and generation and release of growth factors (CYR61, CTGF) have also been described in association with alprostadil and may also contribute to long-term effects [13].

Two pilot studies showed positive effects of alprostadil therapy in patients with dAMD: Heidrich *et al.* observed spontaneous improvement of visual acuity after intravenous infusion of PGE_1 in patients with PAOD. Further examination of these patients showed that the preexisting visual impairment was caused by dAMD in most cases [28]. Furthermore a subsequent pilot study with 11 patients with dAMD showed an improvement in visual acuity and contrast sensitivity as well as in the multifocal electroretinogram after intravenous infusion of alprostadil (60 µg/day) over a period of 21 days also at the follow up examination [29].

The primary goal of this study was to confirm the results of the pilot study in a randomized, double-blind and placebo-controlled study design and to assess efficacy and safety of intravenous alprostadil infusion in patients with dAMD. Primary objective was to show a superior effect of alprostadil compared to placebo on visual acuity at 3 months after the end of the study drug infusion. Additional exploratory comparisons were performed on visual acuity immediately after and 6 months after study drug infusion, on progression of dAMD and development of nAMD, as well as on contrast sensitivity and color vision.

2. Patients/materials and methods

2.1 Study design

This prospective, randomized, double-blind, placebo-controlled, parallel groups study was conducted at six sites in Germany and Austria. The study was conducted using a 2-stage group sequential adaptive design with possible sample size adjustment after the interim analysis.

The study was conducted under the auspices of an independent ethics committee or institutional review board (IEC/IRB) in accordance with the current version of the applicable regulatory and International Conference on Harmoniation-Good Clinical Practice (ICH-GCP) requirements, the ethical guidelines under the Declaration of Helsinki, and the local laws of the countries involved. Prior to participation in the study, the written, informed and signed consent of each patient had to be obtained and documented according to these regulatory requirements.

2.2 Study population

Eligible patients were male or female subjects older than 50 years of age with dAMD with hard drusen and possibly beginning geographic atrophy limited to the perifoveal area in one eye. Visual acuity assessed with Early Treatment Diabetic Retinopathy Study charts (ETDRS charts [30,31]) had to be within 0.2 – 0.7 (logMAR). Key ophthalmologic

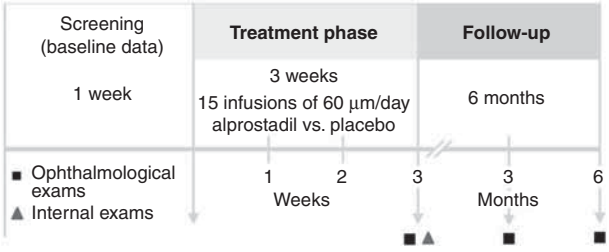

Figure 1. Schematic diagram of study schedule.

exclusion criteria included nAMD in at least one eye, and detachment of the retinal pigment epithelium (RPE). Also AREDS III patients with large soft drusen had to be excluded due to the possible pro-inflammatory effect of alprostadil. Other eye diseases such as glaucoma, uveitis, diabetic retinopathy as well as medical history of retinal vein occlusion, retinal hemorrhage, vitrectomy and cataract surgery (during study or within last 12 months) were also exclusion criteria. Key medical exclusion criteria were cardiac failure, myocardial infarction within the past 6 months, inadequately controlled heart disease, cardiac arrhythmia or hypertension as well as indications of pulmonary edema or pulmonary infiltration, chronic obstructive pulmonary disease, veno-occlusive lung disease, peripheral edema, hepatic disease and malignant disease. Further exclusion criteria were known hypersensitivity to PGE_1 or to any component of study medication, intake of vasoactive medication within the last 2 days of screening or intake of prostaglandins within the past 3 months.

2.3 Concomitant treatment

Treatments of diseases already present at screening and considered no exclusion criteria were continued. Treatments and medications such as AREDS medication [6], ophthalmologic dietary supplements, vasoactive medication or prostaglandins and any other dAMD treatment were prohibited during the study.

2.4 Study schedule and drug administration

The study was conducted on an ambulatory basis and compromised a screening phase (3 – 7 days), a treatment phase (3 weeks) and a follow up phase (6 months). At first day of screening phase (baseline) and immediately after treatment phase all patients had a detailed ophthalmological examination as well as a physical examination. The ophthalmological examination included determination of visual acuity (ETDRS/logMAR), intraocular pressure, slitlamp examination, binocular ophthalmoscopy and fundus photography, fluorescein angiography, multifocal electroretinogram (optional) and optical coherence tomography as well as the determination of the visual field, contrast sensitivity, color vision. As part of the physical examination routine laboratory parameters, vital signs and ECG at rest were assessed. Detailed ophthalmological examinations were also performed at 3 months (without optical coherence tomography) as well as 6 months after end of treatment phase (**Figure 1**).

On the first day of the treatment phase patients were randomized to treatment with alprostadil or placebo. The therapy consisted of a once-daily regimen of intravenous infusion of either 60 µg alprostadil dissolved in 100 ml of NaCl or 47.5 mg lactose (placebo) dissolved in 100 ml NaCl. Infusion took over 1.5 – 2 hr and was performed with an infusion pump on every weekday, thus 15 infusions were performed in 3 weeks.

2.5 Efficacy measurements

Primary outcome measure was change in best corrected visual acuity (BCVA) (logMAR). This was assessed as difference in lines with the ETDRS charts [30,31], between measurements at 3 months after the end of treatment phase and baseline measurements. The mean differences in lines were compared between study groups.

Secondary outcome measure included the difference in BCVA (logMAR) between measurements immediately after as well as 6 months after the end of treatment phase and measurements at baseline. Moreover, differences in contrast sensitivity (determined with the Pelli-Robson test) and color vision (determined with the panel D15 test) between measurements immediately after as well as 3 and 6 months after the end of treatment phase and measurements at baseline were assessed. The state of dAMD and the presence of nAMD were assessed with binocular ophthalmoscopy, fundus photography and fluorescein angiography at all ophthalmic examinations. Gradings were performed by an experienced ophthalmologist in each center. Results were analyzed exploratory displaying numbers and percentages of the following three classifications: 'Progression' in disease was defined as increase in either number or diameter of drusen. Also, either the development of hyperpigmentation or pigment epithelium detachment or starting geopgraphic atrophy was defined as 'progression'. 'Stabilization' of disease means that all measured parameters remained constant. 'Amelioriation' of disease means that one or two test results showed improvement compared to baseline, but the other parameters had to remain constant.

2.6 Safety measurements

Laboratory safety variables were hemoglobin, hematocrit, red blood count (RBC), white blood count (WBC), platelet count, sodium, potassium, ALAT, ASAT, GGT, creatinine, urea, triglycerides, cholesterol, glucose and fibrinogen. Furthermore vital signs (body weight and height, systolic/diastolic blood pressure, pulse rate, body temperature) and ECG at rest were assessed at screening and immediately after end of treatment phase. Blood pressure and pulse rate were additionally determined immediately pre- and post-infusion as well as at 30 min intervals during infusion.

Adverse events (AE) were classified according to seriousness (serious/non-serious), intensity (mild/moderate/severe), outcome

and causality and had to be recorded. Serious adverse events had to be reported immediately.

2.7 Statistical analysis

Statistical analysis was performed using SAS Version 9.3 and ADDPLAN Version 5.0. The study was stopped prematurely at the first interim analyses, thus, final analysis provided exploratory results only. The primary goal of the study was to test the following null hypothesis: $H_0 = \mu_{Alprostadil} \leq \mu_{Placebo}$, which was tested against the alternative hypothesis: $H_0 = \mu_{Alprostadil} \geq \mu_{Placebo}$, with μ = the mean difference in visual acuity between measurements at 3 months after treatment phase and measurements at baseline as assessed as line difference on the ETDRS charts with best possible correction. The criterion for significance (α) had been set at one-sided at $\alpha = 0.025$. For exploratory hypothesis testing, the analysis of variance-covariance (ANCOVA) F-test with dependent variable 'difference in visual acuity', the fixed factors 'treatment' and 'center' and the covariate 'baseline value' was used. Corresponding 95% two-sided repeated confidence intervals were provided, p-values were provided.

The secondary efficacy variables as described above were analyzed exploratory with a Chi-square test. The occurrence of adverse events (AE) was analyzed descriptively.

2.8 Analysis sets

The safety assessment was based on the safety set, which consisted of all randomized subjects who had received at least on dose of study medication.

For efficacy analysis, two data sets were defined. The full analysis set (FAS) included all randomized subjects who had received at least one dose of study medication and who provided valid baseline and post-baseline measurements immediately after treatment phase (week 3) and/or 3 months after treatment phase.

The per protocol set (PPS), being a subset to the FAS, included all subjects who did not show any protocol deviations important for efficacy.

3. Results

3.1 Study population

Forty patients were screened in six centers in Germany and Austria. A first interim analysis was conducted with 30 subjects. As a result, sample size had to be recalculated, which, in conjunction with a slow recruitment rate, lead to a premature ending of the study. For the final analysis 36 patients were randomized, 18 in the alprostadil group and 18 in the placebo group respectively, and received at least one dose of medication (safety set). Of these, 3 patients (2 vs. 1) had no baseline data for primary outcome measure and were not included in the FAS. Twelve patients (7 vs. 5) had protocol deviations relevant for efficacy and were excluded from the PPS. Protocol deviations relevant for efficacy, safety or study conduct had been defined during a blinded data review meeting. Patient demographics and baseline characteristics were comparable between the two groups in all three analysis sets (**Table 1**). Baseline laboratory values indicated no major health problems. Also with regard to blood pressure and pulse rate no clinically relevant differences were found between the two groups, however, the systolic blood pressure varied slightly more in the alprostadil group (**Table 1**).

3.2 Efficacy outcome (visual acuity)

In the FAS the change in BCVA 3 months after treatment revealed a numerical difference in favor of the alprostadil group, which was even more pronounced after 6 months. The mean difference in BCVA was provided according to ANCOVA in least square means (LS mean ± standard error). Between 3 months after end of treatment and baseline a mean difference of 0.89 ± 0.537 ETDRS lines, with a [-0.21; 1.99] 95% CI and a p-value = 0.1090 resulted in the alprostadil group. In the placebo group a mean difference of -0.05 ± 0.578 ETDRS lines, with a [-1.24; 1.14] 95% CI and a p-value = 0.9334 was analyzed. The exploratory testing of H_0 resulted in a one-sided p-value of 0.122, which is above the limit of 0.025.

In the PPS, the numerical difference in favor of the alprostadil group was even more pronounced than in the FAS. The mean difference in BCVA (according to ANCOVA) between 3 months after end of treatment and baseline, was 0.94 ± 0.568 ETDRS lines, with a [-0.27; 2.15] 95% CI and a p-value = 0.1189 in the alprostadil group and a LS mean of -0.42 ± 0.596 ETDRS lines, with a [-1.69; 0.85] 95% CI and a p-value = 0.49 in the placebo group. The exploratory testing of H_0 resulted in a one-sided p-value of 0.0625 (> 0.025).

Differences in BCVA according to ANCOVA between 'immediately after treatment' as well as '6 months after end of treatment' and baseline values in the FAS and in the PPS are summarized in **Table 2**. Differences in BCVA according to ANCOVA between all measuring times and baseline values are presented for the FAS in **Figure 2** and for the PPS in **Figure 3** respectively. In summary, there was a numerical treatment effect in favor of alprostadil visible, which lasted after infusion until the end of follow up (6 months). These findings were even more pronounced in the PPS.

Regarding the variables 'progression of dAMD', 'development of nAMD', 'contrast sensitivity' and 'color vision' the results were similar in both treatment groups. In the FAS progression of dAMD was recorded in 11/16 (68.8%) patients of the alprostadil group and in 12/17 (70.6%) patients of the placebo group at least once. Stabilization or amelioration at all study visits was reported in 5/16 (31.3%) vs. 5/17 (29.4%) of patients. No patient developed a nAMD of the study eye. Contrast sensitivity in the study eye (according to Pelli-Robson) was impaired in all patients at screening already (**Table 1**) and showed only minor changes in both study groups at all measuring times (**Table 3**). All scores measured in this study were 1.65 or

Table 1. Demographic and baseline characteristics.

	Safety set		Full analysis set (FAS)		Per protocol set (PPS)	
	Alprostadil (n = 18)	**Placebo (n = 18)**	**Alprostadil (n = 16)**	**Placebo (n = 17)**	**Alprostadil (n = 9)**	**Placebo (n = 12)**
Demographic data						
Gender (male/female)	10/8	8/10	10/6	8/9	5/4	5/7
Age, mean ± SD, y	76.5 ± 8.3	71.8 ± 7.8	76.1 ± 8.5	71.7 ± 8.1	76.4 ± 7.8	69.3 ± 7.9
Range	63 – 95	58 – 85	63 – 95	58 – 85	63 – 86	58 – 82
BMI [kg/mm^2]	25.65 ± 3.64	26.73 ±3.23	26.2 ± 3.38	26.7 ± 3.32	26.88 ± 4.35	26.98 ± 3.55
Risk factors						
Alcohol (no/yes)	5/13	2/16	3/13	2/15	1/8	1/11
Smoking (no/yes)	16/2	18/0	14/2	17/0	8/1	12/0
Caffeine (no/yes)	3/15	3/15	3/13	3/14	2/7	1/11
Baseline data						
Systolic blood pressure [mmHg]	146.06 ± 23.73	142.28 ± 13.26	143.69 ± 24.11	142.76 ± 13.5	155.89 ± 22.61	138.5 ± 13.35
Diastolic blood	79.89 ± 9.16	80.44 ± 7.01	78.69 ± 9.01	80.35 ± 7.22	81.00 ± 6.65	79.5 ± 8.31
Pressure (mmHg)	71.50 ± 11.65	71.50 ± 8.07	72.38 ± 12.04	71.00 ± 8.02	74.22 ± 12.02	71.17 ± 7.94
Pulse (bpm)						
BCVA (ETDRS), mean ± SD (median)			7,81 ± 1,28 (8,0)	7,29 ± 1,16 (7,0)	7,67 ±1,58 (7,0)	7,25 ± 1,06 (6,0)
Contrast sensitivity, (Pelli-Robson), study eye, mean ± SD (median)			1,153 ± 0,308 (1,2)	1,085 ± 0,329 (1,2)	1,017 ± 0,288 (1,050)	1,075 ± 0,337 (1,125)
Color vision (Panel D15) normal/pathologic			3/13	3/14	2/7	3/9

BMI: Body mass index; SD: Standard deviation; y: Year.

Table 2. Mean difference in BCVA.

		Δ BCVA immediately after treatment*			Δ BCVA at 6 months after end of treatment*		
		LS mean ± SE	95% CI	p-value		95% CI	p-value
FAS	Alprostadil	0.86 ± 0.615	[-0.41; 2.18]	0.174	1.47 ± 0.569	[0.30; 2.64]	0.0155
	Placebo	-0.12 ± 0.630	[-1.42; 1.189]	0.8555	-0.04 ± 0.613	[-1.30; 1.22]	0.9510
PPS	Alprostadil	1.20 ± 0.571	[-0.02; 2.24]	0.0529	1.03 ± 0.664	[-0.38; 2.45]	0.1404
	Placebo	-0.18 ± 0.483	[-1.21; 0.85]	0.7137	-0.86 ± 0.697	[-2.35; 0.62]	0.2338

*As differences in ETDRS lines from baseline; based on ANCOVA.
CI: Confidence interval; FAS: Full analysis set; LS mean: Least square mean; SE: Standard error; PPS: PER protocol set.

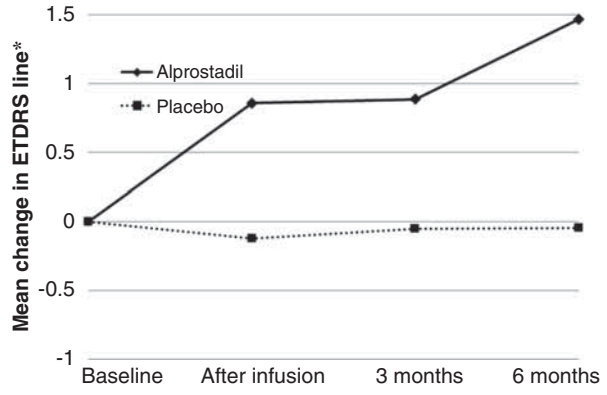

Figure 2. Mean change in BCVA (according to ANCOVA) from baseline at all measuring times in the Full Analysis Set (FAS; n = 33). Changes in BCVA were assessed as ETDRS lines.

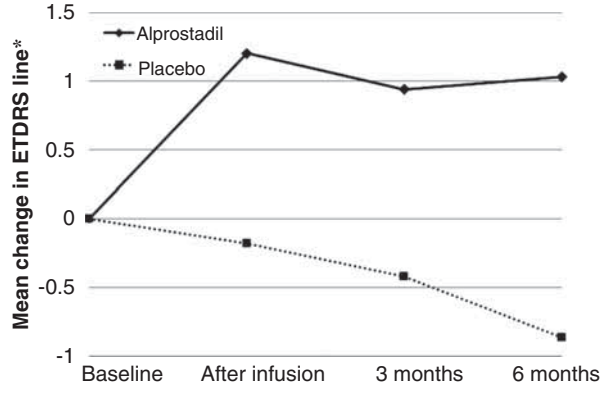

Figure 3. Mean change in BCVA (according to ANCOVA) from baseline at all measuring times in the Per Protocol Set (PPS; n = 21). Changes in BCVA were assessed as ETDRS lines.

less, indicating visual impairment. Color vision was also restricted at screening already in most of the patients (**Table 1**). In the FAS 13/16 (81.3%) patients in the alprostadil group and 14/17 (82.4%) patients in the placebo group showed pathologic results. Of these, 3/16 (18.8%) patients in the alprostadil group and 2/17 (11.8%) in the placebo group had normal results at last study visit (**Table 4**).

3.3 Safety outcome

All AEs reported in both treatment groups were of mild or moderate intensity only and no serious adverse events (SAEs) or AEs leading to premature termination of the study were reported. With regard to overall treatment emerged adverse events (TEAEs), the number of subjects with AEs as well as the number of events was slightly lower in the alprostadil group than in the placebo group. In the alprostadil group, 2 patients (11.1%) reported a total of 4 events while 6 patients (33.3%) from the placebo group reported 9 events. The only AE with a probable or highly probable relation to the study medication in the alprostadil group was a phlebitis that lasted over one day and recovered afterwards. Only in the placebo group 3 ophthalmological AEs were reported. Two of them were assessed as unlikely or not related to the study medication. One of them (mild visual disturbances from day 15) was assessed possibly related to the study drug.

The laboratory values revealed no remarkable changes after treatment with alprostadil or placebo. Also, with regard to vital signs (blood pressure and pulse rate) neither major differences between the treatment groups nor clinically relevant trends were reported. Moreover, results from physical examinations indicated neither any deterioration of an existing pathological change nor new pathological alterations after treatment in both groups.

4. Discussion

This clinical study was performed to show the efficacy and safety of alprostadil in the treatment of dAMD. The target criterion for efficacy was the change of visual acuity as measured with the ETDRS charts at different measuring times. ETDRS charts are a validated and reliable tool to measure visual acuity even in patients with low vision and allow precise quantification of vision and reliable measures of vision change [30-32]. The study was designed as a confirmatory study. However, as the interim analysis showed need for extended recruitment in order to reach adequate power to yield statistical significant results, the study was prematurely

Table 3. Contrast Sensitivity of the study eye (Pelli Robson).

		After treatment		3 months		6 months	
		Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI
FAS	Alprostadil (n = 16)	1.163 ± 0.331	[0.99; 1.34]	1.238 ± 0.282	[1.09; 1.39]	1.81 ± 0.299	[1.02; 1.34]
	Placebo (n = 17)	1.103 ± 0.304	[0.95; 1.26]	1.059 ± 0.293	[0.91; 1.21]	1.094 ± 0.224	[0.98; 1.21]
PPS	Alprostadil (n = 9)	1.050 ± 0.344	[0.79; 1.31]	1.133 ± 0.282	[0.92; 1.35]	1.050 ± 0.290	[0.83; 1.27]
	Placebo (n = 12)	1.050 ± 0.332	[0.84; 1.26]	1.050 ± 0.271	[0.88; 1.22]	1.038 ± 0.217	[0.90; 1.18]

CI: Confidence interval; FAS: Full analysis set; PPS: Per protocol set; SD: Standard deviation.

Table 4. Color Vision (Panel-D15 test): change from baseline.

	Full analysis set (FAS)			Per protocol set (PPS)		
	Alprostadil (n = 16)	Placebo (n = 17)	p-value*	Alprostadil (n = 9)	Placebo (n = 12)	p-value*
After treatment						
Normal → patholog	1	0		1	0	
Unchanged	15	13		8	10	
Patholog. → normal	0	4	0.0774	0	2	0.2403
3 months						
Normal → patholog.	1	0		1	0	
Unchanged	13	14		7	11	
Patholog. → normal	2	3	0.5467	1	1	0.4746
6 months						
Normal → patholog.	1	0		1	0	
Unchanged	12	15		7	11	
Patholog. → normal	3	2	0.4713	1	1	0.4746

*Two sided Chi-square test.

stopped and the final analysis was performed on the basis of the interim analysis. Accordingly, due to small patient numbers of the final analysis (n = 36), only exploratory results can be provided here. Thus, the null hypothesis ($H_0 = \mu_{Alprostadil} \leq \mu_{Placebo}$) cannot be rejected so far. Nevertheless, we identified numerical differences between both groups which are in good agreement with prior study results and can be considered clinically relevant.

In the FAS, the alprostadil group revealed a mean improvement in visual acuity from baseline at all measuring times, whereas in the placebo group almost no change (slight impairment) was detected according to ANCOVA. Three months after treatment patients with alprostadil infusion revealed a mean improvement in visual acuity from baseline by 0.89 ETDRS lines, while in the placebo group a slight impairment by -0.05 ETDRS lines in average was detected. Thus, patients with alprostadil infusion benefited from a mean improvement equivalent to 0.94 ETDRS lines as compared to non-treated patients after 3 months. After 6 months this effect was even more pronounced with a mean improvement equivalent to 1.51 ETDRS lines between the alprostadil group and the placebo group (**Figure 2**). Comparing the results obtained from the FAS with those from the PPS, it can be stated that the positive effect in the alprostadil group was even more pronounced in the PPS: 3 months after treatment patients with alprostadil infusion revealed a mean improvement in visual acuity from baseline by 0.94 ETDRS lines according to ANCOVA, while the placebo group exhibited a mean impairment by -0.42 ETDRS lines, resulting in a difference of 1.36 ETDRS lines between the two groups. After 6 months this effect was even more pronounced and patients with alprostadil infusion benefited from a mean improvement equivalent to 1.89 ETDRS lines in comparison to the placebo group (**Figure 3**).

In general our findings are in good agreement with the results of prior pilot studies: Also Ladewig *et al.* found that alprostadil infusion (60 µg in a once-daily regimen over 3 weeks) was associated with a mean improvement in visual acuity by 0.36 lines after 6 months, while in the placebo group a 0.8 line impairment was detected in average. Thus, patients with alprostadil infusion benefited from an improvement equivalent to 1.2 lines, as compared to non-treated patients after 6 months in this study [29]. In our study we used the same dosage (60 µg alprostadil/day) but in comparison to Ladewig *et al.* adapted the total number of infusions from 21 to 15, in order to allow free weekends for study participants. This administration scheme has been used in peripheral artery occlusive disease (PAOD) with

good results and therefore was taken over for this study as well [33]. As our results are comparable to those of Ladewig *et al.* it is not to be expected that this administration scheme would influence results. We detected an improvement equivalent to 1.51 lines (FAS) or 1.89 lines (PPS) respectively in the treatment group in comparison to the placebo group after 6 months. Even if our results, due to small patient numbers, exhibited no statistical significance, they could be considered clinically relevant. Especially in patients with low vision gaining even one line can have a great impact on their visual and life quality and might make the difference between being able to perform certain vision related activities or not. This is also reflected by the results of Heidrich *et al.* who assessed improvement of subjective visual capacity in six from seven patients after alprostadil infusion (40 µg in a twice-daily regimen over 4 weeks in average) [28].

The results for secondary efficacy parameters (progression of dAMD; development of nAMD, contrast sensitivity and color vision) in our study did not provide any considerable hints for a difference between the alprostadil and the placebo group in terms of visual parameters. However, this might be due to small numbers of subjects per treatment group, which were not expected to provide a sufficient basis for the proof of efficacy. Moreover, a follow up time of 6 months might not be sufficient to detect changes of dAMD, which progresses more slowly than nAMD. In terms of safety, all observed events and abnormalities were of minor clinical importance as expected. The safety results are in line with the known good safety profile of alprostadil, which is in clinical use for > 30 years now.

Within future studies on the effect of alprostadil in dAMD inclusion criteria will be dAMD in at least one eye including GA, whereas patients with high conversion risk to nAMD (e.g., large soft drusen) should be excluded from the study. Defining the best clinical trial endpoint for showing efficacy in the shortest period of time is still difficult in investigating dAMD. As patients with early stages of dAMD, but sometimes even in the late atrophic stages, can maintain good central visual acuity until the disease progresses to involve the foveal center, it might require a long time (or large patient populations) to detect differences in visual acuity outcomes. Therefore in addition to BCVA the evaluation of secondary efficacy parameters is important. Important 'secondary physiological parameters' include contrast vision and color vision. Of course these parameters also have been evaluated in this study; however our results so far are restricted due to low patient numbers. Regarding 'secondary anatomical endpoints' the evaluation of new endpoints might be of great interest. One interesting option might be the enlargement rate of GA as endpoint, because it represents the loss of photoreceptors, RPE and choriocapillaris and thus can indicate disease progression even before visual acuity, contrast vision and color vision are affected. Several imaging modalities like color fundus photography, fluorescein angiography, fundus autofluorescence and spectral domain optical coherence tomography (SD-OCT), exist for the detection of GA [34]. Recently a new SD-OCT software analysis tool has been developed, which allows for automated and quantitative assessment of changes of GA areas and may become a powerful tool in diagnosing and monitoring AMD, because it might offer the feasibility to automatically and objectively quantitate GA and the progression of GA [35]. Of course, in this context it is of utmost importance to define and evaluate reliable and reproducible parameters that allow for grading AMD using SD-OCT.

5. Conclusion

In summary, our results further support the results of two pilot studies which also showed positive effects of alprostadil treatment in dAMD [28,29]. Our study revealed numerical differences in mean BCVA of 1.51 (FAS) to 1.89 (PPS) ETDRS lines in favor of alprostadil compared to placebo 6 months after treatment. Safety results were in line with the good safety profile of alprostadil. Taking also in account the growing evidence that decreased choroidal blood flow might be involved in AMD progression and the multifarious pharmacological effects of alprostadil, it can be stated that it is obviously worthwhile to further continue investigating the benefit of alprostadil in patients with dAMD. This is all the more important as there is still no established treatment for the most prevalent form of dAMD yet. Of course, appropriate patient population as well as appropriate clinical trial end points should be selected for further studies.

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•• **This article provides a short overview of developments in optical coherence technology (OCT) and highlights the advantages of spectral-domain OCT (SD-OCT) and presents a new analysis tool, which should allow for automated, quantitative assessment of drusen and atrophic lesions could potentially provide more objective and easier classification of AMD.**

Affiliation

Albert J Augustin[†1] PhD, Curt Diehm[2] PhD, Frank Grieger[3] Dipl Stat & Juergen Bentz[3] PhD
[†]Author for correspondence
[1]Professor,
Direktor der Augenklinik, Klinikum Karlsruhe, Moltkestrasse 90, 76133 Karlsruhe, Germany
Tel: +49 721 9742001;
Fax: +49 721 9742009;
E-mail: albertjaugustin@googlemail.com
[2]SRH Klinikum Karlsbad-Langensteinbach GmbH, Akademisches Lehrkrankenhaus der Universität Heidelberg, Guttmannstr. 1, 76307 Karlsbad, Germany
[3]UCB Pharma SA, Chemin de Croix-Blanche 10, CH-1630 Bulle, Switzerland