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Efficacy and Safety of Alprostadil in Patients with Peripheral Arterial Occlusive Disease Fontaine Stage IV: Results of a Placebo Controlled Randomised Multicentre Trial (ESPECIAL)

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WHAT THIS PAPER ADDS

This was the largest controlled, multicentre, randomised clinical trial investigating the efficacy and safety of intravenous administration of alprostadil in patients with Stage IV PAOD. In contrast to prior publications, superiority of alprostadil over placebo was not shown; both treatment groups showed good clinical results. Despite certain limitations in study design and conduct this evidence should be taken into account and use of intravenous administration of alprostadil should be critically questioned in patients with Stage IV PAOD.

Objectives: The aim was to assess the efficacy and safety of alprostadil in patients with peripheral arterial occlusive disease (PAOD) Fontaine Stage IV.

Methods: This was a multinational, prospective, randomised, double blind, placebo controlled, parallel group trial. Patients with Stage IV PAOD were equally randomised to either 4 weeks of alprostadil treatment twice daily or to placebo treatment twice daily. The primary efficacy variables were the rate of complete healing of all necrosis and ulceration 12 weeks after the end of treatment and the frequency of major amputations 24 weeks after the end of treatment.

Results: A total of 840 patients were randomised between 2004 and 2013. At baseline, no major differences between treatment groups were found. The rate of "complete healing" was 18.4% in patients on alprostadil and 17.2% in patients on placebo. The rates of "major amputations" were 12.6% in patients on alprostadil and 14.6% in patients on placebo. The adjusted difference between alprostadil and placebo including their 95% confidence intervals was 1.1 (−4.0 to 6.3) for "complete healing" and −2.1 (−6.7 to 2.5) for "major amputations." In the subgroup of diabetic patients the rates of major amputations were numerically lower in the alprostadil than placebo group (10.6% vs. 17.4%). Within the total cohort a non-significant difference in "decrease in ulcer area ≥50%" was reached in 30.2% of patients on alprostadil and in 24.3% of patients on placebo at end of treatment.

Conclusions: In this study, superiority of alprostadil over placebo could not be shown. Nevertheless, a slight numerical but not clinically relevant advantage for alprostadil emerged from the "area decrease of ulcers by ≥ 50%," indicating that a healing effect may have started. The results have to be considered in the light of several limitations in study design and conduct.

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INTRODUCTION

Peripheral arterial occlusive disease (PAOD) Fontaine Stage IV, the most serious form of critical limb ischaemia (CLI), is the clinical endpoint of PAOD. Despite its subacute or chronic appearance immediate action is necessary since tissue perfusion is markedly reduced and there is the threat of major amputation within 1 year.[1,2] The main focus of all therapeutic efforts for patients with CLI is pain reduction and leg retention and the first line treatment is arterial revascularisation either by endovascular or open surgical procedures.[3] However, in about one third of patients revascularisation procedures are impossible, carry a poor

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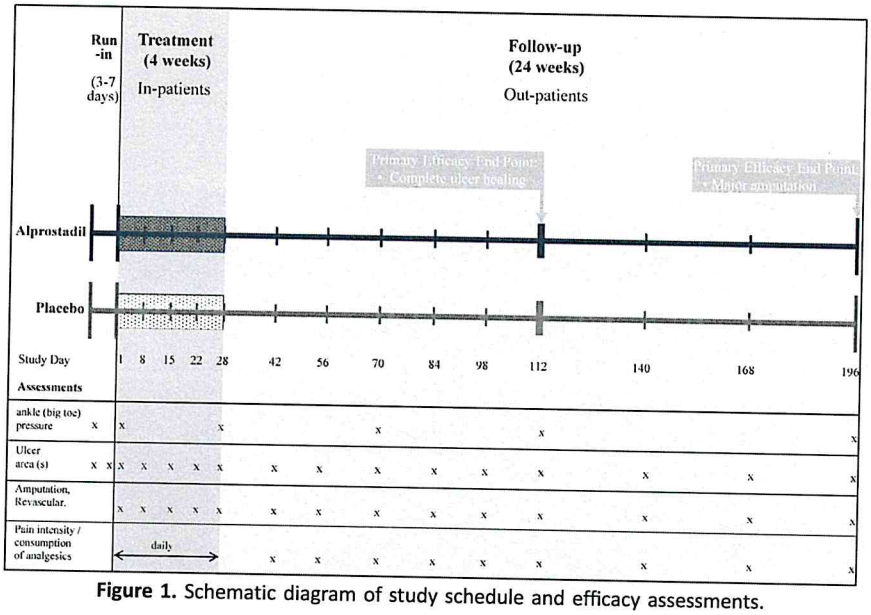

Figure 1. Schematic diagram of study schedule and efficacy assessments.

chance of success, or have previously failed.[4] In these patients not amenable to revascularisation, prostanoids are recommended to accelerate ulcer healing, reduce pain, and avoid amputation.[2,3,5] Several older studies, among them seven randomised, placebo or reference controlled clinical studies, have shown clinical efficacy of alprostadil (prostaglandin E1) in patients with PAOD stage III/IV.[6–12] All studies followed legal regulations regarding the conduct of clinical studies effective at that time. However, up to date studies complying with current regulations are lacking. A recent Cochrane review stated the need for larger studies to confirm the efficacy of prostanoids for CLI.[13]

The purpose of the present study was to confirm a superior effect of alprostadil compared with placebo on the rate of complete healing of ischaemic necrosis and ulceration as well as on the frequency and level of major amputations in patients suffering from Stage IV PAOD. The study was designed in compliance with the current EU Note for PAOD.[14] When planning and designing this study, data on the fate of patients with Stage IV PAOD showed large variations, with amputation rates from approximately 20% to ≥50%, and only few data were available on the rate of complete ulcer healing; therefore, an adaptive test design with an interim sample size adjustment was chosen.[3]

PATIENTS AND METHODS

This was a multinational, prospective, randomised, double blind, placebo controlled, parallel group trial (clinical trial registration number: NCT00596752 (https://clinicaltrials.gov); EudraCT: 2005-001970-29). Ethics approval for the study was granted by a national, regional, or independent ethics committee or institutional review board and full informed consent from patients was obtained in accordance with local regulations and the International Conference on Harmonisation and good clinical practice requirements, and the principles of the Declaration of Helsinki. Non-diabetic and diabetic (II) male or female patients of ≥45 years of age with proven Fontaine Stage IV PAOD in one leg with up to two ischaemic skin lesions for more than 2 weeks with or without rest pain, who were not in the position to be primarily revascularised or who had refused surgery, were considered eligible for the study. Maximum skin lesions diameter was up to 6 cm^2, at least one lesion had to be larger than 1 cm,[2] and the patient's life expectancy had to be ≥ 180 days. Key exclusion criteria were an imminent or foreseeable amputation, a major amputation in the affected extremity, and use of vasoactive medication or other prostaglandins concomitantly or within 3 months prior this study. Also patients with acute ischaemia and peripheral vascular disorders of inflammatory or immunological origin, venous or neuropathic ulcers, Buerger's disease, a myocardial infarction within 6 months of the start of treatment, inadequately controlled cardiac disorders, severe renal dysfunction (KDIGO 4 and more), or severe pulmonary diseases were also excluded.

Randomisation and blinding

Each eligible patient was assigned a random number on Study Day 1. Patients were stratified according to whether or not they had diabetes. Within both strata, the method of randomly permuted blocks with each block containing an equal number of patients allocated to alprostadil and placebo treatment was used. A randomisation list was generated by Aptiv Solutions GmbH for each stratum by a computer program (SAS versions 8.2 and 9.2, SAS Institute Inc., Cary, NC, USA) using a seed dependent random number generator. The randomisation list was provided to the sponsor for preparation of study medication. Study

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medication for each subject displayed the random number. Alprostadil and placebo were identical in appearance and both medical staff and patients were blinded.

Study schedule and intervention

The study schedule is presented in Fig. 1. During the run-in phase, patient data and medical history were recorded and eligibility was checked. During the treatment phase, the patients were hospitalised and randomised to treatment with 40 μg of alprostadil or placebo (containing 95 mg lactose) intravenously twice daily over 2 h in 50–150 ml of isotonic sodium chloride solution. After every infusion patients were questioned about adverse events (AEs). They were also asked to report AEs whenever they occurred. Intensity of rest pain, consumption of analgesics, and concomitant medication were recorded once daily. Digital picture(s) of the ulcer(s) together with a calibrated ruler were taken on Day 28 as well as 12 and 24 weeks after the end of treatment in the subsequent follow-up phase. During hospitalisation an in house standard wound treatment was performed daily. Antibiotic treatment was provided if necessary and antiplatelet drugs were allowed. Further concomitant treatment primarily comprised treatment of comorbidity and cardiovascular risk factors such as arterial hypertension, hypercholesterolemia, and diabetes mellitus.

Outcomes

Primary efficacy outcome measures were the rate of complete healing of ischaemic necrosis and ulceration 12 weeks after the end of treatment as assessed by the investigators, as well as the frequency and level of major amputations 24 weeks after the end of the treatment (Fig. 1).

Secondary efficacy outcome measures were the rate of complete healing of ischaemic necrosis and ulceration 24 weeks after the end of treatment, the intensity of rest pain assessed with a visual analogue scale (VAS) ranging from 0 cm (no pain) to 10 cm (maximum conceivable pain), consumption of analgesic medication, systolic pressure at ankle level (big toe pressure in diabetics with medial sclerosis of the lower limb artery), minor amputations (amputations of toes or of part of the foot), revascularisation procedures, and the number of patients with an increase or decrease in ulcer area of ≥50% as assessed by the investigator. Amputations were regarded as major if they were performed at or above the ankle joint and were classified according to their level (amputation below, at, or above knee). Efficacy outcomes were analysed on an intention to treat (ITT) basis; to impute missing efficacy values the last observation carried forward (LOCF) approach was applied.

Safety outcome measures were any AE that occurred during any phase of the study. An AE was any adverse, noxious, or pathological change compared with pre-existing conditions. AEs were assessed by the investigators following a standardised AE assessment sheet for seriousness, intensity, outcome, and causality. Laboratory values (haematology, clinical chemistry, and urinalysis) that were out of reference range or changed from baseline and were of clinical concern were also considered AEs. Also included were pre-existing physical findings such as vital signs (systolic and diastolic blood pressure, pulse rate), electrocardiograms (ECGs), and physical examination that worsened compared with baseline and was of clinical concern. Moreover, all-cause mortality, cardiovascular mortality, and cardiovascular events were recorded.

Statistical analyses

The study was conducted using a two stage group sequential adaptive design with possible sample size adjustment after the interim analysis. Statistical analysis was performed using SAS Version 9.3 (SAS Institute Inc.) and ADDPLAN Version 6.0. (ADDPLAN GmbH, Cologne, Germany).The null hypotheses were as follows: H_{01} = proportion of patients with complete ulcer healing under alprostadil ≤ proportion of patients with complete ulcer healing under placebo and H_{02} = proportion of patients with major amputation under alprostadil ≥ proportion of patients with major amputation under placebo. They were tested against the alternative hypotheses: H_{11} = proportion of patients with complete ulcer healing under alprostadil > proportion of patients with complete ulcer healing under placebo and H_{12} = proportion of patients with major amputation under alprostadil < proportion of patients with major amputation under placebo.

For confirmatory hypothesis testing at the interim analysis, as well as at the final analysis, the inverse normal method of combining the *p* values of the normal approximation test comparing two rates was used. The analyses were carried out stratified by diabetic/non-diabetic patients assuming no significant effect of the stratum. All group comparisons except testing of H_{01} and H_{02} were interpreted in the exploratory sense. A normal approximation test statistic for the difference of rates was calculated for each stratum and a combined test statistic was derived using a one sided version of the Cochran–Mantel–Haenszel statistic and adjusted for stratification. For estimation of the treatment effect, the difference between the healing rates (amputation rates, respectively) in the two treatment groups along with its corresponding 97.5% two sided repeated confidence interval is provided.

Safety data were analysed based on the safety set (SS) including all patients who had received at least one dose of study medication. Safety analysis was done on the treatment as actually received. Efficacy data were analysed based on the full analysis set including all patients who had received at least one dose of study medication with valid assessments for at least one primary efficacy variable. Efficacy analysis followed the ITT principle. If a patient terminated prematurely, the LOCF principle was applied. No imputation was done for missing data. Data from patients who withdrew their consent during the study were included in the analysis until the day of their withdrawal.

Sample size determination and adaptation

Assuming a placebo ulcer healing rate of 5% and an ulcer healing rate under alprostadil treatment of 12%, with a

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proposed maximum sample size of 300 in each treatment group (i.e., 250 patients for the first stage and 50 patients for the second stage) the study has 80% power to yield a statistically significant result concerning the hypothesis H_{01}.[15] Assuming a major amputation rate of 50% in the placebo group versus 35% in the alprostadil group,[3] the sample size provides 93% power concerning hypothesis H_{02}. At the first interim analysis on March 2009, including a total of 505 patients, both primary efficacy variables showed slightly better results in the alprostadil group, but the critical value was not exceeded. The number of patients in the second stage was therefore increased from 50 to 170 patients, resulting in an estimated sample size of 420 patients per treatment arm.

RESULTS

Study population

The first patient's first visit was in March 2004 and the last patient's last visit in July 2013. A total of 1484 patients were screened and 840 patients were randomised (Fig. 2). Of these, 406 patients were randomised in Russia, 335 in the Ukraine, 90 in Poland, five in Mexico, and four in Germany.

Table 1. Demographic characteristics and risk factors (ITT).

Demographic data	Alprostadil (n = 414)	Placebo (n = 424)
Age (years) (mean ± SD)	66.8 ± 8.6	66.4 ± 9.3
< 65 years (%)	36.7	40.1
≥ 65 years (%)	63.3	59.9
Gender (male/female) (number)	292/122	306/118
Height (cm) (mean ± SD)	170 ± 8.2	170.5 ± 8.1
Weight (kg) (mean ± SD)	75.4 ± 11.9	76.6 ± 12.6
BMI (kg/m^2) (mean ± SD)	26.2 ± 3.6	26.3 ± 4.0
Risk factors and diabetes status (%)		
Diabetes	43.0	43.4
Tobacco use	26.3	24.1
Alcohol	7.0	7.1
Caffeine	51.2	52.8

BMI = body mass index; ITT = intention to treat; SD = standard deviation.

A total of 839 patients received at least one study treatment, and 571 of these patients (68.1%) completed the study. The ITT analysis comprised 414 patients on alprostadil and 424 patients on placebo. Patient demographics and baseline characteristics for the ITT analysis are

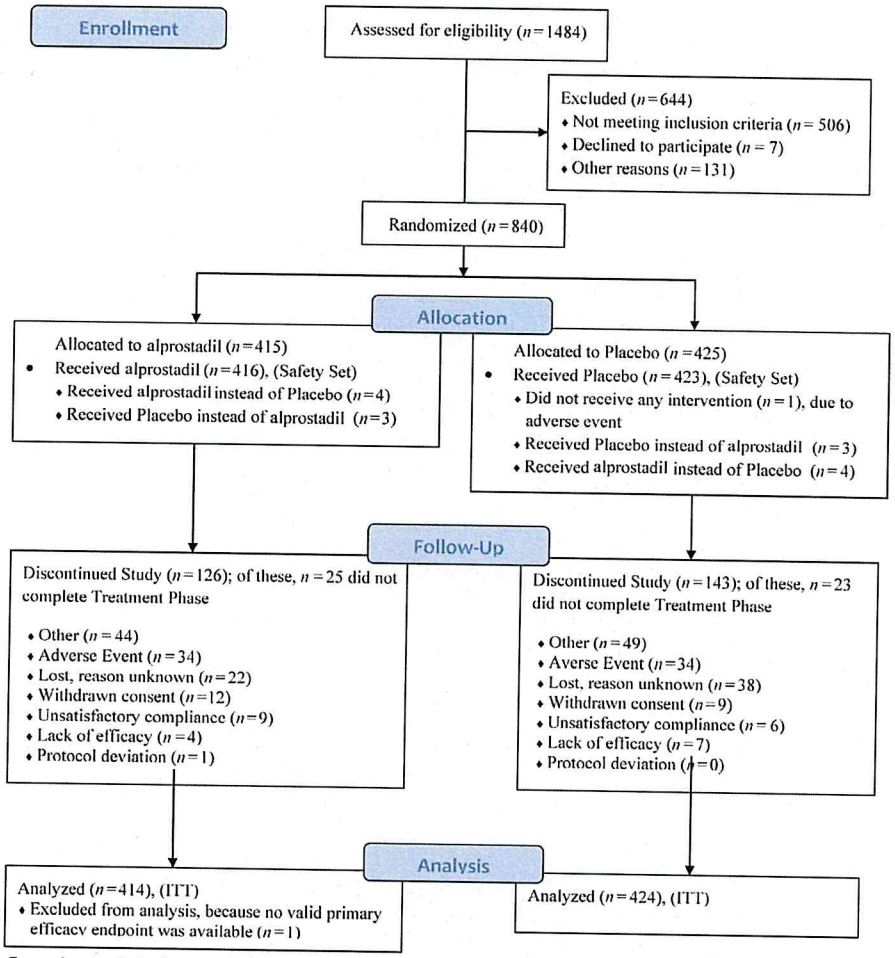

Figure 2. Participant flow chart of study population according to CONSORT. Seven subjects did not receive the treatment according to their randomisation and were reallocated for the efficacy analysis in order to follow the intention to treat principle.

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summarised in Table 1. There were no remarkable differences between the two groups regarding demographic features, diabetes status, and prevalence of risk factors. Also, both groups had similar baseline characteristics of the primary disease (Table 2).

Table 2. Baseline characteristics of PAOD (ITT).

	Alprostadil ($n = 414$)	Placebo ($n = 424$)
Duration of PAOD (years), mean ± SD	4.4 ± 4.5	4.4 ± 4.3
Intensity of rest pain (mmVAS), mean ± SD	39.7 ± 25.8	40.2 ± 25.8
Systolic pressure at ankle level (mmHg), mean ± SD	39.4 ± 24.1	36.7 ± 23.4
Analgesic medication, *n* (%)	292 (70.5)	314 (74.5)
Past treatment for PAOD		
Medical treatment, *n* (%)	272 (65.7)	270 (63.7)
Revascularisation, *n* (%)	89 (21.5)	84 (19.8)
Amputations, *n* (%)	76 (18.4)	67 (15.8)
Ischaemic skin lesions		
Number of lesions, *n* (%)[a]	502 (100)	519 (100)
Size (cm^2) (mean ± standard deviation)	2.28 ± 1.32	2.38 ± 1.42
Type		
Ulcer, *n* (%)[a]	362 (72.1)	375 (72.3)
Necrosis, *n* (%)[a]	140 (27.9)	144 (27.7)
Base		
Clean, *n* (%)[a]	186 (37.1)	178 (34.3)
Granulating, *n* (%)[a]	82 (16.3)	81 (15.6)
Infected, *n* (%)[a]	229 (45.6)	252 (48.6)
Missing, *n* (%)[a]	5 (1.0)	8 (1.5)

ITT = intention to treat; PAOD = peripheral arterial occlusive disease; SD = standard deviation; VAS = visual analogue scale.
[a] Percentages are based on the number of ischaemic skin lesions in the respective group.

Primary efficacy outcomes

The results for both primary efficacy variables are provided in Table 3. With regard to "complete healing at 12 weeks" the adjusted difference between alprostadil and placebo for all patients was 1.1 with a 95% confidence interval (−4.0 to 6.3). Regarding "rates of major amputation at 24 weeks" the adjusted difference was −2.1 with a 95% confidence interval (−6.7; 2.5). In summary, the results for both primary efficacy variables did not show superiority of alprostadil compared with placebo when regarding the whole ITT population. In a pre-specified analysis of the subgroup of diabetic patients, the rate of major amputations was numerically lower in the alprostadil group than in the placebo group (Table 3).

Secondary efficacy outcomes of interest

The results of the secondary efficacy outcomes "complete healing of all necrosis and ulceration", "cumulative rates of revascularisation procedures", "systolic pressure at ankle level", "intensity of rest pain", and "level of major amputation" were similar in both treatment groups 24 weeks after the end of study drug treatment, whereas "minor amputations" appeared to be more frequent in the alprostadil group (Table 4). The "consumption of analgesic medication" decreased between baseline and the immediate follow-up phase (Study Day 29 to Study Day 42) in both treatment groups: in the alprostadil group, 70.5% of patients consumed analgesic medication at baseline and 48.9% consumed analgesic medication in the immediate follow-up phase compared with 74.1% and 54.0% in the placebo group respectively (Tables 2 and 4). A small numerical difference in "area decrease of ulcers by ≥ 50%" was observed in favour of alprostadil in the alprostadil group compared with placebo at Study Day 28 in particular;

Table 3. Primary efficacy outcomes (ITT).

	Complete healing[a]				Major amputations[b]			
	Alprostadil *n/N*	%	Placebo *n/N*	%	Alprostadil *n/N*	%	Placebo *n/N*	%
Interim analysis								
Diabetics	17/103	16.5	20/105	19.0	8/103	7.8	22/105	21.0
Non-diabetics	32/150	21.3	23/146	15.8	24/150	16.0	27/146	18.5
All	49/253	19.4	43/251	17.1	32/253	12.6	49/251	19.5
Overall analysis								
Diabetics	30/178	16.9	33/184	17.9	15/178	8.4	25/184	13.6
Non-diabetics	46/236	19.5	40/240	16.7	37/236	15.7	37/240	15.4
All	76/414	18.4	73/424	17.2	52/414	12.6	62/424	14.6
	Cochran–Mantel–Haenszel (repeated 97.5% CI)[c]	*p*	Statistic**		Cochran–Mantel–Haenszel (repeated 97.5% CI)[c]	*p*	Statistic[d]	
Interim analysis (all patients)	(−6.4 to 10.9)	.2587	0.647		(−15.1 to 1.3)	.0173	2.112	
Final analysis (all patients)	(−4.8 to 7.7)	.3463	0.533		(−8.9 to 2.4)	.1154	1.294	

CI = confidence interval; ITT = intention to treat; *N* = number of study subjects in stage.
[a] At Week 12 after treatment.
[b] At Week 24 after treatment.
[c] Two sided.
[d] Inverse normal method; critical value to exceed is 2.520 at interim analysis and 2.296 at study end.

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Table 4. Secondary efficacy outcomes (ITT).

	Alprostadil ($n = 414$)		Placebo ($n = 424$)	
	n/N[a]	%	n/N[a]	%
Complete healing of all necrosis and ulcerations[b]	108/289	37.4	103/279	36.9
Cumulative rates of revascularisation procedures[b]	6/294	2.0	7/283	2.5
Cumulative rates of minor amputations[b,c]	65/316	20.6	40/297	13.5
Decrease in ulcer area of ≥50%				
At Study Day 28 (end of treatment)	106/351	30.2	90/370	24.3
At Study Day 112	84/270	31.1	78/275	28.4
Analgesic medication at Study Days 29–42	170/348	48.9	191/354	54.0
Height of major amputation[b,c]				
Above knee joint	38/414	9.2	46/424	10.8
At knee joint	0/414	0	1/424	0.2
Below knee joint	14/414	3.4	15/424	3.5
Intensity of rest pain[b]				
absolute value (mmVAS), mean ± SD	17.6 ± 25.3		16.4 ± 25.1	
change from baseline (mmVAS), mean ± SD	−22.2 ± 30.4		−23.9 ± 31.5	
Systolic pressure at ankle level at the end of treatment[a]				
Subjects with data, *n*	383		394	
absolute value (mmHg), mean ± SD	42.7 ± 28.2		40.5 ± 27.5	
change from baseline[d] (mmHg), mean ± SD	3.4 ± 14.1		3.8 ± 12.3	

ITT = intention to treat; SD = standard deviation; VAS = visual analogue scale.

[a] Only patients with Fontaine Stage IV in one leg were included in the study.

[b] At 24 weeks after end of treatment.

[c] Comparison of time to amputation did not show a clinically relevant difference for any amputation or for major amputations only.

[d] Worst change analysis of A. posterior tibial or A. dorsalis pedis.

however, this was not statistically significant nor clinically relevant (Table 4). The complete list of secondary outcome measures can be found in https://clinicaltrials.gov.

Safety outcomes

The SS comprised 416 patients on alprostadil and 423 patients on placebo. Treatment emerged adverse events (TEAEs) were reported in 53.8% of patients in the alprostadil group and 48.5% of patients in the placebo group. Patients reporting TEAEs were slightly more frequent in the alprostadil group than the placebo group during the treatment phase; however, this was assessed as not clinically meaningful. Regarding serious TEAEs and unexpected TEAEs comparable frequencies were reported in both treatment groups (Table 5). For the majority of TEAEs the intensity was

Table 5. Safety outcomes (SS).

	Alprostadil ($n = 416$)		(AE)	Placebo ($n = 423$)		(AE)
	n	(%)		*n*	(%)	
TEAEs, overall	224	53.8	510	205	48.5	470
Events in the treatment phase	147	35.3	298	134	31.7	260
Events in the follow-up phase	133	32.0	212	118	27.9	210
Serious TEAEs, overall	87	20.9	129	62	14.7	89
Events in the treatment phase	34	8.2	45	25	5.9	31
Events in the follow-up phase	59	14.2	84	41	9.7	58
Unexpected TEAEs, overall	216	51.9	445	195	46.1	397
Events in the treatment phase	136	32.7	248	128	30.3	218
Events in the follow-up phase	131	31.5	197	109	25.8	179
All-cause mortality, overall	20	4.8	22	15	3.5	15
Events in the treatment phase	5	1.2	5	5	1.2	5
Events in the Follow-up Phase	15	3.6	17	10	2.4	10
Cardiovascular mortality, overall	11	2.6	11	14	3.3	14
Events in the treatment phase	4	1.0	4	5	1.2	5
Events in the follow-up phase	7	1.7	7	9	2.1	9
Myocardial infarctions, overall	5	1.2	5	6	1.4	6
Events in the treatment phase	2	0.5	2	5	1.2	5
Events in the follow-up phase	3	0.7	3	1	0.2	1
Strokes, overall	3	0.7	3	3	0.7	3
Events in the treatment phase	0	0	0	1	0.2	1
Events in the follow-up phase	3	0.7	3	2	0.5	2

AE = adverse event; SS = safety set; TEAE = treatment emergent adverse event.

evaluated "mild" or "moderate" in both treatment groups, severe TEAEs during the treatment phase were reported in 22 (5.3%) patients in the alprostadil group and in 22 patients (5.2%) in the placebo group. Frequencies of drug related TEAEs during the treatment phase were reported in 10.6% of patients with alprostadil and 7.8% of patients with placebo. Discontinuations during the treatment phase due to TEAEs were reported in similar percentages of patients (5.5% in the alprostadil group and 6.4% in the placebo group). Also the all-cause mortality, the cardiovascular mortality, and the incidence of cardiovascular events (cardiovascular mortality, myocardial infarction, or stroke) were similar in both treatment groups (Table 5). Both treatment groups showed comparable results for ECG, vital signs, and laboratory parameters except for C-reactive protein (CRP): baseline CRP was slightly higher in the alprostadil group (22.6 ± 75.0 mg/dL) compared with placebo

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(17.9 ± 52.3 mg/dL), and at the end of treatment the change from baseline was −4.2 ± 60.0 mg/dL in the alprostadil group compared with −0.5 ± 41.6 mg/dL with placebo.

DISCUSSION

This study investigated the efficacy and safety of alprostadil compared with placebo in patients with PAOD Fontaine Stage IV and up to two ischaemic skin lesions. A total of 840 patients were randomised and 68.1% of patients completed the study. This low adherence rate may be explained by the long study duration, especially the follow-up period where no treatment was administered.

Although at interim analysis a positive trend was evaluated for the primary efficacy endpoints, at final analysis superiority of alprostadil could not be shown. For "complete ulcer healing rate 12 weeks after treatment start" and "rate of major amputation 24 weeks after treatment start" a small, non-statistically significant difference in favour of alprostadil was observed (18.4% vs. 17.2% and 12.6% vs. 14.6% respectively; Table 3). However, further subgroup analyses revealed that diabetic status was associated with a numerically lower amputation rate in the alprostadil group than the placebo group (8.4% vs. 13.6%; Table 3). For most secondary efficacy variables both treatment groups showed comparable results (Table 4). In both treatment groups the "consumption of analgesic medication" decreased by ~20% between baseline and the early post treatment phase, also rest pain levels were equally reduced (Tables 2 and 4). A slight, numerical advantage for alprostadil emerged from the "area decrease of ulcers by ≥ 50%", suggesting there may have been an improved healing effect under alprostadil in comparison with placebo. The evaluation of the safety variables was in line with the known safety profile of alprostadil. The results regarding ulcer healing and pain reduction agree with the Cochrane Review, in which an improved healing effect under prostanoids and a reduction of pain in patients with CLI was shown.[13] The efficacy results in the present study were contrary to our general experience in daily clinical practice and in contrast with the results of numerous clinical trials, among them seven prospective randomised trials, which provided evidence of efficacy of alprostadil in patients with PAOD Stage III/IV.[6–12]

The study has the following major limitations. First, the study duration was long with over 10 years between study design and final analysis. During this period, clinically relevant improvements in wound treatment and cardiovascular medication, as well as general progress in anti-hyperglycemic, and antithrombotic medication occurred, improving the underlying diseases. This resulted in markedly better outcomes and prognoses for patients with CLI at the end of the study. As a result, overall efficacy outcomes for both groups were far better and treatment differences were smaller than anticipated at the start of the study. Secondly, a systematic review describes complete ulcer healing following successful surgical revascularisation after 4 months and following endovascular revascularisation after 7 months in diabetic patients.[16] It is, therefore, not surprising that complete ulcer healing was not achieved by a single application of PGE1 due to multiple confounders influencing wound healing.

In clinical practice alprostadil is used to start healing, therefore decreases in ulcer area may be considered a more meaningful parameter. Regarding "area decrease of ulcers by ≥50%," a numerical difference in favour of alprostadil was observed in the present study, particularly at the end of study treatment. As this effect became smaller during the follow-up phase, a second treatment interval, representing current clinical practice, might have been advantageous to help maintain the improvements achieved by the first series of infusions.

Some critical aspects regarding the study population, as well as basic PAOD treatment may also have affected the results. First, the basic treatment of PAOD including treatment of comorbidities such as arterial hypertension, hypercholesterolemia, cardiovascular disorders, and diabetes mellitus varied in the participating countries. This may be related to the timing of participation in the trial, because the treatment of PAOD has evolved over the past decade to include a broad approach, focusing on the reduction of adverse cardiovascular events, improving symptoms in claudication, and preventing tissue loss in CLI.[17] In addition, treatment of wounds and general infections was not consistent across sites. For example, in Russia, which contributed nearly half the study population, a substantial improvement in wound treatment and co-medication took place between 2007 and 2009.

Secondly, the study population consisting of patients between 64 and 68 years of age, with alcohol consumption in <10%, and only 25% smokers does not reflect the typical CLI patient population from a clinical practice point of view. In a German nationwide analysis based on 1.3 million hospitalisations of PAOD the patients with CLI were older, ~50% being >75 years.[18] The younger age and lower percentage of people reporting alcohol and cigarette consumption in the present study, compared with the typical patient demographic, suggests a better prognosis for this study population even without PAOD medication. This may also have contributed to the low mortality rate in comparison with other studies. Moreover, as the age group of the younger patients (<65 years) was larger in the placebo group (40.2 vs. 36.8%; Table 1) this might additionally have had a positive impact on the efficacy results in this group.

Finally, the decrease in CRP from baseline to the end of treatment was more pronounced in the alprostadil group (−4.16 mg/dL) versus placebo (−0.51 mg/dL) potentially indicating better healing with alprostadil, which was also apparent in the subgroup analysis. Diabetic patients, who in general show higher CRP concentrations and higher ulcer rates with more extended wound areas, were associated with a numerically lower amputation rate with alprostadil than placebo (Table 3).

In conclusion, conservative treatment options for this patient population are still limited with minor impact on prognosis, quality of life and amputation rate. Although

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superiority of alprostadil compared with placebo could not be demonstrated in this study, our experience in daily practice in no-option patients remains in contrast with the outcome of this study.

CONFLICT OF INTEREST

J.W.G. Bentz, F. Grieger, O. Randerath and G. Hamm are employees of UCB Pharma. H. Lawall received honoraria from UCB Pharma for lectures and participation in an advisory board.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2016.12.035.

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