Efficacy and Safety of DP-R202 in Patients with Chronic Artery Occlusive Disease: Multicenter Randomized Double-blind Active-controlled Parallel Group Phase III Clinical Study

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ABSTRACT

Purpose: Sarpogrelate hydrochloride, a selective 5-hydroxytryptamine 2A antagonist, is a widely used antiplatelet agent for the treatment of peripheral arterial disease (PAD). DP-R202 is a new sarpogrelate hydrochloride product with an improved dosage regimen compared with the agent in current use. The aim of this study was to compare the efficacy and

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safety profile of DP-R202 and Anplag* Tab in patients with PAD.

Methods: This study was a 12-week, multicenter, randomized, double-blinded, active-controlled, parallel group comparative Phase III clinical trial. One hundred fifty-one volunteer patients with PAD were randomized to receive DP-R202 300 mg once daily or Anplag Table 100 mg TID for 12 weeks. The primary end point was a change in patient assessment of lower leg pain intensity with the use of a visual analog scale (VAS) after 12 weeks of treatment. Results after 4, 8, and 12 weeks of treatment were compared with baseline and between treatment groups, and all patients were assessed for adverse events (AEs), clinical laboratory data, and vital signs.

Findings: Two hundred thirty-one patients from 25 medical centers were assessed, and 151 were enrolled and randomly assigned to 1 of 2 treatment groups. Seventy-five patients received DP-R202 300 mg once daily and 76 patients received Anplag Table 100 mg TID for 12 weeks. Analysis of the change in lower leg pain intensity as determined by VAS score between baseline and week 12 (mean [SD], 20.72 [20.06] mm vs 15.55 [21.44] mm) suggested that DP-R202 was not inferior to Anplag Tab, and no significant differences were found in the secondary end points. No significant between-group differences were observed in the prevalence of drug-related clinical- or laboratory-determined AEs. For tolerability, no specific issue was found during the treatment period.

Implication: The results of this study suggest that DP-R202 was not inferior to Anplag Tab for efficacy in patients with PAD and indicated a good safety profile. (*Clin Ther.* 2016;38:557–573) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: Anplag Tab, DP-R202, PAD, sarpogrelate.

INTRODUCTION

Peripheral arterial disease (PAD) causes functional and structural changes in blood vessels by hemadostenosis due to atherosclerotic plaque.[1,2] It occurs most commonly in the descending aorta and lower artery, although it can occur in all blood vessels except those in in the heart and cerebrum.[3] According to the US National Health and Nutrition Examination Survey in 2000, the prevalence of PAD in adults older than 40 years is 4.3%, estimated to be ~500,000 people, and increases with age.[4] PAD is largely classified into asymptomatic, intermittent claudication, critical lower limb ischemia, and acute lower limb ischemia according to symptoms. PAD is a fatal disease that results in reduced functionality and decreased quality of life by causing fatigue, discomfort, and pain due to occurrence of ischemia, accompanying chronic pain, ulcer, or gangrene; PAD requires emergency treatment such as amputation because of the rapid decrease in limb perfusion.[5,6] Therefore, treatment of PAD decreases the mortality rate due to cardiovascular disorders and reduces the symptoms and risk of lower limb amputation in patients with symptoms of lower limb ischemia.[1] Sarpogrelate hydrochloride is a selective 5-hydroxytryptamine 2A (serotonin) antagonist that blocks 5-hydroxytryptamine 2A receptors, which are distributed in vascular cells and platelets, and shows antithrombogenesis, antiplatelet aggregation, and cytostatic effects in vascular endothelial cells carried by serotonin[7,8] and is currently used in patients to ameliorate the pain and symptoms of ulceration that accompany chronic arterial occlusion. (Figure 1)

DP-R202 (sarpogrelate hydrochloride; 300 mg) was developed to improve drug compliance over sarpogrelate TID, because it includes both immediate- and sustained-release components. Therefore, DP-R202 has the advantage of showing both a rapid onset of effect and sustained release.

In earlier bioequivalence and repeated dose tests conducted on healthy male volunteers, when comparing DP-R202 (300 mg, once daily) and Anplag* Tab (100 mg, TID), the C_{max} and T_{max} values of sarpogrelate and the M1 active metabolite were similar, and the AUClast value was greater in the DP-R202 group than in the Anplag Tab group. The antiplatelet aggregation effect and residual platelet aggregation did not differ significantly between the groups. For tolerability, serious adverse events (AEs) were absent among the 34 patients administered DP-R202 or Anplag Tab; furthermore vital signs, ECG, and physical examination indicated no meaningful changes after administration. On the basis of these results, the safety profile and efficacy of DP-R202 in comparison with Anplag Tab in patients with PAD were evaluated in a randomized, active-controlled, and double-blind Phase III clinical study that involved administration of the agents for 12 weeks.

*Trademark: Anplag® Tab (Yuhan Corp, Seoul, Republic of Korea).

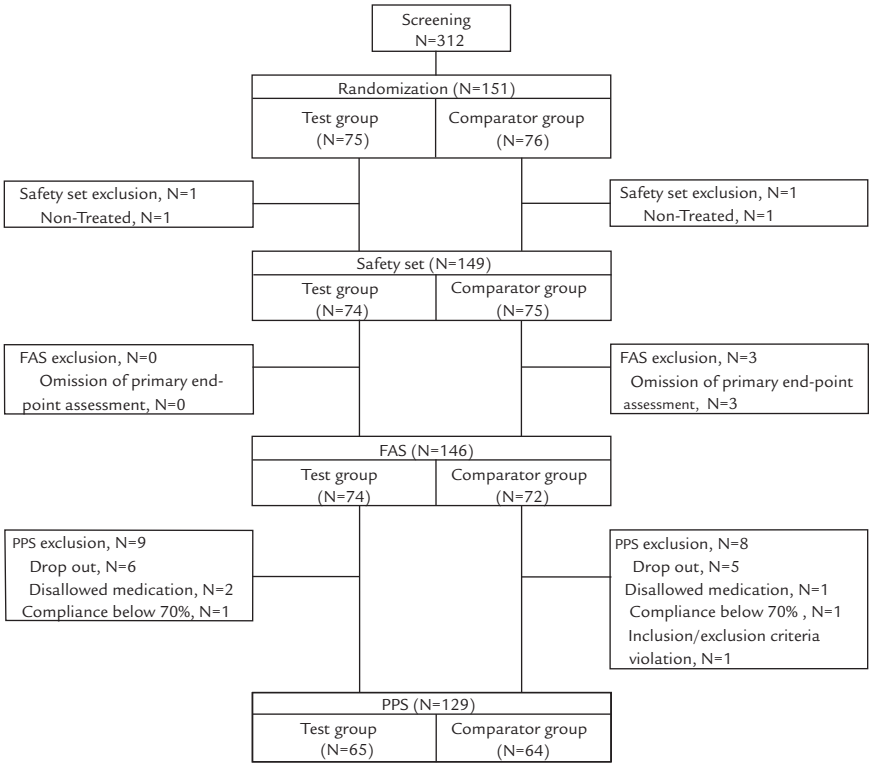

Figure 1. Flow diagram of all patients.

TARGET PATIENTS AND METHODS

Clinical Trial Design and Target Patients

This clinical trial was a 12-week, multicenter, randomized, double-blind, parallel group, Phase III study that enrolled patients in 25 institutions, appointed as national clinical trial institutions, and received the approval of the institutional review boards of all participating institutions.

Patients were men or women with lower limb peripheral artery occlusion aged >20 years with Fontaine stage II/III, who had lower limb pain or symptoms such as leg stretching or numbing, whose lower limb pain degree was >40 mm as evaluated by visual analog scale (VAS) at screening, and with an ankle-brachial index (ABI) ≤ 0.9 or stenosis rate $>50\%$, diagnosed with PAD, and who voluntarily agreed to participate and signed an informed consent form. Patients who underwent peripheral-related surgery within 1 month of study initiation, who were Fontaine stage IV, New York Heart Association class III–IV, had uncontrollable hypertension (systolic blood pressure, ≥ 180 mm Hg, diastolic blood pressure, ≥ 110 mm Hg), a history of cerebrovascular disease (cerebral infarction, cerebral hemorrhage, etc.) within 6 months before clinical trial participation, those with uncontrollable diabetes (glycosylated hemoglobin [HbA_{1c}], $\geq 9\%$), and renal insufficiency (creatinine, >3.0 mg/dL) were excluded from the trial.

Drugs that may affect the efficacy of the investigational product, such as anticoagulants, antiplatelets, thrombolytic agents, prostaglandin E1 preparations, heparin, and aspirin >100 mg/d, were prohibited during the study period. In addition, NSAIDs and analgesics were prohibited within 24 hours of the time of efficacy assessment. NSAID use during the study period was not to exceed a total of 5 days.

Selected patients were stratified in a 1:1 ratio and randomly assigned to receive the investigational product or comparator according to their categorization as Fontaine Stage II or III with the use of a block randomization method. Both the investigators and patients were blinded to the group assignment.

Administration Method

The treatment drug was DP-R202 (sarpogrelate hydrochloride 300 mg; Alvogen Korea Co., Ltd., Seoul, Republic of Korea) and the comparator was Anplag Tab (sarpogrelate hydrochloride 100 mg; Yuhan Corp, Seoul, Republic of Korea). Drugs were administered for 12 weeks. The treatment group took the investigational product of DP-R202, 1 tablet once a day (morning), and took placebo, Anplag Tab, 1 tablet TID. The comparator group took the investigational product of Anplag Tab, 1 tablet TID, and took placebo, DP-R202, 1 tablet once a day (morning). The drugs were administered at a fixed dosage; no dosage fluctuation according to subject condition was performed.

Clinical Trial Compliance

Drug compliance was calculated by checking the quantity of investigational product returned by patients at 2, 8, and 12 weeks. If drug compliance was $<70\%$, the subject was excluded according to the suspension and dropout criteria in the clinical trial plan.

Efficacy and Safety Assessment Variables

Patients visited at 4, 8, and 12 weeks, including the baseline visit (visit 2), for a total of 4 visits and underwent efficacy and quality-of-life assessments.

Variation in lower limb pain (by VAS) between baseline and 12 weeks was the primary efficacy assessment variable. The variation in lower limb pain (by VAS) and coldness (5-point scale) between baseline and 4 and 8 weeks, ABI, ankle systolic pressure (ASP), quality-of-life assessment index (Short Form 36; SF-36), maximum walking distance (MWD), pain-free walking distance (PFWD), and investigator's general assessment (by VAS) at 4, 8, and 12 weeks were the secondary efficacy assessment variables. The pain and coldness tests were performed by assessing the pain and coldness felt by the subject 24 hours before the visit. MWD and PFWD were measured only in patients in whom such measurements were possible, and they were asked to record the degree of lower limb pain every day from baseline until the end of the clinical trial. In addition, AEs, laboratory tests, vital signs, and weight measurements were evaluated for safety assessment. Physical tests and vital signs were conducted at the screening visit, at the time of initiation of administration of the investigational product, and at 4, 8, and 12 weeks thereafter. A urine pregnancy test and laboratory tests were conducted at the screening visit and 12 weeks after the first administration of the investigational product. An ECG test was conducted at the screening visit and at 4, 8, and 12 weeks after the first administration of the investigational product. Hematologic, blood chemical, blood coagulation, and urine tests were also performed.

Statistical Analysis

The per protocol set (PPS) was used as the main analysis method, and the full analysis set (FAS) was used as a secondary analysis of efficacy data in this clinical trial. Tolerability was analyzed with the use of the safety set.

Efficacy Assessment

FAS analysis was conducted on patients who were administered the investigational product at least once and in whom the primary efficacy assessment variable was measured more than once after random assignment. In the PPS analysis, data obtained from patients who completed the clinical trial according to the clinical trial protocol without any major violation were included in the analysis. Those who took a prohibited medication, had a rate of drug compliance $<70\%$, or in whom the primary efficacy assessment variable was not measured were excluded. The primary efficacy assessment variable at baseline and 12 weeks, and the variation in lower limb pain (by VAS) between baseline and 12 weeks are presented with the use of descriptive statistics (number of patients, mean [SD], and median) according to administration group. The 95% 2-sided CI of the variation between the 2 groups was also presented. If the lower limit of the 2-sided 95% CI was >-10, the treatment drug was determined to be noninferior to the comparator drug.

For the secondary efficacy assessment, descriptive statistics (number of patients, mean [SD], and median) of each secondary efficacy assessment variable are presented, and the difference between the 2 groups was analyzed with the use of a 2-sample t test or Wilcoxon rank sum test according to whether the data were normally distributed. The level of significance of all analyses was 0.05, and a 2-tailed test was conducted. Continuous variables are presented as the number of patients, means (SDs), and medians; categorical variables are presented as frequencies and percentages. All P values are presented to 4 decimal places, and a value of $P < 0.05$ was considered to indicate statistical significance. A test of normality was

conducted on all continuous variables, and a 2-sample *t* test, paired *t* test, Wilcoxon rank sum test, or Wilcoxon signed rank test was conducted as appropriate. For categorical variables, on the basis of expected frequency being >5 in a section is $>80\%$, either Pearson χ^2 test or Fisher exact test was performed.

Safety Assessment

The safety set comprised patients who were administered the investigational product at least once, and the analysis was performed as described below.

AEs

Frequency and percentage of AEs after investigational product administration (treatment-emergent AEs), adverse drug reactions (ADRs), serious AEs (SAEs), and AEs that led to dropout were presented, and the homogeneity between administration groups was analyzed with the use of Pearson χ^2 test or Fisher exact test. AEs were coded according to system organ class and preferred term in the Medical Dictionary for Regulatory Activities, and number of occurrences, occurrence rate, and number of occurrences by administration group of coded AEs are also presented.

Laboratory Tests

For comparisons within groups, descriptive statistics (number of patients, means [SDs], medians [range]) at baseline, 12 weeks, and changes between baseline and 12 weeks are presented according to administration group for continuous variables. A paired *t* test or Wilcoxon signed rank test was conducted according to whether the data were normally distributed. For categorical variables, frequencies and percentages are presented, and McNemar test was used for analysis.

For comparison between administration groups, a 2-sample *t* test or Wilcoxon rank sum test was used to analyze changes from baseline to 12 weeks according to whether the data were normally distributed for continuous variables. For categorical variables, Pearson χ^2 test or Fisher exact test was used to analyze the rate of change from a normal baseline result to abnormal at 12 weeks, and the homogeneity between administration groups was determined.

Vital Signs and Weight

For comparison between administration groups, descriptive statistics (number of patients, means [SD], and medians [range]) at baseline and 12 weeks, and changes from baseline to 12 weeks are presented according to administration group. A paired t test or Wilcoxon signed rank test was performed according to whether the data were normally distributed, and a 2-sample t test or Wilcoxon rank sum test was used to analyze changes from baseline to 12 weeks according to whether the data were normally distributed.

RESULTS

A total of 151 patients who met the inclusion criteria were enrolled in this trial (treatment group, 75 patients; comparator group, 76 patients). Of the 151 patients, 135 completed the trial (treatment group, 68 patients; comparator group, 67 patients). Sixteen patients (treatment group, 7 patients; comparator group, 9 patients) terminated the trial prematurely. The reasons for premature termination were protocol deviation in 3 patients (comparator group), withdrawal of informed consent in 8 patients (treatment group, 5 patients; comparator group, 3 patients), failure to follow-up in 1 subject (comparator group), AEs in 3 patients (treatment group, 1 patient; comparator group, 2 patients), and other in 1 patient (treatment group). No subject dropped-out because of lack of effectiveness. The demographic information and other baseline information of the patients were similar between the groups (Table I).

Efficacy Assessment

Assessment Result of Primary Efficacy Assessment Variable

The difference in VAS scores between the 2 groups before and after drug administration is shown in Table II. Lower limb pain was measured with the use of a 100-mm VAS, and the PPS analysis found that the mean VAS change in lower limb pain from baseline to 12 weeks (baseline–12 weeks) was 20.72 (20.06) mm in the treatment group and 15.55 (21.44) mm in the comparator group [95% 2-sided CI, –2.06 to 12.41). The lower limit of the 2-sided CI was –2.06 mm, which exceeded the noninferior limit (–10 mm); therefore, the noninferiority of the treatment drug compared with the comparator product was confirmed.

Assessment Result of Secondary Efficacy Assessment Variable

The secondary efficacy assessment variable results are presented in Tables III–IX. The mean lower limb VAS scores (baseline–12 weeks) were decreased at

Table I. Demographic and baseline characteristics.

Characteristic	DP-R202 (n = 75)	Anplag (n = 76)	*P*
Age, mean [SD], y	70.20 [8.48]	68.92 [9.13]	0.4032*
Male, n (%)	67 (89.33)	62 (81.58)	0.1769†
Risk factor, n (%)			
Hypertension	58 (77.33)	59 (77.63)	0.9650†
Dyslipidemia	39 (52.00)	37 (48.68)	0.6837†
Diabetes	40 (53.33)	32 (42.11)	0.1672†
Cardiovascular disease,‡ n (%)	41 (54.67)	32 (42.11)	0.1225†
Medication use, n (%)			
Vasodilators	57 (76.00)	63 (82.89)	0.2943†
Antiplatelet agents and anticoagulants	11 (14.67)	5 (6.58)	0.1064†
Statin	56 (74.67)	59 (77.63)	0.6690†
Fontaine classification stage, n (%)			
Stage II	65 (86.67)	59 (77.63)	0.1474†
Stage III	10 (13.33)	17 (22.37)	

*Determined by Wilcoxon rank sum test.
†Determined by Pearson χ^2 test.
‡Defined as having myocardial infarction, angina, or coronary artery disease.

baseline compared with those at 4 and 8 weeks (treatment group: 4 weeks, 8.68 [13.80] mm; 8 weeks, 15.62 [18.23] mm vs comparator group: 4 weeks, 8.58 [15.39] mm; 8 weeks, 12.36 [18.49] mm), and no significant difference was found between the groups ($P = 0.8820$, $P = 0.3817$).

The mean change in ABI between baseline and at 4, 8, and 12 weeks was 0.01 (0.13), 0.01 (0.18), and –0.01 (0.13), respectively, in the treatment group and 0.02 (0.11), 0.00 (0.09), and 0.01 (0.11), respectively, in the comparator group. No significant difference was found between the groups ($P = 0.7844$, $P = 0.6241$, and $P = 0.4609$, respectively).

The coldness symptom score on a 5-point scale at baseline compared with at 4, 8, and 12 weeks was reduced by 0.20 (1.13), 0.35 (1.11), and 0.42 (1.30) points, respectively, in the treatment group and by 0.45 (1.10), 0.64 (1.33), and 0.64 (1.26) points, respectively, in the comparator group. No significant difference was found between the groups ($P = 0.1187$, $P = 0.1973$, and $P = 0.3311$, respectively).

The mean change in ASP at baseline compared with at 4, 8, and 12 weeks was –0.60 (23.49), 1.45 (29.01), and –0.70 (24.03) mm Hg, respectively, in the treatment group and 0.56 (19.61), –2.11 (16.97), and –1.53 (20.87) mm Hg, respectively, in the comparator group. No statistically significant difference was found between the groups ($P = 0.9185$, $P = 0.7517$, and $P = 0.6790$, respectively).

The change in MWD at baseline compared with at 12 weeks was 43.10 (162.92) m in the treatment group and 38.93 (154.97) m in the comparator group. The PFWD was increased to 52.13 (176.06) m in the treatment group and 17.09 (143.39) m in the comparator group, respectively, at 12 weeks compared with baseline. The between-group difference was not significant ($P = 0.4279$ and $P = 0.2871$, respectively). The MWD and PFWD found significant differences compared with baseline in the treatment group but not the in comparator group.

The mean general condition of patients assessed by an investigator with the use of a VAS at 4, 8, and 12 weeks was decreased to 11.66 (14.40), 18.45 (17.32), and 21.72 (18.75) mm, respectively, in the treatment group and 10.84 (14.46), 14.28 (16.26), and 18.27

Table II. Changes in VAS of lower leg pain after 12 weeks of treatment.

Pain VAS, mm	DP-R202	Anplag	Mean difference between groups [95% CI]	*P*
PPS, n	65	64		
Baseline				0.3374*
Mean [SD]	61.89 [15.44]	64.25 [15.38]		
Median	60.00	61.00		
Min, Max	40.00, 100.00	40.00, 100.00		
Week 12				
Mean [SD]	41.17 [19.87]	48.70 [19.36]		
Median	40.00	50.00		
Min, Max	10.00, 95.00	11.00, 95.00		
Change (week 12–baseline)			5.18 [–2.06 to 12.41]	0.1592†
Mean [SD]	20.72 [20.06]	15.55 [21.44]		
Median	20.00	10.00		
Min, Max	–20.00, 70.00	–35.00, 70.00		
P	<0.0001†,‡	<0.0001†,‡		
FAS, n	74	72		
Baseline				
Mean [SD]	61.15 [15.54]	64.26 [15.30]		0.1809*
Median	60.00	61.00		
Min, Max	40.00, 100.00	40.00, 100.00		
Week 12				
Mean [SD]	42.32 [19.39]	48.90 [19.30]		
Median	40.00	50.00		
Min, Max	10.00, 95.00	10.00, 95.00		
Change (week 12–baseline)			3.46 [–3.36 to 10.29]	0.3175†
Mean [SD]	18.82 [19.71]	15.36 [21.98]		
Median	19.50 10.00	10.00		
Min, Max	–20.00, 70.00	–35.00, 70.00		
P	<0.0001†,‡	<0.0001†,‡		

FAS = full analysis set; PPS = per protocol set; VAS = visual analog scale.
*Determined by Wilcoxon rank sum test.
†Determined by 2-sample *t* test.
‡Determined by paired *t* test.

(18.98) mm, respectively, in the comparator group. No statistically significant difference was found between the groups ($P = 0.6107$, $P = 0.2359$, and $P = 0.2999$, respectively).

For quality of life assessed with the use of the SF-36, no statistically significant difference between the groups was observed. FAS analysis found a similar result as PPS, and no statistically significant difference was found between the groups.

Final Conclusion on Efficacy

The noninferiority of the study group compared with the comparator group was confirmed by the improvement in lower limb pain with the use of a VAS in patients with PAD of Fontaine stage II/III accompanied by claudication and lower limb pain at rest. No significant difference was found between the groups in terms of coldness, ABI, ASP, quality of life (SF-36), MWD, PFWD, or general assessment performed by an investigator.

Table III. Changes in VAS of lower leg pain after 4 and 8 weeks of treatment.

	PPS			FAS		
Pain VAS, mm	DP-R202	Anplag	*P*	DP-R202	Anplag	*P*
Baseline, n	65	64	0.3374*	74	72	0.1809*
Mean [SD]	61.89 [15.44]	64.25 [15.38]		61.15 [15.54]	64.26 [15.30]	
Median	60.00	61.00		60.00	61.00	
Min, Max	40.00, 100.00	40.00, 100.00		40.00, 100.00	40.00, 100.00	
Week 4						
Mean [SD]	53.22 [16.79]	55.67 [17.70]		53.05 [16.57]	55.57 [17.75]	
Median	50.00	55.00		50.00	55.00	
Min, Max	18.00, 97.00	21.00, 90.00		18.00, 97.00	20.00, 90.00	
Change 1			0.8820*			0.3175†
Mean [SD]	8.68 [13.80]	8.58 [15.39]		8.09 [13.24]	18.69 [16.00]	
Median	10.00	5.00		8.00	5.00	
Min, Max	−20.00, 60.00	−25.00, 51.00		−20.00, 60.00	−25.00, 51.00	
P	<0.0001‡	<0.0001§		<0.0001‡	<0.0001‡	
Week 8						
Mean [SD]	46.28 [18.63]	51.89 [18.89]		46.82 [18.08]	51.90 [18.93]	
Median	47.00	50.00		47.00	50.00	
Min, Max	0.00, 90.00	20.00, 90.00		0.00, 90.00	10.00, 90.00	
Change 2			0.3817*			0.5429*
Mean [SD]	15.62 [18.23]	12.36 [18.49]		14.32 [17.67]	12.36 [19.57]	
Median	15.00	8.00		10.50	7.50	
Min, Max	−20.00, 60.00	−21.00, 69.00		−20.00, 60.00	−21.00, 69.00	
P	<0.0001§	<0.0001‡		<0.0001‡	<0.0001‡	

Change 1 = baseline–week 4; Change 2 = baseline–week 8; FAS = full analysis set; PPS = per protocol set; VAS = visual analog scale.
*Determined by Wilcoxon rank sum test.
†Determined by 2-sample *t* test.
‡Determined by Wilcoxon signed rank test.
§Determined by paired *t* test.

Safety Assessment

Summary of AEs

The frequency of AEs after investigational product administration was 29.73% (22 of 74 patients, 41 cases) in the treatment group, and 40.00% (30 of 75 patients, 49 cases) in the comparator group. The ADR rates in the study and comparator groups were 1.35% (1 of 74 patients, 1 case) and 4.00% (3 of 75 patients, 3 cases), respectively. The SAE rate was 1.35% (1 of 74 patients, 1 cases) and 5.33% (4 of 75 patients, 4 cases) in the study and comparator groups, respectively. The rate of AEs that led to dropout was 2.67% (2 of 75 patients, 2 cases) in the comparator group, and 0.00% (0 of 74 patients, 0 cases) in the treatment group. Therefore, none of the criteria differed significantly between the groups.

Severity of AEs and Cause-and-Effect Relation with the Drug

The severity of AEs and their association with the investigational product were summarized. Events evaluated to be "cannot exclude relevant possibility (possible), high relevant possibility (probable), definitely relevant (definite)" by an investigator were classified as drug-related AEs (ADRs. AEs assessed

Table IV. Changes in ABI after 4, 8, and 12 weeks of treatment.

	PPS			FAS		
ABI	DP-R202	Anplag	*P*	DP-R202	Anplag	*P*
Screening, n	65	64	0.4466*	74	72	0.4522*
Mean [SD]	0.68 [0.15]	0.70 [0.12]		0.68 [0.15]	0.70 [0.12]	
Median	0.70	0.72		0.70	0.72	
Min, Max	0.24, 0.89	0.40, 0.882		0.24, 0.89	0.40, 0.88	
Week 4, n	65	63		73	70	
Mean [SD]	0.69 [0.16]	0.73 [0.15]		0.70 [0.16]	0.73 [0.15]	
Median	0.66	0.72		0.66	0.72	
Min, Max	0.28, 1.18	0.44, 1.20		0.28, 1.18	0.44, 1.20	
Change 1, n	65	63	0.7844*	73	70	0.6214*
Mean [SD]	0.01 [0.13]	0.02 [0.11]		0.01 [0.13]	0.02 [0.11]	
Median	0.01	0.00		0.01	0.00	
Min, Max	−0.25, 0.68	−0.15, 0.41		−0.25, 0.68	−0.15, 0.41	
P	0.8657†	0.5973†		0.8538†	0.3941†	
Week 8, n	65	63		73	70	
Mean [SD]	0.69 [0.17]	0.71 [0.15]		0.70 [0.17]	0.71 [0.16]	
Median	0.68	0.71		0.68	0.717	
Min, Max	0.21, 1.40	0.37, 1.05		0.21, 1.40	−0.23, 0.48	
Change 2	65	63	0.6241*	73	70	0.7017*
Mean [SD]	0.01 [0.18]	0.00 [0.09]		0.01 [0.17]	0.01 [0.11]	
Median	0.00	0.00		0.00	0.01	
Min, Max	−0.22, 1.16	0.28, −0.23		−0.22, 1.16	−0.23, 0.48	
P	0.5786†	0.9026‡		0.7604†	0.8988†	
Week 12, n	63	63		73	70	
Mean [SD]	0.68 [0.15]	0.72 [0.14]		0.70 [0.17]	0.73 [0.15]	
Median	0.69	0.7		0.70	0.73	
Min, Max	0.29, 1.01	0.34, 1.16		0.29, 1.40	0.34, 1.24	
Change 3, n	63	63	0.4609*	73	70	0.5617*
Mean [SD]	−0.01 [0.13]	0.01 [0.11]		0.01 [0.19]	0.02 [0.12]	
Median	−0.01	0.00		−0.01	0.00	
Min, Max	−0.36, 0.35	−0.30, 0.29		−0.36, 1.16	−0.30, 0.48	
P	<0.5626‡	0.8335†		0.9390†	0.6299†	

ABI = ankle-brachial index; Change 1 = week 4–screening; Change 2 = week 8–screening; Change 2 = week 12–screening; FAS = full analysis set; PPS = per protocol set.
*Determined by Wilcoxon rank sum test.
†Determined by Wilcoxon signed rank test.
‡Determined by paired *t* test.

as "not related, or high probability of no relevancy (unlikely)" were classified as non–drug-related AEs (not ADRs). AEs in the treatment group were mostly mild (92.68%, 38 cases); no severe AE was detected. Most cases in the comparator group were also mild (85.71%, 42 cases), only a single severe AE was detected (2.04%, 1 case). Among these, 1 mild ADR occurred in the treatment group

Table V. Changes in coldness 5-point scale after 4, 8, and 12 weeks of treatment.

	PPS			FAS		
Coldness 5-point scale	DP-R202	Anplag	*P*	DP-R202	Anplag	*P*
Baseline, n	65	64	0.4250*	74	72	0.3143*
Mean [SD]	2.55 [1.29]	2.75 [1.30]		2.57 [1.29]	2.79 [1.32]	
Median	3.00	3.00		3.00	3.00	
Min, Max	1.00, 5.00	1.00, 5.00		1.00, 5.00	1.00, 5.00	
Week 4, n	64	64		73	72	
Mean [SD]	2.34 [1.30]	2.30 [1.15]		2.38 [1.31]	2.35 [1.20]	
Median	2.00	2.00		2.00	2.50	
Min, Max	1.00, 5.00	1.00, 5.00		1.00, 5.00	1.00, 5.00	
Change, n	64	64	0.1187*	73	72	0.0898*
Mean [SD]	−0.20 [1.13]	−0.45 [1.10]		0.18 [1.10]	−0.44 [1.06]	
Median	0.00	0.00		0.00	0.00	
Min, Max	−3.00, 3.00	−4.00, 2.00		−3.00, 3.00–	4.00, 2.00	
P	0.1335†	<0.0010†		0.1578†	0.0004†	
Week 8, n	65	64		74	72	
Mean [SD]	2.20 [1.16]	2.11 [1.17]		2.26 [±1.19]	2.18 [1.23]	
Median	2.00	2.00		2.00	2.00	
Min, Max	1.00, 4.00	1.00, 5.00		1.00, 5.00	1.00, 5.00	
Change, n	65	64	0.1973*	74	72	0.1516*
Mean [SD]	−0.35 [1.11]	−0.64 [1.33]		−0.31 [1.08]	−0.61 [1.28]	
Median	0.00	0.00		0.00	0.00	
Min, Max	−3.00, 3.00	−4.00, 3.00		−3.00, 3.00	−4.00, 3.00	
P	0.0077†	<0.0001†		0.0123†	<0.0001†	
Week 12, n	65	64		74	72	
Mean [SD]	2.14 [1.16]	2.11 [1.24]		2.20 [1.19]	2.17 [1.27]	
Median	2.00	2.00		2.00	2.00	
Min, Max	1.00, 5.00	1.00, 5.00		1.00, 5.00	1.00, 5.00	
Change, n	65	64	0.3311*	74	72	0.2168*
Mean [SD]	−0.42 [1.30]	−0.64 [1.26]		−0.36 [1.26]	−0.63 [1.22]	
Median	0.00	0.00		0.00	0.00	
Min, Max	−4.00, 3.00	−4.00, 2.00		−4.00, 3.00	−4.00, 2.00	
P	<0.0001‡	<0.0001†		0.0153†	<0.0001†	

Change 1 = week 4–baseline; Change 2 = week 8–baseline; Change 2 = week 12–baseline; FAS = full analysis set; PPS = per protocol set.
*Determined by Wilcoxon rank sum test.
†Determined by Wilcoxon signed rank test.
‡Determined by paired *t* test.

(2.44%) and 2 ADRs, comprising 1 mild (2.04%) and 2 moderate ADRs, occurred in the comparator group (4.08%). No severe ADR occurred in either group.

AEs According to Organ System

The adverse event rate and number of events per organ system after drug administration are presented in Table X. The proportion of patients who

Table VI. Changes in ASP after 4, 8, and 12 weeks of treatment.

	PPS			FAS		
ASP, mm Hg	DP-R202	Anplag	*P*	DP-R202	Anplag	*P*
Baseline, n	65	64	0.0862*	74	72	0.0899*
Mean [SD]	92.52 [22.74]	98.94 [19.21]		92.41 [23.27]	98.40 [18.88]	
Median	95.00	99.50		99.50	99.00	
Min, Max	39.00, 150.00	57.00, 134.00		39.00, 150.00	57.00, 134.00	
Week 4, n	65	63		73	70	
Mean [SD]	91.92 [23.16]	100.06 [23.79]		93.42 [24.21]	101.06 [23.97]	
Median	87.00	98.00		87.00	99.00	
Min, Max	31.00, 143.00	56.00, 184.00		31.00, 150.00	56.00, 184.00	
Change, n	65	63		73	70	
Mean [SD]	91.92 [23.16]	100.06 [23.79]		93.42 [24.21]	101.06 [23.97]	
Median	87.00	98.00		87.00	99.00	
Min, Max	31.00, 143.00	56.00, 184.00		31.00, 150.00	56.00, 184.00	
P	0.8375†	0.6092‡		0.8741†	0.8845‡	
Week 8, n	65	63		73	70	
Mean [SD]	93.97 [26.26]	97.40 [22.90]		95.79 [27.06]	98.20 [23.54]	
Median	92.00	96.00		93.00	96.00	
Min, Max	26.00, 193.00	44.00, 150.00		26.00, 193.00	44.00, 150.00	
Change, n	65	63	0.7517§	73	70	0.4795§
Mean [SD]	1.45 [29.01]	−2.11 [16.97]		2.79 [28.37]	−0.87 [19.61]	
Median	2.00	−4.00		3.00	−3.50	
Min, Max	−63.00, 154.00	−39.00, 50.00		−63.00, 154.00	−39.00, 71.00	
P	0.7836‡	0.3273†		0.7771‡	0.3703‡	
Week 12, n	63	63		73	70	
Mean [SD]	93.30 [22.62]	97.98 [22.70]		96.33 [25.59]	99.09 [23.85]	
Median	93.00	97.00		94.00	96.50	
Min, Max	36.00, 144.00	52.00, 185.00		36.00, 193.00	52.00, 185.00	
Change, n	63	63	0.6790§	73	70	0.3400§
Mean [SD]	−0.70 [24.00]	−1.53 [20.87]		3.33 [29.65]	0.02 [23.06]	
Median	2.00	−4.00		3.00	−3.50	
Min, Max	−58.00, 51.00	−53.00, 86.00		−58.00, 154.00	−53.00, 86.00	
P	0.8183†	0.2545‡		0.5219‡	0.3869‡	

ASP = ankle systolic pressure; Change 1 = week 4–baseline; Change 2 = week 8–baseline; Change 3 = week 12–baseline; FAS = full analysis set; PPS = per protocol set.
*Determined by 2-sample *t* test.
†Determined by paired *t* test.
‡Determined by Wilcoxon signed rank test.
§Determined by Wilcoxon rank sum test.

experienced AEs after investigational product administration was 29.73% (22 of 74 patients, 41 cases) in the treatment group, and 40.00% (30 of 75 patients, 49 cases) in the comparator group. Infections and infestations exhibited the highest occurrence rate in both groups when AEs were classified into system organ class and preferred term of Medical Dictionary for Regulatory Activities

Table VII. Changes in MWD after 12 weeks of treatment.

	PPS			FAS		
MWD, m	DP-R202	Anplag	*P*	DP-R202	Anplag	*P*
Baseline, n	65	64	0.2012*	74	72	0.1339*
Mean [SD]	313.90 [245.30]	394.15 [286.17]		309.12 [242.29]	388.62 [279.64]	
Median	222.00	302.00		222.00	302.00	
Min, Max	40.00, 800.00	18.00, 800.00		40.00, 800.00	18.00, 800.00	
Week 12, n	48	44		52	48	
Mean [SD]	360.08 [273.93]	435.75 [300.05]		348.62 [269.53]	426.75 [299.54]	
Median	252.00	352.50		240.00	328.00	
Min, Max	48.00, 800.00	24.00, 804.00		48.00, 800.00	24.00, 804.00	
Change, n	48	44	0.4279*	52	48	0.2782*
Mean [SD]	43.10 [162.92]	38.93 [154.97]		40.62 [157.92]	29.88 [152.25]	
Median	12.00	0.00		12.00		
Min, Max	−447.00, 444.00	−420.00, 534.00		−447.00, 444.00	−420.00, 534.00	
P	0.0162†	0.0801†		0.0200†	0.2405†	

Change = week 12–baseline; FAS = full analysis set; MWD = maximum walking distance; PPS = per protocol set.
*Determined by Wilcoxon rank sum test.
†Determined by Wilcoxon signed rank test.

Table VIII. Changes in PFWD after 12 weeks of treatment.

	PPS			FAS		
PFWD, m	DP-R202	Anplag	*P*	DP-R202	Anplag	*P*
Baseline, n	50	46	0.1268*	56	51	0.1058*
Mean [SD]	143.63 [140.73]	178.69 [149.39]		141.11 [135.81]	174.18 [144.12]	
Median	96.50	130.00		96.50	136.00	
Min, Max	20.00, 800.00	26.66, 725.00		20.00, 800.00	26.66, 725.00	
Week 12, n	47	44		51	47	
Mean [SD]	185.74 [168.46]	194.43 [179.34]		180.53 [163.81]	190.89 [175.22]	
Median	120.00	142.00		120.00	135.00	
Min, Max	31.00, 800.00	8.00, 800.00		31.00, 800.00	8.00, 800.00	
Change, n	45	44	0.2871*	49	47	0.2791*
Mean [SD]	52.13 [176.06]	17.09 [143.39]		50.16 [169.34]	14.85 [141.49]	
Median	29.00	8.50		19.00	9.00	
Min, Max	−480.00,708.00	−420.00, 569.00		−480.00, 708.00	−420.00, 569.00	
P	0.0056†	0.2673†		0.0035†	0.2710†	

Change = week 12–baseline; FAS = full analysis set; PFWD = pain-free walking distance; PPS = per protocol set.
*Determined by Wilcoxon rank sum test.
†Determined by Wilcoxon signed rank test.

Table IX. Changes in VAS assessed by investigator after 4, 8, and 12 weeks of treatment.

	PPS			FAS		
VAS	DP-R202	Anplag	*P*	DP-R202	Anplag	*P*
Baseline, n	65	64	0.4266*	74	72	0.3201*
Mean [SD]	61.89 [15.49]	62.86 [13.10]		61.35 [15.18]	62.69 [12.75]	
Median	60.00	60.00		60.00	60.00	
Min, Max	40.00, 100.00	40.00, 92.00		40.00, 100.00	40.00, 92.00	
Week 4, n	65	64		74	72	
Mean [SD]	50.02 [16.01]	52.02 [17.32]		50.50 [15.95]	52.54 [17.72]	
Median	50.00	50.00		50.00	50.00	
Min, Max	10.00, 85.00	6.00, 90.00		10.00, 85.00	6.00, 90.00	
Change 1, n	65	64	0.6107*	74	72	0.6656*
Mean [SD]	−11.66 [14.40]	−10.84 [14.46]		−10.85 [13.97]	−10.15 [15.94]	
Median	−10.00	−7.50		−10.00	−6.00	
Min, Max	−60.00, 22.00	−55.00, 6.00		−60.00, 22.00	−55.00, 30.00	
P	<0.0001†	<0.0001†		<0.0001†	<0.0001†	
Week 8, n	65	64		74	72	
Mean [SD]	43.23 [17.27]	48.58 [18.21]		44.39 [17.10]	49.03 [18.58]	
Median	45.00	46.00		46.00	49.00	
Min, Max	0.00, 86.00	16.00, 89.00		0.00, 86.00	10.00, 90.00	
Change 2, n	65	64	0.2359*	74	72	0.3447*
Mean [SD]	−18.45 [17.32]	−14.28 [16.26]		−16.96 [17.04]	−13.67 [17.40]	
Median	−15.00	−10.00		−15.00	−10.00	
Min, Max	−70.00, 11.00	−65.00, 15.00		−70.00, 11.00	−65.00, 30.00	
P	<0.0001†	<0.0001†		<0.0001†	<0.0001†	
Week 12, n	65	64		74	72	
Mean [SD]	39.95 [19.66]	44.59 [19.08]		41.51 [19.44]	45.49 [19.43]	
Median	40.00	40.00		40.00	40.00	
Min, Max	0.00, 90.00	10.00, 90.00		0.00, 90.00	10.00, 90.00	
Change 3, n	65	64	0.2999‡	74	72	0.4102‡
Mean [SD]	−21.72 [18.75]	−18.27 [18.98]		−19.84 [18.58]	−17.21 [19.88]	
Median	−20.00	−17.00		−20.00	−15.50	
Min, Max	−70.00, 19.00	−65.00, 20.00		−70.00, 19.00	−65.00, 30.00	
P	<0.0001§	<0.0001§		<0.0001§	<0.0001§	

ASP = ankle systolic pressure; Change 1 = week 4–baseline; Change 2 = week 8–baseline; Change 3 = week 12–baseline; FAS = full analysis set; PPS = per protocol set; VAS = visual analog scale.
*Determined by Wilcoxon rank sum test.
†Determined by Wilcoxon signed rank test.
‡Determined by 2-sample *t* test.
§Determined by paired *t* test.

version 17.0. Other AEs occurred in >5% of patients; these were gastrointestinal disorders and metabolism and nutrition disorders in the treatment group, and metabolism and nutrition disorders, general disorders, administration site conditions, and abnormal test values (investigations) in the comparator group.

Table X. Incidence rate and number of AEs reported (treatment-emergent AE, safety set).

System Organ Class/Preferred Term	DP-R202 (n = 74) n (%)	DP-R202 (n = 74) AEs Reported, n	Anplag (n = 75) n (%)	Anplag (n = 75) AEs Reported, n	Total (n = 149) n (%)	Total (n = 149) AEs reported, n
Infections and infestations	8 (10.81)	12	10 (13.33)	12	18 (12.08)	24
Gastrointestinal disorders	4 (5.41)	9	5 (6.67)	6	9 (6.04)	15
General disorders and administration site conditions	2 (2.70)	3	4 (5.33)	5	6 (4.03)	8
Investigations	1 (1.35)	1	5 (6.67)	5	6 (4.03)	6
Metabolism and nutrition disorders	4 (5.41)	5	1 (1.33)	1	5 (3.36)	6
Musculoskeletal and connective tissue disorders	2 (2.70)	2	3 (4.00)	3	5 (3.36)	5
Nervous system disorders	2 (2.70)	2	2 (2.67)	3	4 (2.68)	5
Respiratory, thoracic and mediastinal disorders	1 (1.35)	1	3 (4.00)	3	4 (2.68)	4
Skin and subcutaneous tissue disorders	1 (1.35)	1	3 (4.00)	3	4 (2.68)	4
Vascular disorders	1 (1.35)	1	2 (2.67)	2	3 (2.01)	3
Injury, poisoning and procedural complications	1 (1.35)	1	1 (1.33)	1	2 (1.34)	2
Blood and lymphatic system disorders	0 (0.00)	0	1 (1.33)	1	1 (0.67)	1
Cardiac disorders	1 (1.35)	1	0 (0.00)	0	1 (0.67)	1
Hepatobiliary disorders	0 (0.00)	0	1 (1.33)	1	1 (0.67)	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.00)	0	1 (1.33)	1	1 (0.67)	1
Psychiatric disorders	1 (1.35)	1	0 (0.00)	0	1 (0.67)	1
Renal and urinary disorders	1 (1.35)	1	0 (0.00)	0	1 (0.67)	1
Reproductive system and breast disorders	0 (0.00)	0	1 (1.33)	1	1 (0.67)	1
Surgical and medical procedures	0 (0.00)	0	1 (1.33)	1	1 (0.67)	1

AE = adverse event.

ADRs According to Organ System

The proportion of patients who experienced ADRs in the treatment group and comparator group was 1.35% (1 of 74 patients, 1 case) and 4.00% (3 of 75 patients, 3 cases), respectively. One case of urticaria occurred in the treatment group and 1 case each of pruritus, arthralgia, and dyspnea exertional occurred in the comparator group.

AEs That Led to Dropout

Two patients in the comparator group dropped out of the study because of AEs; pruritus was confirmed as the ADR.

SAEs and Other Important AEs

The proportion of patients who experienced SAEs was 1.35% (1 of 74 patients, 1 case) in the treatment

group and 5.33% (4 of 75 patients, 4 cases) in the comparator group. One case of atrial fibrillation occurred in the treatment group and 1 case each of shock, thromboangiitis obliterans, infectious colitis, and hyponatremia occurred in the comparator group. Serious ADRs were absent in both groups.

Laboratory Tests

For changes in hematologic variables between baseline and 12 weeks, significant reductions in hemoglobin and hematocrit were found in the comparator group, but no statistically significant difference was found between the groups. All other criteria exhibited no significant differences within or between the groups.

Sodium, HDL-C, ALP, and HbA1c exhibited significant differences between screening and 12 weeks in the comparator group, and none in the treatment group. Among these, the difference in HbA1c between screening and 12 weeks was –0.05% (0.50%) in the treatment group and 0.14% (0.42%) in the comparator group; the difference was statistically significant ($P = 0.0048$). No other criteria exhibited statistically significant differences between the groups.

Results of blood coagulation and urine tests indicated no significant differences between and screening and 12 weeks in either the study or comparator group.

Vital Signs and Weight

Vital signs and weight did not differ significantly between screening and 12 weeks in the comparator and treatment groups. Moreover, no significant difference was found in vital signs and weight between the groups.

Final Conclusion on Safety Profile

The safety profile was evaluated on the basis of AEs, laboratory tests, vital signs, and weight (treatment group, 74 patients; comparator group, 75 patients). The AE rate after the investigational product administration was 29.73% (22 of 74 patients, 41 cases) in the treatment group and 40.00% (30 of 75 patients, 3 cases, 49 cases) in the comparator group. The ADR rate was 1.35% (1 of 74 patients, 1 case) in the treatment group and 4.00% (3 of 75 patients, 3 cases) in the comparator group. Most AEs were mild (treatment group, 92.68%, 38 cases vs comparator group, 85.71%, 42 cases), and no severe ADRs occurred in either group. The SAE rate was 1.35% (1 of 74 patients, 1 case) in the treatment group and 5.33% (4 of 75 patients, 4 cases) in the comparator group; no serious ADR was detected. In addition, AEs leading to dropout were absent in the treatment group; however, 2 cases occurred in the comparator group. One case was confirmed to be an ADR. For vital signs and weight, changes were found between baseline and 12 weeks, and no tendency to violate the safety profile in terms of the extent of changes was observed. In addition, the change in HbA1c between baseline and 12 weeks was –0.05% (0.50%) in the treatment group and 0.14% (0.42%) in the comparator group; the difference was significant ($P = 0.0048$). However, no significant difference was found between the groups in the normal/abnormal rate ($P = 0.1445$), and no tendency to violate the safety profile was observed. In the normal/abnormal analysis, no other laboratory test variable differed significantly between the groups. There was no significant difference in safety profile in treatment group compared to comparator group.

CONSIDERATIONS AND GENERAL CONCLUSION

This clinical trial was a 12-week, multicenter, randomized, double-blind, parallel-group, Phase III study that enrolled patients in 25 institutions appointed as national clinical trial institutions and that received the approval of all the institutional review boards.

This clinical study aimed to find the noninferiority of DP-R202 compared with Anplag Tab by assessing their efficacy (in terms of reduction in lower limb pain) and the safety profile after 12 weeks of administration in patients with chronic arterial occlusion.

Of the participants in this study, 60 to 70 were men, and a high proportion had Fontaine stage II; however, several patients with stage III were also included. The demographic characteristics and severity characteristics of patients were similar in the 2 groups.

Lower limb pain in both groups improved significantly between baseline and 12 weeks as assessed by the change in VAS (change in VAS: treatment group, 20.72 [20.06] mm vs comparator group, 15.55 [21.44] mm); therefore, DP-R202 was shown to be noninferior to Anplag Tab. This is in agreement with a previous report of the efficacy of inositol nicotinate (Hexopal[†]) another peripheral vasodilator (inositol vs placebo, 19.9 mm vs 8.8 mm; $P = 0.005$).[9] Pain reduction was defined as an improvement in claudication distance and increases in MWD and

PFWD between baseline and 12 weeks. In both groups, the pain VAS score decreased with increasing treatment duration.

Among secondary efficacy assessment variables, the coldness symptom decreased gradually over time in both groups, therefore confirming the effect of sarpogrelate in improving ischemic symptoms, and no significant difference was found between the groups. For ABI and ASP, modality of change at 4, 8, and 12 weeks was inconsistent, and no significant improvement was found in either group. This result is also in agreement with the above-mentioned previous report.[10] MWD and PFWD increased between baseline and 12 weeks, and no statistically significant difference was found between the groups. In the general assessment performed by an investigator with the use of a VAS, both groups reported gradual improvements over time, and no statistically significant difference was found between the groups. On quality-of-life assessment (SF-36) in terms of the bodily pain and PCS criteria, both groups reported improvements between baseline and at 4, 8, and 12 weeks, and no criterion differed significantly between the groups. However, MWD and PFWD show significant difference from baseline in the DP-R202–administered group, unlike the Anplag Tab–administered group.

For tolerability, the AE, ADR, and SAE rates were lower in the treatment group than in the comparator group. No subject experienced a severe ADR, suggesting that DP-R202 has equal or superior safety than Anplag Tab. In terms of laboratory test results, the increase in HbA1c between baseline and 12 weeks was significantly greater in the treatment group than in the comparator group (treatment group vs comparator group, –0.05% [0.50%] vs 0.14% [0.42%]; $P = 0.0048$). However, this was not considered clinically meaningful because the change was within the normal range. No significant difference was found between the groups in other laboratory test results and vital signs. Therefore, once daily administration of DP-R202 (sarpogrelate 300 mg) to patients with peripheral arterial occlusive disease with Fontaine stage II/III accompanied by claudication or lower limb pain at rest was found to be noninferior to TID administration of Anplag Tab in terms of improvement of lower limb pain; moreover, the 2 regimens exhibited equivalent tolerability. In conclusion, DP-R202 improved symptoms and the drug compliance rate in patients with peripheral arterial occlusive disease who require long-term administration.

CONFLICTS OF INTEREST

Dr. J.W. Lee and Mr. Kim are employees of Alvogen Korea Co., Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article. The sponsor did not participate in the execution of the study or in the analysis of the data.

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