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Selexipag, an oral, selective IP receptor agonist for the treatment of pulmonary arterial hypertension

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Abstract

In this Phase 2 proof-of-concept study we examined the safety and efficacy of selexipag, an orally available, selective prostacyclin receptor (IP receptor) agonist, as a treatment for PAH.

Forty-three adult patients with symptomatic PAH (receiving stable endothelin receptor antagonist and/or a phosphodiesterase type-5 inhibitor therapy) were randomised three to one: selexipag to placebo. Dosage was up-titrated in 200 μg increments from 200 μg twice daily on Day 1 to maximum tolerated dose by Day 35 (maximum allowed dose of 800 μg twice daily). Change in pulmonary vascular resistance at Week 17 expressed as a percentage of the baseline value was the primary efficacy endpoint; analysed on the per protocol set first and then on the all-treated set to assess robustness of results.

A statistically significant 30.3% reduction in geometric mean pulmonary vascular resistance was observed after 17 weeks' treatment with selexipag compared with placebo (95% CL: –44.7, –12.2; p=0.0045, Wilcoxon rank-sum test). This was supported by a similar result from the all-treated set. Selexipag was well tolerated with a safety profile in line with the expected pharmacological effect.

Our results encourage the further investigation of selexipag for the treatment of PAH.

Clinical Trials Registration: http://clinicaltrials.gov/ct2/show/NCT00993408 NCT00993408.

Key Words: Haemodynamics; prostacyclin; pulmonary arterial hypertension; randomised-controlled trial

Introduction

Pulmonary arterial hypertension (PAH) is a life-threatening disease of the pulmonary vasculature defined by an elevated mean pulmonary arterial pressure (mPAP) at rest of ≥25 mm Hg, normal pulmonary capillary wedge pressure (≤15 mmHg) [1,2] in the presence of a normal or reduced cardiac output [1]. Prostacyclin (PGI_2) is a member of the prostaglandin family and dysregulation of prostacyclin pathways has been implicated in the pathogenesis of PAH and provides the rationale for the use of prostacyclin analogues in its treatment [3–6]. These potent vasodilators and inhibitors of platelet aggregation [7,8] also counteract the vasoconstrictor and pro-thrombotic activity of endothelin [9]. They bind to the prostacyclin receptor (IP receptor), a G-protein coupled receptor on the surface of platelets and vascular smooth muscle cells [10]. Activation of the receptor leads to production of cyclic adenosine monophosphate, which induces relaxation of vascular smooth muscle.

Epoprostenol, a synthetic prostacyclin analogue administered as a continuous intravenous infusion, was the first targeted PAH therapy to be approved, and improved prognosis for patients with PAH [11–13]. However, complex administration and potentially serious side effects following acute and chronic administration severely limit its use [3]. Alternatives to epoprostenol include subcutaneously administered treprostinil which is also available for intravenous and inhaled use in the United States and inhaled iloprost. While these prostanoids address some of the limitations associated with epoprostenol, they too have drawbacks with respect to frequent dosing (iloprost), injection site pain (subcutaneous treprostinil), and typical prostanoid-associated side effects such as headache, flushing, diarrhoea, and jaw pain [4,5,14]. An oral prostacyclin analogue would be a major advantage in the treatment of PAH. However,

all studies thus far with oral prostacyclin analogues, such as beraprost and oral treprostinil, have failed to show a persistent treatment effect as determined by the primary efficacy endpoint [14].

Selexipag is an orally available, selective IP receptor agonist. It is rapidly hydrolysed in the hepatic microsomes to an active metabolite [15]. Selexipag, and its active metabolite, have a higher binding affinity for the human IP receptor than for any other prostanoid receptor [16]. The active metabolite of selexipag has a >130-fold higher affinity for the IP receptor than for the prostaglandin receptors [16]. Although selexipag and its metabolite have modes of action similar to that of endogenous prostacyclin (IP receptor agonism), they are chemically distinct from prostacyclin with a different pharmacology. Therefore, selexipag may be an attractive oral alternative to the currently available prostacyclin analogs for the treatment of PAH. The present proof-of-concept study was designed to assess the efficacy, safety and tolerability of selexipag in adult patients with symptomatic PAH.

Methods

Patients

This was a multicentre, multinational, proof-of-concept, Phase 2, randomised, double-blind, placebo-controlled, parallel-group trial of 17 weeks duration.

Eligible patients included male or female adults (≥18 years) with symptomatic PAH of idiopathic or hereditary origin, associated with connective tissue diseases (PAH-CTD), corrected congenital heart disease (congenital systemic-to-pulmonary shunts surgically repaired at least 5 years previously), or anorexigen use. Background targeted treatment with endothelin-receptor antagonists (ERAs) and/or phosphodiesterase type 5 (PDE-5) inhibitors was mandatory and patients had to have been on stable doses for more than 12 weeks before screening. Patients were required to have a baseline PVR of >400 dyn · s · cm^{-5}, and two 6-minute walk tests of 150–500 m inclusive and within ± 15% of each other. Patients were excluded if they had had clinically unstable right heart failure within the last 3 months (World Health Organization functional class [WHO FC] IV), had received or were scheduled to receive long-term epoprostenol within 3 months of screening, had a ventilation-perfusion lung scan or pulmonary angiography indicative of thromboembolic disease, had evidence of left-sided heart disease, or had received any investigational drug within 30 days of screening.

The study was approved by the respective Ethics Committees and was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice. All patients gave written informed consent prior to study participation.

Procedures

The randomisation schedule 3:1 (selexipag:placebo) was computer generated by Penn Pharmaceutical Services Ltd. (Gwent, UK). Eligible patients received selexipag 200 μg twice daily (synthesised by Nippon Shinkyaku Co., Ltd., Kyoto, Japan) or matching placebo on Day 1. Dosage was then up-titrated from 400 μg twice daily on Day 3 to 600 μg twice daily on Day 7, and 800 μg twice daily on Day 21. A slower up-titration schedule was allowed up to Day 35 to allow for a maximum tolerated dose (MTD). Although doses could be temporarily reduced after Day 35 to alleviate adverse events final dosage was required to be stable for at least 4 weeks prior to evaluation at Week 17.

As the study was blinded investigators assessed the relationship between adverse events and study treatment before the treatment code was broken. Medical emergency was the only reason to break the codes. For each patient, treatment remained blinded until the final data for Week 17 were entered and locked. After Week 17data were fixed and locked, patients eligible to enter the open-label extension were unblinded. For patients who discontinued prematurely or otherwise did not enter the open-label extension, study treatment remained blinded until all Week-17 data were cleaned and reconciled. Patients underwent right-heart catheterisation (RHC) at baseline and at Week 17 (Days 112–126 inclusive). Week 17 RHC haemodynamic assessments were conducted 4 hours post-dose. Patients who withdrew prematurely or otherwise did not enter the open-label extension were followed up within 30 days of their last study visit, during which end-of-study assessments were performed along with echocardiography, if possible.

Change in PVR at Week 17 expressed as a percentage of the baseline value was chosen as the primary efficacy endpoint and summarised using geometric mean and its 95% two-sided confidence limits (CL). Additional haemodynamic data obtained from RHC were supported by secondary efficacy endpoints that included established measures of clinical status in PAH patients, such as 6-minute walk distance,[11] and aggravation of PAH (defined as death, transplantation, hospitalisation due to worsening PAH, or aggravation of PAH symptoms, i.e., a 10% or more deterioration in 6-minute walk distance or the need for additional PAH-specific therapies), as well as exploratory endpoints, such as Borg dyspnoea score, WHO FC, and plasma N-terminal pro-brain natriuretic peptide (NT pro-BNP) concentration [17,18].

The overall safety and tolerability of selexipag was evaluated in relation to frequency of treatment-emergent adverse events and premature discontinuation of study treatment, as well as change from baseline to last measurement during the treatment period in vital signs, electrocardiographic (ECG) and laboratory parameters.

Statistical analysis

A sample size estimation of 44 patients was based on the assumption of a 300 dyn · s · cm^{-5} difference in mean change from baseline to Week 17 in PVR between treatment groups, a 300 dyn · s · cm^{-5} common standard deviation, and a 3:1 (selexipag:placebo) randomisation ratio. Such a sample size would provide 80% power to detect a difference between selexipag and placebo based on a two-sided t-test at the 5% significance level. The primary endpoint analysis was based on the per protocol (PP) set, which consisted of all treated patients who did not violate the protocol in a way that might influence the evaluation of the effect of the study drug on the primary endpoint. A sensitivity analysis

was performed on the all-treated test, which consisted of all patients who had received at least one dose of study drug. Secondary and exploratory efficacy analyses were based on the all-treated set.

For each analysis set, missing values at Week 17 were imputed with the closest value in time during the treatment period, unless a patient died or experienced disease worsening, then missing values were imputed with the worse value at Week 17 over all patients in the analysis set. The Wilcoxon rank-sum test with asymptotic approximation to t-distribution (primary) and the t-test (secondary) were used for treatment comparison. Safety and tolerability evaluation was carried out descriptively on the safety set, which consisted of all patients who had received at least one dose of study drug and had at least one post-baseline safety assessment. Post-hoc analyses included prevalence of treatment-emergent adverse events over time and adverse events by PAH background therapy.

Results

Patient demographics and disposition

Of 45 patients screened, 43 were enrolled at 7 centres in 7 European countries and randomised to receive either selexipag 200 μg twice daily (n=33) or placebo (n=10), between April 2008 and June 2009 (Supplementary Figure 1). Forty patients completed the study. Data from 29 patients in the selexipag group and six patients in the placebo group were analysed in the PP set; four patients in each group violated major entry criteria.

Treatment groups were balanced with respect to demographics and aetiologies (Table 1) and patients were on stable background PAH therapy (Table 2). In the PP set 11 (37.9%) patients in the selexipag group were on a combination of ERA and sildenafil therapy versus 1 (16.7%) patient in the placebo group.

Patients on selexipag received treatment for a mean ± standard deviation (SD) of 143.3 ± 28.6 days (median 149.0; range 17–176), compared with 135.1 ± 27.4 days (median 146.0; range 61–152) for patients on placebo. Among selexipag-treated patients, 14 (42.4%) were on a final dosage of 800 μg twice daily, seven (21.2%) were on 600 μg twice daily, six (18.2%) were on 400 μg twice daily, and four (12.1%) were on 200 μg twice daily. The MTD could not be determined for two patients due to premature treatment discontinuation. Nine (90%) patients on placebo reached MTD of 800 μg.

Efficacy

At Week 17, PVR (change in geometric mean expressed as a percentage of the baseline value, 95% CL) in the selexipag and placebo groups was 80.7% (72.8, 89.6; n=29) and

115.9% (106.5, 126.1; n=6), respectively (Figure 1a). This represented a statistically significant treatment effect of −30.3% (95% CL: –44.7, –12.2; Wilcoxon rank-sum test *P*=0.0045). The all-treated analysis, including all 43 patients randomized in the study, confirmed the PP analysis (Figure 1b). Absolute values at baseline, Week 17 and change from baseline to Week 17 for PVR are provided in Supplementary Table 1. Compared with placebo, selexipag treatment seemed to be associated with a mean increase in cardiac index accompanied by a mean decrease in systemic vascular resistance (SVR), with little change in systolic or diastolic blood pressures (Table 3 and 4). The treatment effect on right atrial pressure appeared obscured by the decrease of the high placebo value at baseline (Table 3). At Week 17, the mean (95% CL) change from baseline in 6-minute walk distance was +24.7 m (–1.6, 50.9) and +0.4 m (–19.7, 20.5) in the selexipag and placebo groups, respectively (Figure 2).

One (3.0%) selexipag-treated patient and two (20.0%) placebo-treated patients experienced aggravation of PAH. Five (15.6%) selexipag-treated patients experienced an improvement in WHO FC, compared with one (10%) placebo recipient. Two patients in each group experienced a worsening of WHO FC. There was no difference between treatments with respect to Borg dyspnoea score (mean treatment effect: –0.1 units, 95% CL: –1.4, 1.1) or plasma NT pro-BNP (mean treatment effect: –212.8 pg/mL, 95% CL: –1012.1, 586.5).

Safety

Almost all patients in both treatment groups experienced at least one adverse event with headache, pain in jaw, pain in extremity, nausea, and nasopharyngitis being the most frequently reported in the selexipag group (Table 5). The majority of adverse events in

the selexipag group were classified as mild (n=5; 15.2%) or moderate (n=20; 60.6%). Six (18.2%) patients in the selexipag group and four (40.0%) in the placebo groups experienced at least one serious adverse event (Supplementary Table 2). Serious adverse events considered by the investigator to be at least possibly related to selexipag treatment included headache, nausea, vomiting, myalgia, dyspnoea, and chest pain. None of the events on placebo were considered to be related to study drug. There were no deaths. Post-hoc analysis showed that there was no difference in adverse events between treatment groups when stratified by background therapy ie ERA or PDE-5 inhibitor monotherapy or ERA plus PDE-5 inhibitor combination therapy. Prevalence of adverse events associated with prostacyclin analogue treatment, such as headache, pain in extremity, pain in jaw, nausea, and diarrhoea, decreased over time in patients treated with selexipag (Supplementary Table 3). No clinically relevant changes from baseline to Week 17 in vital signs, including blood pressure, and pulse rate, ECG parameters, including QT interval changes, or laboratory tests were observed.

Discussion

This proof-of-concept Phase 2 study was designed to provide preliminary evidence of the efficacy and tolerability of selexipag in patients with PAH. The study showed a significant 30.3% reduction in PVR after 17 weeks' treatment with selexipag, compared with placebo. PVR has previously been used as an indicator of treatment benefit [19] and likely relates to long term outcomes in PAH [12,13]. Furthermore, marked reductions in PVR have been reported with epoprostenol, the synthetic form of prostacylin [20]. Improvements in other haemodynamic parameters such as an increase in cardiac index and a decrease in SVR, may be explained by the vasodilatory effect of IP receptor agonism. However, the decrease in SVR was not accompanied by systemic hypotension. The beneficial effects with selexipag were observed despite patients receiving background therapy with an ERA and/or sildenafil, with approximately one third of patients on a combination of the two. Patients with PAH often require more than one therapy because of clinical deterioration or failure to achieve specified treatment goals. The efficacy of add-on or combination therapy with drugs of different modalities, such as ERAs and PDE-5 inhibitors, has been evaluated and is recommended in current treatment guidelines [1].

Statistically significant treatment effects were not observed for the secondary parameters of 6-minute walk distance nor the exploratory parameter of NT pro-BNP. Given that the study was not powered to detect differences on these parameters this is not an entirely unexpected result. The magnitude of the placebo-corrected mean treatment effect of +24.2 m on the 6-minute walk distance was similar to that obtained at Week 24 in the phase 2 proof-of-concept study of imatinib; +21.7 m [20]. Statistical

significance on this parameter was not met in this trial either. As in our study patients in the imatinib trial were on background PAH therapies which may have contributed to the lack of significant improvement on 6-minute walk distance. With regards to the NT pro-BNP, there was a baseline difference between placebo- and selexipag-treated patients. This, together with the large standard deviations of the mean at baseline and at study end means it was unlikely that a treatment difference in our study would have been observed.

Seventeen weeks' treatment with selexipag was well tolerated by most patients in this study. Adverse events were consistent with the known side effect profile of IP receptor agonism and were similar in nature to those reported in the 12 week trial of the oral prostacyclin beraprost [21]. There was a marked reduction in the incidence of adverse events in the maintenance phase of the beraprost study compared with the titration phase. . Similarly post-hoc analysis of the selexipag data showed that the prevalence of some adverse events such headache, pain in jaw, pain in extremity and flushing decreased over time. It is likely that they were related to the rapid up-titration to MTD. The up-titration protocol was relatively aggressive and patients could remain hospitalised for one week post first dose. Consequently, 63.6% of selexipag-treated patients achieved a final optimal dose of 600 μg twice daily or higher. However, a longer up-titration phase could have permitted even more patients to reach the highest dose in this study (800 μg twice daily), or potentially even higher doses.

The 3:1 randomisation ratio, together with the small sample size, may have contributed to the imbalances seen between the treatment groups in respect to some of the disease characteristics such as WHO FC, 6MWD and NT pro-BNP, which suggested that patients

on placebo were in a worse condition than those in the active group. Additionally, the PP analysis resulted in an active drug to placebo ratio of 5:1 with 4 patients in each treatment arm excluded due to major protocol violations. This does limit the generalisations of the results of this study. Even so, the treatment effect on PVR was consistent for the PP analysis and the all-treated sensitivity analysis, which included all 43 randomized patients. There were also positive trends on some of the secondary outcomes measures that we consider sufficient in a proof-of-concept study in a rare and fatal disease to support continued investigation of selexipag in larger scale studies. Our study lacked the potential to go beyond a pre-specified maximum dose of selexipag 800 μg twice daily. Although, higher doses of selexipag are being investigated in the current ongoing phase 3 study.

Selexipag is an orally available, selective IP receptor agonist with the potential to address some of the pharmacokinetic and safety limitations associated with prostacyclin analogues. The active metabolite of selexipag has a relatively long elimination half-life of 7.9 hours that permits twice-daily dosing and contrasts with prostacyclin analogues which require continuous or very frequent dosing to achieve a sustained response [16,23]. Adverse events related to prostacyclin analogues are often due to the abrupt changes of the plasma levels of the drug. As selexipag is rapidly hydrolysed in the liver to the active metabolite, peak–trough fluctuations in serum levels of active compound may be reduced, thereby reducing the likelihood of adverse events [16]. In addition, continuous vasodilation induced by exposure to selexipag is not attenuated by repetitive dosing suggesting that severe desensitisation of the IP receptor is unlikely [16]. Thus, there may be less need for dose escalation to maintain efficacy.

In conclusion, this proof-of-concept study showed that treatment with selexipag resulted in a statistically significant 30·3% reduction in PVR after 17 weeks, which was supported by an increase in cardiac index and a decrease in systemic vascular resistance without systemic hypotension. Selexipag was well tolerated, with a safety profile in line with that of the expected pharmacological effect. Overall, the results of this study encourage further investigation of selexipag in PAH.

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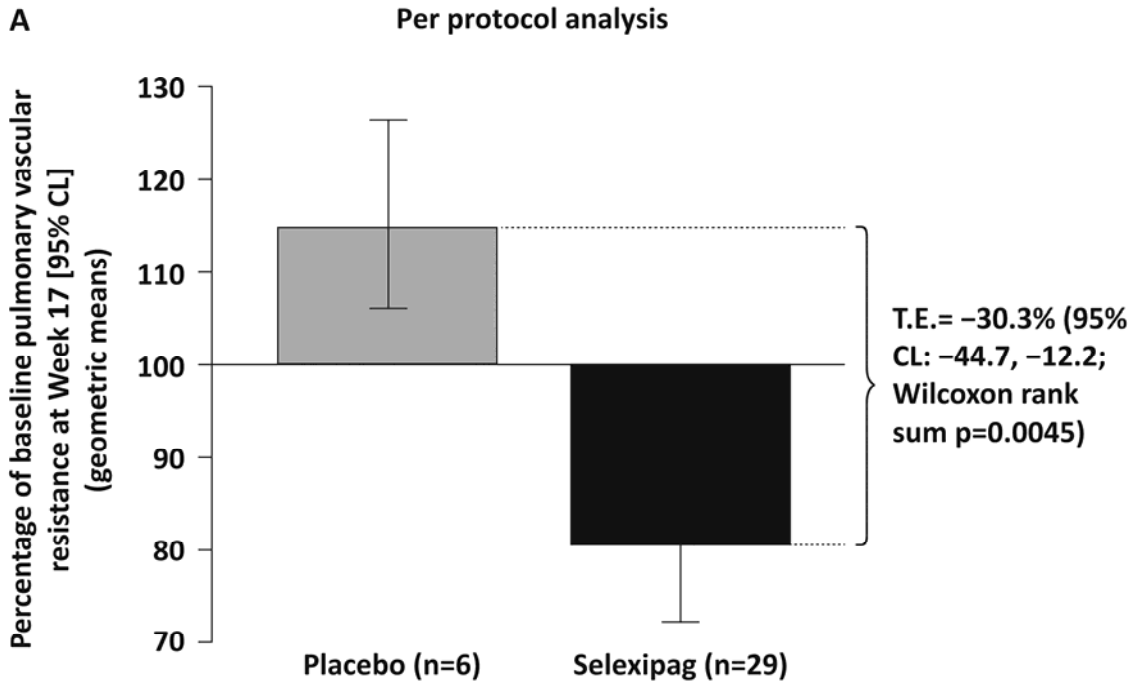
Figure legends

Figure 1. Change in pulmonary vascular resistance (PVR) from baseline to Week 17: a) per protocol set and b) all-treated set. T.E. indicates treatment effect. Geometric mean expressed as a percentage of the baseline value. Baseline PVR values (mean±SD) for per protocol population for selexipag were 951.9±434.5 dyn·s·cm^{-5} and for placebo were 826.8±195.8 dyn·s·cm^{-5}. Baseline PVR values (mean±SD) for all-treated population for selexipag were 948.6±428.0 dyn·s·cm^{-5} and for placebo were 867.2±379.38 dyn·s·cm^{-5}



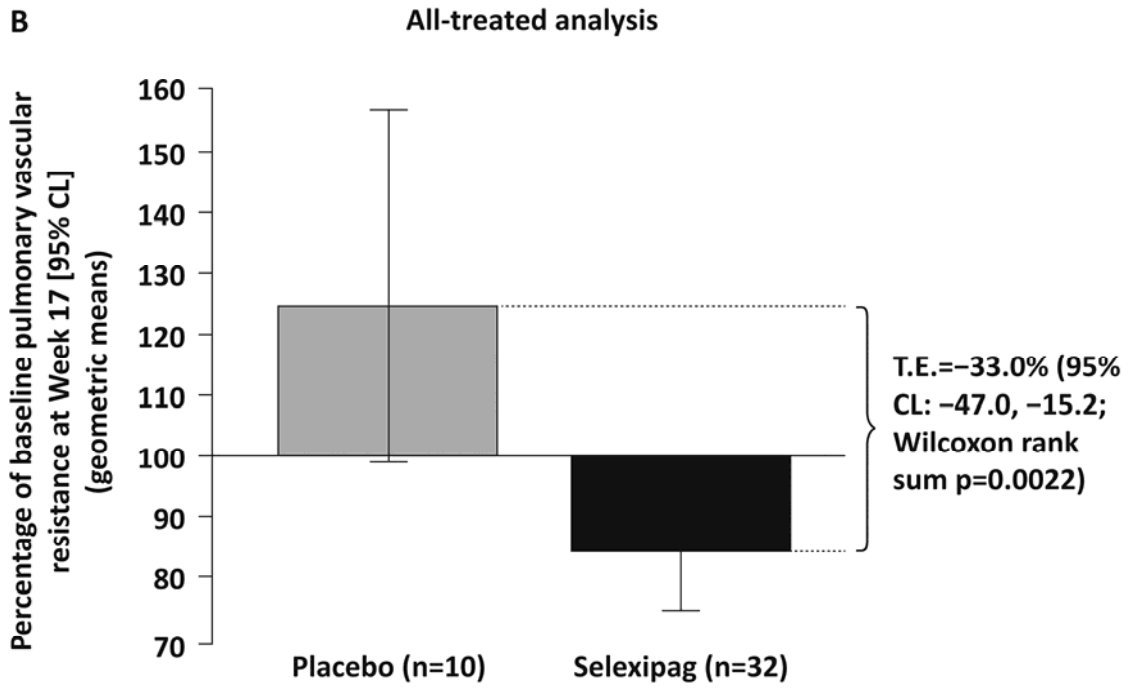
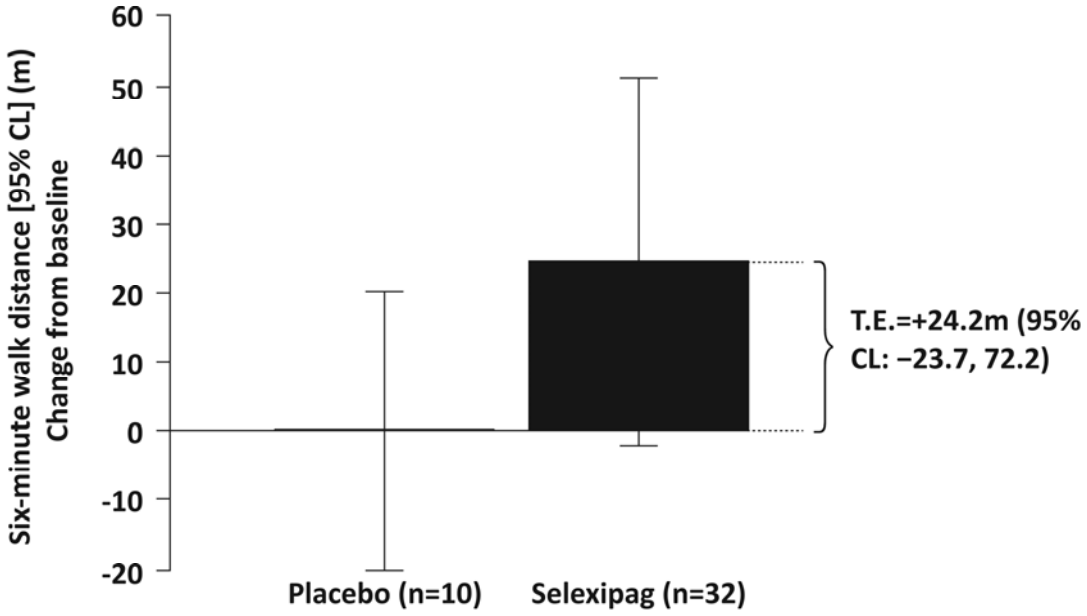


Figure 2. Change in 6-minute walk distance from baseline to Week 17 (all-treated population) T.E. indicates treatment effect. Baseline values (mean±SD) for selexipag were 394.7±72.0 m and for placebo were 350.3±123.5 m. Week 17 values (mean±SD) for selexipag were 419.3±106.3 m and for placebo were 350.7±139.6 m



Supplementary Figure 1. Disposition of patients

Table 1. Demographics and aetiology of pulmonary arterial hypertension (all-treated set)

	Placebo **n=10**	**Selexipag** **n=33**
Demographics		
Male/female, n (%)	2/8 (20.0/80.0)	6/27 (18.2/81.8)
Mean age ± SD, y	53.8 ± 16.3	54.8 ± 16.8
Mean weight ± SD, kg	70.6 ± 13.9	68.7 ± 12.4
Caucasian/other, n (%)	9/1 (90.0/10.0)	29/4 (88.0/12.0)
Aetiology of PAH, n (%)		
Idiopathic PAH	7 (70.0)	24 (72.7)
Hereditary PAH	1 (10.0)	1 (3.0)
Anorexigen-induced PAH	-	2 (6.1)
PAH associated with connective tissue disease	2 (20.0)	4 (12.1)
PAH associated with congenial heart disease	-	2 (6.1)

PAH, pulmonary arterial hypertension; SD, standard deviation

Table 2. Disease characteristics and pulmonary arterial hypertension background therapy (all-treated set)

	Placebo n=10	**Selexipag n=33**
Time from diagnosis ± SD, years	4.0 ± 3.1	5.5 ± 6.1
Mean pulmonary vascular resistance ± SD, dyn · s · cm^{-5}	867.2 ± 379.3	928.6 ± 436.6
Mean 6-minute walk distance (SD), m	350.3 ± 123.5	396.2 ± 71.4
WHO functional class, n (%)		
I	-	-
II	2 (20.0)	15 (45.5)
III	8 (80.0)	18 (54.5)
IV	-	-
Mean Borg dyspnoea score ± SD	4.1 ± 2.6	3.3 ± 2.1*
Mean N-terminal pro-brain natriuretic ± SD, pg · mL**	2400.9 ± 1269.8†	1601.4 ± 2443.0‡
Background PAH therapy, n (%)		
ERA monotherapy	4 (40.0)	12 (36.4)
Sildenafil monotherapy	3 (30.0)	9 (27.2)
ERA plus sildenafil	3 (30.0)	12 (36.4)

*n=32; †n=8; ‡n=27

** Upper reference values are 100 pg/mL and 172 pg/mL for men aged 45–59 and 60-plus years, respectively, and 164 pg/mL and 225 pg/mL for women aged 45–59 and 60-plus years, respectively[18]

ERA , endothelin-receptor antagonists; PAH, pulmonary arterial hypertension; SD, standard deviation; WHO, World Health Organization

Table 4. Baseline, Week 17 and change from baseline to Week 17 in secondary haemodynamic parameters (all-treated set)

Right heart catheterisation parameter	Mean values ± SD at baseline		Mean values ± SD at Week 17		Mean change ± SD from baseline to Week 17		Treatment effect [95% CL; Wilcoxon *P*-value]
	Placebo n=10	Selexipag n=33	Placebo n=10	Selexipag n=33	Placebo n=10	Selexipag n=33	
Pulmonary vascular resistance, dyn · s · cm^{-5}	867.2 ± 379.3	948.6 ± 428.0*	1090.8 ± 421.3	818.8 ± 416.9*	223.6 ± 355.4	−129.8 ± 309.7*	−33.0%§ [−47.0, −15.2; 0.0022]
Cardiac index, L · min · m^{-}	2.5 ± 0.5	2.4 ± 0.6*	2.3 ± 0.4	2.7 ± 0.6*	−0.2 ± 0.2	0.3 ± 0.5*	0.5 [0.13, 0.83; 0.01]
Mean pulmonary arterial pressure, mm Hg	54.6 ± 13.8	54.5 ± 15.3*	60.3 ± 20.2	52.8 ±19.1*	5.7 ± 13.3	−1.7 ± 11.0*	−7.4 [−15.9, 1.1; 0.1]
Right atrial pressure, mm Hg	11.2 ± 5.7	6.9 ± 3.6†	8.3 ± 4.9	7.2 ± 3.6†	−2.9 ± 2.8	0.3 ± 3.5†	3.2 [0.8, 5.7; 0.02]
Pulmonary capillary wedge pressure, mm Hg	10.3 ± 2.5	8.5 ± 3.1‡	8.7 ± 1.7	9.1 ± 2.7‡	−1.6 ± 2.7	0.6 ± 3.4‡	2.2 [−0.2, 4.6; 0.07]
Systemic vascular resistance,	1399.2 ± 475.1	1572.8 ± 544.7†	1687.1 ± 429.2	1452.8 ± 433.6†	287.9 ± 227.8	−119.9 ± 498.8†	−407.8 [−740.2,

dyn · s · cm^{-5}							−75.5; 0.01]
Mixed venous oxygen saturation, %	60.6 ± 8.4	61.0 ± 12.3#	58.4 ± 9.3	62.9 ± 10.0#	−2.1 ± 4.1	1.9 ± 10.6	4.1 [−3.8, 11.9; 0.3]

*n=32; †n=30;‡n=31; #n=26

§Treatment effect calculated at Week 17 as the change in the geometric mean expressed as a percentage of the baseline value

Although *P*-values were calculated for secondary endpoints, they are only exploratory in nature as there was no formal statistical hypothesis for secondary endpoints.

SD; standard deviation

Table 4. Baseline, end of study period and change from baseline to end of study period in vital sign parameters (safety set)

Vital signs parameter*	Mean values ± SD at baseline		Mean values ± SD at end of study period		Mean change ± SD from baseline to end of study period	
	Placebo n=10	Selexipag n=33	Placebo n=10	Selexipag n=33	Placebo n=10	Selexipag n=33
Systolic blood pressure, mmHg	116.2 ± 11.7	117.3 ± 18.5	112.7 ± 17.3	114 ± 15.8	-3.5 ± 17.1	-3.6 ± 17.3
Diastolic blood pressure, mmHg	66.8 ± 10.4	65.9 ± 10.9	70.0 ± 9.8	71.8 ± 9.1	3.2 ± 12.8	5.4 ± 11.2
Heart rate, bpm	74.8 ± 13.2	75.3 ± 15.8	77.9 ± 10.5	75.2 ± 12.1	3.1 ± 6.0	–0.1 ± 7.7

*Treatment effect was not calculated for these safety parameters

SD; standard deviation

Table 5. Treatment-emergent adverse events during the study (safety set)

Adverse events	**Placebo** **n=10**	**Selexipag** **n=33**
Patients with ≥1 adverse event, n	10	31
Adverse events >10% on selexipag, n		
Headache	2	22
Jaw pain	-	12
Pain in extremity	-	10
Nausea	-	9
Nasopharyngitis	2	8
Diarrhoea	1	6
Flushing	-	6
Dizziness	-	5
Cough	-	4
Myalgia	-	4