

ORIGINAL ARTICLE

Selexipag for the Treatment of Pulmonary Arterial Hypertension

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ABSTRACT

BACKGROUND

In a phase 2 trial, selexipag, an oral selective IP prostacyclin-receptor agonist, was shown to be beneficial in the treatment of pulmonary arterial hypertension.

METHODS

In this event-driven, phase 3, randomized, double-blind, placebo-controlled trial, we randomly assigned 1156 patients with pulmonary arterial hypertension to receive placebo or selexipag in individualized doses (maximum dose, 1600 μ g twice daily). Patients were eligible for enrollment if they were not receiving treatment for pulmonary arterial hypertension or if they were receiving a stable dose of an endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both. The primary end point was a composite of death from any cause or a complication related to pulmonary arterial hypertension up to the end of the treatment period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo).

RESULTS

A primary end-point event occurred in 397 patients — 41.6% of those in the placebo group and 27.0% of those in the selexipag group (hazard ratio in the selexipag group as compared with the placebo group, 0.60; 99% confidence interval, 0.46 to 0.78; $P < 0.001$). Disease progression and hospitalization accounted for 81.9% of the events. The effect of selexipag with respect to the primary end point was similar in the subgroup of patients who were not receiving treatment for the disease at baseline and in the subgroup of patients who were already receiving treatment at baseline (including those who were receiving a combination of two therapies). By the end of the study, 105 patients in the placebo group and 100 patients in the selexipag group had died from any cause. Overall, 7.1% of patients in the placebo group and 14.3% of patients in the selexipag group discontinued their assigned regimen prematurely because of adverse events. The most common adverse events in the selexipag group were consistent with the known side effects of prostacyclin, including headache, diarrhea, nausea, and jaw pain.

CONCLUSIONS

Among patients with pulmonary arterial hypertension, the risk of the primary composite end point of death or a complication related to pulmonary arterial hypertension was significantly lower with selexipag than with placebo. There was no significant difference in mortality between the two study groups. (Funded by Actelion Pharmaceuticals; GRIPHON ClinicalTrials.gov number, NCT01106014.)

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PULMONARY ARTERIAL HYPERTENSION IS a severe disease with a poor prognosis despite available treatment options.¹ Current recommendations support the use of a combination of therapies that target the endothelin, nitric-oxide, and prostacyclin pathways.^{2,3} Despite the benefits of intravenous prostacyclin therapy,^{2,4} many patients with pulmonary arterial hypertension die without ever receiving this treatment.^{5,6} The burden and risks related to the administration of prostacyclin therapy are probably contributing factors.⁷

Selexipag is an oral selective IP prostacyclin-receptor agonist that is structurally distinct from prostacyclin.⁸⁻¹¹ In a placebo-controlled, phase 2 trial involving patients who were already receiving treatment for pulmonary arterial hypertension, selexipag increased the cardiac index (at week 17, the treatment effect for the placebo-corrected change from baseline was an increase of 0.5 liters per minute per square meter of body-surface area) and significantly reduced pulmonary vascular resistance by 33% at week 17.¹² We conducted an event-driven, phase 3 trial, the Prostacyclin (PGI₂) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) study, to investigate the safety and efficacy of selexipag in patients with pulmonary arterial hypertension who were not receiving therapy at baseline and those who were already receiving one or two therapies for the disease at baseline.

METHODS

STUDY DESIGN

The GRIPHON study was a multicenter, double-blind, randomized, parallel-group, placebo-controlled, event-driven, phase 3 study. The steering committee, in collaboration with the sponsor (Actelion Pharmaceuticals), designed the trial and oversaw its conduct and the analyses of the data. The study protocol, which is available with the full text of this article at NEJM.org, was approved by the review board or ethics committee at each participating site. The study was monitored by an independent data and safety monitoring committee (see the Supplementary Appendix, available at NEJM.org). The collection, management, and analysis of the data were performed by the sponsor according to a prespecified statistical analysis plan (available with the protocol) that was reviewed by two independent academic statisticians. All drafts of the

manuscript were written by the first author and the last two (senior) authors, as well as the three authors affiliated with the sponsor, and were reviewed and edited by all the authors. The steering committee members, all of whom are authors of this article, and the three authors affiliated with Actelion Pharmaceuticals were involved in the decision to submit the manuscript for publication. All the authors had access to the data and vouch for the accuracy and completeness of the analyses and for the fidelity of this report to the study protocol.

SELECTION OF PATIENTS

The study population included patients 18 to 75 years of age who had idiopathic or heritable pulmonary arterial hypertension or pulmonary arterial hypertension associated with human immunodeficiency virus infection, drug use or toxin exposure, connective tissue disease, or repaired congenital systemic-to-pulmonary shunts. Confirmation of the diagnosis by means of right heart catheterization was required before screening.² Patients were required to have a pulmonary vascular resistance of at least 5 Wood units (400 dyn·sec·cm⁻⁵) and a 6-minute walk distance of 50 to 450 m. Patients who were not receiving treatment for pulmonary arterial hypertension and those who were receiving an endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both at a dose that had been stable for at least 3 months were eligible for enrollment; patients who were receiving prostacyclin analogues were not eligible. Written informed consent was obtained from all the patients.

TRIAL PROCEDURES

Within 28 days after screening, patients were randomly assigned, in a 1:1 ratio (with stratification according to study center), to receive placebo or selexipag. During the 12-week dose-adjustment phase, selexipag was initiated at a dose of 200 μg twice daily and was increased weekly in twice-daily increments of 200 μg until unmanageable adverse effects associated with prostacyclin use, such as headache or jaw pain, developed (Fig. S1 in the Supplementary Appendix). The dose was then decreased by 200 μg in both daily doses, and this reduced dose was considered to be the maximum tolerated dose for that patient. The maximum dose allowed was 1600 μg twice daily. After 12 weeks, patients

entered the maintenance phase of the study. Starting at week 26, doses could be increased at scheduled visits; dose reductions were allowed at any time. The individualized maintenance dose was defined as the dose that a patient received for the longest duration.

Selexipag and placebo were administered in a double-blind fashion. The end of the treatment period was defined for each patient as 7 days after the last intake of selexipag or placebo (Fig. S2 in the Supplementary Appendix). As outlined in Figure 1, the end of the treatment period occurred at the end of the study (for patients who did not have a primary end-point event), after the occurrence of a primary end-point event, or prematurely for various reasons, such as an adverse event. The end of the study was declared when the prespecified number of primary end-point events in the study population was reached (see the Statistical Analysis section below).

Clinical assessments that included the 6-minute walk distance and determination of the World Health Organization (WHO) functional class were performed and laboratory data were collected at screening, at baseline, at weeks 8, 16, and 26, and every 6 months thereafter and when worsening of the disease was suspected. Adverse events and serious adverse events were recorded throughout the treatment period and up to 7 days (for adverse events) and 30 days (for serious adverse events) after the last intake of selexipag or placebo. Vital status was recorded at the end of the study.

Patients who discontinued selexipag or placebo during the double-blind phase of the study and provided written informed consent for further follow-up were followed during a blinded post-treatment observation period up to the end of the study (see Section 7 in the Supplementary Appendix). Patients who had a nonfatal primary end-point event discontinued the double-blind regimen and were eligible to receive open-label selexipag or commercially available drugs; patients who continued to receive selexipag or placebo throughout the double-blind phase were also eligible to receive open-label selexipag or commercially available drugs at the end of the study. The commercially available drugs represented the local standard of care and were not paid for by the sponsor.

OUTCOME MEASURES

The primary end point in a time-to-event analysis was a composite of death or a complication related to pulmonary arterial hypertension, whichever occurred first, up to the end of the treatment period. Complications related to pulmonary arterial hypertension were disease progression or worsening of pulmonary arterial hypertension that resulted in hospitalization, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy as judged by the physician. (Placement on a transplant waiting list represented an acute measure, as confirmed by the critical-event committee, and an actual lung transplantation would also meet this criterion.) Disease progression was defined as a decrease from baseline of at least 15% in the 6-minute walk distance (confirmed by means of a second test on a different day) accompanied by a worsening in WHO functional class (for the patients with WHO functional class II or III at baseline) or the need for additional treatment of pulmonary arterial hypertension (for the patients with WHO functional class III or IV at baseline). An independent critical-event committee whose members were unaware of the study-group assignments adjudicated all events up to the end of the study, including each death, to determine whether it was due to pulmonary arterial hypertension.

Secondary end points, listed in the order of the testing hierarchy, included the change in the 6-minute walk distance from baseline to week 26 (measured at trough levels of the study drug), the absence of worsening of WHO functional class from baseline to week 26, and death due to pulmonary arterial hypertension or hospitalization for worsening of pulmonary arterial hypertension up to the end of treatment period and death from any cause up to the end of the study (both analyzed in a time-to-event analysis). The change in N-terminal pro-brain natriuretic peptide (NT-proBNP) level from baseline to week 26 was analyzed as an exploratory end point. Safety end points included adverse events and abnormal results from laboratory studies.

STATISTICAL ANALYSIS

We initially estimated that 202 primary end-point events would be needed for the study to have 90% power to detect a hazard ratio for the

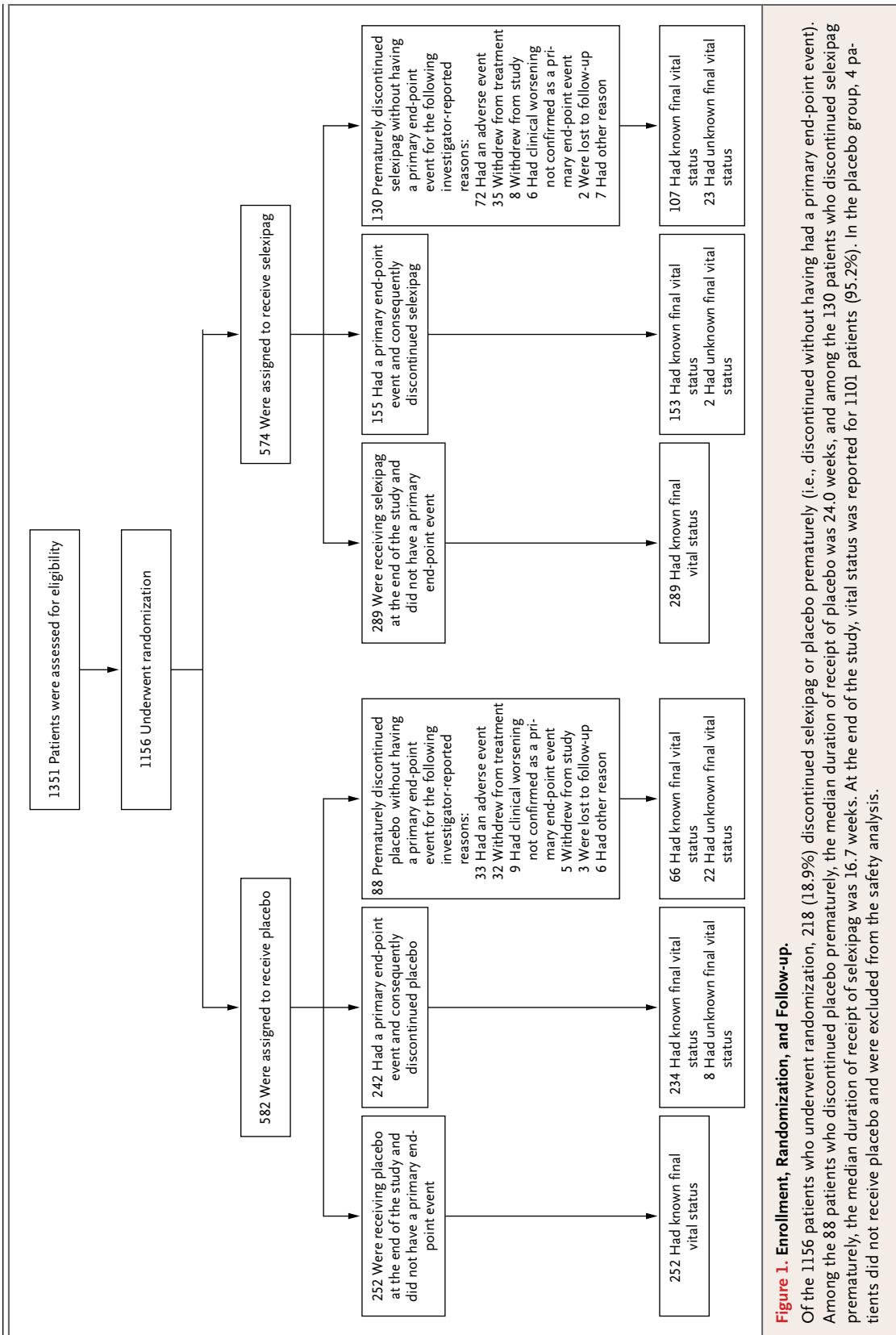


Figure 1. Enrollment, Randomization, and Follow-up.

Of the 1156 patients who underwent randomization, 218 (18.9%) discontinued selexipag or placebo prematurely (i.e., discontinued without having had a primary end-point event). Among the 88 patients who discontinued placebo prematurely, the median duration of receipt of placebo was 24.0 weeks, and among the 130 patients who discontinued selexipag prematurely, the median duration of receipt of selexipag was 16.7 weeks. At the end of the study, vital status was reported for 1101 patients (95.2%). In the placebo group, 4 patients did not receive placebo and were excluded from the safety analysis.

primary end point with selexipag, as compared with placebo, of 0.57 over an estimated study duration of 3.5 years, assuming a hazard rate of 0.22 per year in the placebo group, at a one-sided type 1 error rate of 0.005. We calculated that to reach that number of primary end-point events, we would need to enroll 670 patients over the course of 2 years, assuming an annual rate of attrition of 5%. Twenty months after the study was initiated, a blinded review of baseline data from 154 patients indicated that more patients than expected were receiving background therapy for their disease. Therefore, the hypothesized hazard ratio was changed from 0.57 to 0.65 to reflect a lower anticipated treatment effect. To preserve the type 1 and type 2 error rates and the study duration, the required number of primary end-point events was increased to 331 and the required number of patients was increased to 1150. An independent data and safety monitoring committee performed an interim analysis, which had been planned after 202 events had occurred, with stopping rules for futility and efficacy that were based on Haybittle–Peto boundaries. The final analysis used a one-sided significance level of 0.00499.

The primary end-point analysis was an on-treatment analysis with follow-up data censored at the time selexipag or placebo was discontinued. Secondary end points were tested hierarchically to control for multiplicity. In time-to-event analyses, end points were estimated with the use of the Kaplan–Meier method and were analyzed with the use of the log-rank test. Hazard ratios with 99% confidence intervals (for primary and secondary end points) and 95% confidence intervals (for exploratory end points) were estimated with the use of proportional-hazard models. Sensitivity analyses were performed to account for premature discontinuations of placebo or selexipag, and an analysis of the primary end point was performed that excluded the 45 events that occurred before the sample size was increased (see Section 8 in the Supplementary Appendix). We also performed subgroup analyses that included interaction tests.¹³ In addition, the primary end point was analyzed according to prespecified dose strata: low doses (200 or 400 μg twice daily), medium doses (600, 800, or 1000 μg twice daily), and high doses (1200, 1400, or 1600 μg twice daily).

At week 26, the changes from baseline in the

6-minute walk distance and in the NT-proBNP level were analyzed with use of a nonparametric analysis of covariance that was adjusted for the baseline value; the proportion of patients who did not have a worsening in WHO functional class was assessed with the use of a nonparametric analysis of covariance that was adjusted for the baseline value and a Cochran–Mantel–Haenszel test stratified according to the baseline value. Missing data for the 6-minute walk distance and WHO functional class were imputed according to a worst-case scenario (see Section 9 in the Supplementary Appendix). The analysis of NT-proBNP levels was performed with the use of observed data.

RESULTS

PATIENTS

A total of 1156 patients were enrolled at 181 centers in 39 countries from December 2009 through May 2013 and were randomly assigned to receive placebo (582 patients) or selexipag (574 patients) (Fig. 1). The patients in the placebo group received placebo for a median duration of 63.7 weeks, and the patients in the selexipag group received selexipag for a median duration of 70.7 weeks. The baseline characteristics of the patients are shown in Table 1. Of the 351 patients who discontinued placebo or selexipag after a nonfatal primary end-point event, 170 provided consent for follow-up during the post-treatment observation period (111 in the placebo group and 59 in the selexipag group); of the 218 patients who discontinued placebo or selexipag prematurely without having a primary end-point event, 80 provided consent for follow-up during the post-treatment observation period (26 in the placebo group and 54 in the selexipag group) (see Section 8 in the Supplementary Appendix). Vital status was reported for 1101 patients (95.2%) at the end of the study.

PRIMARY END POINT

Overall, 397 patients had a primary end-point event (242 patients [41.6%] in the placebo group and 155 patients [27.0%] in the selexipag group). The hazard ratio for a primary end-point event in the selexipag group was 0.60 (99% confidence interval [CI], 0.46 to 0.78; $P < 0.001$) (Fig. 2). Disease progression and hospitalization accounted for 81.9% of the events (Table 2). The results of

Characteristic	Placebo (N=582)	Selexipag (N=574)	All Patients (N=1156)
Female sex — no. (%)	466 (80.1)	457 (79.6)	923 (79.8)
Age			
Mean — yr	47.9±15.55	48.2±15.19	48.1±15.37
Distribution — no. (%)			
<65 yr	474 (81.4)	475 (82.8)	949 (82.1)
≥65 yr	108 (18.6)	99 (17.2)	207 (17.9)
Geographic region — no. (%)			
Asia	113 (19.4)	115 (20.0)	228 (19.7)
Eastern Europe	155 (26.6)	149 (26.0)	304 (26.3)
Latin America	56 (9.6)	54 (9.4)	110 (9.5)
North America	98 (16.8)	95 (16.6)	193 (16.7)
Western Europe and Australia	160 (27.5)	161 (28.0)	321 (27.8)
Time since diagnosis of PAH — yr†	2.5±3.75	2.3±3.49	2.4±3.62
PAH classification — no. (%)			
Idiopathic	337 (57.9)	312 (54.4)	649 (56.1)
Heritable	13 (2.2)	13 (2.3)	26 (2.2)
Associated with connective tissue disease	167 (28.7)	167 (29.1)	334 (28.9)
Associated with corrected-congenital shunts	50 (8.6)	60 (10.5)	110 (9.5)
Associated with HIV infection	5 (0.9)	5 (0.9)	10 (0.9)
Associated with drug or toxin exposure	10 (1.7)	17 (3.0)	27 (2.3)
WHO functional class — no. (%)‡			
I	5 (0.9)	4 (0.7)	9 (0.8)
II	255 (43.8)	274 (47.7)	529 (45.8)
III	314 (54.0)	293 (51.0)	607 (52.5)
IV	8 (1.4)	3 (0.5)	11 (1.0)
6-Minute walk distance — m	348.0±83.23	358.5±76.31	353.2±80.01
Use of medications for PAH — no. (%)			
None	124 (21.3)	112 (19.5)	236 (20.4)
Endothelin-receptor antagonists	76 (13.1)	94 (16.4)	170 (14.7)
Phosphodiesterase type 5 inhibitors	185 (31.8)	189 (32.9)	374 (32.4)
Endothelin-receptor antagonists plus phosphodiesterase type 5 inhibitors	197 (33.8)	179 (31.2)	376 (32.5)

* Plus-minus values are means ±SD. Testing of baseline characteristics showed that there were no significant between-group differences at baseline ($P>0.05$). HIV denotes human immunodeficiency virus, PAH pulmonary arterial hypertension, and WHO World Health Organization.

† The diagnosis was confirmed by right heart catheterization.

‡ The WHO functional class ranges from I to IV, with higher numbers indicating greater functional limitations.

sensitivity analyses that were performed to account for premature discontinuations and of an analysis that excluded events that occurred before the sample size was increased were consistent with the results of the primary analysis

(Table S1 and Fig. S3 in the Supplementary Appendix). A total of 133 patients (23.2%) received a maintenance dose of selexipag in the low-dose stratum, 179 (31.2%) received a maintenance dose in the medium-dose stratum, and 246

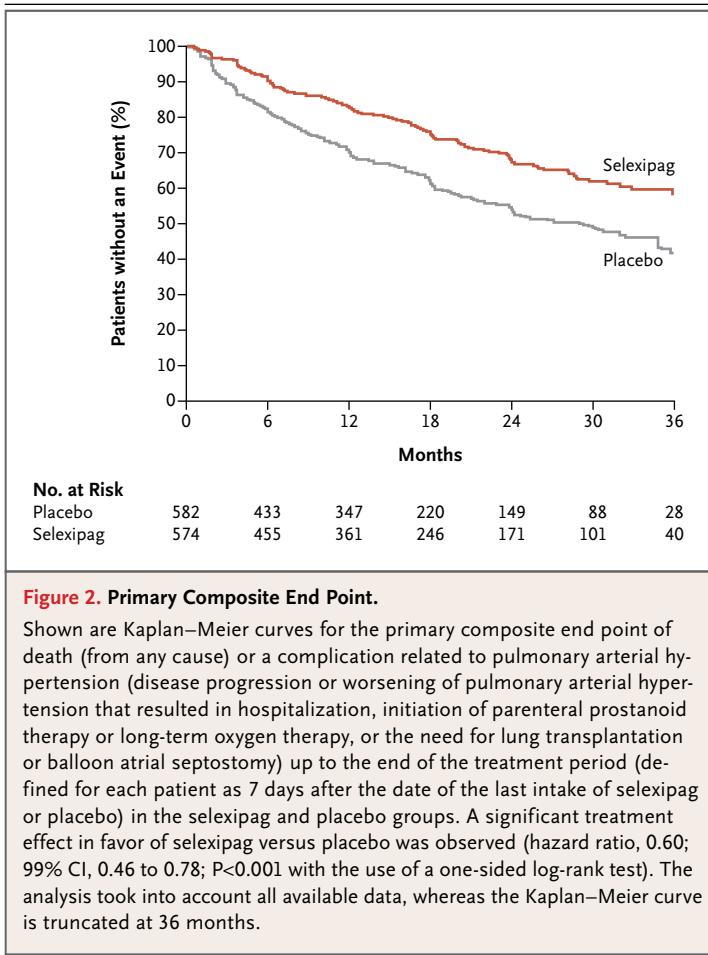


Figure 2. Primary Composite End Point.

Shown are Kaplan–Meier curves for the primary composite end point of death (from any cause) or a complication related to pulmonary arterial hypertension (disease progression or worsening of pulmonary arterial hypertension that resulted in hospitalization, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy) up to the end of the treatment period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo) in the selexipag and placebo groups. A significant treatment effect in favor of selexipag versus placebo was observed (hazard ratio, 0.60; 99% CI, 0.46 to 0.78; $P < 0.001$ with the use of a one-sided log-rank test). The analysis took into account all available data, whereas the Kaplan–Meier curve is truncated at 36 months.

(42.9%) received a maintenance dose in the high-dose stratum (Table S2 in the Supplementary Appendix). The effect of selexipag with respect to the primary end point was consistent across these strata (Fig. S4 in the Supplementary Appendix). The treatment effect with respect to the primary end point was also consistent in the prespecified patient subgroups, with nonsignificant P values for interaction, including in the subgroup of patients who were already receiving two therapies for pulmonary arterial hypertension at baseline (Fig. S5 in the Supplementary Appendix).

SECONDARY AND EXPLORATORY END POINTS

Missing values were imputed for 21.6% of the patients in the analysis of 6-minute walk distance and for 18.3% of the patients in the analysis of WHO functional class. At week 26, the 6-minute walk distance had decreased by a me-

dian of 9.0 m from baseline in the placebo group and had increased by 4.0 m from baseline in the selexipag group (treatment effect, 12.0 m; 99% CI, 1 to 24; $P = 0.003$). At week 26, there was no significant difference between the placebo group and the selexipag group in the proportion of patients with no worsening in WHO functional class (74.9% and 77.8%, respectively; odds ratio, 1.16; 99% CI, 0.81 to 1.66; $P = 0.28$) (Table S3 in the Supplementary Appendix).

On the basis of the testing hierarchy, the following results should be interpreted as exploratory. By the end of the treatment period, death due to pulmonary arterial hypertension or hospitalization for worsening of pulmonary arterial hypertension had occurred in 137 patients (23.5%) in the placebo group and in 102 patients (17.8%) in the selexipag group (hazard ratio in the selexipag group, 0.70; 95% CI, 0.54 to 0.91; $P = 0.003$); 87.4% of these events were hospitalizations (Table 2). By the end of the study, death from any cause had occurred in 105 patients (18.0%) in the placebo group and in 100 patients (17.4%) in the selexipag group (hazard ratio in the selexipag group, 0.97; 95% CI, 0.74 to 1.28; $P = 0.42$). Findings from a sensitivity analysis that assumed that patients with unknown vital status had died (4.8% of patients) were consistent with the findings of the main analysis of death from any cause (Table S4 in the Supplementary Appendix). At week 26, NT-proBNP levels were significantly lower in the selexipag group than in the placebo group (Table S5 in the Supplementary Appendix).

SAFETY AND ADVERSE EVENTS

Overall, 41 patients (7.1%) in the placebo group and 82 patients (14.3%) in the selexipag group discontinued their study regimen prematurely because of an adverse event (Table 3). The most frequent adverse events leading to discontinuation in the selexipag group (events for which there was $>1\%$ difference between the selexipag and placebo groups) were headache (in 3.3% of the patients), diarrhea (in 2.3%), and nausea (in 1.7%). Hyperthyroidism occurred in 8 patients in the selexipag group and led to treatment discontinuation in 1 patient. No serious adverse events were reported more frequently (i.e., at a rate $>1\%$ higher) in the selexipag group than in the placebo group. Table 3 lists the most fre-

Table 2. End Points Related to Pulmonary Arterial Hypertension and Death.*

End Point	Placebo (N=582)	Selexipag (N=574)	Hazard Ratio (99% or 95% CI)†	P Value‡
<i>no. of patients (%)</i>				
Primary end point: composite of death or a complication related to PAH up to the end of the treatment period§				
All events	242 (41.6)	155 (27.0)	0.60 (0.46–0.78)	<0.001
Hospitalization for worsening of PAH	109 (18.7)	78 (13.6)		
Disease progression	100 (17.2)	38 (6.6)		
Death from any cause	18 (3.1)	28 (4.9)		
Initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH	13 (2.2)	10 (1.7)		
Need for lung transplantation or balloon atrial septostomy for worsening of PAH¶	2 (0.3)	1 (0.2)		
Secondary end point: death due to PAH or hospitalization for worsening of PAH up to the end of the treatment period§				
All events	137 (23.5)	102 (17.8)	0.70 (0.54–0.91)	0.003
Hospitalization for worsening of PAH	123 (21.1)	86 (15.0)		
Death due to PAH	14 (2.4)	16 (2.8)		
Secondary end point: death up to the end of the study **				
Death due to PAH	83 (14.3)	70 (12.2)	0.86 (0.63–1.18)	0.18
Death from any cause	105 (18.0)	100 (17.4)	0.97 (0.74–1.28)	0.42

* For the end points evaluated up to the end of the treatment period, the median duration of receipt of placebo was 63.7 weeks and the median duration of treatment with selexipag was 70.7 weeks. For the end points evaluated up to the end of the study, the median follow-up was 98.1 weeks.

† Hazard ratios are for selexipag versus placebo, with a 99% confidence interval (CI) for the primary end point and 95% CIs for secondary end points.

‡ P values were calculated with the use of a one-sided log-rank test.

§ The treatment was defined for each patient as 7 days after the date of the last intake of selexipag or placebo.

¶ The need for lung transplantation or balloon atrial septostomy for worsening of PAH was determined by the physician. (Placement on a transplant waiting list represented an acute measure, as confirmed by the critical-event committee, and an actual lung transplantation would also meet this criterion.)

|| On the basis of the testing hierarchy, these secondary end points were analyzed with 95% CIs, and these results should be interpreted as exploratory.

** The analysis included patients who may have received other treatments for pulmonary arterial hypertension, including open-label selexipag. A total of 155 patients from the placebo group who discontinued placebo after the occurrence of a primary end-point event and 63 patients from the selexipag group who discontinued selexipag after the occurrence of a primary end-point event received open-label selexipag.

quent adverse events reported overall. The most frequent adverse events associated with prostacyclin use that were reported during the dose-adjustment and maintenance phases are listed in Table S6 in the Supplementary Appendix. Adverse events associated with prostacyclin occurred more frequently during the dose-adjust-

ment phase, when they were used to define the individualized maximum tolerated dose.

DISCUSSION

In this event-driven study involving patients with pulmonary arterial hypertension, the risk of the

Table 3. Most Frequent Adverse Events and Abnormal Laboratory Results.*

Variable	Placebo (N=577)	Selexipag (N=575)	P Value
Adverse events — no.	3937	4607	
Patients with ≥1 adverse event — no. (%)	559 (96.9)	565 (98.3)	0.18
Patients with ≥1 serious adverse event — no. (%)†	272 (47.1)	252 (43.8)	0.26
Patients with adverse events leading to discontinuation of study agent — no. (%)	41 (7.1)	82 (14.3)	<0.001
Adverse event — no. of patients (%)‡			
Headache	189 (32.8)	375 (65.2)	<0.001
Diarrhea	110 (19.1)	244 (42.4)	<0.001
Nausea	107 (18.5)	193 (33.6)	<0.001
Pain in jaw	36 (6.2)	148 (25.7)	<0.001
Worsening of PAH	206 (35.7)	126 (21.9)	<0.001
Vomiting	49 (8.5)	104 (18.1)	<0.001
Pain in extremity	46 (8.0)	97 (16.9)	<0.001
Dyspnea	121 (21.0)	92 (16.0)	0.03
Myalgia	34 (5.9)	92 (16.0)	<0.001
Dizziness	85 (14.7)	86 (15.0)	0.93
Peripheral edema	104 (18.0)	80 (13.9)	0.06
Upper respiratory tract infection	80 (13.9)	75 (13.0)	0.73
Nasopharyngitis	63 (10.9)	75 (13.0)	0.28
Flushing	29 (5.0)	70 (12.2)	<0.001
Arthralgia	44 (7.6)	62 (10.8)	0.07
Cough	67 (11.6)	56 (9.7)	0.34
Fatigue	59 (10.2)	46 (8.0)	0.22
Right ventricular failure	58 (10.1)	46 (8.0)	0.26
Other adverse events and laboratory findings of interest — no. of patients (%)§			
Hyperthyroidism	0	8 (1.4)	0.004
Hypotension	18 (3.1)	29 (5.0)	0.10
Anemia	31 (5.4)	48 (8.3)	0.05
Syncope	51 (8.8)	37 (6.4)	0.15
Major bleeding event¶	12 (2.1)	14 (2.4)	0.70
Hemoglobin <8 g/dl	4 (0.7)	7 (1.3)	0.38

* Patients could have more than one event. Among the patients randomly assigned to the placebo group, four did not receive the study agent and were excluded from the safety analysis and one received a single dose of eight tablets of selexipag and was assigned to the selexipag group for the safety analysis.

† Serious adverse events were recorded throughout the treatment period and up to 30 days after placebo or selexipag was discontinued.

‡ Adverse events are listed for those that occurred in more than 10% of the patients in any study group during the double-blind period and up to 7 days after placebo or selexipag was discontinued.

§ The incidence of adverse events of interest that led to discontinuation of the study regimen included the following: hyperthyroidism (none with placebo and one with selexipag), hypotension (two with placebo and none with selexipag), syncope (two with placebo and one with selexipag), and major bleeding event (four with placebo and two with selexipag). No events of anemia resulted in discontinuation of the study regimen.

¶ Bleeding events were adjudicated by an independent committee according to the criteria of the International Society on Thrombosis and Hemostasis.¹⁴

|| Hemoglobin values were obtained for 563 patients in the placebo group and for 555 patients in the selexipag group.

primary composite end point of death or a complication related to pulmonary arterial hypertension was lower among those who received selexipag than among those who received placebo. The treatment effect was driven by differences in disease progression and hospitalization. There was no significant difference in mortality between the two study groups. The effect of selexipag was consistent in all prespecified patient subgroups, including those defined according to the cause of the pulmonary arterial hypertension, disease severity, and baseline treatment. The addition of selexipag to a baseline regimen of two medications for pulmonary arterial hypertension resulted in benefits that were consistent with the overall treatment effect.

It has been postulated that the density of prostacyclin receptors varies substantially among patients¹⁵ and may influence the individualized dose required for each patient. In our study, selexipag showed similar efficacy among patients who received a low-dose, medium-dose, and high-dose selexipag regimen. These data support the dose adjustment of selexipag to the highest dose at which the patient has manageable side effects and reflect the approach to dosing used with other therapies that target the prostacyclin pathway.² This approach precludes us from evaluating whether a fixed dose of selexipag would be equally effective in all patients.

Clinical deterioration typically occurs in patients with pulmonary arterial hypertension before they die. For this reason, the results for the primary end point included only a few deaths as first events. Deaths that happened after the occurrence of a complication were also evaluated. The analysis of all-cause mortality up to the end of the study showed no significant difference between the selexipag and placebo groups. The study was designed in such a way that a substantial proportion of patients who had a primary end-point event crossed over to open-label selexipag or to a commercially available drug. The evaluation of death is subject to this limitation.

The magnitude of improvement in the 6-minute walk distance was in the lower range of that observed (10 to 36 m) in other randomized, controlled trials.¹⁶⁻²² This finding may reflect the extent of imputed data, the strict imputation rules, and our study population that included a large number of patients in WHO functional class II and a high proportion of patients already

receiving treatment at baseline, for whom improvements in 6-minute walk distance may be difficult to achieve.

The adverse events observed with selexipag were consistent with those typically observed with prostacyclin therapies.²³ Headache, diarrhea, and nausea led to discontinuation of the study regimen more frequently in the selexipag group than in the placebo group. Overall, these adverse events were typically mild to moderate in severity and resulted in discontinuation in only a minority of cases.

Our study has several limitations. First, the study included an optional post-treatment observation period after placebo or selexipag was discontinued. As a result, the follow-up of patients who discontinued placebo or selexipag was somewhat limited and potentially biased by the patients' choice to provide consent. Second, 18.9% of patients discontinued placebo or selexipag prematurely. This rate of premature discontinuation was anticipated, and the results of sensitivity analyses of the primary end point that were performed to account for this anticipated rate and the previous limitation of a limited and potentially biased follow-up were consistent with the findings of the primary analysis. Third, the primary end point was based on recommendations for primary end points in pivotal randomized, controlled trials in pulmonary arterial hypertension²⁴ and included a number of subjective components. To address this potential limitation, the disease progression component was stringently defined, and all events were adjudicated by a three-person critical-event committee. Furthermore, as was the case in a previous event-driven study involving patients with pulmonary arterial hypertension,¹⁹ the results for the primary end point were consistent with the results for the secondary composite end point of death from pulmonary arterial hypertension or hospitalization due to pulmonary arterial hypertension. Therefore, future recommendations may evolve to reflect studies of heart failure²⁵ and consider this two-component end point as the primary outcome measure.

In conclusion, among patients with pulmonary arterial hypertension, the risk of the primary composite end point of death or a complication related to pulmonary arterial hypertension was significantly lower among patients who received selexipag than among those who received

placebo. There was no significant difference in mortality between the two study groups.

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APPENDIX

From Assistance Publique–Hôpitaux de Paris, Hôpital de Bicêtre, INSERM Unité Mixte de Recherche en Santé 999, Université Paris-Sud, Université Paris-Saclay, Le Kremlin-Bicêtre, France (O.S., G.S.); Massachusetts General Hospital, Boston (R.C.); UT Southwestern Medical Center, Dallas (K.M.C.); Actelion Pharmaceuticals, Allschwil, Switzerland (A.F., R.P., L.D.S.); National Pulmonary Hypertension Unit, Mater Misericordiae University Hospital, Dublin (S.G.); the Department of Experimental, Diagnostic and Specialty Medicine (DIMES) University of Bologna, Bologna, Italy (N.G.); University of Giessen and Marburg Lung Center, German Center of Lung Research, Giessen (H.-A.G.), and the Department of Respiratory Medicine, Hannover Medical School and German Center of Lung Research, Hannover (M.M.H.) — both in Germany; the Department of Medicine, Imperial College London, London (H.-A.G.); Medical University of Vienna, Department of Internal Medicine II, Division of Cardiology, Allgemeines Krankenhaus, Vienna (I.M.L.); the Division of Pulmonary and Critical Care Medicine, University of California, San Diego (L.J.R.); the Division of Pulmonary and Critical Care Medicine, Cedars-Sinai Medical Center, Los Angeles (V.T.); Minsk Regional Clinical Hospital, Minsk, Belarus (I.A.); the Department of Pulmonary Circulation, Shanghai Pulmonary Hospital, Shanghai (J.L.), and the Department of Rheumatology, Peking Union Medical College Hospital, Beijing (X.Z.) — both in China; Federal Almazov North-West Medical Research Center, St. Petersburg, Russia (O.M.); and the Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan Health System, Ann Arbor (V.V.M.).

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