CHEST

Relationship Between Time From Diagnosis and Morbidity/Mortality in Pulmonary Arterial Hypertension

Results From the Phase III GRIPHON Study

Sean Gaine, MD; Olivier Sitbon, MD; Richard N. Channick, MD; Kelly M. Chin, MD; Rafael Sauter, PhD; Nazzareno Galiè, MD; Marius M. Hoeper, MD; Vallerie V. McLaughlin, MD; Ralph Preiss, MD; Lewis J. Rubin, MD; Gérald Simonneau, MD; Victor Tapson, MD; Hossein-Ardeschir Ghofrani, MD; and Irene Lang, MD

BACKGROUND: Early initiation of pulmonary arterial hypertension (PAH) therapies is associated with improved long-term outcomes, yet data on the early use of prostacyclin pathway agents are limited. In these post hoc analyses of the Prostacyclin (PGI_2) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) study, the largest randomized controlled trial for PAH to date, the prognostic value of time from diagnosis and its impact on treatment response were examined.

RESEARCH QUESTION: How does time from diagnosis impact morbidity/mortality events and response to selexipag treatment in patients with PAH?

STUDY DESIGN AND METHODS: The GRIPHON study randomly assigned 1,156 patients with PAH to selexipag or placebo treatment. Patients were categorized post hoc into a time from diagnosis of $\leq$ 6 months and $>$ 6 months at randomization. Hazard ratios (selexipag vs placebo) were calculated for the primary end point of morbidity/mortality by time from diagnosis using Cox proportional hazard models.

RESULTS: Time from diagnosis was $\leq$ 6 months in 34.9% and $>$ 6 months in 65.1% of patients. Time from diagnosis was prognostic of morbidity/mortality, with newly diagnosed patients having a poorer long-term outcome than patients diagnosed for longer. Compared with placebo, selexipag reduced the risk of morbidity/mortality in patients with a time from diagnosis of $\leq$ 6 months and $>$ 6 months, with a more pronounced effect in newly diagnosed patients (hazard ratio, 0.45 [95% CI, 0.33-0.63] and 0.74 [95% CI, 0.57-0.96], respectively; $P = .0219$ for interaction).

INTERPRETATION: In the GRIPHON study, newly diagnosed PAH patients had a worse prognosis than patients with a longer time from diagnosis. The benefit of selexipag treatment on disease progression was more pronounced in patients treated earlier than in patients treated later.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01106014; URL: www.clinicaltrials.gov

CHEST 2021; 160(1):277-286

KEY WORDS: pulmonary arterial hypertension; selexipag; time from diagnosis

FOR EDITORIAL COMMENT, SEE PAGE 25

ABBREVIATIONS: PAH = pulmonary arterial hypertension; WHO FC = World Health Organization functional class

AFFILIATIONS: From the National Pulmonary Hypertension Unit (S. Gaine), Mater Misericordiae University Hospital, Dublin, Ireland; the Hôpital Universitaire de Bicêtre (O. Sitbon and G. Simonneau), Université Paris-Sud, Le Kremlin Bicêtre, France; the David Geffen School of Medicine at UCLA (R. N. Channick), Los Angeles, CA; the UT Southwestern Medical Center (K. M. Chin), Dallas, TX; Actelion

Take-home Points

Study Question: These post hoc analyses of the GRIPHON study examined how time from diagnosis impacts morbidity/mortality and response to selexipag treatment in patients with PAH.

Results: Compared with placebo, selexipag reduced the risk of morbidity/mortality in patients with a time from diagnosis of ≤ 6 months and > 6 months, with a more pronounced effect in newly diagnosed patients.

Interpretation: Both patient subgroups benefited from selexipag, with the newly diagnosed patients showing a more pronounced treatment effect.

Pulmonary arterial hypertension (PAH) is a progressive disease with no available cure.[1] Currently, therapies for PAH target 3 well-characterized pathways implicated in disease pathogenesis: the endothelin, nitric oxide, and prostacyclin pathways.[2] Initiation of combination therapy, with an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor, is recommended by the European Society of Cardiology/European Respiratory Society guidelines[2,3] and the proceedings from the 6th World Symposium on Pulmonary Hypertension[4] for patients with a low- or intermediate-risk status at diagnosis. Initial use of IV prostacyclin is recommended for high-risk patients with severe disease.[2-4]

The benefits of prostacyclin pathway agents[5-7] are well documented, yet administration often is delayed, and a significant proportion of patients never receive a drug targeting this pathway.[8,9] Key factors delaying the use of prostacyclin and prostacyclin analogs include their adverse event profile, the need for titration to an individualized dose, and for some agents, the complexity of their administration.[8] In addition, studies examining early treatment with these therapies are limited.[6,10,11] Selexipag, a selective prostacyclin receptor agonist,[7] provides an opportunity for early targeting of the prostacyclin pathway with an orally available medication. Herein, we further evaluated its optimal use as part of the PAH treatment armamentarium.

The Prostacyclin (PGI_2) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) study was a long-term, event-driven, randomized, placebo-controlled, phase III trial evaluating selexipag use in 1,156 PAH patients.[7] The study demonstrated a statistically significant 40% reduction in the risk of a primary composite outcome of morbidity and mortality ($P < .001$) with selexipag compared with placebo.[7] These post hoc analyses of the GRIPHON study investigated associations of time from PAH diagnosis with morbidity/mortality and with the response to treatment with selexipag.

Methods

The data sharing policy of the sponsor is available at https://www.janssen.com/clinical-trials/transparency. As noted on this website, requests for access to the study data can be submitted through the Yale Open Data Access Project site at https://yoda.yale.edu.

Study Population and Study Design

PAH patients with a diagnosis confirmed by right heart catheterization 18 to 75 years of age and with a pulmonary vascular resistance of ≥ 400 dyn·s·cm^{-5} were eligible for inclusion in the GRIPHON study.[7] At screening, patients were required to have a 6-min walk distance of 50 to 450 m and to be treatment naïve or receiving a phosphodiesterase type 5 inhibitor, endothelin receptor antagonist, or both at stable doses for at least 3 months before randomization. Patients receiving a prostacyclin analog were not eligible. All patients provided written informed consent before participation.

Pharmaceuticals, Ltd. (R. Sauter and R. Preiss), Allschwil, Switzerland; the Department of Experimental, Diagnostic and Specialty Medicine—DIMES (N. Galiè), University of Bologna, Bologna, Italy; the Department of Respiratory Medicine (M. M. Hoeper), Hannover Medical School and German Center for Lung Research, Hannover, Germany; the Department of Internal Medicine (V. V. McLaughlin), Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI; the Division of Pulmonary and Critical Care Medicine (L. J. Rubin), University of California, San Diego, CA; the Cedars-Sinai Medical Center (V. Tapson), Los Angeles, CA; the University of Giessen and Marburg Lung Center (H.-A. Ghofrani), Giessen, Germany, and member of the German Center for Lung Research, and Department of Medicine, Imperial College London, London, UK; and the Department of Internal Medicine II (I. Lang), Division of Cardiology, Medical University of Vienna, Allgemeines Krankenhaus, Vienna, Austria.

This article was presented as a poster at ATS International Conference, Dallas, TX, May 2019 (Gaine S, et al. *Am J Respir Crit Care Med.* 2019;199:A2502); as a poster and slide presentation at Pulmonary Hypertension Association PH Professional Network (PHPN) Symposium, Washington, DC, September 2019; as a published abstract for the Canadian Cardiovascular Congress, 2019 (Langleben D, et al. *Can J Cardiol.* 2019;35:S77); as a poster at the Pulmonary Vascular Research Institute Annual World Congress, Lima, Peru, January 2020; as a published abstract for the German Society of Cardiology—Cardiovascular Research (DGK) annual meeting, 2020 (*Clin Res Cardiol.* 2020;109:1); and as a published abstract for the Congress of the German Society for Pneumology and Respiratory Medicine eV (DGP), 2020 (Gaine S, et al. *Pneumologie.* 2020;74:S63).

FUNDING/SUPPORT: This study was funded by Actelion Pharmaceuticals, Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson.

CORRESPONDENCE TO: Sean Gaine, MD; email: sgaine@mater.ie

DOI: https://doi.org/10.1016/j.chest.2021.01.066

The GRIPHON study (ClinicalTrials.gov Identifier: NCT01106014) was a global, double-blind, randomized, placebo-controlled, event-driven phase III study assessing the safety and efficacy of selexipag in patients with PAH. Patients were randomized 1:1 to receive selexipag or placebo twice daily. The study drug was titrated over a 12-week period, with patients reaching their individualized maintenance dose ranging between 200 and 1600 μg twice daily. Patients continued to receive double-blind treatment until a primary end point event was experienced, until premature discontinuation of the study drug, or until the end of the study. On reaching the prespecified number of primary end point events (n = 331), the end of the study was declared. The trial adhered to the principles outlined in the amended Declaration of Helsinki, with protocol approval from local institutional review boards or independent ethics committees (e-Appendix 1).

Outcome Measures

The primary composite end point in the GRIPHON study was the time from randomization to the first morbidity or mortality event up to the end of the double-blind treatment plus 7 days. Morbidity events were defined as disease progression or worsening of PAH that resulted in hospitalization, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy. Disease progression was defined as a ≥ 15% decrease in 6-min walk distance from baseline, which was confirmed by a second test on a different day, together with a worsening in World Health Organization functional class (WHO FC; for patients in WHO FC II/III at baseline) or the need for additional PAH therapy (for patients in WHO FC III/IV at baseline). All end point events were adjudicated by a blinded, independent committee.

Categorization by Time From Diagnosis

All randomized patients in the GRIPHON study were categorized post hoc according to their time from PAH diagnosis to baseline (date of study randomization) using a 6-month threshold. This threshold was based on the range in time from diagnosis (0-12 months) that previously was used to define incident vs prevalent PAH patients[12-16] and on the recommendation of the European Society of Cardiology/European Respiratory Society guidelines to have a follow-up assessment up to 6 months after initial diagnosis.[2,3] Time from diagnosis was based on the investigator-reported date of the diagnostic right heart catheterization. A time from diagnosis of ≤ 6 months was used to define newly diagnosed patients treated earlier with selexipag, with later treatment defined as those patients with a time from diagnosis of > 6 months before selexipag initiation.

Statistical Analyses

Post hoc analyses of the GRIPHON study primary composite end point (morbidity or mortality events) were performed for patients grouped according to time from diagnosis at baseline of ≤ 6 months or > 6 months. Descriptive baseline characteristics were compiled for each subgroup. Kaplan-Meier estimates were used to determine the impact of time from diagnosis at baseline on the risk of a primary end point event across the treatment arms and subgroups. Hazard ratios with 95% CIs were calculated using Cox proportional hazard models. Cox proportional hazard models included treatment group and time from diagnosis (≤ 6 months and > 6 months) as covariates and were unadjusted or adjusted for a number of other baseline covariates. A full list of covariates and interaction terms can be found in e-Appendix 2. In these post hoc analyses, no adjustments were made for multiple testing. Safety outcomes were reported descriptively for data collected up to 7 days and 30 days after the end of treatment for adverse events and serious adverse events, respectively.

Results

Patient Characteristics

Mean ± SD time from diagnosis for the 1,156 patients in the GRIPHON study was 2.4 ± 3.62 years,[7] with 404 (34.9%) diagnosed ≤ 6 months and 752 (65.1%) diagnosed > 6 months from randomization (Fig 1). As shown in Table 1, newly diagnosed patients (≤ 6 months) generally were younger than those with a longer time from diagnosis (> 6 months; mean age ± SD, 44.2 ± 15.7 years vs 50.1 ± 14.8 years, respectively). In addition, newly diagnosed patients were more likely

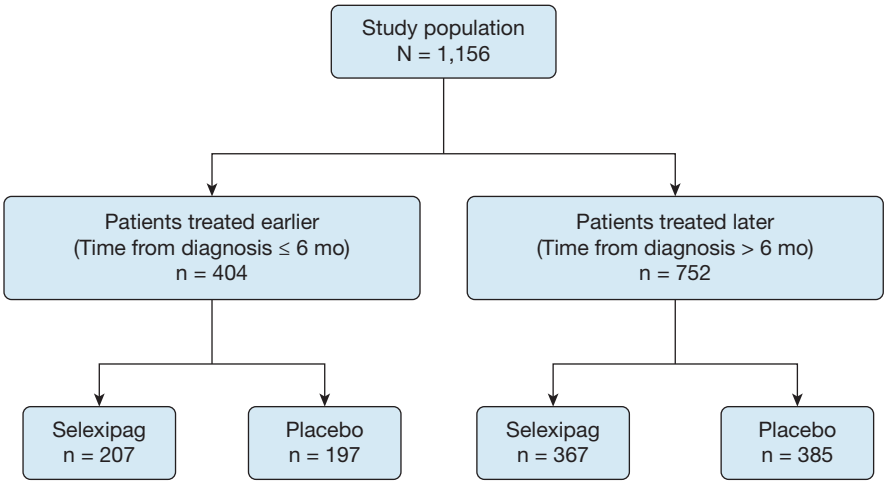

Figure 1 – *Flow chart showing patient disposition.*

TABLE 1] Baseline Characteristics According to Time From PAH Diagnosis at Baseline

	Time From Diagnosis					
	≤ 6 mo			> 6 mo		
Variable	Placebo (n = 197)	Selexipag (n= 207)	Total (N= 404)	Placebo (n= 385)	Selexipag (n= 367)	Total (N= 752)
Female sex	156 (79.2)	163 (78.7)	319 (79.0)	310 (80.5)	294 (80.1)	604 (80.3)
Age, y	44.1 ± 16.1	44.4 ± 15.3	44.2 ± 15.7	49.9 ± 14.9	50.4 ± 14.7	50.1 ± 14.8
Time since PAH diagnosis, y						
Mean ± SD	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	3.6 ± 4.1	3.6 ± 3.9	3.6 ± 4.0
Median (range)	0.1 (0.0-0.5)	0.1 (0.0-0.5)	0.1 (0.0-0.5)	2.1 (0.5-38.9)	2.1 (0.5-37.3)	2.1 (0.5-38.9)
Geographical region						
Asia	57 (28.9)	49 (23.7)	106 (26.2)	56 (14.5)	66 (18.0)	122 (16.2)
Eastern Europe	85 (43.1)	91 (44.0)	176 (43.6)	70 (18.2)	58 (15.8)	128 (17.0)
Latin America	19 (9.6)	26 (12.6)	45 (11.1)	37 (9.6)	28 (7.6)	65 (8.6)
North America	12 (6.1)	15 (7.2)	27 (6.7)	86 (22.3)	80 (21.8)	166 (22.1)
Western Europe/Australia	24 (12.2)	26 (12.6)	50 (12.4)	136 (35.3)	135 (36.8)	271 (36.0)
PAH classification						
Idiopathic	113 (57.4)	106 (51.2)	219 (54.2)	224 (58.2)	206 (56.1)	430 (57.2)
Associated with connective tissue disease	60 (30.5)	66 (31.9)	126 (31.2)	107 (27.8)	101 (27.5)	208 (27.7)
Associated with congenital heart disease	22 (11.2)	25 (12.1)	47 (11.6)	28 (7.3)	35 (9.5)	63 (8.4)
Drug or toxin induced, heritable, HIV infection	2 (1.0)	10 (4.8)	12 (3.0)	26 (6.8)	25 (6.8)	51 (6.8)
WHO FC						
I	4 (2.0)	3 (1.4)	7 (1.7)	1 (0.3)	1 (0.3)	2 (0.3)
II	96 (48.7)	114 (55.1)	210 (52.0)	159 (41.3)	160 (43.6)	319 (42.4)
III	95 (48.2)	89 (43.0)	184 (45.5)	219 (56.9)	204 (55.6)	423 (56.3)
IV	2 (1.0)	1 (0.5)	3 (0.7)	6 (1.6)	2 (0.5)	8 (1.1)
6-min walk distance, m	339.3 ± 87.6	348.9 ± 79.7	344.2 ± 83.6	352.4 ± 80.7	363.9 ± 73.9	358.0 ± 77.6

(Continued)

TABLE 1 (*Continued*)

Variable	Time From Diagnosis					
	≤ 6 mo			> 6 mo		
	Placebo (n = 197)	Selexipag (n= 207)	Total (N= 404)	Placebo (n= 385)	Selexipag (n= 367)	Total (N= 752)
Background PAH therapy						
None	82 (41.6)	75 (36.2)	157 (38.9)	42 (10.9)	37 (10.1)	79 (10.5)
ERA	21 (10.7)	21 (10.1)	42 (10.4)	55 (14.3)	73 (19.9)	128 (17.0)
PDE-5i	77 (39.1)	88 (42.5)	165 (40.8)	108 (28.1)	101 (27.5)	209 (27.8)
ERA and PDE-5i	17 (8.6)	23 (11.1)	40 (9.9)	180 (46.8)	156 (42.5)	336 (44.7)
NT-proBNP, ng/L[a]	726.0 (204.0-2,015.0)	517.0 (135.5-1,560.0)	563.0 (167.0-1,678.0)	522.0 (195.0-1,608.0)	578.0 (194.5-1,444.5)	546.0 (195.0-1,521.0)

Data are presented as No. (%), or mean ± SD, or median (interquartile range), unless otherwise indicated. Percentages may not add up to 100% because of rounding. ERA = endothelin receptor antagonist; NT-proBNP = N-terminal pro brain natriuretic peptide; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; WHO FC = World Health Organization functional class.
[a]Missing data: ≤ 6 mo for placebo (n = 2), selexipag (n = 3); > 6 mo for placebo (n = 6), selexipag (n = 3).

to be in WHO FC I/II (53.7%) than patients with a longer time from diagnosis (42.7%). A regional difference also was observed in relation to time from diagnosis, with a higher proportion of newly diagnosed patients from Asia (26.2%) and Eastern Europe (43.6%) compared with patients with a longer time from diagnosis, of whom 16.2% were from Asia and 17.0% from Eastern Europe. A higher proportion of patients with a longer time from diagnosis were receiving background double-combination therapy than those newly diagnosed (44.7% vs 9.9%, respectively).

Time From Diagnosis and Morbidity/Mortality

In the placebo group, up to the end of double-blind treatment, 50.3% of newly diagnosed patients experienced a morbidity or mortality event compared with 37.1% of patients diagnosed for a longer period (Table 2). The Kaplan-Meier estimates indicated that at month 12, 64.1% (95% CI, 56.6%-70.6%) of newly diagnosed patients in the placebo group were event free compared with 74.0% (95% CI, 69.1%-78.3%) of patients with a longer time from diagnosis (Fig 2A, 2B). The percentage of patients who experienced a morbidity or mortality event in the selexipag group was similar for those with a shorter or longer time from diagnosis (27.5% and 26.7%, respectively) (Table 2). At month 12, Kaplan-Meier estimates indicated that 79.4% (95% CI, 72.8%-84.6%) of newly diagnosed selexipag patients were event-free compared with 85.2% (95% CI, 80.8%-88.7%) of selexipag patients with a longer time from diagnosis (Fig 2A, 2B). In line with results from the overall GRIPHON population,[7] hospitalization for PAH worsening and disease progression were the most common primary end point events, with the current analysis highlighting that this was regardless of time from diagnosis or treatment (Table 2).

In the overall population, time from diagnosis was prognostic of morbidity/mortality events ($P = .0053$, adjusted Cox regression model). The prognostic relevance of time from diagnosis was not dependent on age ($P = .3660$ for interaction) or on the number of low-risk criteria at baseline ($P = .9703$ for interaction), and no statistical evidence was found for an influence of PAH background therapy ($P = .0798$ for interaction). Consistent results were observed in sensitivity analyses that were unadjusted for baseline covariates (e-Table 1).

Time From Diagnosis and Treatment Response

Compared with placebo treatment, selexipag reduced the risk of morbidity/mortality by 55% in newly

TABLE 2] End Points Related to PAH and Death According to Time From PAH Diagnosis at Baseline

Variable	Time From Diagnosis			
	≤ 6 mo (n = 404)		> 6 mo (n = 752)	
	Placebo (n = 197)	Selexipag (n = 207)	Placebo (n = 385)	Selexipag (n = 367)
Patients with morbidity or mortality event	99 (50.3)	57 (27.5)	143 (37.1)	98 (26.7)
First morbidity or mortality event				
Hospitalization for PAH worsening	39 (19.8)	24 (11.6)	70 (18.2)	54 (14.7)
Disease progression	48 (24.4)	15 (7.2)	52 (13.5)	23 (6.3)
Death	10 (5.1)	14 (6.8)	8 (2.1)	14 (3.8)
Parenteral prostanoid therapy or chronic oxygen therapy	2 (1.0)	4 (1.9)	11 (2.9)	6 (1.6)
PAH worsening resulting in need for lung transplantation or balloon atrial septostomy	0	0	2 (0.5)	1 (0.3)

Data are presented as No. (%). First morbidity or mortality events up to end of double-blind treatment plus 7 days are included. PAH = pulmonary arterial hypertension.

diagnosed patients (hazard ratio, 0.45 [95% CI, 0.33-0.63]) and by 26% in patients with a longer time from diagnosis (hazard ratio, 0.74 [95% CI, 0.57-0.96]) (Fig 3, e-Table 2). The low interaction *P* value (.0219) suggested a more pronounced treatment effect in newly diagnosed patients. In an effort to account for the potential impact of differences in background PAH therapy use at baseline, an analysis adjusting for this variable was conducted and a similar pattern for the treatment effect was observed, although small group sizes may have contributed to the higher interaction *P* value of .1805 (Fig 3, e-Table 3). Consistent results were observed in sensitivity analyses that were unadjusted for baseline covariates (e-Tables 2, 3).

Exposure, Safety, and Tolerability

Similar percentages of patients with a time from diagnosis of ≤ 6 months and > 6 months were in the low- (23.2% and 23.1%), intermediate- (30.9% and 31.3%), and high-individualized maintenance dose groups (43.0% and 42.7%) (e-Table 4). Mean ± SD exposure time in the placebo group was 64.4 ± 45.7 weeks in newly diagnosed patients compared with 74.7 ± 49.3 weeks in patients with a longer time from diagnosis. By contrast, exposure to selexipag was similar

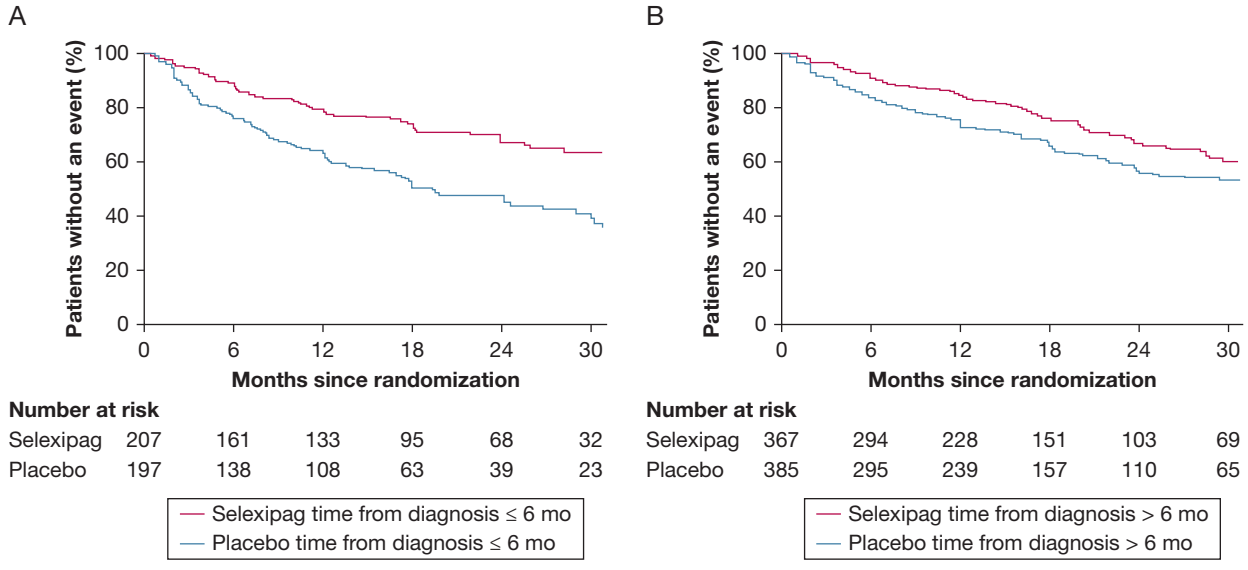

Figure 2 – *A, B, Kaplan-Meier estimates of time from baseline to first morbidity or mortality event in patients stratified by time from diagnosis. Time from baseline to first morbidity or mortality event up to the end of double-blind treatment plus 7 days in patients with a time from pulmonary arterial hypertension diagnosis at baseline of (A) ≤ 6 months and (B) > 6 months.*

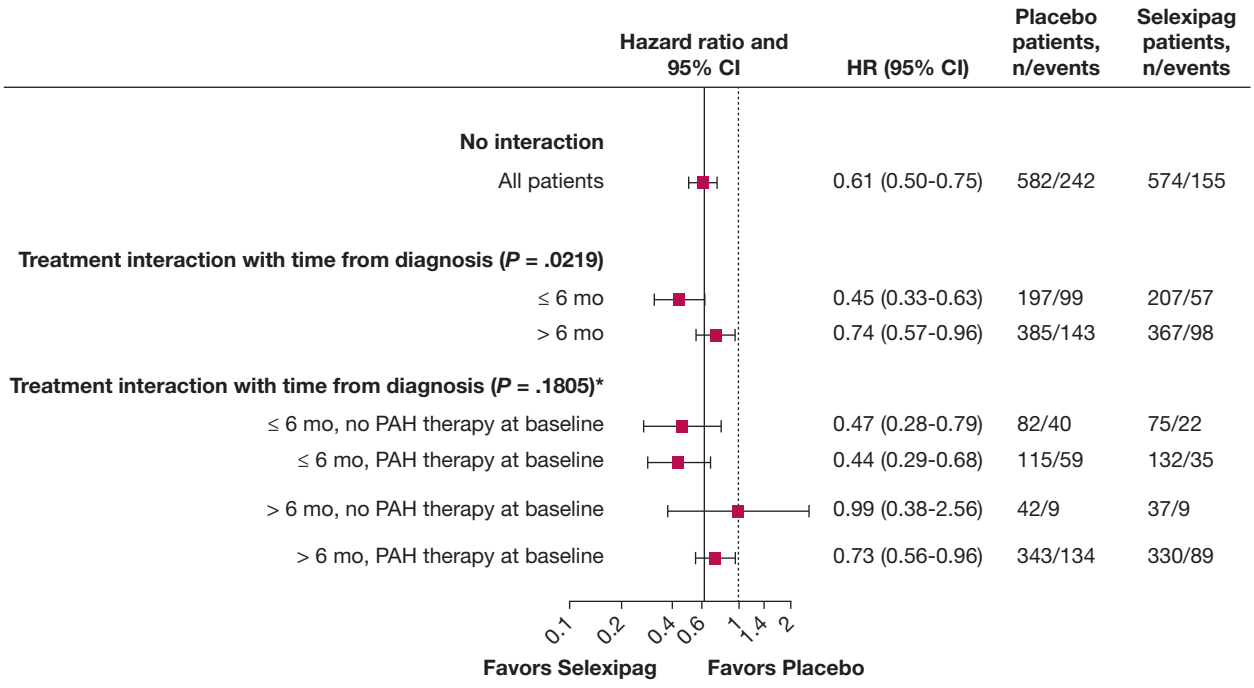

Figure 3 – *Forest plot showing treatment effects of selexipag on time from baseline to first morbidity or mortality event. Treatment effect of selexipag on time from baseline to first morbidity or mortality event up to end of double-blind treatment plus 7 days by time from diagnosis and by time from diagnosis according to PAH background therapy at baseline. Three separate Cox models were used for this analysis. All models were adjusted for baseline 6-min walk distance, age, World Health Organization functional class, sex, race, etiology, geographical region, and baseline N-terminal pro brain natriuretic peptide (see e-Appendix 2). *Model also adjusted for background PAH therapy (categorized as yes or no). HR = hazard ratio; PAH = pulmonary arterial hypertension.*

in both the newly diagnosed patients and those with a longer time from diagnosis (76.7 ± 49.4 weeks and 76.3 ± 51.1 weeks, respectively). In total, 23.7% of selexipag and 16.3% of newly diagnosed placebo patients discontinued treatment, compared with 26.9% of selexipag and 17.1% of placebo patients with a longer time from diagnosis. The percentage of patients who discontinued because of an adverse event and the percentage of patients experiencing at least one serious adverse event were comparable between treatment groups and were not influenced by time from diagnosis (Table 3). Up to the end of the study, in the newly diagnosed subgroup, 38 selexipag patients and 44 placebo patients had died; in patients with a longer time from diagnosis, 62 selexipag patients and 61 placebo patients had died.

Discussion

The results of these post hoc analyses from the randomized controlled GRIPHON trial confirm that newly diagnosed PAH patients have a worse prognosis than those with a longer time from diagnosis. This study also showed that selexipag reduced the risk of a morbidity or mortality event (primary composite end point) both in patients with a time from diagnosis of ≤ 6 months and of > 6 months when compared with placebo, with a more pronounced effect in newly diagnosed patients. These results highlight the potential benefits of early addition of an oral prostacyclin pathway agent to a patient's treatment regimen.

The prognostic value of time from diagnosis for disease progression demonstrated in these analyses is consistent with registry data and findings from the Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) study.[12,13] Our results add to this body of evidence by showing that the prognostic value of time from diagnosis was not influenced by differences in age and risk status at baseline. Furthermore, no evidence was found that PAH background therapy influenced the prognostic value of time from diagnosis, although a potential impact cannot be ruled out entirely. The better prognosis in the subgroup of patients with a time from diagnosis of > 6 months may reflect survivor bias, whereby patients with rapidly progressive disease or those who do not respond well to treatment are more likely to die at an earlier stage. This poor prognosis for newly diagnosed patients highlights the need for early treatment in this population.

TABLE 3] Adverse Events and Serious Adverse Events According to Time From PAH Diagnosis at Baseline[a]

Variable	Time From Diagnosis			
	≤ 6 mo (n = 403)		> 6 mo (n = 749)	
	Placebo (n = 196)	Selexipag (n = 207)	Placebo (n = 381)	Selexipag (n = 368)
No. of adverse events	1,019	1,292	2,918	3,315
Patients with ≥ 1 adverse event	187 (95.4)	203 (98.1)	372 (97.6)	362 (98.4)
Patients with ≥ 1 serious adverse events	90 (45.9)	89 (43.0)	182 (47.8)	163 (44.3)
Patients with ≥ 1 adverse event leading to discontinuation[b]	13 (6.6)	23 (11.1)	28 (7.3)	59 (16.0)
Adverse events[c]				
Headache	53 (27.0)	126 (60.9)	136 (35.7)	249 (67.7)
Diarrhea	28 (14.3)	67 (32.4)	82 (21.5)	177 (48.1)
Nausea	20 (10.2)	48 (23.2)	87 (22.8)	145 (39.4)
PAH	86 (43.9)	41 (19.8)	120 (31.5)	85 (23.1)
Edema peripheral	32 (16.3)	34 (16.4)	72 (18.9)	46 (12.5)
Pain in jaw	7 (3.6)	34 (16.4)	29 (7.6)	114 (31.0)
Vomiting	14 (7.1)	32 (15.5)	35 (9.2)	72 (19.6)
Pain in extremity	4 (2.0)	29 (14.0)	42 (11.0)	68 (18.5)
Dyspnea	39 (19.9)	27 (13.0)	82 (21.5)	65 (17.7)
Myalgia	14 (7.1)	27 (13.0)	20 (5.2)	65 (17.7)
Arthralgia	11 (5.6)	26 (12.6)	33 (8.7)	36 (9.8)
Dizziness	21 (10.7)	25 (12.1)	64 (16.8)	61 (16.6)
Nasopharyngitis	13 (6.6)	21 (10.1)	50 (13.1)	54 (14.7)
Upper respiratory tract infection	26 (13.3)	19 (9.2)	54 (14.2)	56 (15.2)
Cough	20 (10.2)	17 (8.2)	47 (12.3)	39 (10.6)
Flushing	7 (3.6)	17 (8.2)	22 (5.8)	53 (14.4)
Right ventricular failure	17 (8.7)	11 (5.3)	41 (10.8)	35 (9.5)
Syncope	11 (5.6)	11 (5.3)	40 (10.5)	26 (7.1)
Fatigue	12 (6.1)	9 (4.3)	47 (12.3)	37 (10.1)

Data are presented as No. (%), unless otherwise indicated. Data presented for the safety analysis set. PAH = pulmonary arterial hypertension.
[a]Among the patients randomly assigned to placebo, four did not receive the study drug 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.
[b]Includes study drug discontinuations before the end of the study in patients without a primary end point morbidity or mortality event with onset date before the study drug end date.
[c]Values provided for events occurring in ≥ 10% of patients in any group. Ordered by incidence in the patients treated earlier with selexipag.

Selexipag delayed disease progression in patients treated earlier and those treated later, with a more pronounced effect seen when selexipag was used within 6 months after diagnosis. In both subgroups, the treatment effect on the primary end point was driven by reductions in hospitalization for PAH worsening and disease progression. A similar pattern for the treatment effect was observed when PAH background therapy was taken into account in our analysis. To our knowledge, this is the first analysis to demonstrate that prostacyclin pathway agents can reduce the risk of disease progression in both newly diagnosed and prevalent patient populations.

From a clinical perspective, these data indicate that, despite their poorer prognosis, newly diagnosed PAH patients can respond to and benefit from early targeting of the prostacyclin pathway with selexipag, adding to the body of evidence showing that newly diagnosed patients benefit from early initiation of therapy.[13,17,18]

Safety findings in both newly diagnosed patients and in patients with a longer time from diagnosis were consistent with those observed previously for the overall GRIPHON population,[7] with selexipag treatment generally well tolerated, other than the known side effects of targeting the prostacyclin pathway.[19] The

shorter exposure time recorded for newly diagnosed placebo patients most likely is related to the higher rate of primary end point events experienced by this group, given that the study design stipulated discontinuation of double-blind therapy after a disease progression event. It should be noted that the post hoc analyses presented here are exploratory in nature and therefore are subject to limitations.

Interpretation

These post hoc analyses of the GRIPHON trial confirm earlier data[12,13] that newly diagnosed PAH patients have a worse prognosis than patients with a longer time from diagnosis. Selexipag showed beneficial effects on disease progression in patients who were treated more than or less than 6 months from diagnosis, with a more pronounced treatment effect seen in patients treated earlier.

Acknowledgments

Author contributions: S. G. is the guarantor of the manuscript and takes responsibility for the content of the manuscript, including the data and analysis. S. G., O. S., R. N. C., K. M. C., N. G., M. M. H., V. V. M., L. J. R., G. S., V. T., H.-A. G., and I. L. (members of the study steering committee) contributed to the conception and design of the study in collaboration with the funders and were involved in the collection and interpretation of the data. R. S. was involved in the statistical analyses. S. G., R. S., and R. P. were involved in development of the first draft of the manuscript, with medical writing assistance funded by the sponsor and provided by eluSCIdate Ltd. All authors had access to the data, reviewed and edited the manuscript, approved the final draft, and were involved in the decision to submit the manuscript for publication. All authors vouch for the accuracy and completeness of the analyses and for the fidelity of this report to the study protocol.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: S. G. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson, has received speaker fees from Janssen Pharmaceutical Companies of Johnson & Johnson, has received advisory board fees from Janssen Pharmaceutical Companies of Johnson & Johnson and Daiichi-Sankyo, and has served on a data and safety monitoring board for United Therapeutics. O. S. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has served as an advisory board member for and received research grants from Janssen Pharmaceutical Companies of Johnson & Johnson, Bayer, GlaxoSmithKline, and Merck Sharp & Dohme; has received consultancy fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Arena, Bayer, GlaxoSmithKline, and Merck Sharp & Dohme; has received speaker fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Bayer, GlaxoSmithKline, and Merck Sharp & Dohme; has served on a scientific advisory board for Arena Pharmaceuticals and Gossamer Bio; and has received writing assistance from Janssen Pharmaceutical Companies of Johnson & Johnson and GlaxoSmithKline. R. N. C. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson, has served on an advisory board for Janssen Pharmaceutical Companies of Johnson & Johnson and Bayer, has received consultancy fees from Bayer and Arena Pharmaceuticals, and has received research grants from Janssen Pharmaceutical Companies of Johnson & Johnson and United Therapeutics. K. M. C. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received research grants from Janssen Pharmaceutical Companies of Johnson & Johnson, the National Institutes of Health, Ironwood Pharmaceuticals, and SoniVie Ltd.; has served on an advisory board for Bayer Healthcare (through UCSD) and Flowonix; has served as an adjudication committee member for Arena Pharmaceuticals; is *Circulation* Associate Editor for the American Heart Association; and has received consultancy fees from Janssen Pharmaceutical Companies of Johnson & Johnson. R. S. is an employee of Actelion Pharmaceuticals, Ltd. N. G. is a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received grant support, personal fees, and non-financial support from Janssen Pharmaceutical Companies of Johnson & Johnson; and has received grant support and personal fees from Bayer Healthcare, Pfizer, and GlaxoSmithKline. M. M. H. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received speaker and consultancy fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and Pfizer; and has received research grants from Janssen Pharmaceutical Companies of Johnson & Johnson. V. V. M. reports grants, personal fees, and nonfinancial support from Janssen Pharmaceutical Companies of Johnson & Johnson and Bayer; grants from Eiger and SoniVie Ltd.; and personal fees from United Therapeutics, Arena, Caremark, Medtronic, and Merck Sharp & Dohme. R. P. is an employee of Actelion Pharmaceuticals, Ltd., in the past held stock/stock options for Actelion Pharmaceuticals, Ltd., and currently holds stock/stock options in the parent company Johnson & Johnson. L. J. R. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson and has received consultancy fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Arena Pharmaceuticals, GENO Pharmaceuticals, Gilead, Karos Pharmaceuticals, Pfizer, and SoniVie, Ltd. G. S. has served as a steering committee member for and received research grants from Janssen Pharmaceutical Companies of Johnson & Johnson and Bayer and has received speaker and consultancy fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and Pfizer. V. T. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson, Bayer, and United Therapeutics; has received consultancy fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Arena Pharmaceuticals, Bayer, Daiichi-Sankyo, EKOS/BTG, Gilead Sciences, Janssen, Reata, and United Therapeutics; has received research grants from Arena Pharmaceuticals, Arena, Bayer, EKOS/BTG, and Riata; and has received speaker fees from Bayer, Gilead Sciences, and Janssen. H.-A. G. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received advisory board and speaker fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Bayer, GlaxoSmithKline, Novartis, and Pfizer; has received consultancy fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Bayer, Bellerophon Pulse Technologies, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, and Pfizer; and has received research grants from Janssen Pharmaceutical Companies of Johnson & Johnson and Deutsche Forschungsgemeinschaft. I. L. has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received speaker fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Merck Sharp & Dohme, and AOP Orphan Pharmaceuticals; and has received research grants from Janssen Pharmaceutical Companies of Johnson & Johnson and AOP Orphan Pharmaceuticals.

Role of sponsors: Actelion Pharmaceuticals Ltd., a Janssen Pharmaceutical Company of Johnson & Johnson, funded the study and participated in the design of the study, data analysis, interpretation, and preparation of the manuscript.

Other contributions: The authors thank the patients and the investigators for their

contribution to the study. Medical writing support was provided by Carly Taylor of nspm, Ltd. (Meggen, Switzerland), and Iain Haslam of eluSCIdate, Ltd. (Meggen, Switzerland), and was funded by Actelion Pharmaceuticals, Ltd., Switzerland a Janssen Pharmaceutical Company of Johnson & Johnson.

Additional information: The e-Tables and e-Appendixes can be found in the Supplemental Materials section of the online article.

References

1. Humbert M, Guignabert C, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J*. 2019;53:1801887.
2. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J*. 2015;46:903-975.
3. Galiè N, Humbert M, Vachiéry JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67-119.
4. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J*. 2019;53:1801889.
5. Simonneau G, Barst RJ, Galiè N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002;165:800-804.
6. Olsson KM, Richter MJ, Kamp JC, et al. Intravenous treprostinil as an add-on therapy in patients with pulmonary arterial hypertension. *J Heart Lung Transplant*. 2019;38:748-756.
7. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373:2522-2533.
8. Del Pozo R, Hernandez Gonzalez I, Escribano-Subías P. The prostacyclin pathway in pulmonary arterial hypertension: a clinical review. *Expert Rev Respir Med*. 2017;11:491-503.
9. Farber HW, Miller DP, Meltzer LA, et al. Treatment of patients with pulmonary arterial hypertension at the time of death or deterioration to functional class IV: insights from the REVEAL Registry. *J Heart Lung Transplant*. 2013;32:1114-1122.
10. Sitbon O, Jaïs X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J*. 2014;43:1691-1697.
11. Badagliacca R, Pezzuto B, Poscia R, et al. Prognostic factors in severe pulmonary hypertension patients who need parenteral prostanoid therapy: the impact of late referral. *J Heart Lung Transplant*. 2012;31:364-372.
12. Humbert M, Sitbon O, Yaïci A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J*. 2010;36:549-555.
13. Simonneau G, Channick RN, Delcroix M, et al. Incident and prevalent cohorts with pulmonary arterial hypertension: insight from SERAPHIN. *Eur Respir J*. 2015;46:1711-1720.
14. Escribano-Subias P, Blanco I, Lopez-Meseguer M, et al. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. *Eur Respir J*. 2012;40:596-603.
15. Jansa P, Jarkovsky J, Al-Hiti H, et al. Epidemiology and long-term survival of pulmonary arterial hypertension in the Czech Republic: a retrospective analysis of a nationwide registry. *BMC Pulm Med*. 2014;14:45.
16. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med*. 1991;115:343-349.
17. Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373:834-844.
18. Sitbon O, Cottin V, Canuet M, et al. Initial combination therapy of macitentan and tadalafil in pulmonary arterial hypertension. *Eur Respir J*. 2020;56:2000673.
19. Kingman M, Archer-Chicko C, Bartlett M, et al. Management of prostacyclin side effects in adult patients with pulmonary arterial hypertension. *Pulm Circ*. 2017;7:598-608.