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ORIGINAL INVESTIGATIONS

Three- Versus Two-Drug Therapy for Patients With Newly Diagnosed Pulmonary Arterial Hypertension

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ABSTRACT

BACKGROUND In pulmonary arterial hypertension (PAH), there are no data comparing initial triple oral therapy with initial double oral therapy.

OBJECTIVES TRITON (The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension; NCT02558231), a multicenter, double-blind, randomized phase 3b study, evaluated initial triple (macitentan, tadalafil, and selexipag) versus initial double (macitentan, tadalafil, and placebo) oral therapy in newly diagnosed, treatment-naive patients with PAH.

METHODS Efficacy was assessed until the last patient randomized completed week 26 (end of main observation period). The primary endpoint was change in pulmonary vascular resistance (PVR) at week 26.

RESULTS Patients were assigned to initial triple (n = 123) or initial double therapy (n = 124). At week 26, both treatment strategies reduced PVR compared with baseline (by 54% and 52%), with no significant difference between groups (ratio of geometric means: 0.96; 95% confidence interval: 0.86-1.07; $P = 0.42$). Six-minute walk distance and N-terminal pro-brain natriuretic peptide improved by week 26, with no difference between groups. Risk for disease progression (to end of main observation period) was reduced with initial triple versus initial double therapy (hazard ratio: 0.59; 95% confidence interval: 0.32-1.09). Most common adverse events with initial triple therapy included headache, diarrhea, and nausea. By the end of the main observation period, 2 patients in the initial triple and 9 in the initial double therapy groups had died.

CONCLUSIONS In patients with newly diagnosed PAH, both treatment strategies markedly reduced PVR by week 26, with no significant difference between groups (primary endpoint not met). Exploratory analyses suggested a possible signal for improved long-term outcomes with initial triple versus initial double oral therapy. (J Am Coll Cardiol 2021;78:1393-1403)

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

AE = adverse event

CI = confidence interval

ERA = endothelin receptor antagonist

FC = functional class

NT-proBNP = N-terminal pro-brain natriuretic peptide

PAH = pulmonary arterial hypertension

PDE5i = phosphodiesterase type-5 inhibitor

PVR = pulmonary vascular resistance

Pulmonary arterial hypertension (PAH) is a relentlessly advancing disease, with many pathophysiological mechanisms contributing to its progression (1,2). Among those identified, the prostacyclin, endothelin, and nitric oxide pathways can be targeted by medical treatment (3-5). Combination therapy to target multiple pathways is an essential part of PAH management. Initial double therapy with an endothelin receptor antagonist (ERA) and phosphodiesterase type 5 inhibitor (PDE5i) delays PAH progression versus initial monotherapy (6) and is recommended for patients with newly diagnosed PAH at low or intermediate risk for 1-year mortality (3-5).

Patients receiving double oral therapy, including initial double therapy, continue to experience PAH progression (6-8), providing a rationale for more intensive treatment. Uncontrolled retrospective analyses showed that initial triple therapy including a parenteral prostacyclin analog improved hemodynamic status and functional capacity compared with baseline in patients newly diagnosed with severe PAH, with excellent survival rates (9,10). Furthermore, in the GRIPHON (Selexipag [ACT-293987] in Pulmonary Arterial Hypertension) randomized controlled trial, administration of selexipag, an oral, selective prostacyclin receptor (IP receptor) agonist, to patients receiving double oral therapy at baseline reduced the risk for composite morbidity and mortality endpoint events (11). However, there are no data comparing initial triple versus initial double therapy in patients with PAH.

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TRITON (The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension) evaluated the efficacy and safety of initial triple oral therapy with macitentan, tadalafil, and selexipag compared with initial double oral therapy with macitentan and tadalafil in newly-diagnosed, treatment-naive patients with PAH.

METHODS

The data-sharing policy of the sponsor is available at Janssen (12). Requests for access to study data can be submitted through the Yale Open Data Access Project site (13).

STUDY DESIGN. TRITON (NCT02558231) was a multicenter, double-blind, randomized, placebo-controlled phase 3b study. The steering committee, in collaboration with the sponsor (Actelion Pharmaceuticals), designed the trial and oversaw its conduct and data analyses. The protocol (Supplemental Appendix) was approved by the Institutional Review Board or independent ethics committee at each study site. The study was monitored by an independent data and safety monitoring committee (sections 4 and 5 in the Supplemental Appendix). Covance oversaw the collection of data and performed data management, and Datamap analyzed the data according to a prespecified statistical analysis plan (available with the protocol). All authors had access to the data, contributed to data interpretation and writing of the manuscript, reviewed and approved the final manuscript, and made 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 manuscript to the protocol.

SELECTION OF PATIENTS. Patients (18-75 years of age) diagnosed with PAH (group 1 pulmonary hypertension), including idiopathic, heritable, or drug- and toxin-induced PAH, or PAH associated with connective tissue disease, human immunodeficiency virus infection, or corrected congenital heart disease (simple systemic-to-pulmonary shunts ≥1 year after repair) confirmed by right heart catheterization within 6 months prior to randomization were eligible. Patients had 6-minute walk distance (6MWD) ≥50 m and pulmonary vascular resistance (PVR) ≥6 WU and were excluded if previously treated with PAH therapy. Eligibility criteria are listed in the protocol in the Supplemental Appendix. Written informed consent was obtained from all patients.

TRIAL PROCEDURES. Patients were randomized 1:1 to initial triple oral therapy (macitentan, tadalafil, and selexipag) or initial double oral therapy (macitentan, tadalafil, and placebo) within 28 days of screening (Supplemental Figure 1). Randomization was stratified by region (rest of the world vs North America) and World Health Organization functional class (FC) at baseline (I and II vs III and IV).

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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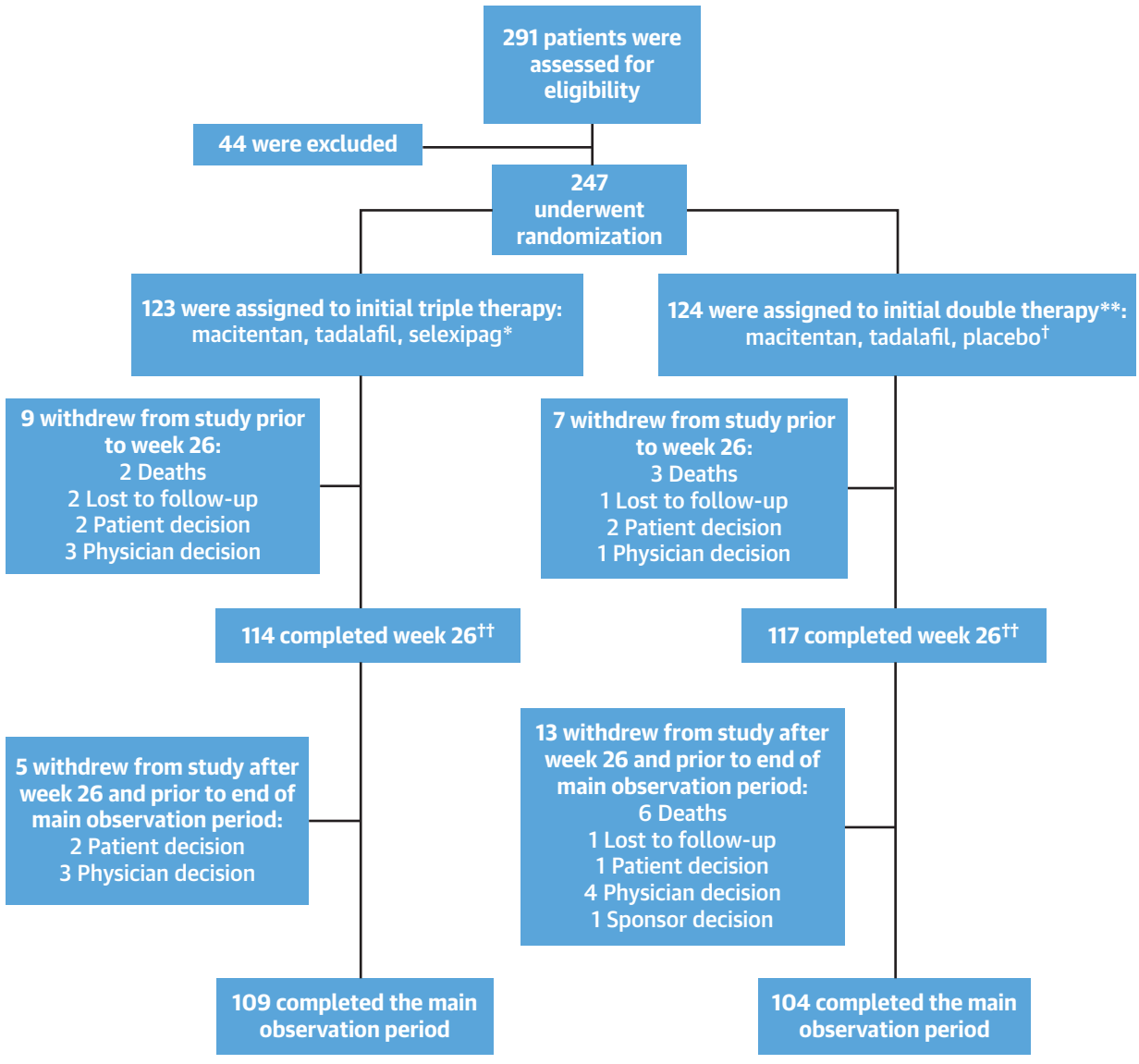
FIGURE 1 Patient Disposition



*19 patients received selexipag; the 4 patients who did not receive selexipag were allocated to initial double therapy for the safety analysis. **1 patient randomized to initial double therapy did not receive any treatment and was excluded from the safety analysis set. †120 patients received placebo. ††112 patients in the initial triple therapy group and 117 patients in the initial double therapy group completed the primary endpoint assessment at week 26. Treatment discontinuations are described in Supplemental Table 2.

Macitentan 10 mg once daily and tadalafil 20 mg once daily were initiated open label on day 1. On day 8 ± 3, the tadalafil dose was increased to 40 mg once daily according to tolerability. On day 15 ± 3, double-blinded selexipag or placebo was initiated at 200 μg twice daily. Until week 12, the dose was increased, typically at weekly intervals in increments of 200 μg twice daily to reach an individualized maintenance dose (range: 200-1,600 μg twice daily) (Supplemental Figure 2). All 3 study treatments were administered until the end of the main observation period. The end of the main observation period was declared when the last patient randomized reached week 26. Follow-up of patients continued in a blinded fashion until the end of the main observation period regardless of discontinuation of any study treatment(s).

Right heart catheterization was performed at screening and week 26. FC, 6MWD, and N-terminal

TABLE 1 Baseline Characteristics

	Initial Triple Therapy (n = 123)	Initial Double Therapy (n = 124)	Overall (N = 247)
Female	93 (75.6)	94 (75.8)	187 (75.7)
Age, y	52.2 ± 13.5	51.6 ± 13.9	51.9 ± 13.7
Race[a]			
White	102 (82.9)	108 (87.1)	210 (85.0)
Asian	7 (5.7)	3 (2.4)	10 (4.0)
Black or African American	5 (4.1)	5 (4.0)	10 (4.0)
Other	3 (2.4)	3 (2.4)	6 (2.4)
American Indian or Alaska Native	1 (0.8)	0	1 (0.4)
Geographical region[b]			
North America	69 (56.1)	70 (56.5)	139 (56.3)
Rest of the world	54 (43.9)	54 (43.5)	108 (43.7)
Time from diagnosis of PAH, ds	23.9 ± 32.5	19.8 ± 26.7	21.9 ± 29.8
PAH classification			
Idiopathic	53 (43.1)	62 (50.0)	115 (46.6)
Associated with connective tissue disease	43 (35.0)	42 (33.9)	85 (34.4)
Drug or toxin induced	14 (11.4)	6 (4.8)	20 (8.1)
Heritable	9 (7.3)	7 (5.6)	16 (6.5)
Associated with HIV infection	3 (2.4)	5 (4.0)	8 (3.2)
Associated with congenital heart disease	1 (0.8)	2 (1.6)	3 (1.2)
6MWD, m[a]	345 ± 121.0	347 ± 116.9	346 ± 118.7
FC[b]			
I or II	25 (20.3)	25 (20.2)	50 (20.2)
III or IV[c]	98 (79.7)	99 (79.8)	197 (79.8)
Hemodynamic variables			
PVR, WU	11.8 ± 5.0	12.3 ± 4.4	12.0 ± 4.7
mPAP, mm Hg	51.8 ± 9.8	52.4 ± 11.4	52.1 ± 10.6
Cardiac index, L/min/m^2	2.2 ± 0.66	2.1 ± 0.56	2.2 ± 0.61
TPR, WU	14.0 ± 5.6	14.6 ± 4.9	14.3 ± 5.3
mRAP, mm Hg	8.0 ± 4.3	8.2 ± 4.1	8.1 ± 4.2
SvO_2, %[a]	62.0 ± 7.5	62.3 ± 7.7	62.2 ± 7.6
PAWP, mm Hg	8.4 ± 2.9	8.5 ± 3.3	8.4 ± 3.1

Values are n (%) or mean ± SD. Data are presented for the full analysis set. [a]Data were missing for 5 double, 5 triple (race); 3 double (6MWD); and 3 triple, 6 double (SvO_2). [b]Randomization stratification factor. [c]Number of FC IV patients: 1 triple, 5 double. Percentages may not add to 100 because of rounding.

6MWD = 6-minute walk distance; FC = World Health Organization functional class; HIV = human immunodeficiency virus; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; SvO_2 = mixed venous oxygen saturation; TPR = total pulmonary resistance; WU = wood units.

pro-brain natriuretic peptide (NT-proBNP) levels were assessed at screening, week 12, week 26, every 6 months thereafter, the end of the main observation period, and the end of all study treatments. Disease progression events were collected throughout the study. Safety monitoring included adverse events (AEs) and laboratory testing until 30 days after the end of all study treatments.

OUTCOME MEASURES. The primary endpoint was change in PVR at week 26, expressed as ratio of baseline. Secondary endpoints assessed at week 26 were change from baseline in 6MWD, NT-proBNP, and other right heart catheterization variables (mean pulmonary arterial pressure, cardiac index, mean right atrial pressure, mixed venous oxygen saturation, total pulmonary resistance), and absence of worsening in FC from baseline. The secondary endpoint of time from randomization to first disease progression event (composite endpoint) was assessed up to the end of the main observation period + 7 days (adjudicated by a clinical events committee). Disease progression events were defined as all-cause death; hospitalization for worsening PAH; initiation of prostacyclin, a prostacyclin analog, or prostacyclin receptor agonist for worsening PAH; or clinical worsening, defined as a postbaseline decrease in 6MWD of >15% from the highest 6MWD obtained at or after screening and FC III or IV (both conditions confirmed at 2 consecutive postbaseline visits 1-21 days apart).

STATISTICAL ANALYSES. It was estimated that 238 patients randomized 1:1 would provide 90% power to detect a 20% improvement in PVR at week 26 favoring triple therapy (difference of −0.223 on log scale and within-group SD of 0.5 on log scale) at a 2-sided significance level of 0.05. This assumed 1 efficacy interim analysis for futility when 33% of patients had completed the week 26 PVR assessment or prematurely discontinued the study. Efficacy analyses used the intention-to-treat population, which included all randomized patients (full analysis set; Supplemental Table 1). The safety set included patients who received at least 1 dose of any of the 3 study treatments.

Change from baseline to week 26 in log-transformed PVR was analyzed using analysis of covariance including treatment group, region, baseline FC, and log-transformed baseline value as covariates and expressed as a ratio. The treatment group difference (ratio of geometric means) and 95% confidence interval (CI) were estimated by exponentiation. Secondary endpoints were tested hierarchically in the following order: change in 6MWD and treatment group difference were analyzed using analysis of covariance including the same covariates as the primary endpoint analysis, without log transformation; NT-proBNP was analyzed as for PVR; time from randomization to first disease progression event was analyzed using the Kaplan-Meier method, stratified log-rank test, and Cox regression model with factors for treatment group, region, and baseline FC; and absence of worsening in FC was analyzed using logistic regression with factors for treatment group, region, and baseline FC, excluding patients in FC IV at baseline. Changes in other right heart catheterization variables and treatment group differences were analyzed outside of the testing hierarchy using

TABLE 2 Primary and Secondary Endpoints

	Initial Triple Therapy (n = 123)[a]				Initial Double Therapy (n = 124)[a]				Treatment Effect
	Baseline	Week 26[b]	Geometric Mean (95% CI) of Ratio (Week 26/ Baseline)[c]	Change (%)	Baseline	Week 26[b]	Geometric Mean (95% CI) of Ratio (Week 26/ Baseline)[c]	Change (%)	Ratio[c] (95% CI)
PVR, WU	11.8 ± 5.0	5.9 ± 4.4	0.46 (0.42 to 0.50)	−54	12.3 ± 4.4	6.1 ± 2.9	0.48 (0.44 to 0.53)	−52	0.96 (0.86 to 1.07), $P = 0.42$
NT-proBNP, ng/L	2,073 ± 2,387	675 ± 1,277	0.26 (0.21 to 0.33)	−74	1,932 ± 2,104	697 ± 1,351	0.25 (0.20 to 0.32)	−75	1.03 (0.77 to 1.37)
	Baseline	Week 26[b]	Mean (95% CI) Change From Baseline to Week 26[d]		Baseline	Week 26[b]	Mean (95% CI) Change From Baseline to Week 26[d]		Difference[d] (95% CI)
6MWD, m	345.3 ± 121.0	403.9 ± 124.5	+55.0 (40.4 to 69.5)		347.2 ± 116.9	407.2 ± 116.8	+56.4 (41.4 to 71.3)		−1.4 (−19.4 to 16.5)
mPAP, mm Hg	51.8 ± 9.8	39.4 ± 10.9	−12.9 (−14.6 to −11.2)		52.4 ± 11.4	40.4 ± 10.1	−12.2 (−13.9 to −10.5)		−0.72 (−2.8 to 1.4)
Cardiac index, L/min/m^2	2.2 ± 0.7	3.2 ± 1.0	+0.97 (0.81 to 1.13)		2.1 ± 0.6	3.0 ± 0.8	+0.84 (0.68 to 1.00)		0.13 (−0.07 to 0.33)
TPR, WU	14.0 ± 5.6	7.8 ± 4.9	−6.4 (−7.1 to −5.7)		14.6 ± 4.9	8.0 ± 3.2	−6.4 (−7.1 to −5.7)		0.03 (−0.87 to 0.93)
mRAP, mm Hg	8.0 ± 4.3	6.5 ± 4.4	−1.78 (−2.51 to −1.05)		8.2 ± 4.1	6.6 ± 3.4	−1.69 (−2.43 to −0.96)		−0.09 (−1.00 to 0.83)
SvO_2, %	62.0 ± 7.5	68.0 ± 7.3	+5.6 (4.4 to 6.8)		62.3 ± 7.7	69.4 ± 6.8	+6.8 (5.6 to 8.0)		−1.2 (−2.7 to 0.3)
	Patients Without FC Worsening From Baseline to Week 26				Patients Without FC Worsening From Baseline to Week 26				Odds Ratio[e] (95% CI)
Absence of FC worsening	121 (99.2%)[f]				116 (97.5%)[f]				3.2 (0.3 to 31.8)

Values are mean ± SD unless otherwise stated. Analyses were performed in the full analysis set. Variables are ordered differently to the testing hierarchy. [a]6MWD: n = 121 initial double therapy; NT-proBNP: n = 121 initial triple therapy, n = 122 initial double therapy; mRAP: n = 123 initial double therapy; SvO_2: n = 120 initial triple therapy, n = 118 initial double therapy. [b]Missing values were imputed using LOCF: 11 triple, 7 double (PVR, mPAP, TPR, cardiac index); 13 triple, 11 double (6MWD); 12 triple, 12 double (NT-proBNP); 12 triple, 7 double (mRAP); and 15 triple, 9 double (SvO_2). [c]Ratio of geometric least squares mean (and treatment effect) calculated using ANCOVA on log-transformed data with treatment group, region, baseline FC, and log-transformed baseline parameter as covariates. [d]Least squares mean change (and treatment effect) calculated using ANCOVA with treatment group, region, baseline FC, and baseline value as covariates. [e]Calculated using logistic regression with treatment group, region, and baseline FC as covariates. [f]Values are n (%); patients in FC IV at baseline were excluded (1 triple, 5 double); missing values at week 26 were imputed using LOCF: 10 triple, 7 double.

ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; other abbreviations as in Table 1.

analysis of covariance, including the same covariates as the primary endpoint analysis, without log transformation. Post hoc exploratory endpoints included time from randomization to all-cause death up to the end of the main observation period analyzed as for disease progression and all disease progression events, including recurrent events, captured up to end of main observation period + 7 days analyzed using a negative binomial model.

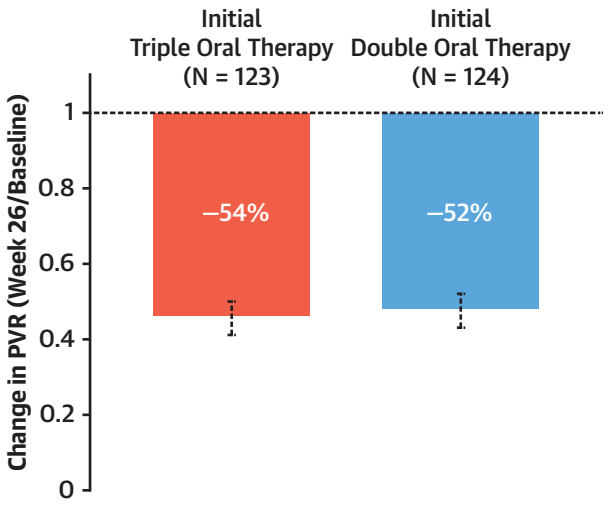
Missing PVR at week 26 was imputed using the last observation carried forward. Imputation rules and sensitivity analyses are described in the Supplemental Appendix. Subgroup analyses were performed for the primary endpoint. Safety variables were reported descriptively until the end of the main observation period.

RESULTS

PATIENTS CHARACTERISTICS AND FOLLOW-UP. From March 7, 2016, to December 28, 2018, 291 patients were screened at 67 sites. A total of 247 patients were randomized (123 to initial triple oral therapy, 124 to initial double oral therapy), and the full analysis set comprised all randomized patients (Figure 1). Most patients were female (75.7%), and the majority had idiopathic (46.6%) or connective tissue disease-associated (34.4%) PAH (Table 1). Baseline characteristics were balanced between treatment groups.

Nine patients (7.3%) in the initial triple and 7 (5.6%) in the initial double therapy groups discontinued the study prior to week 26 (Figure 1). Right heart catheterization and other assessments were performed at week 26, after which patients continued follow-up in a blinded manner until the end of the main observation period (up to 3.1 years); median follow-up duration was 77.6 weeks (interquartile range: 45.9-110.1 weeks) and 75.8 weeks (interquartile range: 49.9-103.2 weeks) in the initial triple and initial double therapy groups, respectively. Treatment discontinuations to the end of the main observation period are in Supplemental

FIGURE 2 Change in Pulmonary Vascular Resistance From Baseline to Week 26



Analyses were performed in the full analysis set. **Bar chart** illustrating the geometric mean of the ratio (week 26/baseline) for pulmonary vascular resistance (PVR) with **error bars** representing 95% confidence intervals. Missing values were imputed using the last observation carried forward for 11 patients receiving initial triple therapy and 7 patients receiving initial double therapy.

Table 2, and selexipag dosing information is in Supplemental Table 3.

PRIMARY AND SECONDARY ENDPOINTS. From baseline to week 26, the primary endpoint of PVR decreased by 54% for initial triple therapy (geometric mean ratio: 0.46; 95% CI: 0.42-0.50) and 52% for initial double therapy (geometric mean ratio: 0.48; 95% CI: 0.44-0.53), corresponding to a treatment effect of 0.96 (95% CI: 0.86-1.07; $P = 0.42$) (**Table 2, Figure 2**). Findings were consistent across prespecified subgroups and in sensitivity analyses (Supplemental Figure 3, Supplemental Table 4).

Secondary endpoint results should be interpreted as exploratory, on the basis of the testing hierarchy. At week 26, 6MWD increased from baseline by +55.0 m for initial triple therapy and +56.4 m for initial double therapy (treatment effect −1.4 m; 95% CI: −19.4 to 16.5) (**Table 2**). The geometric mean for the ratio of baseline to week 26 NT-proBNP was 0.26 (95% CI: 0.21-0.33; 74% reduction) for initial triple therapy and 0.25 (95% CI: 0.20-0.32; 75% reduction) for initial double therapy (treatment effect 1.03; 95% CI: 0.77-1.37) (**Table 2**).

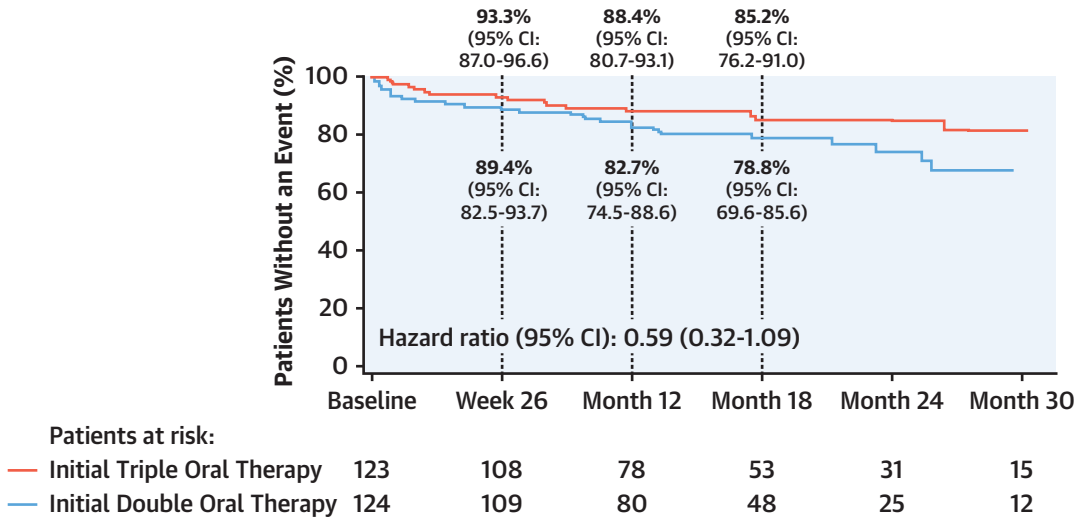
In the initial triple therapy group, 16 patients (13.0%) had a first disease progression event, compared with 27 (21.8%) in the initial double therapy group. In a time-to-event analysis, the hazard ratio for initial triple versus initial double therapy for the occurrence of a first event was 0.59 (95% CI: 0.32-1.09) (**Figure 3**). The difference was driven by hospitalizations for worsening PAH, which occurred as the first event in 10 patients (8.1%) in the initial triple therapy group versus 19 patients (15.3%) in the initial double therapy group, and by all-cause deaths, with no deaths occurring as a first event in the initial triple therapy group versus 4 (3.2%) in the initial double therapy group (**Table 3**). Sensitivity analyses provided consistent results (Supplemental Table 5).

At week 26, there was no significant difference between initial triple and initial double therapy in the proportion of patients without worsening in FC (99.2% and 97.5%, respectively; odds ratio: 3.2; 95% CI: 0.3-31.8) (**Table 2,** Supplemental Table 6). Other hemodynamic parameters markedly improved between baseline and week 26, with no difference between groups (**Table 2**).

POST HOC EXPLORATORY ENDPOINTS. To investigate the impact of premature treatment discontinuation on the results for time to disease progression, a post hoc sensitivity analysis was performed that included patients only for the time that they received their assigned treatment regimens. In this analysis, 14 patients (11.4%) in the initial triple therapy group had a first disease progression event compared with 25 patients (20.2%) in the initial double therapy group. The hazard ratio for risk for a first disease progression event was 0.59 (95% CI: 0.30-1.13) for initial triple versus initial double therapy (Supplemental Figure 4, Supplemental Table 5), consistent with the main analysis. Analysis of all disease progression events (including recurrent events) showed 31 events in 16 patients in the initial triple therapy group and 67 events in 27 patients in the initial double therapy group. The rate ratio for all disease progression events was 0.39 (95% CI: 0.15-1.00) for initial triple versus initial double therapy; the difference was driven by PAH-related hospitalizations and initiation of prostacyclin for worsening PAH and all-cause deaths (**Table 4**). Two patients in the initial triple therapy group and 9 patients in the initial double therapy group died. The hazard ratio for risk for all-cause death up to end of the main observation period was 0.23 (95% CI: 0.05-1.04) for initial triple versus initial double therapy (Supplemental Figure 5).

SAFETY. Exposure up to the end of main observation period is in Supplemental Table 7. All patients in the initial triple therapy group and 96.9% of patients in the initial double therapy group experienced at least 1 AE. Most common treatment-emergent AEs reported were headache, diarrhea, nausea, and peripheral

FIGURE 3 Time to First Disease Progression Event



Analyses were performed in the full analysis set. Kaplan-Meier curves illustrating the time from randomization to first disease progression event in the initial triple therapy and the initial double therapy groups up to the end of the main observation period + 7 days (or end of study, whichever was earliest). Kaplan-Meier estimates (95% confidence interval [CI]) at week 26, month 12, and month 18 are shown. Hazard ratio estimate obtained using a Cox regression model with factors for treatment group, region, and baseline World Health Organization functional class. Graph is cut when <10% of patients are at risk in both treatment groups.

edema; except for peripheral edema, all were more frequent with initial triple versus initial double therapy (Supplemental Table 8). AEs occurring with selexipag or placebo were reported less frequently in the maintenance versus titration period (Supplemental Table 9). The most common serious AEs are in Supplemental Table 8; 42.9% of patients in the initial triple therapy group and 31.5% in the initial double therapy group experienced at least 1 serious AE. Overall, 19 patients (16.0%) discontinued selexipag and 17 (14.2%) discontinued placebo due to AEs (Supplemental Table 8). The only AE leading to discontinuation with >1% difference between treatment groups was headache (1.7% vs 0%). Two patients (1.7%) in the initial triple and 9 (7.1%) in the initial double therapy group died up to the end of the main observation period.

DISCUSSION

TRITON is the first randomized controlled trial comparing initial triple oral and initial double oral therapy in PAH in newly diagnosed patients. The primary endpoint of change in PVR at week 26 was not met. Hemodynamic status, NT-proBNP, and functional parameters markedly improved from baseline to week 26 with both treatment strategies, but there was no significant difference between groups. Exploratory analyses suggested a signal for reduced risk for disease progression with initial triple compared with initial double oral therapy (**Central Illustration**).

The marked improvements in hemodynamics, NT-proBNP, and functional parameters observed with initial double oral therapy in this study build upon the body of evidence supporting the beneficial effect of initial ERA and PDE5i combination therapy, as previously shown in the AMBITION (A Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects With Pulmonary Arterial Hypertension) and OPTIMA (Clinical Study Evaluating the Effects of First-Line Oral Combination Therapy of Macitentan and Tadalafil in Patients With Newly Diagnosed Pulmonary Arterial Hypertension) trials (6,14). Although TRITON provides the only existing data on initial triple oral therapy, selexipag has been shown to improve PVR in prevalent patients established on an ERA and/or PDE5i (15). For initial triple therapy including a parenteral prostacyclin analog, uncontrolled data in newly diagnosed patients with severe PAH showed a reduction in PVR from baseline of approximately 67% to 69% (9,10). The baseline values and the decrease from baseline observed in those studies were greater than in TRITON, but the absolute

TABLE 3 First Disease Progression Events

	Initial Triple Therapy (n = 123)	Initial Double Therapy (n = 124)
First disease progression event	16 (13.0)	27 (21.8)
Hospitalization for worsening of PAH	10 (8.1)	19 (15.3)
Clinical worsening of PAH[a]	5 (4.1)	2 (1.6)
Initiation of prostacyclin for worsening of PAH	1 (0.8)	2 (1.6)
Death	0	4 (3.2)

Values are n (%) and are presented up to the end of the main observation period + 7 days. [a]Defined as a postbaseline decrease in 6MWD by >15% from the highest 6MWD obtained at or after screening, accompanied by FC III or IV (both conditions confirmed at two consecutive postbaseline visits separated by 1-21 days). Analyses were performed in the full analysis set.

Abbreviations as in Table 1.

values reached were comparable (PVR reduced to approximately 5.5 to 6.2 WU [9,10]). Collectively, these findings suggest that targeting the prostacyclin, endothelin, and nitric oxide pathways simultaneously substantially improves PVR and may normalize hemodynamic status in some patients.

Exploratory and post hoc analyses on long-term outcomes suggest a signal for reduced risk for disease progression with initial triple versus initial double oral therapy. Although these findings should be interpreted with caution because of their exploratory nature, they build on the results from the long-term GRIPHON randomized controlled trial, in which selexipag versus placebo reduced risk for disease progression by 40% (hazard ratio: 0.60; 99% CI: 0.46-0.78) in a large, predominantly prevalent population, with consistent outcomes in patients already treated with an ERA and PDE5i (hazard ratio: 0.63; 95% CI: 0.44-0.90) (7,11). A recent analysis from GRIPHON demonstrated a more pronounced treatment effect for selexipag on disease progression in patients treated within 6 months from diagnosis (hazard ratio: 0.45; 95% CI: 0.33-0.63) versus those with a longer time from diagnosis (hazard ratio: 0.74; 95% CI: 0.57-0.96) (16). Furthermore, previous data showed that initial double oral therapy slows PAH progression compared with monotherapy (6). Our data build on these by suggesting that initial triple oral therapy may add incremental benefit over initial double therapy for further delaying disease progression.

TABLE 4 All Disease Progression Events

	Initial Triple Therapy (n = 123)	Initial Double Therapy (n = 124)
Patients with disease progression event		
≥1 event	16 (13.0)	27 (21.8)
≥2 events	11 (8.9)	15 (12.1)
≥3 events	3 (2.4)	10 (8.1)
Events	31	67
Hospitalization for worsening of PAH	14	34
Clinical worsening of PAH[a]	8	8
Initiation of prostacyclin for worsening of PAH[b]	7	16
Death	2	9
Negative binomial model		
Mean annualized rate of disease progression events[c]	0.224 (0.112-0.448)	0.577 (0.295-1.127)
Rate ratio (95% CI)	0.39 (0.15-1.00)	

Values are n (%), n, or mean (95% CI), unless otherwise indicated. Analyses were performed in the full analysis set and are presented up to the end of the main observation period + 7 days. [a]Defined as a postbaseline decrease in 6MWD by >15% from the highest 6MWD obtained at or after screening, accompanied by FC III or IV (both conditions confirmed at two consecutive postbaseline visits separated by 1-21 days). [b]Patients who initiated parenteral prostacyclin: 7 initial triple therapy (1 as first event, 6 as subsequent events), 8 initial double therapy (all as subsequent events). [c]Total number of disease progression events/cumulative time on study (years) up to the end of the main observation period + 7 days (or end of study, whichever occurs earliest). All events were confirmed by the clinical events committee.

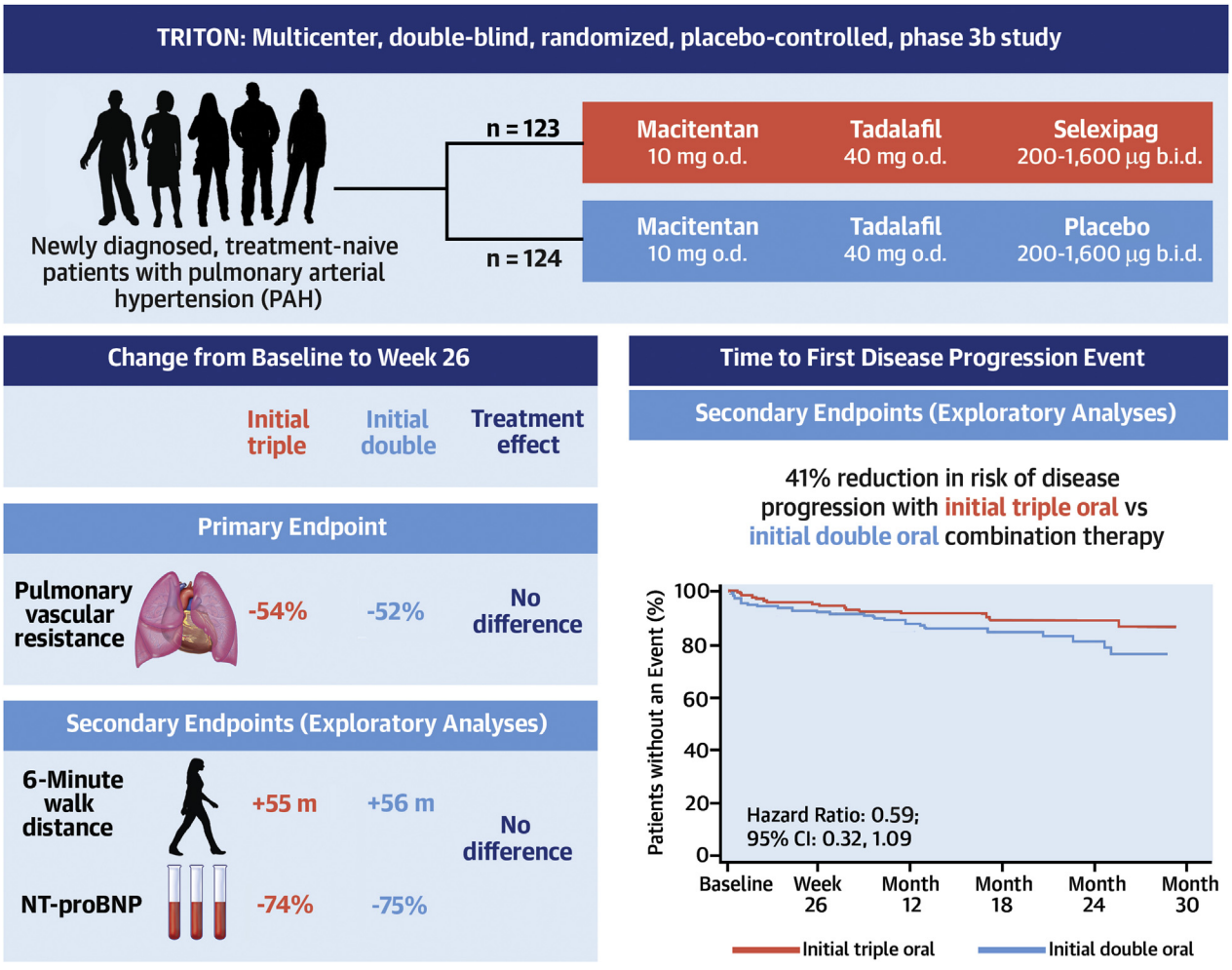
Abbreviations as in Tables 1 and 2.

Despite no treatment effect between groups on the week 26 endpoints of hemodynamic status and functional capacity, a signal for a treatment effect on disease progression until the end of the main observation period was suggested. Observing a benefit on outcome without a consistent effect on functional parameters is not unusual in other disease areas, for example, in heart failure with beta-blocker treatment (17,18), but is a recent observation in PAH. The reasons for the difference observed in our study are unclear. One hypothesis is that the improvements in hemodynamic status and functional parameters at week 26 are sustained for a longer duration with initial triple versus initial double therapy. Alternatively, triple oral therapy may delay disease progression through an unknown mechanism, which is not captured by the week 26 endpoints in TRITON.

As the safety profiles of the study drugs are well characterized (8,11,19,20), the novelty of our data relates to the timing of treatment initiation. This is the first randomized controlled trial to confirm that newly diagnosed patients can tolerate initiation of 3 oral therapies within 2 weeks, a shorter time frame than previously used for initial double oral therapy (6).

STUDY LIMITATIONS AND STRENGTHS. The main limitation of our findings was that analyses of disease progression and mortality were either exploratory, because of the testing hierarchy, or their post hoc nature; in addition, the study was not event driven or powered to assess long-term outcome. The interpretation of the subgroup analyses of the primary endpoint was limited by the small size of the subgroups assessed. There was also a small number of patients who discontinued prior to the primary endpoint assessment. Their missing values were

CENTRAL ILLUSTRATION **Initial Triple Versus Double Oral Combination Therapy in Pulmonary Arterial Hypertension**



Chin, K.M. et al. J Am Coll Cardiol. 2021;78(14):1393–1403.

Newly diagnosed, treatment-naive patients with pulmonary arterial hypertension were randomized to either initial triple or initial double oral therapy. Changes in pulmonary vascular resistance, 6-minute walk distance, and N-terminal pro-brain natriuretic peptide from baseline to week 26 are shown, alongside the treatment effect on the risk for disease progression (up to end of main observation period). NT-proBNP = N-terminal pro–brain natriuretic peptide.

imputed as prespecified in the protocol and were unlikely to affect the findings.

The strengths of the TRITON study design were the evaluation of both short- and long-term outcomes and the collection and adjudication of all disease progression events, rather than just the first event (6,8,11). The analysis of all disease progression events in TRITON can inform future clinical trial design in PAH. Subsequent long-term studies should consider a similar approach, as collection of all disease progression events, rather than only the first event, provides further information on outcomes relevant to prognosis and quality of life and can offer insights into the burden of PAH for patients.

CONCLUSIONS

In TRITON, the primary endpoint of change in PVR at week 26 was not met. Although marked improvements from baseline were observed in hemodynamic parameters and other clinical variables at week 26 following both initial triple and initial double oral therapy, there was no significant difference between groups. Our study shows that initial triple and

double oral therapy in patients with newly diagnosed PAH are well tolerated, with the nature of reported AEs generally consistent with these well-characterized medications. Exploratory analyses suggested a signal for reduced risk for disease progression with initial triple versus initial double oral therapy, suggesting that incremental long-term benefit can be gained by oral targeting of 3 rather than 2 pathways.

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This study was funded by Actelion Pharmaceuticals, a Janssen Pharmaceutical Company of Johnson & Johnson. Dr Chin 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; has served on advisory boards for Bayer Healthcare (through the University of California, San Diego) and Flowonix; has served as an adjudication committee member for Arena Pharmaceuticals; is an associate editor of *Circulation* for the American Heart Association; and has received consultancy fees from Janssen Pharmaceutical Companies of Johnson & Johnson. Prof Sitbon has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; and has served as an advisory board member for and received research grants from Janssen Pharmaceutical Companies of Johnson & Johnson. Dr Doelberg is an employee of Actelion Pharmaceuticals. Dr Feldman has received speaker and consultancy fees from Bayer and United Therapeutics; and has received consultancy fees from Gilead, Gossamer, Acceleron, Altavant, Janssen Pharmaceutical Companies of Johnson & Johnson, and Bellerophon. Dr Gibbs has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson, Complexa, and Acceleron; has received consultancy fees from Arena; has received speaker fees from GlaxoSmithKline and Merck Sharp & Dohme; has served as a clinical endpoints committee member for Pfizer, Bayer, Bellerophon, Janssen Pharmaceutical Companies of Johnson & Johnson, and United Therapeutics; and has served as a data and safety monitoring board member for Janssen Pharmaceutical Companies of Johnson & Johnson. Prof Grünig has received grants and personal fees from Bayer, Janssen Pharmaceutical Companies of Johnson & Johnson, Merck Sharp & Dohme, and GlaxoSmithKline; and has received grants from Janssen Pharmaceutical Companies of Johnson & Johnson, Bayer/Merck Sharp & Dohme, GlaxoSmithKline, and United Therapeutics. Prof Hoeper 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. Mr Martin is an employee of Actelion Pharmaceuticals. Dr Mathai has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; and has served as a consultant for Arena, Liquidia, and United Therapeutics. Prof McLaughlin has served as a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received grants, personal fees, and nonfinancial support from Janssen Pharmaceutical Companies of Johnson & Johnson and Bayer; has received grants from Eiger and SoniVie; and has received personal fees from United Therapeutics, Arena, Caremark, Medtronic, and Merck Sharp & Dohme. Dr Perchenet is an employee of Actelion Pharmaceuticals; has previously held stock and stock options with Actelion Pharmaceuticals; and currently holds stock and stock options in the parent company Johnson & Johnson. Dr Poch has received speaker and consultancy fees from Bayer Healthcare. Dr Saggar has received consultancy fees and research funding from United Therapeutics and Janssen Pharmaceutical Companies of Johnson & Johnson. Prof Simonneau 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. Prof Galiè is a steering committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received grant support, personal fees, and nonfinancial support from Janssen Pharmaceutical Companies of Johnson & Johnson; and has received grant support and personal fees from Bayer Healthcare, Pfizer, and GlaxoSmithKline.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: During initial oral drug therapy for patients with PAH, targeting the endothelin and nitric oxide pathways is associated with similar improvements in hemodynamic status and functional capacity as targeting 3 pathways (the endothelin, nitric oxide, and prostacyclin pathways). Initial triple therapy may offer a potential benefit with respect to disease progression.

TRANSLATIONAL OUTLOOK: Future studies should compare rates of disease progression and long-term outcomes with triple- versus double-pathway regimens for initial treatment of patients with PAH.

REFERENCES

1. Hemnes AR, Humbert M. Pathobiology of pulmonary arterial hypertension: understanding the roads less travelled. *Eur Respir Rev*. 2017;26(146):170093.

2. 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(1):1801887.

3. 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(4):903–975.

4. 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(1):67–119.

5. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J*. 2019;53:1801889.

6. Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373(9):834–844.

7. Coghlan JG, Channick R, Chin K, et al. Targeting the prostacyclin pathway with selexipag in patients with pulmonary arterial hypertension receiving double combination therapy: Insights from the randomized controlled GRIPHON study. *Am J Cardiovasc Drugs*. 2018;18(1):37–47.

8. Pulido T, Adzerikho I, Channick R, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369(9):809–818.

9. D'Alto M, Badagliacca R, Argiento P, et al. Risk reduction and right heart reverse remodeling by upfront triple combination therapy in pulmonary arterial hypertension. *Chest*. 2020;157(2):376–383.

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(6):1691–1697.

11. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373(26):2522–2533.

12. Clinical Trial Data Transparency. Accessed September 14, 2021. https:/www.janssen.com/clinical-trials/transparency.

13. Yale Open Data Access [YODA] Project site. Accessed September 14, 2021. http://yoda.yale.edu.

14. 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.

15. Simonneau G, Torbicki A, Hoeper MM, et al. Selexipag, an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. *Eur Respir J*. 2012;40(4):874–880.

16. Gaine S, Sitbon O, Channick RN, et al. Relationship between time from diagnosis and morbidity/mortality in pulmonary arterial hypertension: results from the phase III GRIPHON study. *Chest*. 2021;160(1):277–286.

17. de Milliano P, Tijssen J, van Zwieten PA, Lie KI. Beta blockers in heart failure haemodynamics, clinical effects and modes of action. *Neth Heart J*. 2001;9(8):334–342.

18. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet*. 1997;349(9049):375–380.

19. Galiè N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009;119(22):2894–2903.

20. Kim N, Channick R, Chin K, et al. Macitentan in pulmonary hypertension (PH): data from OPUS and OrPHeUS real-world data sets. *Eur Respir J*. 2019;54:PA5458.

KEY WORDS macitentan, pulmonary arterial hypertension, randomized controlled trial, selexipag, triple combination therapy

APPENDIX For lists of TRITON investigators and committee members, imputation rules, supplemental figures and tables, and the protocol and statistical analysis plan, please see the online version of this paper.