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Macitentan Improves Health-Related Quality of Life for Patients With Pulmonary Arterial Hypertension

Results From the Randomized Controlled SERAPHIN Trial

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BACKGROUND: Pulmonary arterial hypertension (PAH) leads to reduced health-related quality of life (HRQoL). The objectives of this analysis were to evaluate the effect of macitentan on HRQoL in patients with PAH in the Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) study. The association between baseline HRQoL and long-term outcomes was also investigated.

METHODS: Patients were randomized to placebo, macitentan 3 mg, or macitentan 10 mg once daily. Patients aged 14 years or older completed the 36-Item Short Form Survey (SF-36) at baseline, at month 6 and month 12, and at the end of treatment (EOT). The absolute change from baseline to month 6 in SF-36 scores was calculated. The time to a clinically meaningful deterioration in the SF-36 physical component summary and mental component summary (PCS and MCS) scores and associations between baseline PCS/MCS scores and time to morbidity/mortality events were also assessed.

RESULTS: At month 6, macitentan 10 mg significantly improved seven of eight SF-36 domains and the PCS and MCS scores vs placebo. Macitentan 10 mg significantly reduced the risk of a three-point or greater deterioration in PCS (hazard ratio [HR], 0.60; 95% CI, 0.47-0.76; $P < .0001$) and MCS scores (HR, 0.76; 95% CI, 0.61-0.95; $P = .0173$) until EOT vs placebo. Patients with a baseline PCS score greater than the median baseline value had a significantly reduced risk of morbidity/mortality compared with patients with a PCS score less than the median; a similar result was observed for the MCS score.

CONCLUSIONS: Macitentan significantly improved HRQoL in patients with PAH compared with placebo and significantly reduced the risk of a clinically meaningful HRQoL deterioration. An association between better baseline HRQoL and improved long-term outcomes was shown.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT00660179; URL: clinicaltrials.gov.

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KEY WORDS: health-related quality of life; pulmonary arterial hypertension; pharmacotherapy

ABBREVIATIONS: 6MWD = 6-min walk distance; EOT = end of treatment; HRQoL = health-related quality of life; MCS = mental component summary; PAH = pulmonary arterial hypertension; PCS = physical component summary; SERAPHIN = Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome; SF-36 = 36-Item Short Form Survey; WHO = World Health Organization

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Pulmonary arterial hypertension (PAH) is a debilitating progressive disease that imposes a significant burden on patients and caregivers.[1-3] In PAH, elevations in pulmonary vascular resistance and pulmonary arterial pressure lead to symptoms, including dyspnea and fatigue, that impact patients' daily activities and reduce their health-related quality of life (HRQoL).[1-9]

PAH symptoms affect not only the physical aspects of patients' HRQoL but also social, emotional, and psychological aspects.[1,3,10] The impairment experienced in PAH is comparable to other serious conditions, including COPD and renal failure,[8,11] and increases with PAH severity as measured by World Health Organization (WHO) functional class.[2] In addition to PAH symptoms, HRQoL is negatively impacted by hospitalizations,[12] treatment-related side effects, and route of administration of PAH therapies (eg, IV epoprostenol).[12-14]

In the Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN), an event-driven randomized placebo-controlled study in PAH, macitentan 10 mg reduced the risk of the composite primary end point of morbidity/mortality by 45% ($P < .001$) vs placebo.[15] SERAPHIN included an evaluation of HRQoL among patients with PAH. Here we present both the short-term and long-term impact of macitentan on HRQoL and the prognostic relevance of baseline HRQoL on long-term outcomes in PAH.

Methods

Study Design

SERAPHIN was a multicenter, double-blind, placebo-controlled, long-term, event-driven, phase III trial of macitentan in patients with PAH (NCT00660179). The primary composite end point was the time from initiation of treatment to the first morbidity event (PAH worsening, initiation of treatment with IV or subcutaneous prostanoids, lung transplantation, or atrial septostomy) or all-cause mortality event until end of treatment (EOT). The PAH worsening component has been defined previously.[15] All primary end point events were adjudicated by a blinded independent clinical event committee.

The study design has been described in detail elsewhere.[15] Briefly, patients were randomly assigned (1:1:1 ratio) to receive placebo, macitentan 3 mg, or macitentan 10 mg once daily. Patients were followed from randomization to the EOT visit, which occurred at (1) the end of the study (declared when the predefined number of 285 primary end point events was reached), (2) at the time a patient experienced a primary end point event, or (3) at the time of premature double-blind treatment discontinuation (eg, due to an adverse event). The study was conducted in accordance with the amended Declaration of Helsinki, and the protocol was approved by local institutional review boards or independent ethics committees (e-Table 1).

Patients

Patients aged 12 years or older with a diagnosis of WHO group 1 PAH[16] were eligible for inclusion into the study. Concomitant treatment with phosphodiesterase type 5 inhibitors, oral/inhaled prostanoids, calcium channel blockers, or L-arginine was allowed. Additional inclusion criteria were WHO functional class II to IV and a 6-min walk distance (6MWD) of 50 m or more. All patients provided written informed consent prior to study entry.

HRQoL Outcome Measure

The 36-Item Short Form Survey (SF-36) (version 2) comprises 36 questions, which are summarized in eight health domain scores: physical functioning, role limitations due to physical health, role limitations due to emotional problems, mental health, bodily pain, general health perceptions, vitality, and social functioning. The domain scores are combined into a physical component summary (PCS) and a mental component summary (MCS) score.[17,18] Domain and component summary scores are converted to norm-based scores based on the 1998 US general population (mean, 50; SD, 10).[18] A higher SF-36 score denotes better HRQoL (scale, 0-100).

Patients aged 14 years or older completed validated translations of the standard SF-36 questionnaire, licensed from the developer, at baseline, at month 6 and month 12, and at the EOT visit. The change from baseline to month 6 in domain and component summary scores was evaluated as a prespecified secondary outcome measure. Because of the limited amount of available data at month 12 (e-Table 2), which would require imputation of missing values for about 30% of the patients, analyses at this time point have the potential for bias and would yield results that may not be meaningful. Analysis of change from baseline to EOT also has the potential for bias, as EOT could be different for each patient (as SERAPHIN was an event-driven study), and therefore patients' exposure time is not consistent. To determine the long-term

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effect on HRQoL, post hoc analyses were conducted to assess the effect of macitentan on time to a clinically meaningful deterioration in SF-36 PCS and MCS scores from baseline until EOT vs placebo. For the SF-36, the minimal important difference considered to show clinically meaningful effect varies across diseases; the generally accepted threshold is two to three norm-based points for PCS and three points for MCS. In the absence of a PAH-specific minimal important difference for the SF-36 derived using anchor-based methods, a three-point threshold was used.[18]

Statistical Analyses

The analyses included patients with complete baseline HRQoL data (ie, patients with baseline scores for all eight SF-36 health domains and the PCS and MCS scores).

Changes from baseline to month 6 in individual domain scores and PCS and MCS scores for the three treatment groups were calculated as mean (data plotted represent the mean scores ± SEM). Missing month 6 values were imputed based on the last observation carried forward or, for patients who experienced a morbidity/mortality event before month 6, the worst value observed in the total population up to month 6. In addition, a more conservative approach of last observation carried forward for missing data was also used. For further information related to imputation rules, see e-Table 3. The treatment effect was evaluated according to sex, age, race, geographic region, 6MWD (greater than/less than median), WHO functional class (I/II and III/IV), PAH therapy at baseline, and cause of PAH. Results of these exploratory analyses are presented in forest plots as medians with 95% CIs; interaction *P* values (based on general linear models) are also reported.

Time to a clinically meaningful decrease (≥ three points) from baseline in the PCS and MCS scores is presented in Kaplan-Meier plots, with Kaplan-Meier estimates (hazard ratio [HR] and 95% CI) reported for the entire treatment duration (until EOT) and tested using a log-rank test without inclusion of covariates. Patients who experienced a primary end point event and subsequently discontinued double-blind treatment without completing the HRQoL assessment at the time of the event were assigned a three-point deterioration in PCS and MCS scores at the time of the event. Patients who prematurely discontinued without experiencing a primary end point event and without completing the HRQoL assessment were censored at the time of treatment discontinuation. A sensitivity analysis was performed for the assessment of time to a clinically meaningful deterioration in PCS and MCS scores only in patients for whom HRQoL data were available at the time of the primary end point event.

Further exploratory analyses were performed to assess the prognostic significance of HRQoL. The association between baseline SF-36 PCS or MCS score and the occurrence of a morbidity or mortality event was evaluated using the Cox regression model for assessing covariates and illustrated using Kaplan-Meier plots. Interaction tests were used to evaluate potential heterogeneity across the treatment groups (placebo, macitentan 3 mg, and macitentan 10 mg) with respect to the associations between PCS and MCS scores and long-term outcome. As the *P* values for interaction indicated no heterogeneity ($P < .1161$ and $P < .4268$ for PCS and MCS scores), the associations between PCS and MCS scores and long-term outcome were analyzed combining all treatment groups.

Results

Baseline Characteristics

Of the 742 patients randomized in SERAPHIN, 710 were included in this analysis and received placebo (n = 239), macitentan 3 mg (n = 237), or macitentan 10 mg (n = 234) (Fig 1).

The patient population analyzed was predominantly female (76.9%) and white (55.2%) and had a mean age of 45.5 years (Table 1). Demographics and baseline clinical characteristics, including SF-36 scores, were similar across the treatment groups (Table 1).

Change in HRQoL

The treatment effect of macitentan 10 mg vs placebo and 3 mg vs placebo on SF-36 domain scores and PCS and MCS scores at month 6 is shown in Figure 2. In the placebo group, individual SF-36 domain scores (physical functioning, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health) as well as PCS and MCS scores deteriorated from baseline to month 6. Treatment with macitentan 10 mg significantly improved seven of the eight SF-36 domains (all domains except general health perceptions) compared with placebo. Improvements in the PCS and MCS scores from baseline to month 6 after treatment with macitentan 10 mg compared with placebo were also significant (Fig 2). Significant improvements in seven of eight SF-36 individual domain scores and PCS and MCS scores were also shown after treatment with macitentan 3 mg compared with placebo. Consistent results were also shown when using the more conservative imputation approach of last observation carried forward (data not shown).

Change in HRQoL by Prespecified Subgroups

The placebo-corrected treatment effect of macitentan 10 mg on PCS and MCS scores by protocol prespecified subgroups is shown in Figure 3. The nonsignificant *P* values for interaction indicate that the treatment effect was consistent across the majority of subgroups, including PAH background therapy. For the PCS, the interaction test between treatment and subgroups was nonsignificant for all subgroups (Fig 3A), and for the MCS, the interaction test was nonsignificant for all except sex (interaction $P = .0289$) (Fig 3B). With respect to the SF-36 domain scores, the treatment effect of macitentan 10 mg compared with placebo at month 6 was consistent across all subgroups except 6MWD (role limitations due to emotional problems and general health perceptions domains), sex (bodily pain and vitality domains), and cause of PAH (bodily pain domain)

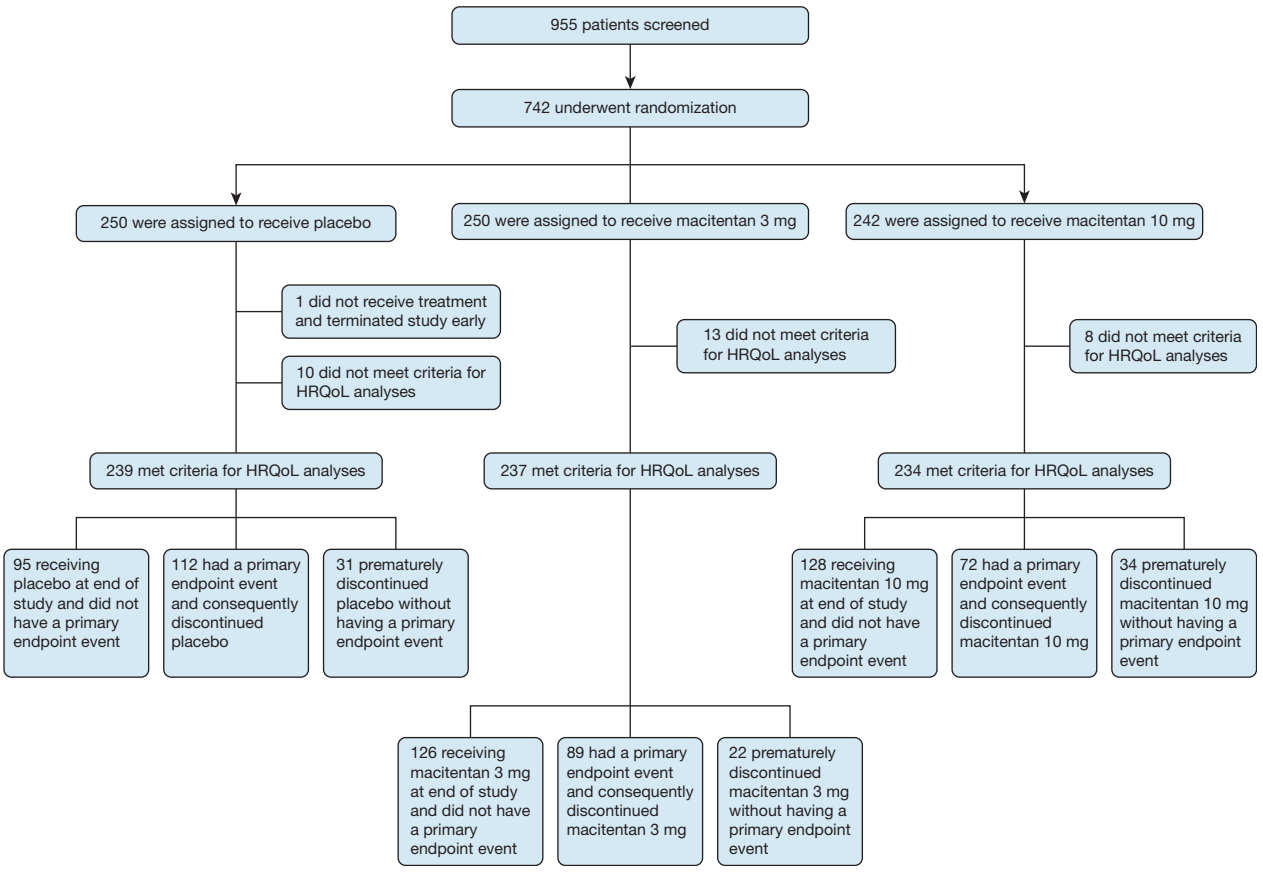


Figure 1 – *Patient disposition. The quality of life analysis included all randomized patients 14 years of age or older with complete baseline health-related quality of life (HRQoL) data (ie, patients with baseline scores for all eight 36-Item Short Form Survey [SF-36] health domains, the physical component summary [PCS] score, and the mental component summary [MCS] score). This resulted in 10, 13, and 8 patients being excluded from the placebo, macitentan 3 mg, and macitentan 10 mg groups, respectively, for the quality of life analysis.*

(e-Table 4). The treatment effect of macitentan 3 mg on the PCS and MCS scores at month 6 was consistent across subgroups (e-Fig 1).

Time to Deterioration in HRQoL

Time to a clinically meaningful deterioration (≥ three points) in PCS and MCS scores for patients receiving placebo, macitentan 3 mg, and macitentan 10 mg is shown in Figure 4. Treatment with macitentan 10 mg (vs placebo) significantly reduced the risk of a three-point or greater deterioration in PCS scores (HR, 0.60; 95% CI, 0.47-0.76; log-rank test $P < .0001$) (Fig 4A) and MCS scores (HR, 0.76; 95% CI, 0.61-0.95; $P = .0173$) (Fig 4B) until EOT. Significant reductions in the risk of a three-point or greater deterioration in PCS (HR, 0.71; 95% CI, 0.56-0.89; log-rank test $P = .0026$) and MCS (HR, 0.79; 95% CI, 0.64-0.99; $P = .0395$) scores were also observed with macitentan 3 mg vs placebo. Results of the sensitivity analysis excluding patients with a missing HRQoL assessment at the time of the primary end point event showed a similar treatment effect (e-Table 5).

Association Between HRQoL and Long-Term Outcome

When analyzed as continuous variables, the PCS and MCS scores at baseline were associated with the risk of a primary end point event. Every five-unit increase in PCS and MCS score at baseline was associated, respectively, with a 17% (HR, 0.83; 95% CI, 0.77-0.89) and a 6% (HR, 0.94; 95% CI, 0.89-0.99) lower risk of experiencing a morbidity/mortality event. To illustrate this result, the association between time to first morbidity/mortality event and baseline values greater than/less than the median SF-36 PCS and MCS scores was also analyzed (Fig 5). For patients with a PCS score greater than the median baseline value (35.5), the risk of a morbidity or mortality event was significantly reduced by 39% compared with patients who had a PCS score less than the median baseline value (Fig 5A). For patients

TABLE 1] Baseline Characteristics

Characteristic	Placebo (n = 239)	Macitentan 3 mg (n = 237)	Macitentan 10 mg (n = 234)	All Patients (N = 710)
Sex, female, No. (%)	176 (73.6)	184 (77.6)	186 (79.5)	546 (76.9)
Age, mean ± SD, y	46.4 ± 16.8	44.7 ± 15.9	45.5 ± 14.9	45.5 ± 15.9
Race/ethnicity, No. (%)				
White	129 (54.0)	133 (56.1)	130 (55.6)	392 (55.2)
Black	8 (3.3)	5 (2.1)	6 (2.6)	19 (2.7)
Asian	68 (28.5)	64 (27.0)	63 (26.9)	195 (27.5)
Hispanic	32 (13.4)	35 (14.8)	34 (14.5)	101 (14.2)
Other	2 (0.8)	. . .	1 (0.4)	3 (0.4)
Time from PAH diagnosis, mean ± SD, y	2.6 ± 3.8	3.0 ± 4.6	2.6 ± 3.7	2.7 ± 4.0
PAH classification, No. (%)				
Idiopathic	119 (50.2)	134 (56.8)	130 (55.8)	383 (54.2)
Heritable	3 (1.3)	8 (3.4)	1 (0.4)	12 (1.7)
Associated with CTD	79 (33.3)	69 (29.2)	72 (30.9)	220 (31.2)
Associated with congenital shunts	26 (11.0)	15 (6.4)	21 (9.0)	62 (8.8)
Associated with HIV infection	3 (1.3)	1 (0.4)	5 (2.1)	9 (1.3)
Associated with drug use/toxin exposure	7 (3.0)	9 (3.8)	4 (1.7)	20 (2.8)
6MWD, mean ± SD, m	353.3 ± 110.9	365.0 ± 97.1	362.8 ± 93.4	360.4 ± 100.8
WHO functional class, No. (%)[a]				
I	. . .	. . .	1 (0.4)	1 (0.1)
II	126 (52.7)	133 (56.1)	117 (50.0)	376 (53.0)
III	109 (45.6)	99 (41.8)	111 (47.4)	319 (44.9)
IV	4 (1.7)	5 (2.1)	5 (2.1)	14 (2.0)
Hemodynamic parameters, mean ± SD				
RAP, mm Hg	8.8 ± 5.6	9.0 ± 5.2	9.0 ± 5.8	9.0 ± 5.5
PAP, mm Hg	53.2 ± 18.1	54.9 ± 16.7	53.6 ± 17.8	53.9 ± 17.5
PAWP, mm Hg	9.6 ± 3.4	9.7 ± 3.3	9.5 ± 3.4	9.6 ± 3.4
Cardiac index, L/min/m^2	2.5 ± 0.8	2.4 ± 0.8	2.4 ± 0.8	2.4 ± 0.8
PVR, Wood units	12.4 ± 9.9	12.9 ± 7.7	13.0 ± 8.4	12.8 ± 8.7
Background PAH therapy, No. (%)[b]	149 (62.3)	156 (65.8)	150 (64.1)	455 (64.1)
PDE-5 inhibitors	145 (60.7)	147 (62.0)	146 (62.4)	438 (61.7)
Oral or inhaled prostanoids	7 (2.9)	17 (7.2)	13 (5.6)	37 (5.2)
Anticoagulant therapy, No. (%)	115 (48.1)	129 (54.4)	119 (50.9)	363 (51.1)
SF-36 domain score, mean ± SD				
Physical functioning	32.7 ± 9.8	31.9 ± 9.5	33.1 ± 9.8	32.6 ± 9.7
Role-physical	34.8 ± 10.8	33.1 ± 10.7	34.4 ± 10.8	34.1 ± 10.8
Bodily pain	45.6 ± 11.9	44.7 ± 11.2	44.0 ± 11.6	44.8 ± 11.6

(Continued)

TABLE 1] *(Continued)*

Characteristic	Placebo (n = 239)	Macitentan 3 mg (n = 237)	Macitentan 10 mg (n = 234)	All Patients (N = 710)
General health	34.8 ± 9.0	35.1 ± 9.2	35.4 ± 8.5	35.1 ± 8.9
Vitality	43.9 ± 10.3	43.4 ± 9.7	44.3 ± 9.7	43.8 ± 9.9
Social functioning	38.5 ± 11.3	38.7 ± 11.5	39.3 ± 11.7	38.8 ± 11.5
Role-emotional	36.3 ± 13.3	35.2 ± 13.7	35.8 ± 13.8	35.8 ± 13.6
Mental health	41.8 ± 11.3	41.8 ± 11.2	43.4 ± 10.2	42.4 ± 10.9
SF-36 component summary score, mean ± SD				
Physical component summary	36.5 ± 8.5	35.5 ± 8.9	35.9 ± 8.7	36.0 ± 8.7
Mental component summary	42.1 ± 11.3	42.0 ± 11.7	43.1 ± 11.0	42.4 ± 11.3

All randomized patients with complete HRQoL data included those patients 14 years of age or older with baseline data for all eight health domains and physical and mental component summary scores of the SF-36. Overall, 32 patients from SERAPHIN (11 in the placebo group, 13 in the macitentan 3 mg group, and 8 in the macitentan 10 mg group) were not included, as they did not have complete HRQoL data as defined. CTD = connective tissue disease; HRQoL = health-related quality of life; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PDE-5 inhibitor = phosphodiesterase type 5 inhibitor; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SF-36 = 36-Item Short Form Survey; WHO = World Health Organization.

[a]Although only patients in WHO functional class II, III, or IV were permitted into the study according to the protocol, one patient in WHO functional class I was erroneously included.

[b]Patients may have received more than one type of background PAH therapy.

with an MCS score greater than the median baseline value (42.7), the risk of a morbidity/mortality event was significantly reduced by 22% compared with patients who had an MCS score less than the median baseline value (Fig 5B). However, an exploratory analysis found no significant association between change from baseline to month 6 in PCS and MCS and a subsequent morbidity/mortality event (data not shown).

Discussion

In the SERAPHIN study, macitentan improved HRQoL by month 6, with significant placebo-corrected treatment

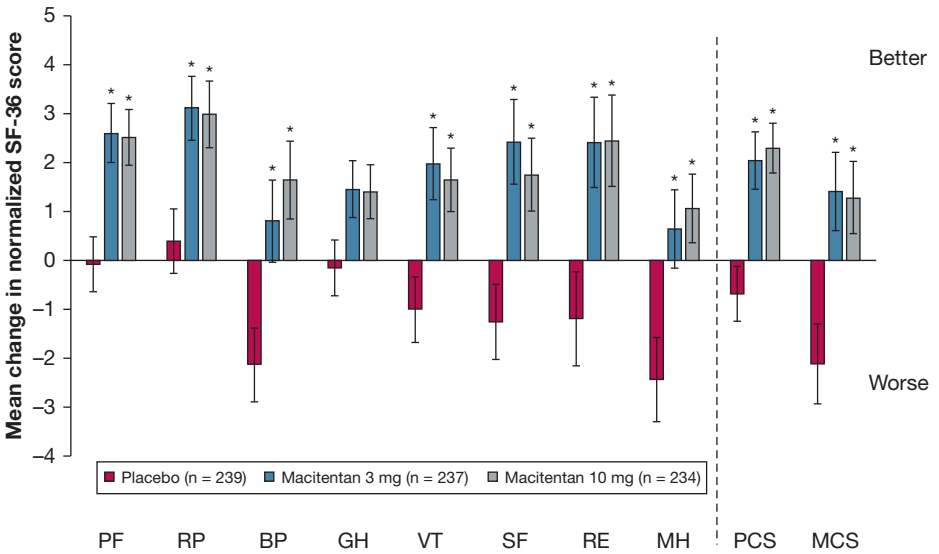


Figure 2 – *Change from baseline to month 6 in individual SF-36 domains as well as physical and mental component summary scores with placebo, macitentan 3 mg, or macitentan 10 mg. Patient population used for this analysis included all randomized patients with complete HRQoL data. In this analysis, the HRQoL assessment was not available for 134 (18.9%) patients. Imputation for missing data was used for these patients. *Data are significantly different compared with placebo (P < .05). Data represent the mean scores ± SEM. BP = bodily pain; GH = general health; MCS = mental component summary; MH = mental health; PCS = physical component summary; PF = physical functioning; RE = role-emotional; RP = role-physical; SF = social functioning; VT = vitality. See Figure 1 legend for expansion of other abbreviations.*

A

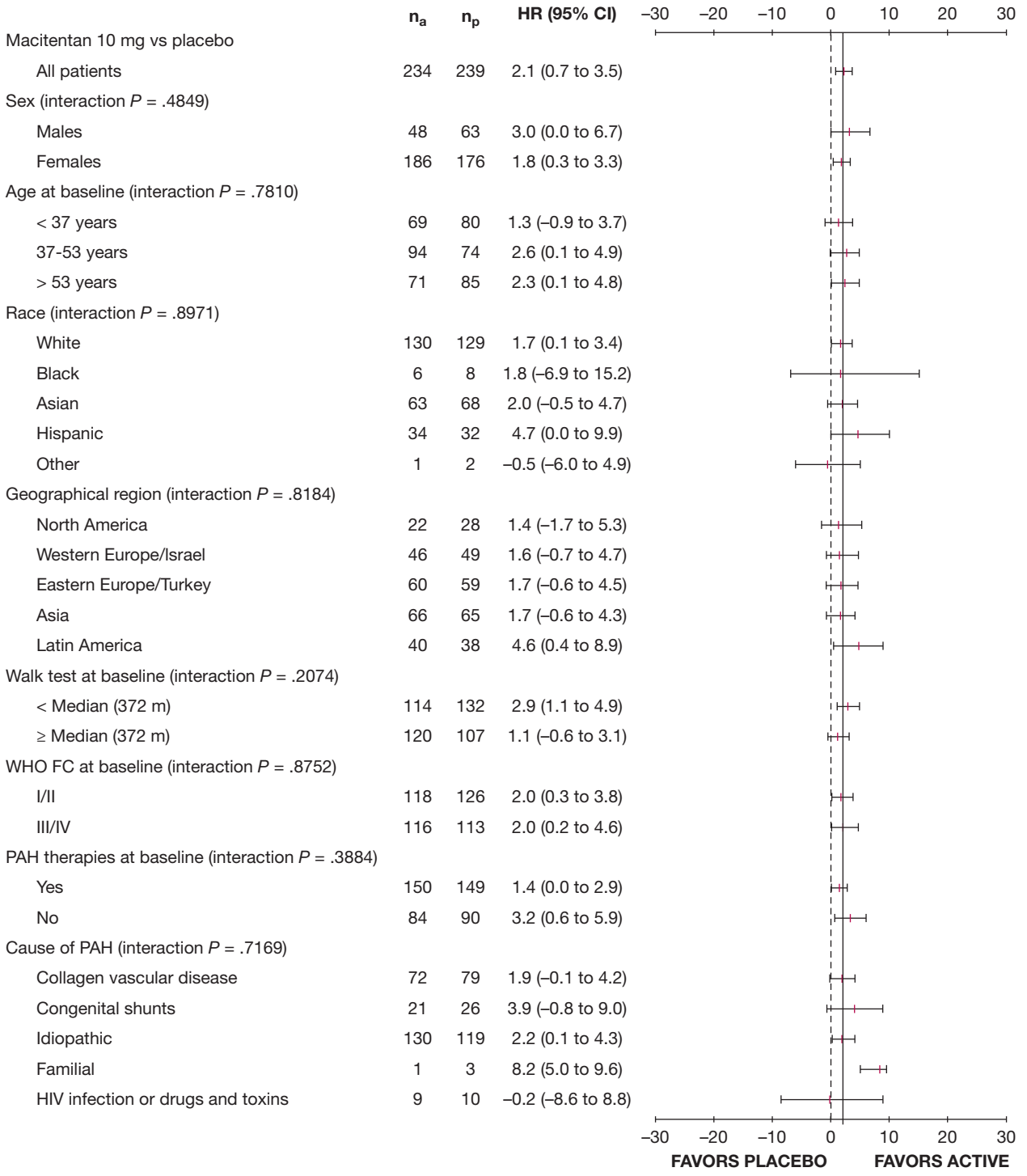


Figure 3 – *Patient subgroup analyses of change in SF-36 summary component scores with macitentan 10 mg vs placebo according to baseline demographic or clinical characteristics. A, Physical component summary. Patient population used for this analysis included all randomized patients with complete HRQoL data. B, Mental component summary. Patient population used for this analysis included all randomized patients with complete HRQoL data. Norm-based SF-36 summary scores with imputation of missing data. Median plus 95% CI Hodges Lehmann. Interaction P value from analysis of variance model on ranks including baseline characteristics by treatment interaction term.* n_a *= number of patients in active treatment group;* n_p *= number of patients in placebo group; PAH = pulmonary arterial hypertension; WHO FC = World Health Organization functional class. See Figure 1 legend for expansion of other abbreviations.*

B

	n_a	n_p	HR (95% CI)
Macitentan 10 mg vs placebo			
All patients	234	239	1.9 (0.1 to 3.8)
Sex (interaction *P* = .0289)			
Males	48	63	5.6 (1.4 to 10.1)
Females	186	176	0.8 (–0.9 to 2.8)
Age at baseline (interaction *P* = .7420)			
< 37 years	69	80	2.2 (–0.8 to 5.8)
37-53 years	94	74	0.9 (–0.2 to 4.1)
> 53 years	71	85	2.1 (–0.3 to 5.6)
Race (interaction *P* = .1678)			
White	130	129	0.1 (–2.3 to 2.3)
Black	6	8	7.8 (–18.0 to 25.3)
Asian	63	68	5.2 (1.6 to 9.0)
Hispanic	34	32	2.1 (–1.8 to 8.5)
Other	1	2	0.6 (–3.5 to 4.7)
Geographical region (interaction *P* = .1773)			
North America	22	28	–2.5 (–7.9 to 1.7)
Western Europe/Israel	46	49	2.7 (–1.4 to 7.6)
Eastern Europe/Turkey	60	59	0.2 (–3.3 to 3.9)
Asia	66	65	4.4 (0.8 to 8.1)
Latin America	40	38	2.7 (–0.9 to 8.8)
Walk test at baseline (interaction *P* = .0958)			
< Median (372 m)	114	132	3.8 (0.9 to 7.1)
≥ Median (372 m)	120	107	0.3 (–1.8 to 2.6)
WHO FC at baseline (interaction *P* = .7085)			
I/II	118	126	2.0 (0.0 to 4.3)
III/IV	116	113	2.3 (–0.8 to 5.2)
PAH therapies at baseline (interaction *P* = .5766)			
Yes	150	149	1.5 (–0.5 to 3.8)
No	84	90	2.9 (0.0 to 6.1)
Cause of PAH (interaction *P* = .1303)			
Collagen vascular disease	72	79	0.5 (–2.0 to 3.4)
Congenital shunts	21	26	0.9 (–3.2 to 8.1)
Idiopathic	130	119	3.9 (1.1 to 6.9)
Familial	1	3	2.6 (0.7 to 10.1)
HIV infection or drugs and toxins	9	10	–7.8 (–17.6 to 3.8)

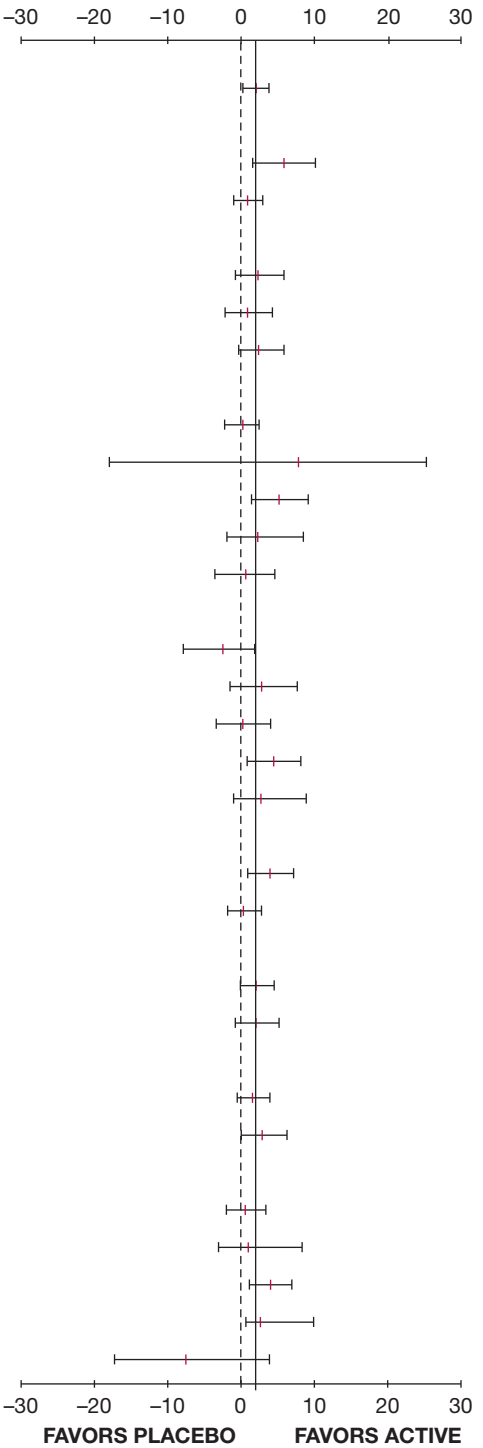
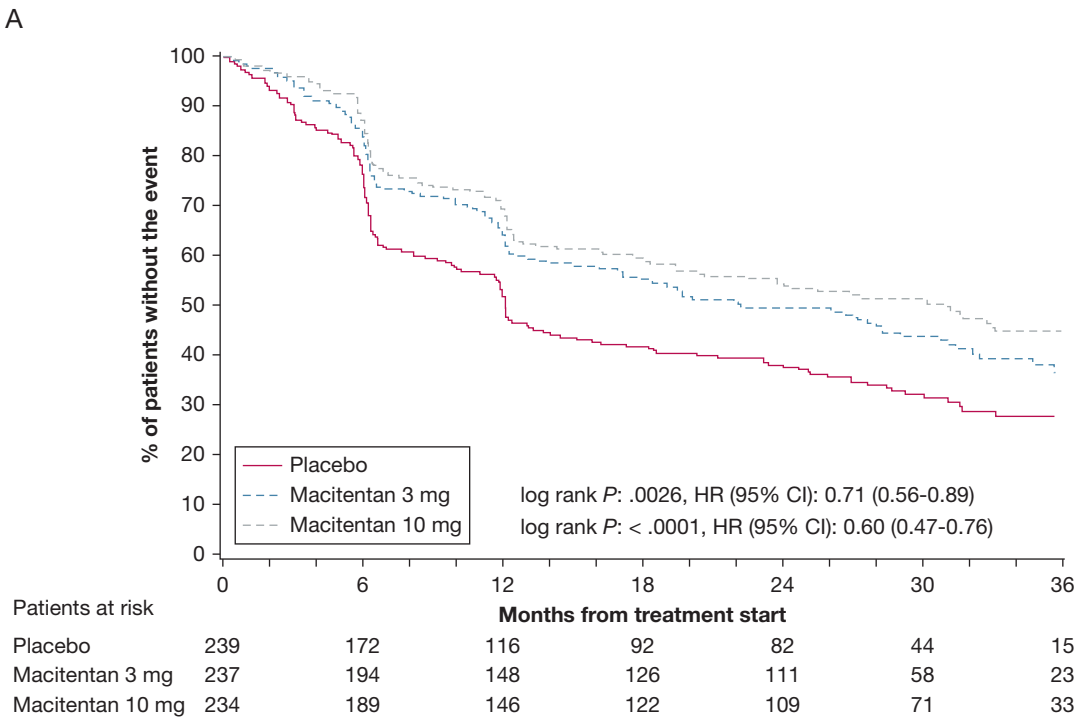


Figure 3 – *Continued.*

effects observed for seven of the eight SF-36 domain scores and for both the PCS and MCS scores. Treatment with macitentan also led to a significantly lower risk for clinically relevant worsening of HRQoL compared with placebo over the long-term duration of the study. With respect to HRQoL and long-term outcome, patients with higher baseline HRQoL had improved long-term outcomes compared with those with lower baseline HRQoL.



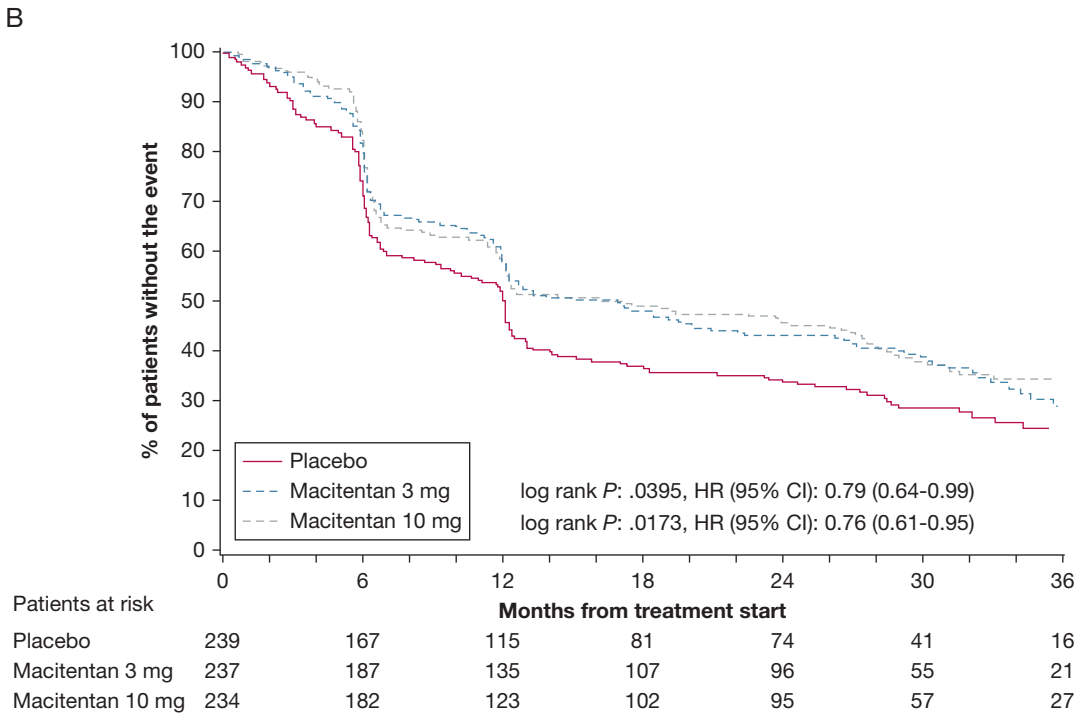


Figure 4 – *Kaplan-Meier analyses of time to a three-point or greater deterioration in SF-36 component summary scores for macitentan 10 mg or 3 mg vs placebo. A, Physical component score. Macitentan 3 mg vs placebo (hazard ratio [HR], 0.71; 95% CI, 0.56-0.89; log-rank P = .0026). Macitentan 10 mg vs placebo (HR, 0.60; 95% CI, 0.47-0.76; log-rank P < .0001). Patient population used for this analysis included all randomized patients with complete HRQoL data. The analysis took into account all available data up to end of treatment (EOT), but the Kaplan-Meier curve is truncated at 36 months because of the small number of patients remaining in the analysis after this time point. B, Mental component summary. Macitentan 3 mg vs placebo (HR, 0.79; 95% CI, 0.64-0.99; log-rank P = .0395). Macitentan 10 mg vs placebo (HR, 0.76; 95% CI, 0.61-0.95; log-rank P = .0173). Patient population used for this analysis included all randomized patients with complete HRQoL data. The analysis took into account all available data up to EOT, but the Kaplan-Meier curve is truncated at 36 months because of the small number of patients remaining in the analysis after this time point. See Figure 1 legend for expansion of abbreviations.*

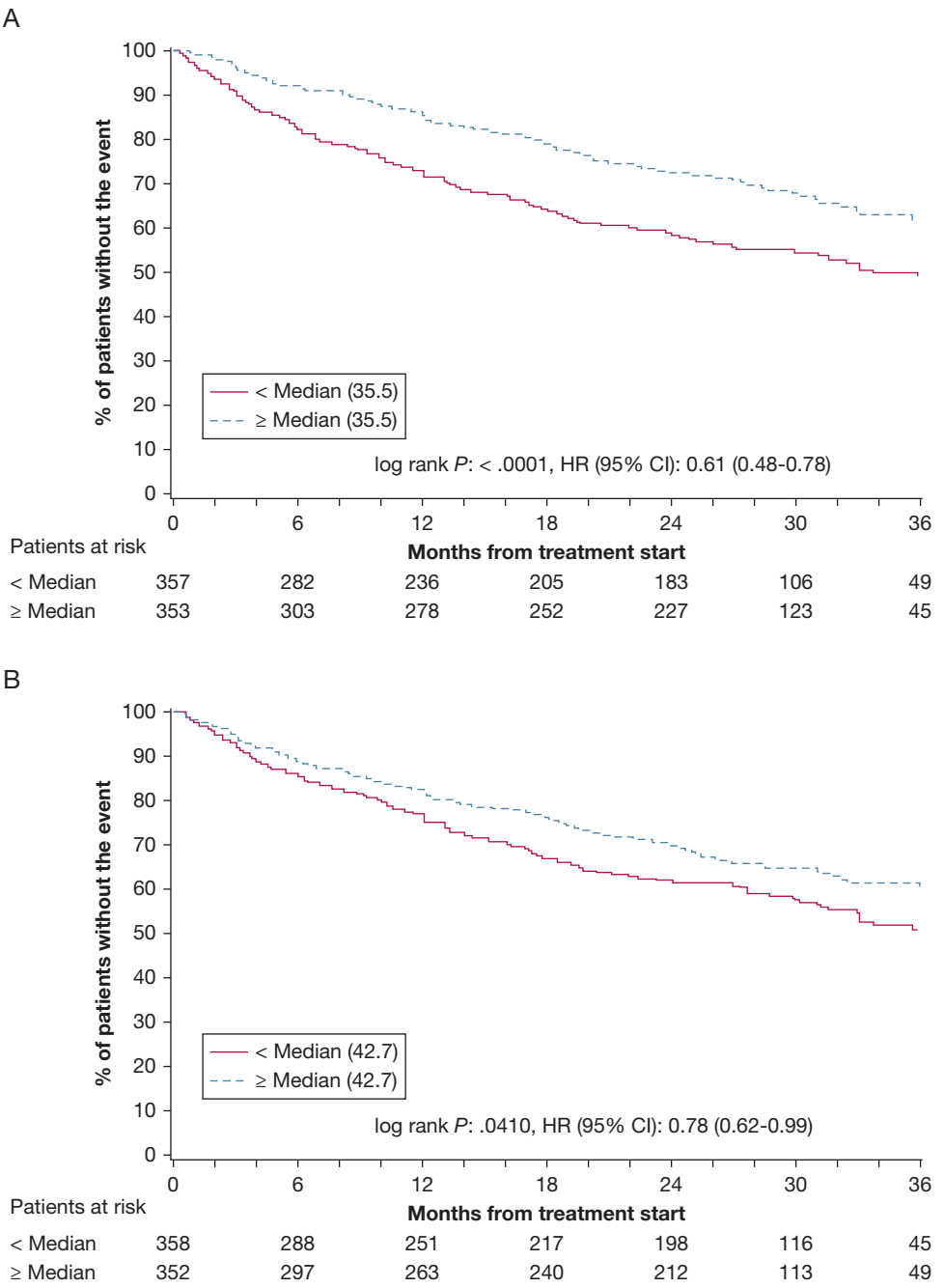


Figure 5 – *Kaplan-Meier analyses of time to first confirmed morbidity or mortality event according to median baseline SF-36 component summary score. A, Physical component summary. Median difference (HR, 0.61; 95% CI, 0.48-0.78; log-rank test P < .0001). Patient population used for this analysis included all randomized patients with complete HRQoL data. The analysis took into account all available data up to EOT, but the Kaplan-Meier curve is truncated at 36 months because of the small number of patients remaining in the analysis after this time point. B, Mental component summary. Median difference (HR, 0.78; 95% CI, 0.62-0.99; log-rank P = .0410). Patient population used for this analysis included all randomized patients with complete HRQoL data. The analysis took into account all available data up to EOT, but the Kaplan-Meier curve is truncated at 36 months because of the small number of patients remaining in the analysis after this time point. See Figure 1 legend for expansion of abbreviations.*

The number of PAH clinical trials that included HRQoL as an outcome measure has recently increased. Although some of these studies were long-term, event-driven trials, the majority were of short duration, usually 12 to 26 weeks.[5] Both generic HRQoL instruments, such as the SF-36,[5,19] and disease-specific instruments developed for cardiac or pulmonary diseases (or both), such as the Cambridge Pulmonary Hypertension Outcomes Review (CAMPHOR),[19,20] have been used in PAH trials. Improvements in HRQoL have been reported to varying

degrees; however, comparisons between studies are challenging because of differences in trial design and variation in instruments used to assess HRQoL.[5] Nevertheless, it is encouraging that the importance of evaluating the impact of PAH therapies on patients' HRQoL is now well recognized.

SERAPHIN, using the SF-36, is the first study to demonstrate a benefit of PAH-targeted therapy in seven of the eight domains. Macitentan also improved both the physical and mental component summary scores. The effect on mental domains is important, as several studies have shown that patients with PAH suffer a decline in psychological health, often experiencing feelings of anxiety, depression, and stress.[1,3,9] The improvement in HRQoL in patients receiving macitentan is paralleled by improved functional parameters such as 6MWD and WHO functional class,[15] as seen in other studies.[6,8] In addition, macitentan's convenient oral administration and its well-tolerated adverse event profile[15] may contribute to the HRQoL benefits, compared with therapies that require parenteral administration or close monitoring for side effects.

Although short-term improvements in HRQoL with treatment are encouraging, it is perhaps more important to determine the long-term impact of treatment regarding delaying the deterioration of HRQoL over time. Macitentan reduced the risk of a clinically relevant deterioration of HRQoL in SERAPHIN; this result complements the impact of macitentan on delaying disease progression (reduced risk of morbidity/mortality and PAH-related hospitalization/death).[15]

These analyses show that both macitentan 3 mg and 10 mg significantly reduced the risk for HRQoL deterioration. Similarly, the treatment effect of macitentan on change in HRQoL at month 6 was comparable for both doses. In contrast, only the 10 mg dose of macitentan had a significant treatment effect on the risk of a morbidity/mortality event.[15] This finding suggests that although improving HRQoL is important, the change in HRQoL may not be predictive of long-term outcome in PAH. Supporting this, recent data have shown that the change from baseline in SF-36 PCS score after PAH treatment was not predictive of survival.[21]

Although the change from baseline in HRQoL may not be predictive of outcome, the absolute HRQoL thresholds at baseline did have prognostic relevance in SERAPHIN. The analysis showed that patients with better baseline HRQoL had better long-term outcomes evidenced by a reduced risk of morbidity/mortality compared with patients whose PCS and MCS scores were less than the median baseline values. This observation parallels previous findings for 6MWD, whereby the change in 6MWD was not predictive of outcome, but absolute values at baseline were.[22] Recent evidence also suggests an association between better baseline SF-36 PCS scores and improved survival[21,23]; however one retrospective analysis showed that the predictive value of baseline total CAMPHOR scores for clinical deterioration in patients with idiopathic PAH was lost following adjustment for baseline WHO functional class and 6MWD.[24]

These analyses have potential limitations. First, the SF-36 is a generic measure of HRQoL and is not tailored to specifically assess the impact of PAH-specific symptoms. However, the SF-36 has frequently been used to evaluate HRQoL in PAH studies,[8,25,26] and findings from a cross-sectional study of 93 patients with PAH who completed the SF-36 suggest that this instrument is sensitive to PAH-related symptoms.[27] Second, the extent of missing data at month 12 precluded meaningful analysis of the SF-36 change from baseline to month 12. Nevertheless, the analysis of the time to a deterioration in HRQoL over the course of the entire study gives insight into the long-term impact of macitentan on HRQoL; the observed benefit of macitentan over placebo was maintained throughout the study. Third, other than the prespecified analysis of change from baseline to month 6 in the SF-36, all other exploratory analyses were post hoc and not adjusted for multiple comparisons.

In conclusion, results from this study indicate significant improvements in HRQoL in patients with PAH treated with macitentan compared with placebo. Treatment with macitentan significantly reduced the risk of experiencing a clinically meaningful reduction in PCS and MCS scores vs placebo. In addition, an association between better baseline HRQoL and improved long-term outcomes was shown.

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

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