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ORIGINAL RESEARCH

Macitentan in Pulmonary Arterial Hypertension Associated with Connective Tissue Disease (CTD-PAH): Real-World Evidence from the Combined OPUS/OrPHeUS Dataset

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ABSTRACT

Introduction: Data on real-world clinical practice and outcomes of patients with pulmonary arterial hypertension associated with connective tissue disease (CTD-PAH) are scarce. The OPUS/OrPHeUS studies enrolled patients newly initiating macitentan, including those with CTD-PAH. This analysis describes patient characteristics, treatment patterns, outcomes, and safety profiles of patients with CTD-PAH newly initiating macitentan in the US using the OPUS/OrPHeUS combined dataset.

Methods: OPUS was a prospective, US, multicenter, long-term, observational drug registry (April 2014–June 2020). OrPHeUS was a retrospective, US, multicenter medical chart review (October 2013–March 2017). The characteristics, treatment patterns, safety, and outcomes during macitentan treatment of patients with CTD-PAH and its subgroups systemic sclerosis (SSc-PAH),

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systemic lupus erythematosus (SLE-PAH), and mixed CTD (MCTD-PAH) were descriptively compared to patients with idiopathic/heritable PAH (I/HPAH).

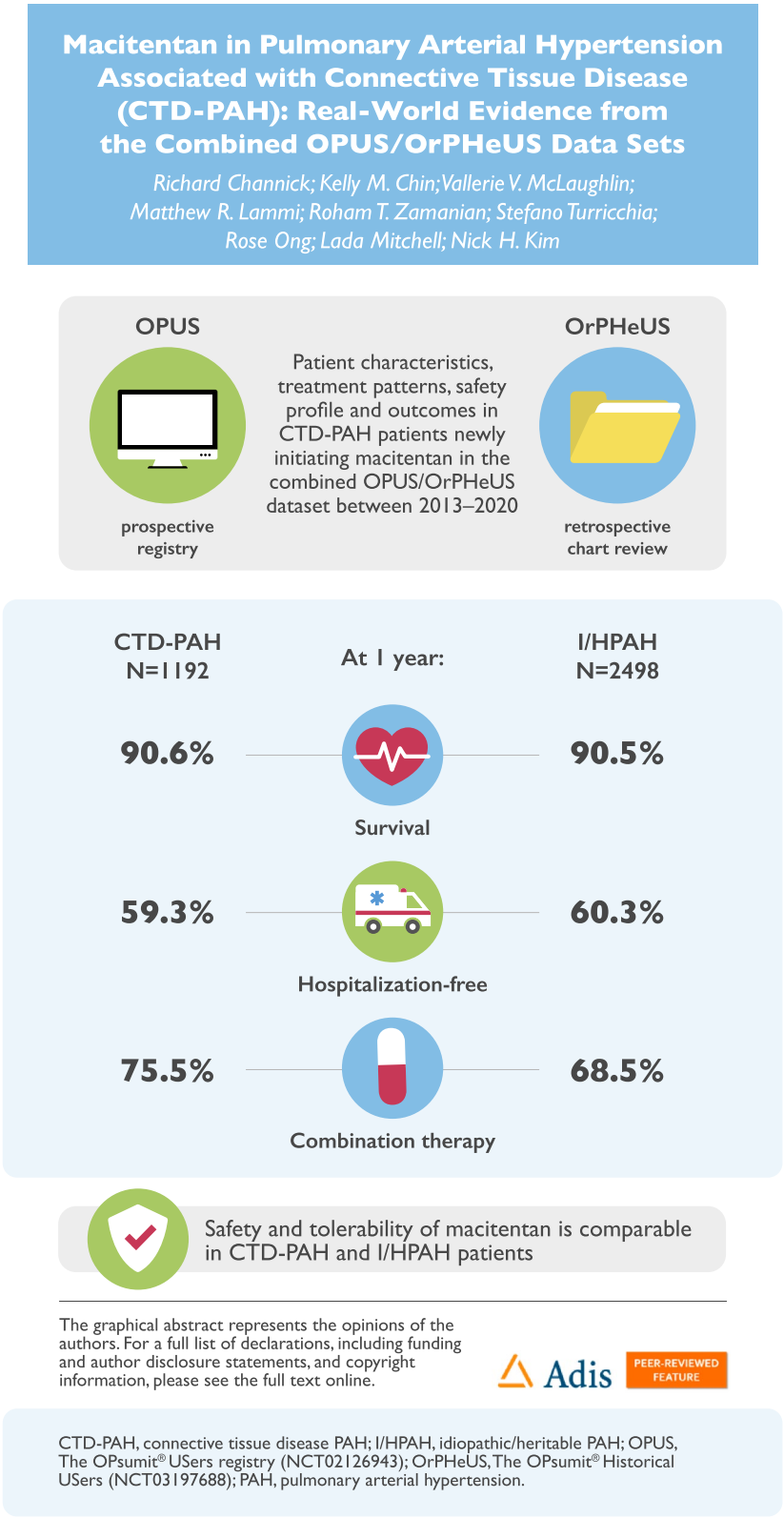
***Results*:** The combined OPUS/OrPHeUS population included 2498 patients with I/HPAH and 1192 patients with CTD-PAH (708 SSc-PAH; 159 SLE-PAH; 124 MCTD-PAH, and 201 other CTD-PAH etiologies). At macitentan initiation for patients with I/HPAH and CTD-PAH, respectively: 61.2 and 69.3% were in World Health Organization functional class (WHO FC) III/IV; median 6-min walk distance was 289 and 279 m; and 58.1 and 65.2% received macitentan as combination therapy. During follow-up, for patients with I/HPAH and CTD-PAH, respectively: median duration of macitentan exposure observed was 14.0 and 15.8 months; 79.0 and 83.0% experienced an adverse event; Kaplan–Meier estimates (95% confidence limits [CL]) of patients free from all-cause hospitalization at 1 year were 60.3% (58.1, 62.4) and 59.3% (56.1, 62.3); and Kaplan–Meier estimates (95% CL) of survival at 1 year were 90.5% (89.1, 91.7) and 90.6% (88.6, 92.3).

***Conclusions*:** Macitentan was used in clinical practice in patients with CTD-PAH and its subgroups, including as combination therapy. The safety and tolerability profile of macitentan in patients with CTD-PAH was comparable to that of patients with I/HPAH.

***Trial Registration*:** OPsumit® Users Registry (OPUS): NCT02126943; Opsumit® Historical Users cohort (OrPHeUS): NCT03197688; www.clinicaltrials.gov

Graphical abstract available for this article.

Graphical Abstract:



Keywords: Connective tissue disease; Macitentan; Mixed connective tissue disease; Pulmonary arterial hypertension; Real-world evidence; Scleroderma; Systemic lupus erythematosus; Systemic sclerosis

Key Summary Points

Why carry out this study?

Patients with connective tissue disease associated with pulmonary arterial hypertension (CTD-PAH) form the largest PAH etiological subgroup after idiopathic/heritable PAH (I/HPAH).

However, patient characteristics, treatment patterns, safety profile, and outcomes of patients with CTD-PAH (including patients with systemic sclerosis [SSc], systemic lupus erythematosus [SLE], and mixed connective tissue disease [MCTD]-PAH) newly initiating macitentan are not well understood.

The OPUS/OrPHeUS studies provide detailed insight into real-world clinical practice and management of patients with CTD-PAH and its subgroups, with differing disease severities and comorbidity burdens.

What was learned from the study?

Macitentan was used as part of combination therapy in most patients with CTD-PAH; however, contrary to guideline recommendations, a considerable proportion remained on monotherapy therapy at follow-up.

Outcomes were similar between patients with CTD-PAH and I/HPAH and there were no unexpected safety findings, supporting the safety and tolerability of macitentan, including as a combination therapy in patients with CTD-PAH.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.25196996.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive and debilitating disease characterized by elevated pressure in arteries in the lungs, and can manifest as a complication of connective tissue diseases (CTD) [1–3]. The most common causes of CTD associated PAH (CTD-PAH) are systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD), while less common causes are rheumatoid arthritis, dermatomyositis, and Sjögren's syndrome [1]. The CTD-PAH patient population is the largest PAH etiological subgroup after patients with idiopathic PAH (IPAH) [2, 3], accounting for approximately 15–30% of the PAH population [4–6]. Data from REVEAL show that within the CTD-PAH population, 62, 17, and 8% of patients had SSc-PAH, SLE-PAH, and MCTD-PAH, respectively [7], with 1- and 5-year survival estimates of 80 and 44% for patients with CTD-PAH versus 88 and 64% for patients with IPAH [8]. The long-term trials SERAPHIN, GRIPHON, and AMBITION have shown that patients with CTD-PAH respond to PAH-specific therapies, including combination therapy [1, 9, 10]. In the pivotal randomized controlled trial (RCT) SERAPHIN, patients with PAH including those with CTD-PAH (which accounted for 30.5% of the enrolled patients) were treated with the oral endothelin receptor antagonist (ERA) macitentan 10 mg as part of a monotherapy or combination therapy regimen, which resulted in a significant reduction (by 45%; $p < 0.001$) in the risk of a composite mortality/morbidity events [10]. Results from REPAIR also demonstrate the beneficial effects of macitentan on right ventricular function and structure in patients with PAH, including

those with CTD-PAH [11]. Furthermore, a recent meta-analysis that included RCTs evaluated the addition of a PAH-specific therapy to a patient's current care. In this analysis, patients were stratified according to whether they were receiving no PAH-specific treatment, monotherapy, or dual combination therapy; additional PAH-specific therapy resulted in a 36% reduction in the risk of morbidity/mortality events compared to controls, in patients with CTD-PAH, and in the overall PAH population [12].

In addition to progress in therapeutic development, early detection of PAH through systematic screening and timely treatment of patients with CTD-PAH is advocated due to potential survival benefits, especially in the SSc-PAH subpopulation, which have been shown to have worse survival compared to other CTD-PAH patient subgroups [1, 13, 14]. However, despite these recent advances, there is still a lack of data on real-world clinical practices, on clinical outcomes, and the use of PAH-specific therapies in patients with CTD-PAH, including with macitentan.

Opsumit® (macitentan) is an oral ERA administered once daily for the treatment of PAH to reduce the risks of disease progression and hospitalization for patients with PAH [15, 16]. The prospective Opsumit® Users (OPUS) registry was set up in 2014 to enable further evaluation of the hepatic safety profile of macitentan. OPUS was designed to characterize the safety, clinical characteristics, and outcomes of patients newly treated with macitentan in routine clinical practice [17]. The Opsumit® Historical Users cohort study (OrPHeUS) was initiated to supplement the OPUS registry data. Data from both studies provide a unique insight into contemporary real-world clinical practice for the management of a broad range of patients with PAH, including those with CTD-PAH, and report real-life clinical outcomes of these patients, complementing the findings of RCTs and other registries. This article describes the baseline characteristics, treatment patterns, safety profile, and outcomes in terms of hospitalizations and survival in patients with CTD-PAH newly treated with macitentan in the combined OPUS/OrPHeUS population. The overall CTD-PAH population and the CTD-PAH patient subgroups are descriptively compared with the idiopathic/heritable PAH (I/HPAH) population.

METHODS

OPUS and OrPHeUS Study Design

As previously described, OPUS was a prospective, multicenter, long-term, US, observational drug registry (NCT02126943) that ran between April 2014 and June 2020. OrPHeUS was a retrospective, multicenter, US, medical chart review (NCT03197688) that captured individual patient data from October 2013 to March 2017 [17]. Both studies enrolled patients newly initiating macitentan. Data collection in OrPHeUS was designed to be similar to that of OPUS. Patients were excluded from OPUS if they were enrolled in an ongoing clinical trial, and from OrPHeUS if they were enrolled in a clinical trial involving macitentan; patients enrolled in OPUS were not allowed to participate in OrPHeUS. OPUS and OrPHeUS were initiated as a post-marketing requirement to evaluate the potential for hepatic risks with macitentan. The FDA announced in September 2019 that the post-marketing requirement had been fulfilled.

Monitoring and Ethical Approval

OPUS and OrPHeUS were executed in accordance with Good Pharmacoepidemiology Practices [18] and the 2008 Declaration of Helsinki ethical principles. Ethical approval was received from independent ethics committees/institutional review boards of participating centers (Supplementary Material I). The protocols were reviewed by the US FDA with written informed consent obtained from all patients in OPUS, including for publication of anonymized patient data (informed consent was not required in OrPHeUS as an Institutional Review Board [IRB] waiver was obtained). IRB approvals were provided by

the Western IRB and Quorum (now Advarra) (OPUS registry; Western IRB approval number 2014-0816, Quorum Review File number 29120/Advarra Pro00035124) and WCG-IRB (OrPHeUS study; IRB numbers 2017-8051 and 2017-2348).

Observations and Assessments

Data collection (on demographics, baseline characteristics, treatment patterns, safety, hospitalizations, and deaths) during macitentan treatment in OPUS and OrPHeUS has been previously described [17]. Information was collected per routine clinical practice and no assessments were mandated. The observation period was from the date of macitentan initiation (which may not have coincided with the date of diagnosis) to study end, or until the first of death, loss to follow-up, withdrawal of consent, or macitentan discontinuation plus 30 days. For both OPUS and OrPHeUS, follow-up data were defined as at least one observation after macitentan initiation. In OPUS, adverse events (AEs) were recorded. In OrPHeUS, hepatic adverse events (HAEs) and HAEs of special interest (HAESIs) were identified from the clinical data collected; however, due to the retrospective design, no other AE reporting was conducted. For OPUS, the Independent Liver Safety Data Review Board (ILSDRB) reviewed and assessed all reported HAESIs. The ILSDRB additionally reviewed all HAESIs identified in OrPHeUS that met the biochemical criteria of a potential Hy's law case, using available information from the electronic case report form (Supplementary Material II). As edema and anemia are common (occurring in ≥ 1 in 10 patients) side effects associated with ERA and macitentan use [15, 16], the AEs of special interest (AESIs) of edema and anemia/hemoglobin decrease were also investigated in OPUS.

Statistical and Other Analyses

Statistical and other analyses in OPUS and OrPHeUS have been previously described [17]. All analysis groups described here were derived from the OPUS/OrPHeUS PAH population, and included patients with follow-up data who had PAH entered as the only reason for macitentan prescription; patients with multiple pulmonary hypertension (PH) diagnoses or PAH etiologies were excluded. The reasons for macitentan prescription were investigator-assessed and were used to classify patients with CTD-PAH etiology into the CTD-PAH subgroups SSc-PAH, SLE-PAH, and MCTD-PAH; patients with other forms of CTD-PAH were included in the overall CTD-PAH group only. An I/HPAH patient group is included for reference, as it is the most well-characterized form of PAH. Patient and treatment characteristics were found to be similar in the OPUS and OrPHeUS datasets following heterogeneity analyses, and it was deemed appropriate to combine both into one dataset [17].

For this analysis from the combined OPUS/OrPHeUS population, the CTD-PAH group and CTD-PAH subgroups SSc-PAH, SLE-PAH, MCTD-PAH are presented, and descriptively compared with the I/HPAH group. Analyses of clinical characteristics and treatment patterns were descriptive. All analyses were conducted until the end of the observation period. Event rates (for HAEs, HAESIs, AEs [OPUS only], discontinuation of macitentan, hospitalization, and death) were calculated using time to the first event. Patients were included in each analysis until the first occurrence of the specified event, or until the end of observation period, whichever occurred first. Patients experiencing non-fatal events who did not discontinue macitentan treatment were able to continue in the study (i.e., they were not censored from other event analyses). All Poisson models included log (exposure time) as an offset to account for varying length of patients' time on treatment. Confidence limits (CL [95%]) for rates per person-year were estimated using an unadjusted Poisson model. Treatment escalation, hospitalizations and deaths are presented using Kaplan–Meier (KM) estimates; curves were truncated at the time point when < 10% of patients in any of the cohorts were at risk, in accordance with Pocock's stopping rule [19]. Imputations for missing values were applied for incomplete or missing dates; no other data imputations were

Table 1 Demographics and baseline characteristics at macitentan initiation

	I/HPAH, *N* = 2498	CTD-PAH, *N* = 1192[a]	SSc-PAH, *N* = 708	SLE-PAH, *N* = 159	MCTD-PAH, *N* = 124
Age, median (Q1, Q3) years	64 (53, 73)	62 (52, 70)	64 (55, 71)	49 (38, 62)	57 (48, 65)
Female sex, *n* (%)	1826 (73.1)	1028 (86.2)	603 (85.2)	152 (95.6)	109 (87.9)
Race, *n* (%)					
Black or African American	390 (15.7)	234 (19.9)	96 (13.7)	51 (32.7)	38 (30.9)
White	1936 (77.9)	844 (71.7)	558 (79.7)	82 (52.6)	67 (54.5)
Other[b]	159 (6.4)	99 (8.4)	46 (6.6)	23 (14.7)	18 (14.6)
Missing	13 (0.5)	15 (1.3)	8 (1.1)	3 (1.9)	1 (0.8)
Ethnicity, *n* (%)					
Hispanic or Latino	252 (10.1)	127 (10.7)	60 (8.5)	32 (20.1)	19 (15.4)
Not Hispanic or Latino	2131 (85.7)	1019 (85.7)	624 (88.3)	119 (74.8)	96 (78.0)
Unknown	105 (4.2)	43 (3.6)	23 (3.3)	8 (5.0)	8 (6.5)
Missing	10 (0.4)	3 (0.3)	1 (0.1)	0	1 (0.8)
Time from diagnosis, *n* (%)	2440 (97.7)	1156 (97.0)	688 (97.2)	153 (96.2)	116 (93.5)
Median (Q1, Q3) months	7.0 (1.3, 36.8)	6.3 (1.1, 35.1)	7.9 (1.2, 38.7)	6.0 (0.9, 44.3)	4.6 (1.0, 27.8)
≤ 6 months before macitentan initiation (incident), *n* (%)	1154 (47.3)	573 (49.6)	325 (47.2)	77 (50.3)	61 (52.6)
> 6 months before macitentan initiation (prevalent), *n* (%)	1286 (52.7)	583 (50.4)	363 (52.8)	76 (49.7)	55 (47.4)
WHO functional class, *n* (%)	1383 (55.4)	654 (54.9)	380 (53.7)	89 (56.0)	68 (54.8)
I[c]	117 (8.5)	49 (7.5)	28 (7.4)	8 (9.0)	2 (2.9)
II[c]	419 (30.3)	152 (23.2)	90 (23.7)	30 (33.7)	10 (14.7)
III[c]	761 (55.0)	412 (63.0)	233 (61.3)	46 (51.7)	54 (79.4)
IV[c]	86 (6.2)	41 (6.3)	29 (7.6)	5 (5.6)	2 (2.9)
Missing	1115 (44.6)	538 (45.1)	328 (46.3)	70 (44.0)	56 (45.2)
6-min walk distance, *n* (%)	900 (36.0)	454 (38.1)	275 (38.8)	62 (39.0)	46 (37.1)
Median (Q1, Q3) m	289 (193, 375)	279 (184, 362)	274 (187, 360)	344 (237, 397)	286 (152, 362)
Missing	1598 (64.0)	738 (61.9)	433 (61.2)	97 (61.0)	78 (62.9)

Table 1 continued

	I/HPAH, *N* = 2498	CTD-PAH, *N* = 1192[a]	SSc-PAH, *N* = 708	SLE-PAH, *N* = 159	MCTD-PAH, *N* = 124
BNP/NT-proBNP risk category, *n* (%)	813 (32.5)	502 (42.1)	293 (41.4)	62 (39.0)	55 (44.4)
Low[d]	225 (27.7)	113 (22.5)	54 (18.4)	17 (27.4)	14 (25.5)
Intermediate[d]	302 (37.1)	187 (37.3)	116 (39.6)	19 (30.6)	21 (38.2)
High[d]	286 (35.2)	202 (40.2)	123 (42.0)	26 (41.9)	20 (36.4)
Missing	1685 (67.5)	690 (57.9)	415 (58.6)	97 (61.0)	69 (55.6)
Relevant medical history[e], *n* (%)					
Hypertension	929 (37.2)	405 (34.0)	251 (35.5)	47 (29.6)	35 (28.2)
Obesity (BMI ≥ 30 kg/m^2)	851 (34.1)	245 (20.6)	128 (18.1)	35 (22.0)	21 (16.9)
Anemia[f]	223 (8.9)	166 (13.9)	101 (14.3)	27 (17.0)	17 (13.7)
Edema[f]	317 (12.7)	156 (13.1)	108 (15.3)	14 (8.8)	11 (8.9)
Diabetes mellitus	697 (27.9)	153 (12.8)	78 (11.0)	18 (11.3)	17 (13.7)
Renal insufficiency	196 (7.8)	82 (6.9)	54 (7.6)	4 (2.5)	12 (9.7)
Hepatic comorbidities	191 (7.6)	77 (6.5)	36 (5.1)	17 (10.7)	9 (7.3)
≥ 1 commonly prescribed therapy, *n* (%)	1910 (76.5)	938 (78.7)	565 (79.8)	111 (69.8)	98 (79.0)
Diuretic	1417 (56.7)	673 (56.5)	396 (55.9)	79 (49.7)	76 (61.3)
Oxygen therapy	890 (35.6)	464 (38.9)	285 (40.3)	34 (21.4)	50 (40.3)
Anticoagulation agent	767 (30.7)	227 (19.0)	133 (18.8)	33 (20.8)	24 (19.4)
Calcium channel blocker	377 (15.1)	225 (18.9)	161 (22.7)	26 (16.4)	12 (9.7)

AESI adverse event of special interest, *BMI* body mass index, *BNP/NT-proBNP* brain natriuretic peptide/N-terminal pro-brain natriuretic peptide, *CTD-PAH* PAH associated with connective tissue disease, *ESC/ERS* European Society of Cardiology/European Respiratory Society, *I/HPAH* idiopathic/heritable PAH, *MCTD-PAH* PAH associated with mixed connective tissue disease, *PAH* pulmonary arterial hypertension, *Q1, Q3* interquartile range, *SLE-PAH* PAH associated with systemic lupus erythematosus, *SSc-PAH* PAH associated with systemic sclerosis

[a]The 201 patients with CTD-PAH classified other than SSc-PAH, SLE-PAH, or MCTD-PAH were: PAH-associated with: rheumatoid arthritis (*n* = 78), undifferentiated CTD (*n* = 50), Sjögren's syndrome (*n* = 23), polymyositis/dermatomyositis/antisynthetase syndrome (*n* = 20), Raynaud's disease/phenomenon (*n* = 12), overlap syndrome (*n* = 11), psoriasis/psoriatic arthritis (*n* = 3), inflammatory bowel disease/Crohn's disease/ulcerative colitis (*n* = 1), digital ulcers (*n* = 1), and missing (*n* = 2); no further information was available on the limited cutaneous or diffuse cutaneous SSc subtypes

[b]Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other

[c]Percentages are based on *n*

[d]BNP/NT-proBNP risk category defined as per the 2015 ESC/ERS guidelines [26, 27]

[e]≥ 10% in any group [17]

[f]The cause of anemia and edema was not recorded in OPUS/OrPHeUS. This information is included to contextualize the proportion of patients who experienced AESIs of anemia/hemoglobin decrease or edema following macitentan treatment

made (see Supplementary Material III for more details). Fixed imputations were used based on other information (e.g., 1st or 15th of the month if the day of the month was missing). Rules were added to avoid conflicts (e.g., between start and stop dates). If the patient died or was lost to follow-up and no discontinuation date was provided, the discontinuation date was the date of death (for deaths) or date of last information (for loss to follow-up), respectively.

RESULTS

Study Population and Characteristics

As previously described, 155 sites contributed patients to the combined OPUS and OrPHeUS database [17]. Of these, 150 sites enrolled patients with I/HPAH and 121 enrolled patients with CTD-PAH. The combined OPUS/OrPHeUS population consisted of 5654 patients of whom 81.9% ($N=4626$) had a diagnosis that included PAH (WHO Group 1) and had follow-up data [17]. Out of these, there were 4459 patients with PAH as the only reason for macitentan prescription: 2498 (56.0%) patients had I/HPAH and 1192 (26.7%) patients had CTD-PAH, including 708 patients with SSc-PAH, 159 with SLE-PAH, and 124 with MCTD-PAH. There were 201 patients with CTD-PAH subgroup etiologies other than SSc-PAH, SLE-PAH, or MCTD-PAH. To note, as the current analysis excluded patients with multiple PH diagnoses or PAH etiologies, the CTD-PAH and I/HPAH groups herein comprise 47 and 100 patients less than the populations reported in McLaughlin et al., 2022 [17].

Patient characteristics at macitentan initiation are shown in Table 1. The majority of patients in all groups were White (range 52.6–79.7%). Compared to patients with I/HPAH, patients with CTD-PAH were more likely to be female (73.1 vs. 86.2%), in World Health Organization functional class (WHO FC) III/IV (61.2 vs. 69.3%) and were less likely to be obese (34.1 vs. 20.6%) and diabetic (27.9 vs. 12.8%). In all groups at baseline, data were frequently missing for 6-min walk distance (6MWD) and brain natriuretic peptide/N-terminal pro-brain natriuretic peptide (BNP/NT-proBNP) risk category. Compared to the other CTD-PAH subgroups, patients with SSc-PAH tended to be older (median age 64 years) and had the longest time from diagnosis to macitentan initiation (7.9 months). They had more impaired functional status (median 6MWD 274 m, 68.9% in WHO FC III/IV) and the highest proportion of patients with hypertension and edema. Patients with SLE-PAH were the youngest (median age 49 years), mostly female (95.6%), comprised a larger proportion of Black or African American (32.7%) and Hispanic-Latino (20.1%) patients, had less severe disease (median 6MWD 344 m, 57.3% in WHO FC III/IV) and the highest proportion of obesity and anemia compared to the other CTD-PAH subgroups. Patients with MCTD-PAH had the shortest time from diagnosis (4.6 months), with proportionally more patients in WHO FC III/IV (82.4%), and higher proportion of patients with diabetes, and renal insufficiency compared to the other CTD-PAH subgroups. At macitentan initiation, approximately half of patients across all groups had been diagnosed less than 6 months before enrollment (incident patients). Other relevant medical history at macitentan initiation is described in Table S1.

Treatment Patterns

Prior to macitentan initiation, 61.4% of patients with I/HPAH and 68.4% of patients with CTD-PAH had received at least one previous PAH-specific therapy (Table 2). At macitentan initiation, compared to patients with I/HPAH a higher proportion of patients with CTD-PAH received macitentan as part of combination therapy (58.1 vs. 65.2%, respectively; Fig. 1), most commonly

Table 2 Treatment patterns prior to and at macitentan initiation and Kaplan–Meier estimates of percentage escalating PAH-specific therapy up to 1 and 2 years

	I/HPAH, *N* = 2498	CTD-PAH, *N* = 1192	SSc-PAH, *N* = 708	SLE-PAH, *N* = 159	MCTD-PAH, *N* = 124
PAH-specific therapies prior to macitentan initiation					
No previous PAH therapy, *n* (%)	965 (38.6)	377 (31.6)	221 (31.2)	55 (34.6)	33 (26.6)
≥ 1 previous PAH therapy, *n* (%)	1533 (61.4)	815 (68.4)	487 (68.8)	104 (65.4)	91 (73.4)
PDE5i	1206 (48.3)	662 (55.5)	396 (55.9)	85 (53.5)	69 (55.6)
ERA	417 (16.7)	203 (17.0)	133 (18.8)	24 (15.1)	18 (14.5)
Bosentan	280 (11.2)	126 (10.6)	82 (11.6)	19 (11.9)	10 (8.1)
Ambrisentan	144 (5.8)	78 (6.5)	52 (7.3)	5 (3.1)	8 (6.5)
i.v./s.c. prostanoid	305 (12.2)	142 (11.9)	87 (12.3)	22 (13.8)	15 (12.1)
Inhaled prostanoid	142 (5.7)	95 (8.0)	62 (8.8)	13 (8.2)	11 (8.9)
sGC stimulator	105 (4.2)	40 (3.4)	23 (3.2)	3 (1.9)	8 (6.5)
Oral prostanoid	59 (2.4)	30 (2.5)	18 (2.5)	2 (1.3)	2 (1.6)
Investigational drug[a]	5 (0.2)	2 (0.2)	2 (0.3)	0	0
PAH-specific therapies ongoing at macitentan initiation					
No concomitant PAH-specific therapy, *n* (%)	1021 (40.9)	410 (34.4)	250 (35.3)	58 (36.5)	36 (29.0)
≥ 1 concomitant PAH-specific therapy, *n* (%)	1477 (59.1)	782 (65.6)	458 (64.7)	101 (63.5)	88 (71.0)
ERA[b]	64 (2.6)	16 (1.3)	9 (1.3)	4 (2.5)	1 (0.8)
PDE5i	1197 (47.9)	670 (56.2)	397 (56.1)	87 (54.7)	70 (56.5)
i.v./s.c. prostanoid	305 (12.2)	136 (11.4)	81 (11.4)	20 (12.6)	15 (12.1)
Inhaled prostanoid	122 (4.9)	88 (7.4)	56 (7.9)	11 (6.9)	10 (8.1)
sGC stimulator	108 (4.3)	39 (3.3)	24 (3.4)	3 (1.9)	7 (5.6)
Oral prostanoid	56 (2.2)	26 (2.2)	15 (2.1)	3 (1.9)	1 (0.8)
Investigational drug[a]	5 (0.2)	1 (0.1)	1 (0.1)	0	0

Table 2 continued

	I/HPAH, *N* = 2498	CTD-PAH, *N* = 1192	SSc-PAH, *N* = 708	SLE-PAH, *N* = 159	MCTD-PAH, *N* = 124
Kaplan–Meier estimates for time to additional PAH-specific therapy, % (95% CL)[c]					
Monotherapy to combination therapy					
Patients receiving monotherapy at macitentan initiation, *n*	1044	412	253	58	35
Patients who escalated therapy up to 1 year	31.8 (28.7, 35.1)	39.2 (34.3, 44.5)	40.0 (33.8, 46.9)	17.0 (9.2, 30.2)	48.3 (32.1, 67.5)
Patients who escalated therapy up to 2 years	40.7 (36.9, 44.6)	49.4 (43.7, 55.3)	49.7 (42.6, 57.3)	31.4 (18.7, 49.7)	53.5 (36.2, 72.9)
Double to triple therapy					
Patients receiving double therapy at macitentan initiation, *n*	1118	595	336	79	71
Patients who escalated therapy up to 1 year	13.9 (11.8, 16.4)	22.8 (19.2, 26.9)	20.7 (16.3, 26.1)	24.2 (15.5, 36.5)	23.6 (14.6, 36.8)
Patients who escalated therapy up to 2 years	22.0 (18.9, 25.5)	31.3 (26.9, 36.2)	28.7 (23.2, 35.2)	27.0 (17.4, 40.3)	36.4 (23.7, 53.0)

CL confidence limits, *CTD-PAH* PAH associated with connective tissue disease, *ERA* endothelin receptor antagonist, *I/HPAH* idiopathic/heritable PAH, *i.v./s.c.* intravenous/subcutaneous, *MCTD-PAH* PAH associated with mixed connective tissue disease, *PAH* pulmonary arterial hypertension, *PDE5i* phosphodiesterase-5 inhibitor, *sGC* soluble guanylate cyclase, *SLE-PAH* PAH associated with systemic lupus erythematosus, *SSc-PAH* PAH associated with systemic sclerosis

[a]Only in OrPHeUS

[b]Other ERA can be the result of the entry of the same end date/start date for previous/current therapies, or due to imputation of one or both of the dates

[c]Two patients with I/HPAH, three patients with CTD-PAH, and two patients with MCTD-PAH who only received macitentan for 1 day are not included in these analyses

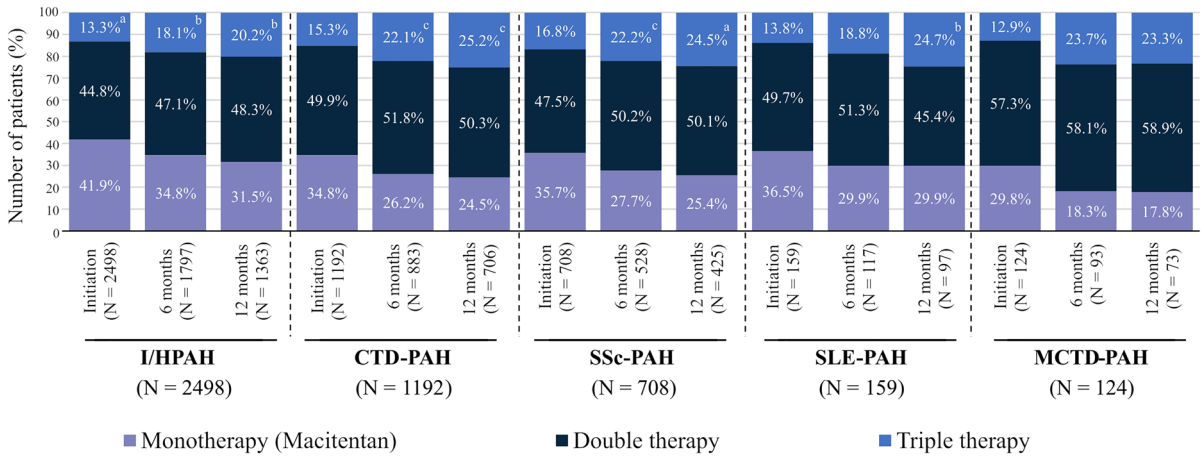


Fig. 1 Treatment regimen at macitentan initiation, 6 months and 12 months after macitentan initiation. Percentages may not add to 100% due to rounding. Double therapy includes macitentan in combination with one other class of PAH therapy; triple therapy includes macitentan in combination with two other classes of PAH therapy. Classes of PAH therapy include PDE5i, prostanoids (oral, inhaled, or intravenous/subcutaneous), sGCs, and investigational drug (≥ 3 PAH therapies only; OrPHeUS only). [a]Includes two patients receiving > 3 classes of PAH therapy; [b]Includes one patient receiving > 3 classes of PAH therapy; [c]Includes three patients receiving > 3 classes of PAH therapy. *CTD-PAH* PAH associated with connective tissue disease, *I/HPAH* idiopathic/heritable PAH, *MCTD-PAH* PAH associated with mixed connective tissue disease, *PAH* pulmonary arterial hypertension, *PDE5i* phosphodiesterase-5 inhibitor, *sGCs* soluble guanylate cyclase stimulator, *SLE-PAH* PAH associated with systemic lupus erythematosus, *SSc-PAH* PAH associated with systemic sclerosis

combining macitentan with a phosphodiesterase 5 inhibitor (PDE5i; Table 2). This trend was similar at 6- and 12-month follow-up. Across the CTD-PAH subgroups, patients with MCTD-PAH had the highest rate of combination therapy at all three timepoints, while patients with SLE-PAH had the lowest (Fig. 1). At 1 and 2 years, patients with CTD-PAH were more likely to escalate from monotherapy to combination therapy, and from double to triple therapy, compared to patients with I/HPAH, with the MCTD-PAH patient group being the most likely to escalate at 2 years, compared to all other groups (Table 2; Fig. 2). Across all CTD-PAH groups, patients were more likely to escalate from monotherapy to double combination therapy, compared to double to triple therapy, with the exception of the SLE-PAH group at 1 year. Patterns of treatment changes over time are also shown in more detail in Figs. S1 and S2.

Safety and Tolerability

The safety and tolerability profile of macitentan was similar between patients with I/HPAH and CTD-PAH. During follow-up, the median duration of macitentan exposure observed was 14.0 and 15.8 months for the I/HPAH and CTD-PAH groups, respectively. A comparable proportion of patients with I/HPAH and CTD-PAH discontinued macitentan due to an AE (17.4 and 16.3%, respectively), with the lowest discontinuations observed in the SLE-PAH and MCTD-PAH groups (12.6 and 12.9%, respectively). AEs were recorded only in OPUS; 79.0 and 83.0% of patients with I/HPAH and

CTD-PAH, respectively, experienced an AE. The most common AEs are described in Table 3. The proportion of patients experiencing an AESI of edema was similar between those with I/HPAH (27.7%) and with CTD-PAH (30.3%); this was slightly higher for patients with SSc-PAH (34.2%) and lower for those with SLE-PAH (23.1%). The proportion of patients experiencing an AESI of anemia/hemoglobin decrease was also similar for patients with I/HPAH and CTD-PAH (9.8 and 13.0%, respectively), with the highest levels for patients with SSc-PAH (15.6%) and lowest for patients with MCTD-PAH (5.0%). In the combined OPUS/OrPHeUS dataset, 7.8 and 7.7% of patients with I/HPAH and CTD-PAH, respectively, experienced an HAE. Similar to the I/HPAH group, the proportion and incidence rates of HAEs, HAESIs, and liver abnormalities were low in the CTD-PAH group (Table 4).

Hospitalization and Survival

At 1 year, KM estimates showed that 60.3% (95% CL 58.1, 62.4) of patients with I/HPAH, and 59.3% (95% CL 56.1, 62.3) of patients with CTD-PAH were free from all-cause hospitalization. Similar KM estimates were observed for the SSc-PAH and SLE-PAH groups, with more hospitalizations in the MCTD-PAH group at 1 year. At 30 months, patients with SLE-PAH had the highest free from all-cause hospitalization KM estimate (95% CL), at 49.5% (39.4, 58.8), and patients with MCTD-PAH had the lowest, at 35.9% (24.8, 47.2) (Fig. 3; Table 5).

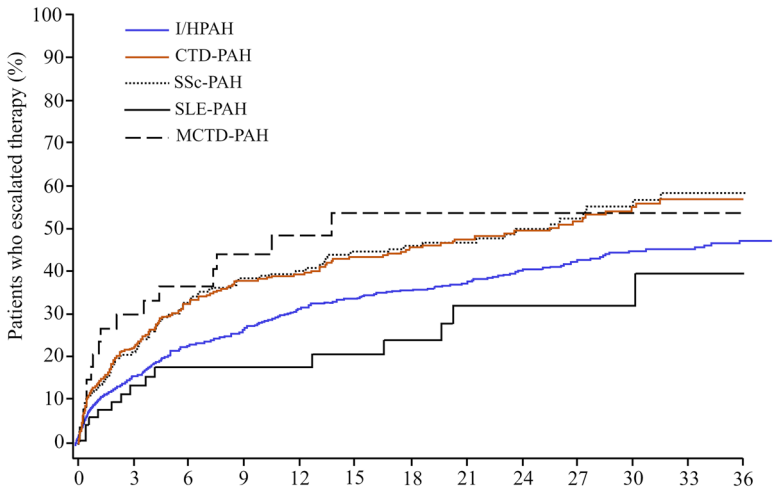
The KM estimates (95% CL) of survival at 1 year for patients with I/HPAH and CTD-PAH were 90.5% (89.1, 91.7) and 90.6% (88.6, 92.3), respectively. Similar estimates were observed for patients with SSc-PAH (89.8% [86.9, 92.0]), SLE-PAH (92.5% [86.4, 95.9]), and MCTD-PAH (93.8% [86.7, 97.2]). At 3 years, the KM survival estimates (95% CL) for patients with I/HPAH and CTD-PAH were 75.7% (73.1, 78.2) and 74.3% (70.5, 77.7), respectively, with the highest survival in patients with SLE-PAH (84.7% [74.7, 91.0]) (Fig. 4; Table 5).

DISCUSSION

The combined OPUS/OrPHeUS dataset is the largest new-users database for macitentan in the US, and includes a large proportion of patients with CTD-PAH. Data collection spanned the years 2013–2020, providing contemporary, real-world data on the management and outcomes of patients with CTD-PAH, albeit limited to those receiving macitentan. Here, we show that macitentan is used in newly diagnosed and prevalent patients with CTD-PAH, including in those with SSc-PAH, SLE-PAH, and MCTD-PAH, as part of a combination therapy regimen in the majority of patients, and tolerability and safety are comparable to the I/HPAH patient population and consistent with previous safety reports [10, 20].

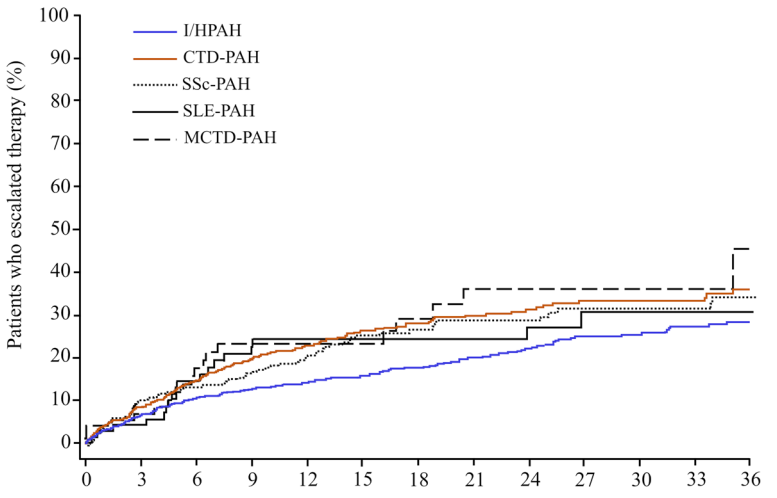
In OPUS/OrPHeUS, patients with CTD-PAH comprised approximately a quarter of the PAH follow-up cohort. This is similar to previous reports where patients with CTD-PAH represented 24–34% of patients with PAH [5, 7]. In our analyses, the median ages for the overall CTD-PAH group and I/HPAH group were similar (62 vs. 64 years), while the median ages differed between the CTD subgroups: patients with SLE-PAH and MCTD-PAH were younger compared to patients with SSc-PAH (49, 57, and 64 years, respectively). This similarity in age between the overall CTD-PAH and I/HPAH groups in OPUS/OrPHeUS contrasts with earlier registries where patients with CTD-PAH were older than patients with IPAH (mean age 57 for patients with CTD-PAH versus 50 years for IPAH)[7], and older than other patients with PAH (mean age 56 for patients with CTD-PAH versus 51 years for PAH) [12]. This may reflect the changing demographics of patients with PAH, however, as OPUS and OrPHeUS were macitentan drug registries, there

A)



Patients at risk:													
I/HPAH	1044	719	587	483	396	323	280	241	200	164	140	114	87
CTD-PAH	412	279	216	186	159	132	119	94	75	61	51	40	34
SSc-PAH	253	175	136	117	99	81	73	59	43	35	30	23	19
SLE-PAH	58	43	32	29	27	24	21	17	17	13	9	6	6
MCTD-PAH	35	21	17	14	12	9	9	9	7	6	6	5	3

B)



Patients at risk:													
I/HPAH	1118	841	696	597	510	437	376	324	269	232	198	162	127
CTD-PAH	595	464	375	321	275	234	201	166	138	119	105	85	65
SSc-PAH	336	258	211	184	160	132	109	91	79	70	62	54	43
SLE-PAH	79	66	55	47	40	38	35	32	25	19	16	13	10
MCTD-PAH	71	59	44	35	31	28	23	17	14	14	13	11	5

◂**Fig. 2** Kaplan–Meier estimates of percentage escalating from **A** monotherapy to combination therapy and **B** double to triple therapy. *CTD-PAH* PAH associated with connective tissue disease, *I/HPAH* idiopathic/heritable PAH, *MCTD-PAH* PAH associated with mixed connective tissue disease, *PAH* pulmonary arterial hypertension, *SLE-PAH* PAH associated with systemic lupus erythematosus, *SSc-PAH* PAH associated with systemic sclerosis

was the potential for bias in patient selection and therefore the study population may not be directly comparable with disease registries. In OPUS/OrPHeUS, patients with CTD-PAH were less likely to be obese and diabetic than patients with I/HPAH and the proportion of Black or African-American patients in the SLE-PAH group and the proportion of White patients in the SSc-PAH group were consistent with previous reports [21]. Additionally, the demographics and characteristics of patients with SSc-PAH and SLE-PAH were similar to previous reports from disease registries [22, 23], despite OPUS/OrPHeUS being a drug registry.

The current 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) PH treatment guidelines, as well as those effective at the time of study conduct, recommend that patients with CTD-PAH be treated according to the same algorithm as patients with IPAH [24–29]. Compared to patients with I/HPAH, a higher proportion of patients with CTD-PAH initiated macitentan as part of combination therapy and were more likely to escalate therapy up to 2 years after macitentan initiation. Overall, the MCTD-PAH group had the highest proportion of patients who escalated treatment up to 2 years after macitentan initiation. The MCTD-PAH group had the worst clinical presentation at macitentan initiation among the other subgroups; with a high proportion of patients with a low baseline 6MWD (a quarter of patients with a 6MWD < 152 m), and the highest proportion of patients in WHO FC III/IV at macitentan initiation (82.4%). Additionally, the MCTD-PAH group had a high proportion of patients with hospitalizations (50.8%). These factors could have contributed to the urgency to escalate therapy in these patients.

Exposure to macitentan was similar in patients with I/HPAH and CTD-PAH, with comparable proportions of patients discontinuing treatment due to an AE/HAE. AE profiles in OPUS were similar across the groups, and comparable to observations in previous RCTs assessing PAH therapies [1, 9], including ERAs. The incidence of HAEs, HAESIs, and liver abnormalities were low, and in line with the known safety profile of macitentan [10, 20]. Overall, these data show that the administration of macitentan, including as part of a combination therapy regimen, is well tolerated in newly diagnosed and prevalent patients with CTD-PAH and subgroups with varying characteristics.

We found the overall rates of first hospitalization and survival were similar between patients with I/HPAH and CTD-PAH in OPUS/OrPHeUS, in contrast to the REVEAL registry that enrolled patients from 2006 to 2009, and the recent COMPERA PAH-disease registry [8, 30]. Several recent studies have shown that survival has improved in patients with CTD-PAH in the last 10 years, which may be related to improved screening of patients with CTD for PAH, leading to earlier detection and initiation of initial combination treatment [12, 22, 30–32]. In REVEAL, only 39.5% of patients with CTD-PAH were on combination therapy at enrollment [7], whereas 65.2% were on combination therapy in OPUS/OrPHeUS. The differences in outcomes might also be due to the type of registry (disease versus drug), where patients may enroll in a disease registry at different times along their PAH journey; the time from diagnosis to enrollment for patients with CTD-PAH in REVEAL was mean (standard deviation) 27 (30) months [7], whereas in OPUS/OrPHeUS median (Q1, Q3) time from diagnosis to enrollment for patients with CTD-PAH was 6 (1, 35) months. The outcomes of patients with CTD-PAH in our study indicate progress has been made for early diagnosis and improved treatment options, however, outcomes could be further enhanced with increased use of

Table 3 Discontinuations and adverse events

	I/HPAH, *N* = 2498	**CTD-PAH, *N* = 1192**	**SSc-PAH, *N* = 708**	**SLE-PAH, *N* = 159**	**MCTD-PAH, *N* = 124**
Observed exposure, median (Q1, Q3) months	14.0 (5.1, 29.2)	15.8 (5.6, 29.0)	15.5 (5.9, 30.5)	18.7 (5.6, 30.2)	14.5 (6.2, 27.8)
Patients who discontinued, *n* (%)	1071 (42.9)	485 (40.7)	303 (42.8)	57 (35.8)	39 (31.5)
Due to a non-hepatic AE	434 (17.4)	194 (16.3)	134 (18.9)	20 (12.6)	16 (12.9)
Due to an HAE	5 (0.2)	7 (0.6)	5 (0.7)	1 (0.6)	1 (0.8)
Not due to an AE/HAE	465 (18.6)	182 (15.3)	95 (13.4)	30 (18.9)	12 (9.7)
Missing reason	167 (6.7)	102 (8.6)	69 (9.7)	6 (3.8)	10 (8.1)
AEs (OPUS only), *n*	1240	554	339	78	40
Patients with ≥ 1 AE, *n* (%)	979 (79.0)	460 (83.0)	292 (86.1)	62 (79.5)	30 (75.0)
Most common AEs (≥ 10% in any group), *n* (%)					
Dyspnea	273 (22.0)	140 (25.3)	99 (29.2)	17 (21.8)	8 (20.0)
Headache	143 (11.5)	70 (12.6)	41 (12.1)	13 (16.7)	5 (12.5)
Peripheral edema	129 (10.4)	65 (11.7)	43 (12.7)	5 (6.4)	6 (15.0)
Dizziness	90 (7.3)	59 (10.6)	38 (11.2)	7 (9.0)	5 (12.5)
Pneumonia	104 (8.4)	59 (10.6)	37 (10.9)	7 (9.0)	5 (12.5)
Fatigue	103 (8.3)	57 (10.3)	43 (12.7)	5 (6.4)	1 (2.5)
Anemia	90 (7.3)	55 (9.9)	38 (11.2)	8 (10.3)	2 (5.0)
Nausea	121 (9.8)	51 (9.2)	29 (8.6)	6 (7.7)	4 (10.0)
Edema	94 (7.6)	50 (9.0)	36 (10.6)	7 (9.0)	5 (12.5)
Hypoxia	68 (5.5)	50 (9.0)	31 (9.1)	5 (6.4)	4 (10.0)
Cough	84 (6.8)	50 (9.0)	29 (8.6)	7 (9.0)	5 (12.5)
Aggravated condition	87 (7.0)	47 (8.5)	34 (10.0)	8 (10.3)	1 (2.5)
Chest pain	83 (6.7)	39 (7.0)	28 (8.3)	3 (3.8)	5 (12.5)
Exertional dyspnea	48 (3.9)	31 (5.6)	17 (5.0)	6 (7.7)	5 (12.5)
Vomiting	57 (4.6)	29 (5.2)	14 (4.1)	6 (7.7)	4 (10.0)
Pyrexia	41 (3.3)	28 (5.1)	14 (4.1)	4 (5.1)	4 (10.0)

Table 3 continued

	I/HPAH, *N* = 2498	CTD-PAH, *N* = 1192	SSc-PAH, *N* = 708	SLE-PAH, *N* = 159	MCTD-PAH, *N* = 124
Productive cough	32 (2.6)	27 (4.9)	17 (5.0)	3 (3.8)	5 (12.5)
Peripheral swelling	60 (4.8)	25 (4.5)	15 (4.4)	2 (2.6)	5 (12.5)
AESIs (OPUS only), *n*	1240	554	339	78	40
Patients with ≥ 1 AESI of edema[a], *n* (%)	344 (27.7)	168 (30.3)	116 (34.2)	18 (23.1)	13 (32.5)
Patients with ≥ 1 AESI of anemia/hemoglobin decrease[b], *n* (%)	122 (9.8)	72 (13.0)	53 (15.6)	10 (12.8)	2 (5.0)

AEs are not mutually exclusive, and patients could have multiple AEs

AE adverse event, *AESI* AE of special interest, *CTD-PAH* PAH associated with connective tissue disease, *HAE* hepatic AE, *I/HPAH* idiopathic/heritable PAH, *MCTD-PAH* PAH associated with mixed connective tissue disease, *PAH* pulmonary arterial hypertension, *PT* preferred term, *Q1, Q3* interquartile range, *SLE-PAH* PAH associated with systemic lupus erythematosus, *SMQ* Standardized MedDRA Queries, *SSc-PAH* PAH associated with systemic sclerosis

[a]AESI "Edema" are included in this grouping if their coded PTs are included in the SMQs: "Hemodynamic edema, effusions and fluid overload" or are included in the following list of PTs: eye edema, eyelid edema, face edema, orbital edema, periorbital edema, swelling face

[b]AESI "Anemia/hemoglobin decrease": AEs are included in this grouping if their coded PTs are included in at least one of the following SMQs: hematopoietic erythropenia, hematopoietic cytopenias affecting more than one type of blood cell; or are included in the following list of PTs: anemia hemolytic autoimmune, anemia megaloblastic, hemolytic anemia, iron deficiency anemia

initial combination therapy, as per the 2015 and recent 2022 ESC/ERS guidelines [26–29].

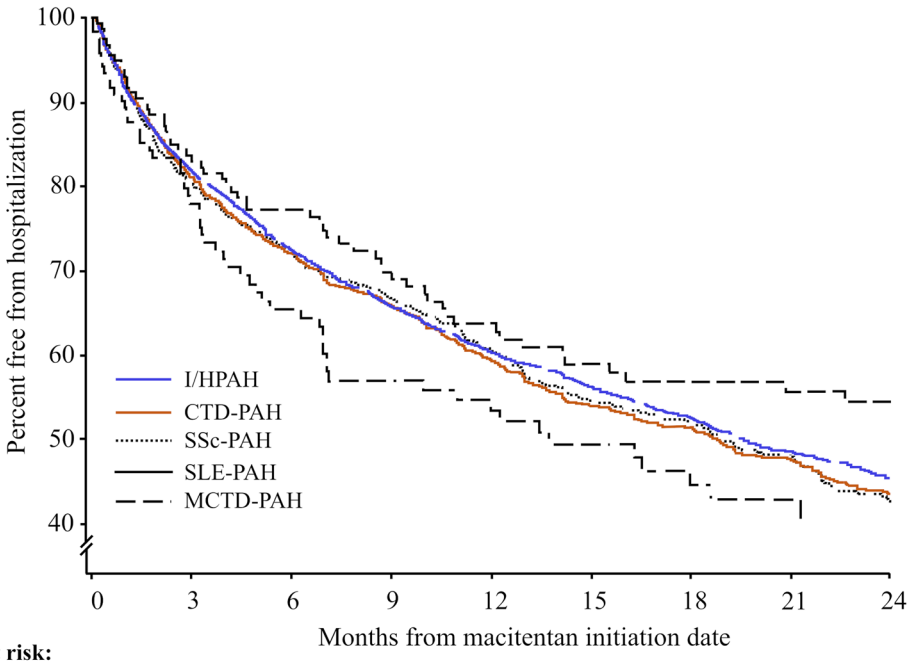
The OPUS and OrPHeUS studies provide valuable insights into the real-world management of patients with PAH newly treated with macitentan, including in patients with CTD-PAH, although their observational nature is associated with limitations. Firstly, as OPUS and OrPHeUS were drug registries, there is the possibility of bias with respect to the type of patients enrolled, and results may not be directly comparable with disease registries. In both studies, follow-up data were collected according to routine clinical practice without protocol-mandated rules or assessments. As such, data on patient baseline and disease characteristics are incomplete, particularly for WHO FC and 6MWD, which may indicate that for a large proportion of patients accurate risk assessment was not performed as recommended in the 2015 ESC/ERS guidelines, relevant at the time of the study [17, 26, 27]. Many parameters

Table 4 Hepatic safety

	I/HPAH, *N* = 2498	CTD-PAH, *N* = 1192	SSc-PAH, *N* = 708	SLE-PAH, *N* = 159	MCTD-PAH, *N* = 124
HAE					
Patients with ≥ 1 HAE, *n* (%)	196 (7.8)	92 (7.7)	59 (8.3)	12 (7.5)	9 (7.3)
Incidence rate, per person-year (95% CL)[a]	0.05 (0.05, 0.06)	0.05 (0.04, 0.06)	0.05 (0.04, 0.07)	0.05 (0.03, 0.08)	0.05 (0.03, 0.10)
HAESI					
Patients with ≥ 1 HAESI, *n* (%)	108 (4.3)	47 (3.9)	27 (3.8)	8 (5.0)	6 (4.8)
Incidence rate, per person-year (95% CL)[a]	0.03 (0.02, 0.04)	0.03 (0.02, 0.03)	0.02 (0.02, 0.03)	0.03 (0.02, 0.06)	0.03 (0.02, 0.08)
Liver enzyme elevations					
Patients with ALT/AST ≥ 3 × ULN, *n* (%)	64 (2.6)	35 (2.9)	24 (3.4)	3 (1.9)	4 (3.2)
Incidence rate, per person-year (95% CL)[a]	0.02 (0.01, 0.02)	0.02 (0.01, 0.03)	0.02 (0.01, 0.03)	0.01 (0.004, 0.03)	0.02 (0.01, 0.06)
Patients with ALT/AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN, *n* (%)	8 (0.3)	3 (0.3)	2 (0.3)	0	1 (0.8)
Incidence rate, per person-year (95% CL)[a]	0.002 (0.001, 0.004)	0.002 (0.001, 0.005)	0.002 (0.0004, 0.007)	0 (0, NE)	0.01 (0.001, 0.040)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CL* confidence limits, *CTD-PAH* PAH associated with connective tissue disease, *HAE* hepatic adverse event, *HAESI* HAE of special interest, *I/HPAH* idiopathic/heritable PAH, *MCTD-PAH* PAH associated with mixed connective tissue disease, *PAH* pulmonary arterial hypertension, *SLE-PAH* PAH associated with systemic lupus erythematosus, *SSc-PAH* PAH associated with systemic sclerosis, *ULN* upper limit of normal

[a]Incidence rates are estimates using Poisson model with log (exposure time) as an offset



Patients at risk:

I/HPAH	2496	1774	1402	1134	939	783	653	556	451
CTD-PAH	1190	855	689	588	472	386	330	276	227
SLE-PAH	159	119	100	83	68	58	52	47	40
SSc-PAH	708	510	414	360	290	233	201	170	138
MCTD-PAH	122	84	63	51	42	34	26	21	18

Fig. 3 Kaplan–Meier estimates of time from macitentan initiation to first all-cause hospitalization. The *y*-axis has been truncated at 40%. *CTD-PAH* PAH associated with connective tissue disease, *I/HPAH* idiopathic/heritable PAH, *MCTD-PAH* PAH associated with mixed connective tissue disease, *PAH* pulmonary arterial hypertension, *SLE-PAH* PAH associated with systemic lupus erythematosus, *SSc-PAH* PAH associated with systemic sclerosis

reported here (e.g., CTD-PAH diagnosis and deaths) were investigator-assessed and were not adjudicated. The sample sizes of the CTD-PAH subgroups are small (with corresponding wide 95% confidence limits), and the results from the time-to-event analysis should be interpreted with caution due to the small number of events. It should also be noted that the comparisons between the populations are descriptive. Finally, there are differences in the data between both studies [17], with decreased robustness in the data from OrPHeUS due to the retrospective nature of a medical chart review.

CONCLUSIONS

The OPUS/OrPHeUS dataset shows that macitentan was used in a heterogenous CTD-PAH population that included patients with SSc-PAH, SLE-PAH, and MCTD-PAH. The majority of patients received macitentan as part of combination

Table 5 Kaplan–Meier estimates of time to first hospitalization and survival

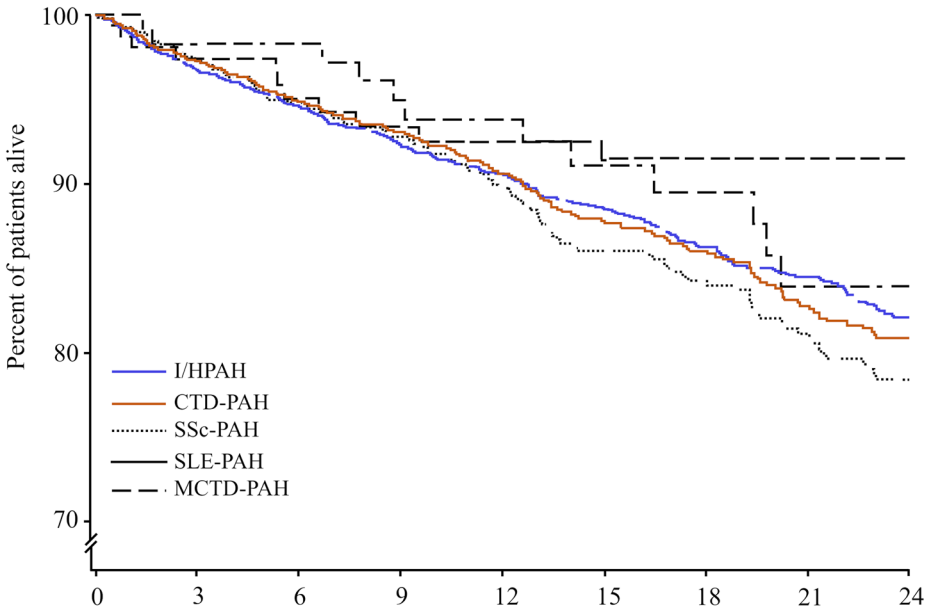
	I/HPAH, *N* = 2498	CTD-PAH, *N* = 1192	SSc-PAH, *N* = 708	SLE-PAH, *N* = 159	MCTD-PAH, *N* = 124
Patients with ≥ 1 hospitalization, *n* (%)	1114 (44.6)	579 (48.6)	350 (49.4)	66 (41.5)	63 (50.8)
Incidence rate, per person-year (95% CL)	0.42 (0.39, 0.46)	0.45 (0.40, 0.50)	0.44 (0.38, 0.51)	0.34 (0.25, 0.47)	0.56 (0.39, 0.80)
Kaplan–Meier estimates of freedom from hospitalization[a], % (95% CL)					
Free from hospitalization at 1 year	60.3 (58.1, 62.4)	59.3 (56.1, 62.3)	60.2 (56.2, 64.1)	63.7 (54.9, 71.3)	53.4 (43.2, 62.5)
Free from hospitalization at 2 years	45.3 (42.8, 47.8)	43.4 (39.9, 46.8)	42.6 (38.1, 47.1)	54.4 (44.9, 62.9)	38.5 (27.5, 49.3)
Free from hospitalization at 30 months[b]	40.5 (37.9, 43.1)	38.8 (35.2, 42.4)	37.2 (32.6, 41.8)	49.5 (39.4, 58.8)	35.9 (24.8, 47.2)
Number of deaths, *n* (%)	365 (14.6)	191 (16.0)	128 (18.1)	15 (9.4)	15 (12.1)
Incidence rate, per person-year (95% CL)	0.10 (0.09, 0.11)	0.10 (0.09, 0.12)	0.11 (0.09, 0.13)	0.05 (0.03, 0.09)	0.08 (0.05, 0.14)

CL confidence limits, *CTD-PAH* PAH associated with connective tissue disease, *I/HPAH* idiopathic/heritable PAH, *MCTD-PAH* PAH associated with mixed connective tissue disease, *PAH* pulmonary arterial hypertension, *SLE-PAH* PAH associated with systemic lupus erythematosus, *SSc-PAH* PAH associated with systemic sclerosis

[a]Two patients with I/HPAH, two patients with CTD-PAH, and two patients with MCTD-PAH who only received macitentan for 1 day were not included in these analyses

[b]Kaplan–Meier curves were truncated at the time point when < 10% of patients in any of the cohorts were at risk, in accordance with Pocock's stopping rule [19]

therapy, and escalation from monotherapy to combination therapy was more likely in patients with CTD-PAH compared to I/HPAH. Outcomes were similar, and a considerable proportion of patients received monotherapy, contrary to the 2015 and 2022 ESC/ERS guidelines. Safety and tolerability of macitentan in patients with CTD-PAH were comparable to I/HPAH, including when administered as part of combination therapy.



Patients at risk:

I/HPAH	2498	2069	1805	1576	1376	1200	1051	936	806
CTD-PAH	1192	1020	890	807	709	611	540	455	389
SLE-PAH	159	140	120	108	98	90	82	74	64
SSc-PAH	708	606	532	484	426	361	319	272	236
MCTD-PAH	124	106	93	83	73	60	51	44	37

Fig. 4 Kaplan–Meier estimate of survival from macitentan initiation. The *y*-axis has been truncated at 70%. *CTD-PAH* PAH associated with connective tissue disease, *I/HPAH* idiopathic/heritable PAH, *MCTD-PAH* PAH associated with mixed connective tissue disease, *PAH* pulmonary arterial hypertension, *SLE-PAH* PAH associated with systemic lupus erythematosus, *SSc-PAH* PAH associated with systemic sclerosis

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Richard Channick served as a scientific committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; served on an advisory board for Janssen Pharmaceutical Companies of Johnson & Johnson and Bayer; received research grants / support from Janssen Pharmaceutical Companies of Johnson & Johnson and United therapeutics; received speaker fees from Janssen Pharmaceutical Companies of Johnson & Johnson, and Bayer; received consultancy fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Bayer and Third pole. Kelly M Chin has served as a scientific committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received research grants / support from Janssen Pharmaceutical Companies of Johnson & Johnson, Altavant, Acceleron, United Therapeutics, Pfizer, Merck, Gossamer Bio; has received support for travel to meetings from Janssen Pharmaceutical Companies of Johnson & Johnson; and has received consultancy fees from Janssen Pharmaceutical Companies of Johnson & Johnson, Altavant, Acceleron, United Therapeutics, Gossamer Bio and Merck. Vallerie V McLaughlin served as a scientific committee member from Janssen Pharmaceutical Companies of Johnson & Johnson; received research grants from Aerovate, Altavant, Gossamer Bio, Janssen Pharmaceutical Companies of Johnson & Johnson, Merck, and SoniVie; and received consultant fees from Aerami, Aerovate, Altavant, Bayer, Caremark, Corvista, Gossamer Bio, Janssen Pharmaceutical Companies of Johnson & Johnson, L.L.C, Merck and United Therapeutics. Matthew R Lammi has received research grants / support from Janssen Pharmaceutical Companies of Johnson & Johnson, Gilead, Bayer, United Therapeutics, Altavant and Acceleron. Roham T Zamanian is a patent holder (FK-506 in PAH); has served as a scientific medical advisor for Morphogenic-IX; has received consulting fees from Vivus, Pfizer, and Selten; and has received grants / support from Janssen Pharmaceutical Companies of Johnson & Johnson and United Therapeutics. Stefano Turricchia and Lada Mitchell are employees of Janssen Pharmaceutical Companies of Johnson & Johnson. Rose Ong is an employee of Janssen Pharmaceutical Companies of Johnson & Johnson; has received support for travel to meetings from Janssen Pharmaceutical Companies of Johnson & Johnson; holds stock or stock options with Janssen Pharmaceutical Companies of Johnson & Johnson; and spouse is an employee of Roche. Nick H Kim has served a scientific committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; has received research grants / support from Janssen Pharmaceutical Companies of Johnson & Johnson, Bellerophon, Eiger, Gossamer Bio, Lung Biotechnology, SoniVie, and Altavant; has received consultant fees from Bayer, Merck, United Therapeutics, Pulnovo, and Polarean; and speaker fees from Janssen Pharmaceutical Companies of Johnson & Johnson and Bayer.

Ethical Approval. OPUS and OrPHeUS were executed in accordance with Good Pharmacoepidemiology Practices [18] and the 2008 Declaration of Helsinki ethical principles. Ethical approval was received from independent ethics committees/institutional review boards of participating centers (Supplementary Material I). The protocols were reviewed by the US FDA with written informed consent obtained from all patients in OPUS (informed consent was not required in OrPHeUS as an Institutional Review Board (IRB) waiver was obtained). OPUS' Informed Consent Form included a confidentiality clause that all records and documents pertaining to the participation of patients in the OPUS registry would be held strictly confidential and their names would not be reported in any publications resulting from the OPUS registry.

IRB approvals were provided by the Western IRB and Quorum (now Advarra) (OPUS registry; Western IRB approval number 2014-0816, Quorum Review File number 29120/Advarra Pro00035124) and WCG-IRB (OrPHeUS study; IRB numbers 2017-8051 and 2017-2348).

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