Adv Ther (2023) 40:5037–5054
https://doi.org/10.1007/s12325-023-02658-z

ORIGINAL RESEARCH

# Real-World Treatment Patterns Among Patients with Connective Tissue Disorder-Related Pulmonary Arterial Hypertension in the United States: A Retrospective Claims-Based Analysis

Therese Sargent · Yuen Tsang · Sumeet Panjabi · Vienica Funtanilla · Hayley D. Germack · Marjolaine Gauthier-Loiselle · Ameur M. Manceur · Martin Cloutier · Patrick Lefebvre

Received: June 19, 2023 / Accepted: August 18, 2023 / Published online: September 20, 2023


## ABSTRACT

***Introduction***: Connective tissue disorders (CTDs) are the most frequent diseases associated with pulmonary arterial hypertension (PAH). Despite advances in treatment, the prognosis of CTD-related PAH remains poor. To help identify areas for improvement in the management of CTD-related PAH, this study assessed real-world PAH treatment patterns in this population in the US.

***Methods***: Eligible adult patients with PAH initiated on a PAH treatment (index date: 1st initiation date) were identified from Optum's de-identified Clinformatics® Data Mart Database (10/01/2015–09/30/2021) and categorized into mutually exclusive cohorts (CTD + PAH; PAH) based on the presence of CTD diagnosis claims. Treatment patterns were assessed from the index date to the earliest of death or end of continuous insurance eligibility, or data availability. Treatment persistence was assessed using Kaplan-Meier analysis.

This manuscript is based on work that has been previously presented at the American College of Rheumatology Convergence 2022 conference, which was held in Philadelphia, PA, USA, from November 10–14, 2022.

T. Sargent
HonorHealth, 8125 N Hayden Road, Scottsdale, AZ 85258, USA
e-mail: tsarge@honorhealth.com

Y. Tsang · S. Panjabi · V. Funtanilla · H. D. Germack
Janssen Scientific Affairs, LLC, 1125 Trenton-Harbourton Road, Titusville, NJ 08560, USA

Y. Tsang
e-mail: ytsang@its.jnj.com

S. Panjabi
e-mail: spanjabi@its.jnj.com

V. Funtanilla
e-mail: vfuntani@its.jnj.com

H. D. Germack
e-mail: hgermack@its.jnj.com

A. M. Manceur · M. Cloutier · P. Lefebvre
Analysis Group, Inc., 1190 Avenue des Canadiens-de-Montréal, Montreal, QC H3B 0G7, Canada

A. M. Manceur
e-mail: ameur.manceur@analysisgroup.com

M. Cloutier
e-mail: martin.cloutier@analysisgroup.com

P. Lefebvre
e-mail: patrick.lefebvre@analysisgroup.com

M. Gauthier-Loiselle (✉)
Analysis Group, Inc., 1190 Avenue des Canadiens-de-Montréal, Tour Deloitte, Suite 1500, Montreal, QC H3B 0M7, Canada
e-mail: Marjolaine.Gauthier-Loiselle@analysisgroup.com

***Results***: A total of 4751 patients were included (CTD + PAH: $n = 728$, mean follow-up of 18.8 months; PAH: $n = 4023$, mean follow-up of 19.6 months). For both cohorts, the most common first treatment regimens were sildenafil (CTD + PAH: 38.7%; PAH: 51.5%), tadalafil (10.0%; 9.4%), and macitentan (8.1%; 5.4%) monotherapy; these were also the most frequent agents included in any of the first 3 treatment regimens. Combination therapy was more frequent in the CTD + PAH versus PAH cohort (any regimen: 40.9% vs. 27.2%; 1st treatment regimen: 26.9% vs. 18.5%; 2nd: 52.8% vs. 42.0%; 3rd: 55.2% vs. 48.5%). Treatment persistence was similar across cohorts and the first three treatment regimens, with persistence rates ranging from 42.6 to 49.7% at 12 months.

***Conclusions***: Treatment patterns were generally similar between the CTD + PAH and PAH cohorts, although combination therapy was more frequent in the CTD + PAH cohort. Both cohorts may benefit from broader use of all available PAH treatment classes, including combination therapy. Considering the life-threatening nature of PAH, our findings also highlight the need to address the low persistence rates with PAH therapies regardless of etiology.

**Keyword:** Combination therapy; Connective tissue disorders; Endothelin receptor antagonists; Phosphodiesterase type 5 inhibitors; Prostacyclin pathway agents; Pulmonary arterial hypertension; Retrospective study; Systemic sclerosis; Treatment patterns; Treatment persistence

**Key Summary Points**

***Why carry out this study?***

Although connective tissue disorders (CTDs) are commonly associated with pulmonary arterial hypertension (PAH) and tend to be associated with poorer outcomes among patients with PAH, there is limited real-world evidence on treatment patterns among patients with CTD-related PAH.

A better understanding of real-world treatment patterns among patients with CTD-related PAH is needed to identify potential gaps and areas for improvement in the management of CTD-related PAH.

Therefore, the present study aimed to describe treatment patterns among patients with CTD-related PAH and PAH from other etiologies in a real-world setting in the US stratified by treatment class and strategy.

***What was learned from the study?***

Treatment patterns were generally similar among patients with CTD-related PAH and PAH from other etiologies, although the use of combination therapy, including triple therapy, was more frequent among those with CTD-related PAH; treatment persistence was similar across cohorts and remained low for the first three treatment regimens, with fewer than one in two patients persistent at 12 months.

Our findings suggest that both patients with CTD-related PAH and PAH from other etiologies may potentially benefit from broader access to all available PAH treatment classes as early as possible, including combination therapy to target the nitric oxide, endothelin, and prostacyclin pathways.

Furthermore, a better understanding of the factors driving low persistence rates with PAH therapies could enable clinicians to devise more effective strategies aimed at improving this outcome among patients, thereby maximizing the benefits of treatment.

## INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, severe, and progressive subtype of pulmonary hypertension (World Health Organization Group 1) [1–3], which may lead to reduced cardiac output, right heart failure, and

ultimately death [1, 2]. In the US, the prevalence of PAH is estimated at 12.4 cases per million adult inhabitants [1, 2]. In terms of etiology, PAH may be idiopathic (46.2%; i.e., with no identifiable cause) or associated with an identifiable factor (50.7%) [4]. Among patients whose PAH is associated with an identifiable factor, these factors may include a primary condition (84.0%; e.g., congenital heart disease, portal hypertension, HIV), drug/toxin exposure (10.5%), or other factors (5.5%; e.g., genetic factors) [4, 5].

Connective tissue disorders (CTDs) are the most frequent conditions associated with PAH, accounting for 11–28% of all PAH cases [6]. Among patients with CTD-related PAH (CTD + PAH), the most common cause, which accounts for approximately three in four cases in the US, is systemic sclerosis (SSc), an autoimmune disease that causes scar tissue to form in the skin, internal organs, and small blood vessels [5, 7]. In addition, PAH may arise as a complication of other CTDs such as systemic lupus erythematosus, dermatomyositis/polymyositis, rheumatoid arthritis, Sjögren's syndrome (Sicca), and mixed CTD, which displays features commonly seen in three different CTDs (i.e., systemic lupus erythematosus, scleroderma, and polymyositis) [8]. CTD + PAH is typically associated with poor clinical outcomes, including worse overall survival than idiopathic PAH (iPAH) [9–13]. Based on the REVEAL registry data, patients with CTD + PAH were found to have a twice greater risk of 1-year fatality relative to those with iPAH (14% vs. 7%, $p < 0.001$), while those with SSc showed the poorest survival outcomes compared to patients with other CTDs [9]. Compared to iPAH, other studies have shown that patients with SSc-PAH had a more than twice greater risk of death at 1 year (12% vs. 5%, $p = 0.002$) and more than three times greater risk of death at 3-years (51% vs. 16%, $p = 0.002$), respectively [11]. Moreover, patients with CTD + PAH may be prone to more severe PAH, as evidenced by higher-risk disease markers (including lower 6min walk distance [6MWD] and higher NT-proB-type natriuretic peptide [BNP] level) compared to patients with iPAH [9, 14, 15].

Randomized controlled trials have demonstrated that the use of modern PAH therapies, including combination therapies with phosphodiesterase type 5 inhibitors (PDE5is), endothelin receptor antagonists (ERAs), and prostacyclin pathway agents (PPAs), improves clinical outcomes in PAH and CTD + PAH [16–22]. Based on this evidence, the use of early combination therapy is recommended for the treatment of PAH regardless of etiology per the American Heart Association (AHA) in 2023 [23] and the CHEST guidelines in 2019 [24], as well as the 2022 guidelines of the European Society of Cardiology (ESC) and European Respiratory Society (ERS) [25]. For instance, in their 2023 update, the AHA recommends initial combination therapy with a PDE5i and an ERA for non-vasoreactive patients without evidence of high-risk disease (e.g., chest pain, syncope, World Health Organization functional class IV, etc.) and initial triple therapy with a PDE5i, ERA, and injectable PPA for those with evidence of high-risk disease [23]. In the absence of cardiopulmonary comorbidities, the 2022 ESC/ERS guidelines recommend initial oral double combination therapy with a PDE5i or ERA for treatment-naïve patients who are low or intermediate risk (for patients who present at intermediate-low risk of death while receiving a PDE5i and ERA, switching from a PDE5i to a soluble guanylate cyclase stimulator [sGC; i.e., riociguat] may also be considered) and initial triple therapy including an injectable PPA for those who are at high-risk) [25]. Among patients with cardiopulmonary comorbidities (i.e., diabetes, systemic hypertension, coronary artery disease, and low lung diffusion capacity for carbon monoxide), the 2022 ESC/ERS guidelines recommend initial monotherapy with a PDE5i or ERA, while the addition of another PAH medication among intermediate-to-high risk patients may be considered on an individual basis [25]. When considering different PAH etiologies, the AHA and CHEST guidelines do not provide specific recommendations [23, 24], while the 2022 ESC/ERS guidelines recommend that patients with CTD + PAH follow a similar treatment algorithm to that of PAH overall [25].

However, given their worse prognosis compared to other PAH etiologies [9, 15, 26], prompt access to the appropriate treatment may be especially critical among patients with CTD + PAH [7].

Regarding treatment patterns in PAH, evidence suggests that monotherapy with PDE5i remains the most commonly used strategy [27, 28] despite meta-analyses reporting that combination therapy significantly reduces the risk of progression by approximately 35% [19, 20]. In contrast to PAH, there is currently limited information on treatment patterns among patients with CTD-related PAH [15]. A paucity of studies have investigated treatment patterns among CTD + PAH patients within the context of prospective, observational studies of specific PAH agents (e.g., selexipag, macitentan) [15, 26, 29]. However, further data regarding the use of all available PAH-specific therapies among the general CTD + PAH population is warranted. Such evidence could help identify potential areas for improvement in the management of CTD-related PAH.

Therefore, the present study aimed to describe real-world treatment patterns in terms of PAH agents (i.e., generic molecules used for the treatment of PAH), treatment classes, and strategy (monotherapy and combination therapy) among patients with CTD-related PAH and PAH from other etiologies in the US.

# METHODS

## Data Source

The Optum's de-identified Clinformatics® Data Mart (CDM) Database was used to identify adult patients diagnosed with CTD + PAH and PAH from other etiologies between October 1, 2015, and September 30, 2021. Optum's CDM database is geographically diverse and represents all 50 states (as well as the District of Columbia and Puerto Rico). It includes adjudicated health insurance claims for commercial and Medicare Advantage enrollees within a large national managed care company affiliated with Optum, as previously described [30]. Using the Expert Determination method and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996, the CDM database was statistically de-identified and managed according to Optum's customer data use agreements; therefore, no review by an institutional review board was required per Title 45 of CFR, Part 46.101(b)(4) (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/#46.101). The present study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

## Study Design

A retrospective cohort study design was used to describe and compare treatment patterns in CTD + PAH and PAH overall (Fig. 1). The index date was defined as the date of the first documented prescription fill for a PAH-related treatment. To increase the likelihood of capturing treatment initiation as of the treatment index date, patients were required to be continuously enrolled in their healthcare plan for ≥ 6 months prior to their index date (i.e., baseline period). Treatment patterns were assessed from the index date until the end of the follow-up, which is the earliest of the end of data availability, end of continuous healthcare plan enrollment, or death, whichever came first. No minimal duration of follow-up was required to limit survival bias.

## Study Population

Adult patients diagnosed with PAH (International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM]: I27.0x, I27.20, I27.21, I27.89) and newly initiated on a PAH-related treatment (i.e., sildenafil citrate [excluding dosage corresponding to Viagra], tadalafil [excluding dosage corresponding to Cialis], ambrisentan, bosentan, macitentan, riociguat, treprostinil, selexipag, iloprost, epoprostenol) were eligible for inclusion in the study if they had at least 6 months of continuous eligibility enrollment in their healthcare plan prior to the index date and no medical claims with a recorded diagnosis for chronic thromboembolic pulmonary hypertension

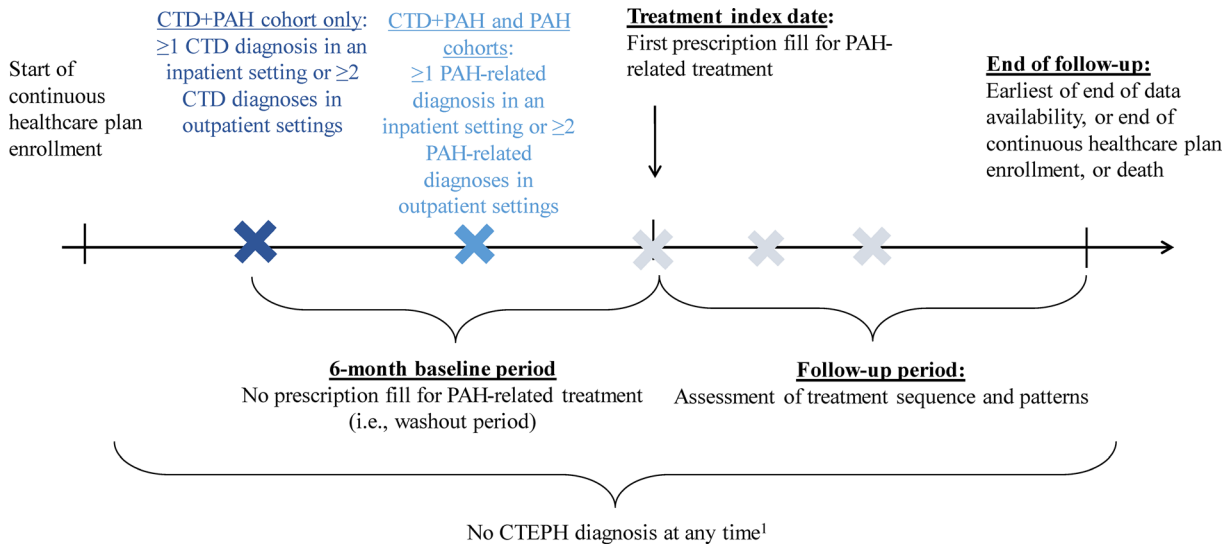



**Fig. 1** Study design. *CTD* connective tissue disorder, *CTEPH* chronic thromboembolic pulmonary hypertension, *PAH* pulmonary arterial hypertension

(ICD-10-CM: I27.24) at any time. Patients were further classified in the mutually exclusive CTD + PAH and PAH cohorts based on the presence of CTD diagnosis (ICD-10-CM: M32, M33, M34, M35.0, M35.1, M35.5, M35.9, M36.8) as described in Fig. 2.

### Measures, Outcomes, and Statistical Analyses

Patients' demographic and clinical characteristics were measured during the 6-month baseline period. Treatment patterns (e.g., sequence of agents received, combination therapy) were assessed separately for each cohort and descriptively summarized. A treatment regimen was defined as all PAH agents (i.e., generic molecules used for the treatment of PAH) observed within 60 days of the first PAH-related agent observed. A treatment change was defined as a treatment discontinuation (i.e., ≥ 90-day gap without any agents from the treatment regimen), drop (i.e., discontinuation of ≥ 1 agent in a regimen while other agents were continued), switch (i.e., initiation of a new agent while other agents in the treatment regimen were discontinued), or augmentation/add-on (i.e., initiation of a new agent while ≥ 1 agent of the treatment regimen was continued). A patient could also remain on the same treatment regimen until the end of the follow-up. PAH-related regimens (i.e., regimens that included ≥ 1 PAH agent) were defined as follows: first treatment regimen was the treatment regimen initiated on the index date, second treatment regimen was defined as the first treatment regimen observed following the first treatment change, and third treatment regimen was defined as the treatment regimen following the second treatment change.

Descriptive statistics were used to assess baseline characteristics and treatment patterns at follow-up among CTD + PAH and PAH cohorts. Kaplan-Meier (KM) analyses of time to combination therapy (time from the index date to initiation of the first treatment regimen with ≥ 2 agents) and treatment persistence (time from treatment initiation to treatment change or the end of the patient follow-up if there was no treatment change [censor date] for the first 3 treatment regimens) were performed. Patients who did not experience the event were censored as of the end of their follow-up.

## RESULTS

After applying the eligibility criteria, the CTD + PAH cohort comprised 728 eligible

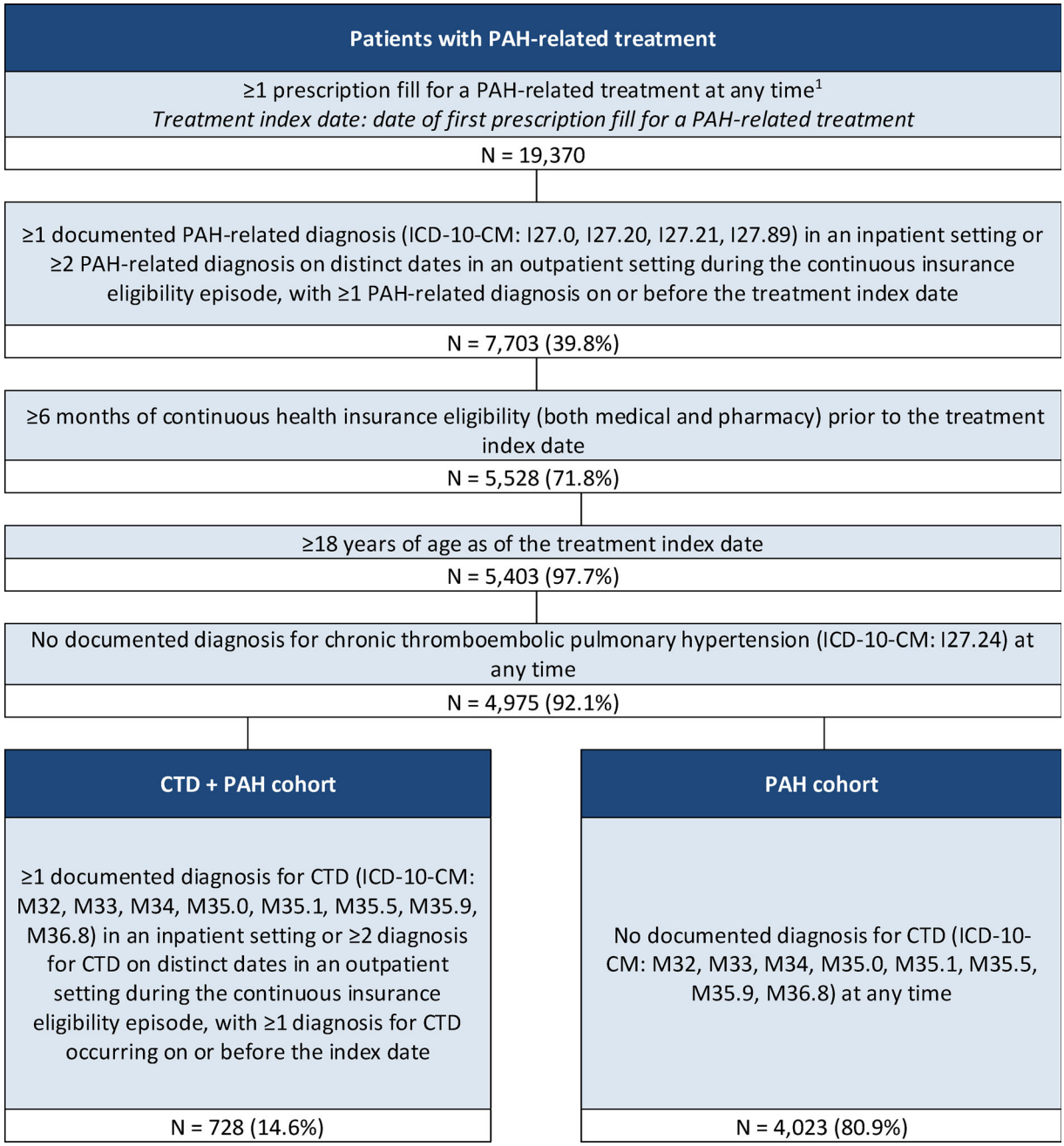



**Fig. 2** Sample selection. *CTD* connective tissue disorder, *ICD-10-CM* International Classification of Diseases, 10th Revision, Clinical Modification, *PAH* pulmonary arterial hypertension. (1) Sildenafil citrate (excluding Viagra), tadalafil (excluding Cialis), ambrisentan, bosentan, macitentan, riociguat, treprostinil, selexipag, iloprost, epoprostenol

patients and the PAH cohort included 4023 patients (Fig. 2).

## Patient Characteristics

Patients in the CTD + PAH and PAH cohorts were observed for an average of 18.8 and

19.6 months following their index date, respectively (Table 1). Patients in the CTD + PAH cohort tended to be younger than in the PAH cohort (64.2 and 69.1 years old, respectively) and were female in a larger proportion (85.7% vs. 60.8%, respectively). Among patients in the CTD + PAH cohort, 57.3% had systemic sclerosis and 24.7% had systemic lupus erythematosus.

### Treatment Patterns

For both cohorts, the most common first treatment regimens observed were sildenafil (CTD+PAH: 38.7%; PAH: 51.5%), tadalafil (10.0%; 9.4%), and macitentan (8.1%; 5.4%) in monotherapy. Sildenafil, tadalafil, and macitentan were also the most frequent agents included in any of the first three treatment regimens (Fig. 3a). Combination therapy was more frequent in the CTD+PAH cohort than in the PAH cohort (any regimen: 40.9% vs. 27.2%; first treatment regimen: 26.9% vs. 18.5%; second: 52.8% vs. 42.0%; third: 55.2% vs. 48.5%); patients with CTD+PAH were also more likely to have triple therapy when having combination therapy (Fig. 3b). KM analysis showed that patients in the CTD+PAH cohort were more likely to be initiated on combination therapy at any time post-index (Fig. 4). At 12 months post-index, 44.8% of patients in the CTD+PAH cohort had been initiated on a combination therapy compared to 30.2% in the PAH cohort. Most patients had cardiologist (83.0% in the PAH+CTD and 81.7% in the PAH cohort, respectively), pulmonologist (71.0% and 61.8%), and/or rheumatologist (59.1% and 5.2%) visits during the baseline period, but time to combination therapy was similar regardless of the type of specialist visits (data not shown). Treatment persistence was similar across cohorts and first three treatment regimens, with 12-month persistence rates of 43.2% and 46.5% in the CTD+PAH and PAH cohorts respectively for the first observed treatment regimen, 49.7% and 44.9% for the second regimen, and 42.6% and 45.9% for the third regimen (Fig. 5). For both cohorts, treatment discontinuation was the most frequent type of treatment change for the first and second treatment regimen, while treatment augmentation (add-on) was the most frequent change for the third treatment regimen for the CTD+PAH cohort (Fig. 6). Among those who discontinued their first treatment regimen, many reinitiated the same treatment after more than 90 days (CTD + PAH: 29.2%; PAH: 22.4%), and the vast majority of those patients restarted a tadalafil or sildenafil monotherapy (CTD + PAH: 86.5%; PAH: 90.1%).

## DISCUSSION

In this real-world study in a US patient population, treatment patterns were generally similar between the CTD + PAH and PAH cohorts. However, the use of combination therapy, including triple therapy, was more frequent among patients in the CTD + PAH cohort. Overall, less than half of patients used combination therapy. This underscores an unmet need for improved access to the full spectrum of available PAH treatment classes as early as possible, including recommended treatment strategies such as combination therapy. Our findings further underscore the low persistence to treatment in real-world clinical practice. Indeed, for the first three treatment regimens, fewer than one in two patients were persistent to their treatment 12 months after initiation.

Given the scarcity of real-world data on treatment patterns among patients with CTD + PAH, the present study findings help to fill an important gap in the literature. In a manner consistent with our findings, a few prior real-world studies have shown that combination therapy remains an underutilized strategy in routine clinical practice.[14, 15, 29, 31] Specifically, in analyses of the combined datasets from the ongoing OPsumit® USers (OPUS) prospective US drug registry study (since 04/2014) and the OPsumit® Historical USers cohort (OrPHeUS) retrospective US chart review study (10/2013–03/2017) [29, 31], a large proportion of patients with PAH and with CTD + PAH initiated on macitentan received monotherapy at initiation, and in most cases, this treatment strategy did not change during the follow-up

**Table 1** Patient characteristics

| Patient characteristics[a] | CTD + PAH cohort *N* = 728 | PAH cohort *N* = 4023 |
|---|---|---|
| **Duration of follow-up, mean ± SD [median]** | 18.8 ± 16.5 [14.4] | 19.6 ± 17.5 [14.1] |
| **Age, mean ± SD [median]** | 64.2 ± 12.8 [66.0] | 69.1 ± 12.8 [71.0] |
| **Female, *n* (%)** | 624 (85.7%) | 2446 (60.8%) |
| **Region, *n* (%)** | | |
| South | 332 (45.6%) | 1873 (46.6%) |
| West | 175 (24.0%) | 961 (23.9%) |
| Midwest | 154 (21.2%) | 768 (19.1%) |
| Northeast | 65 (8.9%) | 417 (10.4%) |
| Unknown | n.r.[c] | n.r.[c] |
| **Insurance type, *n* (%)** | | |
| Medicare advantage | 498 (68.4%) | 3140 (78.1%) |
| Commercial insurance | 230 (31.6%) | 883 (21.9%) |
| **PAH-related procedures, *n* (%)** | | |
| Echocardiography chest/thorax | 530 (72.8%) | 2853 (70.9%) |
| ECG/EKG | 513 (70.5%) | 2911 (72.4%) |
| Right heart catheterization | 394 (54.1%) | 1736 (43.2%) |
| Computer tomography chest/thorax | 314 (43.1%) | 1308 (32.5%) |
| Computed tomography angiography | 153 (21.0%) | 820 (20.4%) |
| Pulmonary angiogram | n.r.[c] | 28 (0.7%) |
| Cardiac magnetic resonance imaging chest/thorax | n.r.[c] | 15 (0.4%) |
| **CTD-diagnoses, *n* (%)** | | |
| Systemic sclerosis | 417 (57.3%) | – |
| Systemic lupus erythematosus | 180 (24.7%) | – |
| Dermatopolymyositis | 35 (4.8%) | – |
| Other systemic disorders of connective tissues | 260 (35.7%) | – |
| Systemic involvement of connective tissue | 142 (19.5%) | – |
| Sjögren's syndrome | 96 (13.2%) | – |
| Other overlap syndrome | 65 (8.9%) | – |
| **Quan–Charlson comorbidity index[b], mean ± SD [median]** | 4.0 ± 2.8 [3.0] | 4.4 ± 3.1 [4.0] |
| 0, *n* (%) | 18 (2.5%) | 376 (9.3%) |
| 1, *n* (%) | 108 (14.8%) | 456 (11.3%) |
| 2, *n* (%) | 130 (17.9%) | 527 (13.1%) |

**Table 1** continued

| Patient characteristics[a] | CTD + PAH cohort *N* = 728 | PAH cohort *N* = 4023 |
|---|---|---|
| 3, *n* (%) | 129 (17.7%) | 502 (12.5%) |
| 4+, *n* (%) | 343 (47.1%) | 2162 (53.7%) |
| **Comorbidities, *n* (%)** | | |
| Systemic hypertension | 524 (72.0%) | 3080 (76.6%) |
| Anemia | 272 (37.4%) | 1479 (36.8%) |
| Chronic obstructive pulmonary disease | 261 (35.9%) | 2025 (50.3%) |
| Renal disease | 243 (33.4%) | 1729 (43.0%) |
| Hypothyroidism | 219 (30.1%) | 891 (22.1%) |
| Pulmonary fibrosis | 216 (29.7%) | 479 (11.9%) |
| Diabetes mellitus | 189 (26.0%) | 1815 (45.1%) |
| Depression | 169 (23.2%) | 771 (19.2%) |
| Rheumatoid arthritis | 153 (21.0%) | 167 (4.2%) |
| Liver disease | 101 (13.9%) | 530 (13.2%) |
| Peripheral vascular disease | 75 (10.3%) | 456 (11.3%) |
| Pulmonary embolism | 69 (9.5%) | 355 (8.8%) |
| Malignancy | 62 (8.5%) | 455 (11.3%) |
| Stroke | 22 (3.0%) | 238 (5.9%) |
| Portal hypertension | 16 (2.2%) | 145 (3.6%) |
| **PAH-related symptoms, *n* (%)** | | |
| Dyspnea | 571 (78.4%) | 3003 (74.6%) |
| Chest pain | 234 (32.1%) | 1325 (32.9%) |
| Fatigue | 214 (29.4%) | 1176 (29.2%) |
| Lower limb edema | 206 (28.3%) | 1276 (31.7%) |
| Light headedness | 75 (10.3%) | 408 (10.1%) |
| Syncope | 60 (8.2%) | 416 (10.3%) |
| Ascites | 37 (5.1%) | 247 (6.1%) |
| **Specialist visits, *n* (%)** | | |
| Cardiologist visits | 604 (83.0%) | 3285 (81.7%) |
| Pulmonologist visits | 517 (71.0%) | 2488 (61.8%) |

**Table 1** continued

| Patient characteristics[a] | CTD + PAH cohort *N* = 728 | PAH cohort *N* = 4023 |
|---|---|---|
| Rheumatologist visit | 430 (59.1%) | 210 (5.2%) |

*CTD* connective tissue disorder, *ECG/EKG* electrocardiogram, *PAH* pulmonary arterial hypertension, *n.r.* not reported, *SD* standard deviation

[a]Unless otherwise specified, patient characteristics were measured on the treatment index date or during the baseline period (i.e., 6-month period prior to the index date)

[b]Based on Quan et al. [48]

[c]Per Optum's policy, cells with fewer than 10 patient counts cannot be reported

period. Among patients with PAH overall (including 44.7% with iPAH and 24.6% with CTD–PAH) in the OPUS/OrPHeUS dataset (data cutoff 02/2020; *N* = 4540) [31], 31–44% were receiving monotherapy at the time of macitentan initiation across the US regions, and 52–60% of them were still receiving monotherapy at 2 years post-macitentan initiation. Among patients with CTD + PAH in the OPUS/OrPHeUS dataset (data cutoff 08/2019; *N* = 1130) [29], 38.3% were receiving monotherapy at the time of macitentan initiation, and 72.9% were still receiving monotherapy at 6 months post-macitentan initiation.

While combination therapy may be underutilized, prior real-world evidence also suggests that it may be more common among patients with CTD + PAH than in those with PAH, which is aligned with the present study findings. For instance, an analysis of the Uptravi® (SelexiPag): tHe usErs dRug rEgistry (SPHERE) study of patients initiated on selexipag in the US (data cutoff of 20/12/2019; *N* = 500) [15] found that double combination therapy was more common in the CTD + PAH cohort (64.9%) [15] than the overall PAH cohort (55.0%) prior to selexipag initiation [32]. Another study analyzed data from the Post-authorization safety study (PASS): observational cohort study of PAH patients newly treated with either Uptravi (selexipag) or any other PAH-specific therapy, in clinical practice (EXPOSURE; EUPAS19085) study of adult patients with CTD + PAH and iPAH initiated on selexipag in Europe and Canada (09/2017–11/2020; *N* = 382) [14]. The results indicate that selexipag was mainly taken as part of triple combination therapy for all patients at the time of initiation. However, triple therapy was slightly more frequent in CTD + PAH vs. iPAH patients (81.0% vs. 74.0%).

In agreement with the present study, treatment persistence was found to be generally low in prior real-world studies regardless of PAH etiology. In the analysis of data from the EXPOSURE study with up to 21 months of follow-up [14], a sizable proportion of patients in CTD + PAH and iPAH cohorts discontinued treatment with selexipag (37% and 28%, respectively) with an average time to discontinuation of 5.5 and 7.6 months. Likewise, the analysis of the SPHERE registry study with up to 18 months of follow-up observed high selexipag discontinuation rates among CTD + PAH and iPAH cohorts (46.3% and 44.9%, respectively) with an average time to discontinuation of 16.4 and 16.9 months [15]. Prior evidence suggests that tolerability issues are a common reason for failed escalation attempts and discontinuation of treatment among patients with PAH [14, 15, 28]. Our findings and these prior ones highlight the need to better understand the low persistence rates with PAH therapies in routine clinical practice.

Prior real-world studies further suggest that patients with CTD+PAH may have more severe disease at treatment initiation and subsequently experience worse clinical outcomes than PAH overall. In the EXPOSURE study [14], patients with CTD+PAH had greater functional impairment (i.e., lower 6MWD) at selexipag initiation. This may have contributed to worse clinical outcomes, including a shorter time to all-cause death over 21 months of follow-up than iPAH

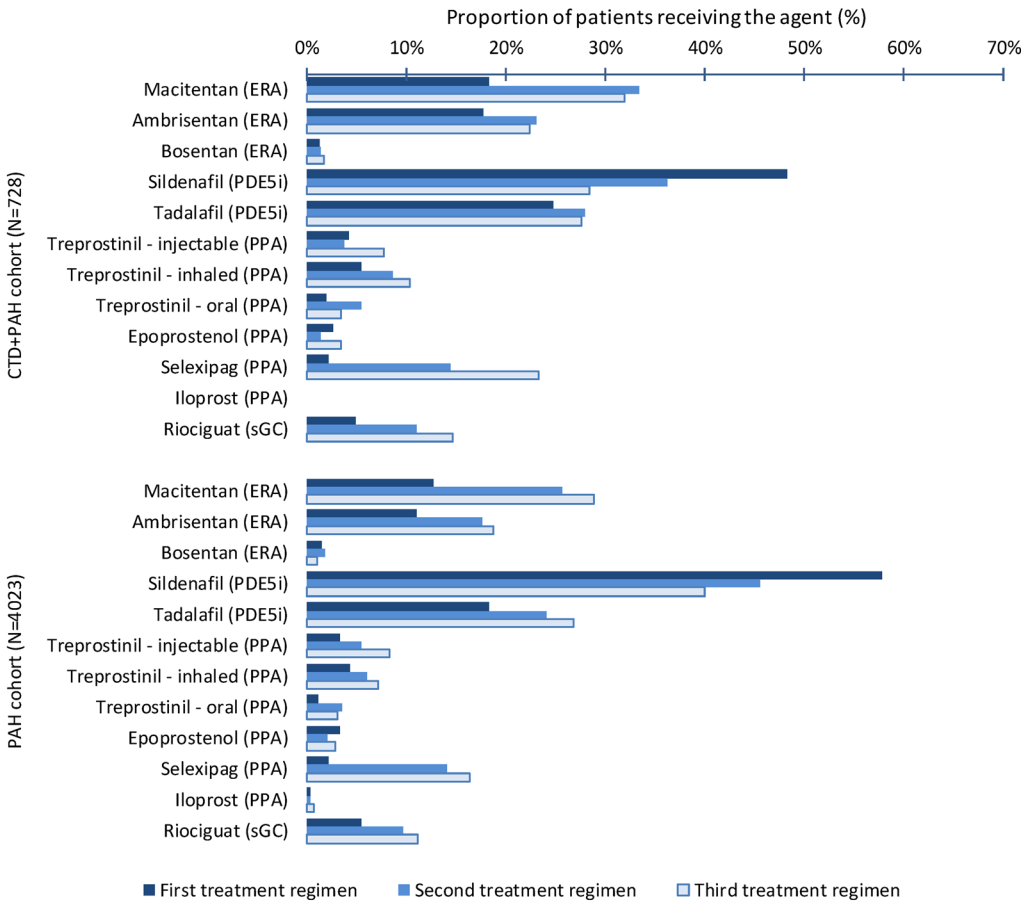
[14]. In the SPHERE registry study [15], the median 18-month survival rate was numerically lower in the CTD+PAH cohort (71.0% [95% CI 53.7%, 82.8%]) than in the iPAH cohort (84.4% [95% CI 71.6%, 91.8%]). Taken together, these prior findings and those of the present study highlight an opportunity for earlier initiation of combination therapy, especially among patients with CTD + PAH.

Our study findings have several important implications for clinical practice. Although early combination therapy is now considered a standard of care for patients with PAH [23–25, 33, 34], the present findings suggest that routine clinical practice may lag behind treatment guidelines. In our study, monotherapy was found to be dominant in the first treatment regimen, despite recommendations for upfront combination therapy among treatment-naïve patients who are non-vasoreactive or high-risk per the 2016 AHA guidelines and 2015 ESC/ERS guidelines that were in effect during the study period [34, 35]. Since the time that our study was conducted, the role for combination therapy in the treatment of PAH has been further expanded. While the 2016 AHA guidance considered monotherapy as a viable alternative to combination therapy for the initial treatment of non-vasoreactive patients at low or intermediate risk [35], the AHA now recommends combination therapy only as an initial treatment for non-vasoreactive patients across all risk levels [23]. Furthermore, the 2022 ESC/ERS guidelines have updated their recommendations for treatment-naïve patients without cardiopulmonary comorbidities to initial oral double combination therapy with a PDE5i or ERA for those who are low or intermediate risk and initial triple therapy with an injectable PPA for those who are high-risk [25]. Moreover, approximately half of patients in our study were not treated with combination therapy in the second and third treatment regimen even though the AHA and the 2015 and 2022 ESC/ERS guidelines recommend treatment escalation following failure on initial therapy (i.e., patients who fail to achieve low-risk status while on therapy) [23, 25, 34, 35].

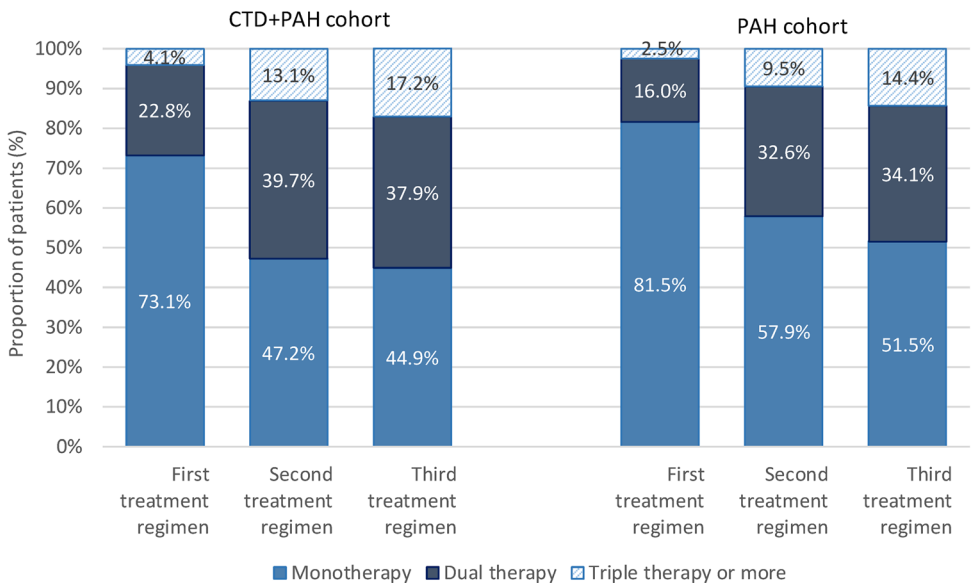
The underutilization of combination therapy in routine clinical practice may reflect several concerns. First, the costs of treatment, including out-of-pocket costs for patients, may act as a deterrent [36, 37]. However, increased pharmacy costs among patients treated with combination therapy are likely to be at least partly offset by a reduction in healthcare resource utilization and costs, which could alleviate these economic concerns [36, 38–40]. Second, combination therapy regimens could lead to additive side effects and reduced tolerability compared with monotherapy, although various strategies have been found to successfully reduce these additive effects (e.g., staggered treatment initiation, careful up-titration, and regular monitoring) in clinical practice [41]. Finally, evidence suggests that patients with cardiopulmonary comorbidities respond less well to PAH medication and are more likely to discontinue this medication due to efficacy failure or lack of tolerability, which could be another factor limiting the use of combination therapy in routine clinical practice [25].

Prior evidence suggests that there may be greater clinical benefits to combination therapy in patients initiated earlier compared to those initiated later [42, 43]. Thus, providing patients with prompt access to all available PAH treatment classes is key to improving long-term outcomes and potentially mitigating any downstream costs associated with disease progression [36, 44]. Early screening and detection among patients at higher risk of developing PAH may help to expedite treatment with combination therapy. Indeed, in their 2023 update, the AHA recommends that clinicians consider the possibility of a PH diagnosis among patients with unexplained dyspnea or tricuspid regurgitant jet velocity $> 2.8$ cm/s on echocardiography (including screening patients for sleep-disordered breathing and assessing exertional hypoxemia) [23]. The 2022 ESC/ERS guidelines recommend screening of asymptomatic individuals with SSc and early detection of symptomatic individuals with non-SSc CTD (as lower prevalence rates do not support asymptomatic screening) [25]. Moreover, the American College of Rheumatology recommends that patients with SSc, mixed CTD, or other CTDs with scleroderma features undergo screening for PAH [45]. For patients with SSc

***A. Agents received in first, second, and third treatment regimen***




***B. Type of therapy in first, second, and third treatment regimen***



◀**Fig. 3** Treatment regimens in the CTD + PAH and PAH cohorts. *CTD* connective tissue disorder, *ERA* endothelin receptor antagonist, *PAH* pulmonary arterial hypertension, *PDE5i* phosphodiesterase type 5 inhibitor, *PPA* prostacyclin pathway agent, *sGC* soluble guanylate cyclase stimulator. (1) All agents received are listed regardless of whether they were used as monotherapy or combination therapy

and scleroderma-spectrum disorders, initial screening evaluation should involve pulmonary function testing (PFT; including DLCO), TTE, and NT-Pro BNP, while TTE and PFT should be performed on an annual basis [45].

Interestingly, our study found that combination therapy, including triple therapy, was more common among patients in the CTD + PAH cohort. On the one hand, this appears to diverge from the 2015 ESC/ERS guidelines in effect at the time of our study and the later 2022 guidelines, which expressly recommend the same treatment algorithm for CTD + PAH and iPAH [25, 34, 46]. On the other hand, the AHA, and CHEST, and ESC/ERS guidelines recommend treatment based on patient disease severity [23–25, 34, 35]. Thus, increased use of combination therapy among CTD+PAH patients in the present study might reflect the use of differing treatment strategies across PAH etiologies due to the potentially greater risk of progressive disease and mortality in CTD+PAH compared to iPAH [9, 14, 15] and/or reflect higher risk at treatment initiation due to other factors besides CTD (e.g., lower 6MWD, higher NT-proBNP levels, etc.).

## Limitations

Patients may have been misclassified in a given cohort because of inaccuracies in health insurance claims data, including regarding diagnosis codes and treatment received (e.g., if they had a rule-out diagnosis or had information recorded incorrectly). For instance, it is possible that some patients might have been incorrectly diagnosed with PAH and treated with a PAH-related medication when in fact they might have had Group 2 PH. However, we note that the likelihood of misclassification may have been lower in the CTD+PAH cohort given that CTD is a strong risk factor for PAH [5–7]. Furthermore, the demographic distribution of

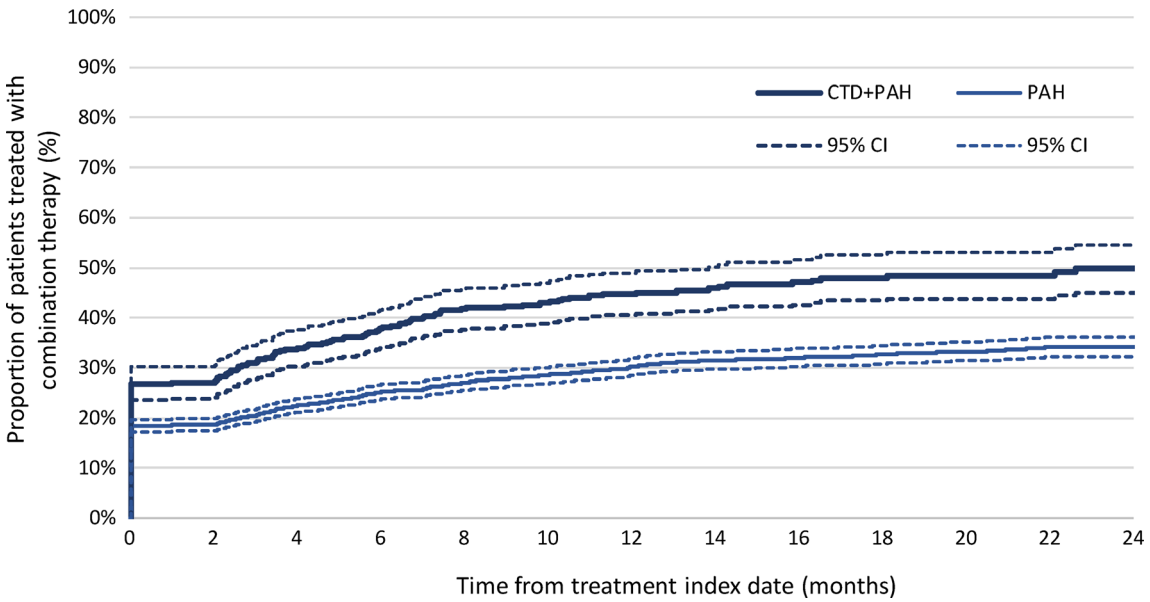



**Fig. 4** Kaplan-Meier analysis of time to first combination treatment regimen in the CTD + PAH and PAH cohorts. *CI* confidence interval, *CTD* connective tissue disorder, *PAH* pulmonary arterial hypertension

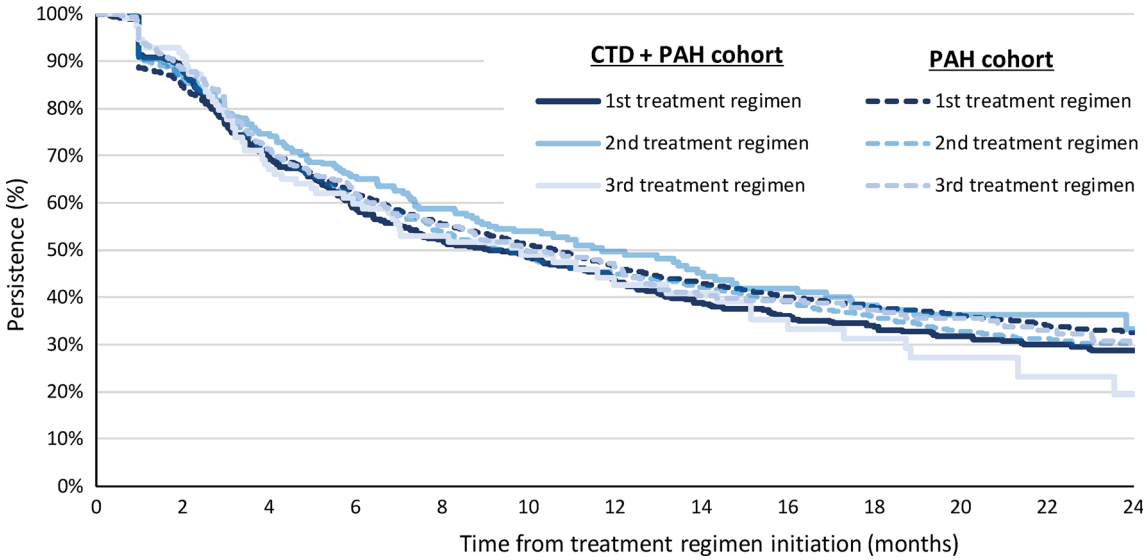



**Fig. 5** Kaplan-Meier analysis of treatment persistence in the CTD + PAH and PAH cohorts. *CTD* connective tissue disorder, *PAH* pulmonary arterial hypertension

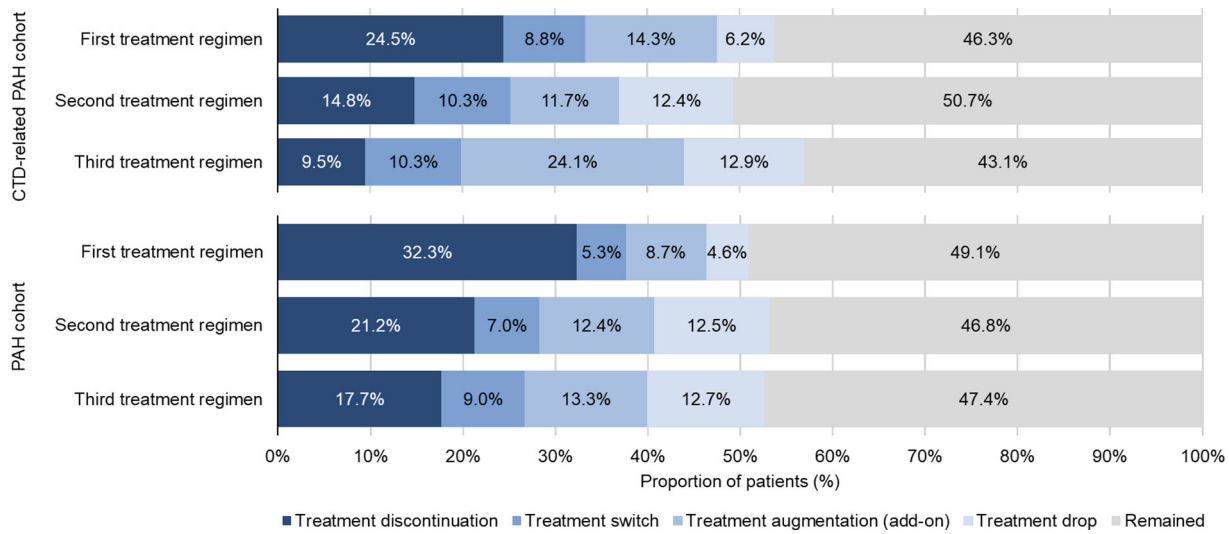



**Fig. 6** Type of treatment change at the end of the first, second, and third treatment regimens in the CTD + PAH and PAH cohorts. *CTD* connective tissue disorder, *PAH* pulmonary arterial hypertension

patients in the CTD+PAH cohort differs from that of Group 2 PH. For instance, patients with CTD+PAH in our study were younger on average relative to those with Group 2 PH in a prior study (e.g., 64 years vs. 72 years) with a higher proportion of females (e.g., 85.7% vs. 54.1%) [47]. Treatment patterns were observed based on prescription fills from pharmacy claims; however, this does not imply that the medication was actually taken. Furthermore, this study only captured medications for which an insurance claim was submitted. As such, it did not capture medications received through patient support programs without a record in an insurance claim. The study results might not be generalizable to patients without health

insurance or those with insurance plans other than commercial ones. Observed differences in treatment patterns might be partly explained by differences in patient characteristics between cohorts, including unobserved variables such as disease severity and hemodynamics. Finally, the reasons behind treatment patterns cannot be obtained from the pharmacy and medical claims; further studies are warranted to assess the rationale for treatment choice and treatment changes in real-world practice.

## CONCLUSION

In this study, real-world treatment patterns were described among patients with CTD + PAH and PAH from other etiologies. Although combination therapy is a cornerstone of PAH treatment per current guidelines [23–25, 34, 35], our findings suggest that it remains underutilized among both patients with CTD + PAH and with PAH in routine clinical practice. Nonetheless, combination therapy was more common in the CTD + PAH cohort, which appears consistent with evidence of the greater medical complexity and/or increased risk of mortality in this population [7, 9, 26]. Overall, our findings suggest that both CTD + PAH and PAH patients may potentially benefit from broader access to all available PAH treatment classes as early as possible, including combination therapy to target the nitric oxide, endothelin, and prostacyclin pathways [23–25, 35, 36, 44]. Our findings also highlight the low persistence rates with PAH therapies, despite the life-threatening nature of this condition. A better understanding of the factors driving treatment discontinuation and/or changes could enable clinicians to devise more effective strategies aimed at improving these metrics of treatment success.

***Medical Writing, Editorial, and Other Assistance*** Medical writing and editorial assistance were provided by professional medical writer, Mona Lisa Chanda, PhD, an employee of Analysis Group, Inc. Support for this assistance was funded by Janssen Scientific Affairs, LLC.

***Author Contributions.*** All named authors have made substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data. Furthermore, all authors have made important contributions to drafting the manuscript and revising it critically for important intellectual content and have provided final approval of this version to be published and agree to be accountable for all aspects of the work.

***Funding.*** Sponsorship for this study was funded by Janssen Scientific Affairs, LLC. The study sponsor was involved in several aspects of the research, including the study design, interpretation of data, writing of the manuscript, the journal's rapid service fee, the open access fee, and decision to submit the manuscript for publication.

***Data Availability.*** The data that support the findings of this study are available from Optum. Restrictions apply to the availability of these data, which were used under license for this study. Data used in this study may be available with the permission of Optum.

### *Declarations*

***Conflict of Interest.*** Yuen Tsang, Sumeet Panjabi, Vienica Funtanilla, and Hayley D Germack are employees of Janssen Scientific Affairs, LLC and may own stock/stock options. Marjolaine Gauthier-Loiselle, Aameu M Manceur, Martin Cloutier, and Patrick Lefebvre are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Janssen Scientific Affairs, LLC, which funded the development and conduct of this study and manuscript. Therese Sargent has received consultancy fees from Janssen Scientific Affairs, LLC. Finally, we note that the study sponsor, Janssen Scientific Affairs, LLC, is a manufacturer of therapies for PH/PAH, including bosentan, epoprostenol, iloprost, macitentan, and selexipag.

***Compliance with Ethics Guidelines.*** Data were de-identified and comply with the patient requirements of the HIPAA of 1996; therefore, no review by an institutional review board was

required per Title 45 of CFR, Part 46.101(b)(4) (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/#46.101). The present study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.



## REFERENCES

1. Thenappan T, Ormiston ML, Ryan JJ, Archer SL. Pulmonary arterial hypertension: pathogenesis and clinical management. BMJ. 2018;360: j5492.

2. Frost AE, Badesch DB, Barst RJ, Benza RL, Elliott CG, Farber HW, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US Contemporary Registries. Chest. 2011;139(1):128–37.

3. Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates from a systematic literature review. Pulm Circ. 2021;11(1):2045894020977300. https://doi.org/10.1177/2045894020977300.

4. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest. 2010;137(2):376–87. https://doi.org/10.1378/chest.09-1140.

5. McGoon MD, Miller DP. REVEAL: a contemporary US pulmonary arterial hypertension registry. Eur Respir Rev. 2012;21(123):8–18. https://doi.org/10.1183/09059180.00008211.

6. Hoeper MM, Simon R, Gibbs J. The changing landscape of pulmonary arterial hypertension and implications for patient care. Eur Respir Rev. 2014;23(134):450–7. https://doi.org/10.1183/09059180.00007814.

7. Zanatta E, Polito P, Famoso G, Larosa M, De Zorzi E, Scarpieri E, et al. Pulmonary arterial hypertension in connective tissue disorders: pathophysiology and treatment. Exp Biol Med (Maywood). 2019;244(2):120–31. https://doi.org/10.1177/1535370218824101.

8. Mathai SC, Hassoun PM. Pulmonary arterial hypertension in connective tissue diseases. Heart Fail Clin. 2012;8(3):413–25. https://doi.org/10.1016/j.hfc.2012.04.001.

9. Chung L, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB, et al. Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. Chest. 2010;138(6):1383–94. https://doi.org/10.1378/chest.10-0260.

10. Clements PJ, Tan M, McLaughlin VV, Oudiz RJ, Tapson VF, Channick RN, et al. The pulmonary arterial hypertension quality enhancement research initiative: comparison of patients with idiopathic PAH to patients with systemic sclerosis-associated PAH. Ann Rheum Dis. 2012;71(2):249–52. https://doi.org/10.1136/annrheumdis-2011-200265.

11. Fisher MR, Mathai SC, Champion HC, Girgis RE, Housten-Harris T, Hummers L, et al. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. Arthritis Rheum. 2006;54(9):3043–50. https://doi.org/10.1002/art.22069.

12. Launay D, Sitbon O, Hachulla E, Mouthon L, Gressin V, Rottat L, et al. Survival in systemic sclerosis-associated pulmonary arterial hypertension in the modern management era. Ann Rheum Dis. 2013;72(12):1940–6. https://doi.org/10.1136/annrheumdis-2012-202489.

13. Ramjug S, Hussain N, Hurdman J, Billings C, Charalampopoulos A, Elliot CA, et al. Idiopathic and systemic sclerosis-associated pulmonary arterial hypertension: a comparison of demographic, hemodynamic, and MRI characteristics and outcomes. Chest. 2017;152(1):92–102. https://doi.org/10.1016/j.chest.2017.02.010.

14. Gaine S, Escribano P, Muller A, Klement R, Söderberg S, Lange T. Selexipag experience in patients with pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD): real-world experience from EXPOSURE. C105 Civic Center Pulmonary Vascular Disease. American Thoracic Society; 2022. p. A4914-A.

15. Chin K, Chakinala M, Hemnes A, Farber H, McLaughlin V, Kim N, et al. Real-world data for selixipag in patients with connective tissue disease-associated pulmonary arterial hypertension: a SPHERE (selexipag: the users drug reigistry) analysis. Chest. 2020;158(4):A2187–90.

16. Sitbon O, Cottin V, Canuet M, Clerson P, Gressin V, Perchenet L, et al. Initial combination therapy of macitentan and tadalafil in pulmonary arterial hypertension. Eur Respir J. 2020. https://doi.org/10.1183/13993003.00673-2020.

17. Galie N, Barbera JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med. 2015;373(9):834–44. https://doi.org/10.1056/NEJMoa1413687.

18. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani HA, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369(9):809–18. https://doi.org/10.1056/NEJMoa1213917.

19. Fox BD, Shtraichman O, Langleben D, Shimony A, Kramer MR. Combination therapy for pulmonary arterial hypertension: a systematic review and meta-analysis. Can J Cardiol. 2016;32(12):1520–30. https://doi.org/10.1016/j.cjca.2016.03.004.

20. Lajoie AC, Lauziere G, Lega JC, Lacasse Y, Martin S, Simard S, et al. Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. Lancet Respir Med. 2016;4(4):291–305. https://doi.org/10.1016/S2213-2600(16)00027-8.

21. Coghlan JG, Galie N, Barbera JA, Frost AE, Ghofrani HA, Hoeper MM, et al. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. Ann Rheum Dis. 2017;76(7):1219–27. https://doi.org/10.1136/annrheumdis-2016-210236.

22. Khanna D, Zhao C, Saggar R, Mathai SC, Chung L, Coghlan JG, et al. Long-term outcomes in patients with connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era: meta-analyses of randomized, controlled trials and observational registries. Arthritis Rheumatol. 2021;73(5):837–47. https://doi.org/10.1002/art.41669.

23. Maron BA. Revised definition of pulmonary hypertension and approach to management: a clinical primer. J Am Heart Assoc. 2023;12(8):e029024. https://doi.org/10.1161/JAHA.122.029024.

24. Klinger JR, Elliott CG, Levine DJ, Bossone E, Duvall L, Fagan K, et al. Therapy for pulmonary arterial hypertension in adults: update of the CHEST guideline and expert panel report. Chest. 2019;155(3):565–86. https://doi.org/10.1016/j.chest.2018.11.030.

25. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2020 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2022. https://doi.org/10.1183/13993003.00879-2022.

26. Gaine S, Chin K, Coghlan G, Channick R, Di Scala L, Galie N, et al. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. Eur Respir J. 2017. https://doi.org/10.1183/13993003.02493-2016.

27. Studer S, Hull M, Pruett J, Koep E, Tsang Y, Drake W 3rd. Treatment patterns, healthcare resource utilization, and healthcare costs among patients with pulmonary arterial hypertension in a real-world US database. Pulm Circ. 2019;9(1):2045894018816294. https://doi.org/10.1177/2045894018816294.

28. Wissmuller M, Xanthouli P, Benjamin N, Grunig E, Richter MJ, Gall H, et al. Profiles and treatment patterns of patients with pulmonary arterial hypertension on monotherapy at experienced centres. ESC Heart Fail. 2022. https://doi.org/10.1002/ehf2.13804.

29. Lammi MR, Chin K, Kim NH, McLaughlin VV, Zamanian R, Flynn M, et al. Real-world mono-, double and triple combination treatment patterns with macitentan in patients with pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD): evidence from the combined OPUS/OrPHeUS dataset. B27 Up-To-Date PAH Assessment and Management. American Thoracic Society; 2020. p. A2914-A.

30. Tsang Y, Panjabi S, Funtanilla V, Germack HD, Gauthier-Loiselle M, Manceur AM, et al. Economic burden of illness among patients with pulmonary arterial hypertension (PAH) associated with connective tissue disorders (CTD). Pulm Circ. 2023;13(2):e12218. https://doi.org/10.1002/pul2.12218.

31. Ravichandran A, Zamanian R, Channick R, Chin K, Kim N, Martinez E, et al. Epidemiology and treatment patterns of pulmonary arterial hypertension (PAH) patients across US regions using real-world data from OPUS/OrPHeUS. TP86 while my guitar gently weeps-novel epidemiologic studies in

pulmonary vascular disease. American Thoracic Society; 2021. p. A3702-A.

32. Kim NH, Hemnes AR, Chakinala MM, Highland KB, Chin KM, McLaughlin V, et al. Patient and disease characteristics of the first 500 patients with pulmonary arterial hypertension treated with selexipag in real-world settings from SPHERE. J Heart Lung Transplant. 2021;40(4):279–88. https://doi.org/10.1016/j.healun.2021.01.006.

33. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th world symposium on pulmonary hypertension. Eur Respir J. 2019. https://doi.org/10.1183/13993003.02148-2018.

34. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, 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. https://doi.org/10.1093/eurheartj/ehv317.

35. Maron BA, Galie N. Diagnosis, treatment, and clinical management of pulmonary arterial hypertension in the contemporary era: a review. JAMA Cardiol. 2016;1(9):1056–65. https://doi.org/10.1001/jamacardio.2016.4471.

36. Burger CD, Ghandour M, Padmanabhan Menon D, Helmi H, Benza RL. Early intervention in the management of pulmonary arterial hypertension: clinical and economic outcomes. Clinicoecon Outcomes Res. 2017;9:731–9. https://doi.org/10.2147/CEOR.S119117.

37. Helgeson SA, Menon D, Helmi H, Vadlamudi C, Moss JE, Zeiger TK, et al. Psychosocial and financial burden of therapy in USA patients with pulmonary arterial hypertension. Diseases. 2020. https://doi.org/10.3390/diseases8020022.

38. Sikirica M, Iorga SR, Bancroft T, Potash J. The economic burden of pulmonary arterial hypertension (PAH) in the US on payers and patients. BMC Health Serv Res. 2014;14:676. https://doi.org/10.1186/s12913-014-0676-0.

39. Berger A, Edelsberg J, Teal S, Mychaskiw MA, Oster G. Changes in healthcare utilization and costs associated with sildenafil therapy for pulmonary arterial hypertension: a retrospective cohort study. BMC Pulm Med. 2012;12:75. https://doi.org/10.1186/1471-2466-12-75.

40. Burger CD, Ozbay B, Riehle E, Montejano LB, White RJ. Health care resource utilization and cost among pulmonary arterial hypertension patients before and after sequential combination therapy initiation. Value Health. 2016;19(3):A49–50.

41. Burks M, Stickel S, Galie N. Pulmonary arterial hypertension: combination therapy in practice. Am J Cardiovasc Drugs. 2018;18(4):249–57. https://doi.org/10.1007/s40256-018-0272-5.

42. Gaine S, Sitbon O, Channick RN, Chin KM, Sauter R, Galie N, 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):277–86. https://doi.org/10.1016/j.chest.2021.01.066.

43. Naranjo M, Hassoun PM. Time is of the essence in PAH therapy. Chest. 2021;160(1):25–6. https://doi.org/10.1016/j.chest.2021.02.009.

44. Burgoyne DS. Reducing economic burden and improving quality of life in pulmonary arterial hypertension. Am J Manag Care. 2021;27(3 Suppl):S53–8. https://doi.org/10.37765/ajmc.2021.88611.

45. Khanna D, Gladue H, Channick R, Chung L, Distler O, Furst DE, et al. Recommendations for screening and detection of connective tissue disease-associated pulmonary arterial hypertension. Arthritis Rheum. 2013;65(12):3194–201. https://doi.org/10.1002/art.38172.

46. Galie N, Channick RN, Frantz RP, Grunig E, Jing ZC, Moiseeva O, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J. 2019. https://doi.org/10.1183/13993003.01889-2018.

47. Wijeratne DT, Lajkosz K, Brogly SB, Lougheed MD, Jiang L, Housin A, et al. Increasing incidence and prevalence of World Health Organization groups 1 to 4 pulmonary hypertension: a population-based cohort study in Ontario, Canada. Circ Cardiovasc Qual Outcomes. 2018;11(2):973. https://doi.org/10.1161/CIRCOUTCOMES.117.003973.

48. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43:1130–9.