

SUPPLEMENTARY MATERIAL

Title: 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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Supplementary Material I. List of investigators and sites that enrolled patients with CTD-PAH and I/HPAH in OPUS and OrPHeUS

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Stewart, Jeffrey	Temple University Hospital	Philadelphia	PA	UNITED STATES
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Wells, Richard	University of Mississippi Medical Center	Jackson	MS	UNITED STATES
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CTD-PAH: PAH associated with connective tissue disease; I/HPAH: idiopathic/heritable PAH; PAH: pulmonary arterial hypertension; PI: principal investigator.

OPUS and OrPHeUS Scientific Committee Members

The Scientific Committee was an independent group of the following 4 experts with expertise in PAH:

- **Richard Channick**, MD, Department of Medicine, University of California at Los Angeles School of Medicine, Los Angeles, CA, USA
- **Kelly Chin**, MD, Associate Professor of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA.
- **Nick H Kim**, MD, Professor of Medicine, Section Chief Pulmonary Vascular Medicine, Medical Director PTE Program, Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego Health, La Jolla, CA, USA
- **Vallerie V McLaughlin**, MD (chairperson), Professor of Medicine and Director Pulmonary Hypertension Program, University of Michigan, Ann Arbor, MI, USA

Supplementary Material II. Independent Liver Safety Data Review Board members

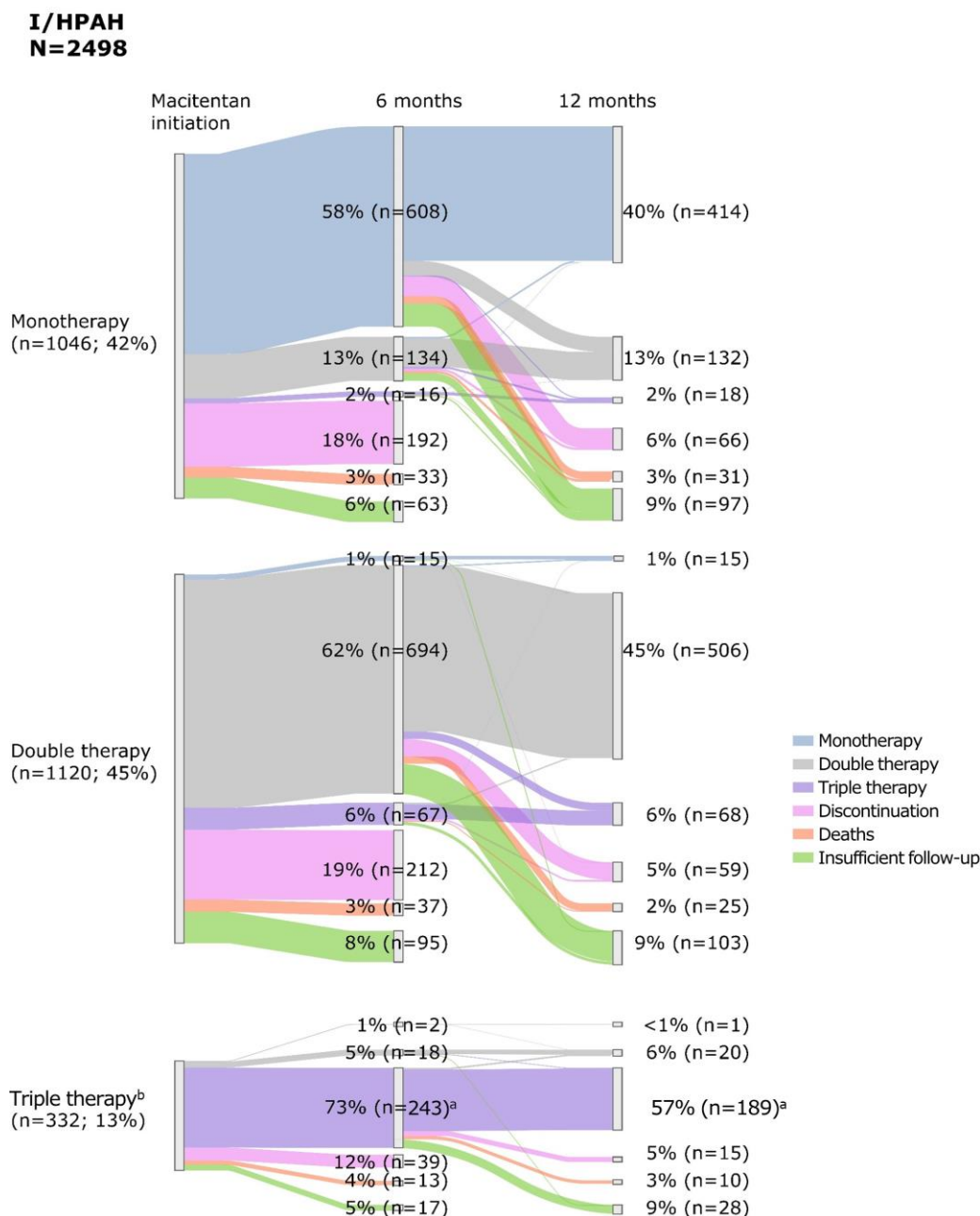
- **Willis Maddrey**, MD (chairperson), Professor of Internal Medicine, University of Texas, Southwestern Medical Center, Dallas, Texas, USA
- **Paul Watkins**, MD, Professor of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA
- **James Freston**, MD, Independent Pharmaceutical Consultant and National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases Council Member.

Supplementary Material III. Imputation rules

Incomplete dates for macitentan start or discontinuation were imputed if only the month and/or year were provided. For macitentan start, the first day of the month was used except when the available information was October 2013, the 19th of the month was used. For macitentan discontinuation, the 15th of the month was used except when the available information was the same as the year and month of disposition, in which case the date of disposition was used. If only the year of macitentan discontinuation was available, the discontinuation date was imputed with 31st December, except if the available year was the same as 1) the year of disposition or, 2) the year of last information prior to database lock in which case, the date of disposition or the date of the last information prior to database lock was used. If the year or the entire date was missing, no imputation was done. In general, for missing dates: where the year and month were present, the day was imputed; where only the year was present, imputation was done for most variables (including dates of clinical characteristic assessments and death, start of hepatic adverse events (HAEs), hepatic adverse events of special interest (HAESIs), laboratory abnormalities, hospitalization, and adverse events (AEs), start and end of comedications, and start of event leading to reason for macitentan prescription); where the date was not required for analysis, there was no imputation (e.g., some end dates, some dates before macitentan initiation); where a date was completely missing, imputation was done where required (e.g., date of death) but not otherwise. Hospitalization with no associated start date was recorded for 58 patients; most of these events were identified from the Sponsor's pharmacovigilance database. As it was not possible to determine whether these events occurred within the study observation period, these events were excluded from the hospitalization analyses.

SUPPLEMENTARY FIGURES AND TABLES

Figure S1. Transition of patients through treatment regimens at macitentan initiation, 6 months and 12 months after macitentan initiation in the I/HPAH population

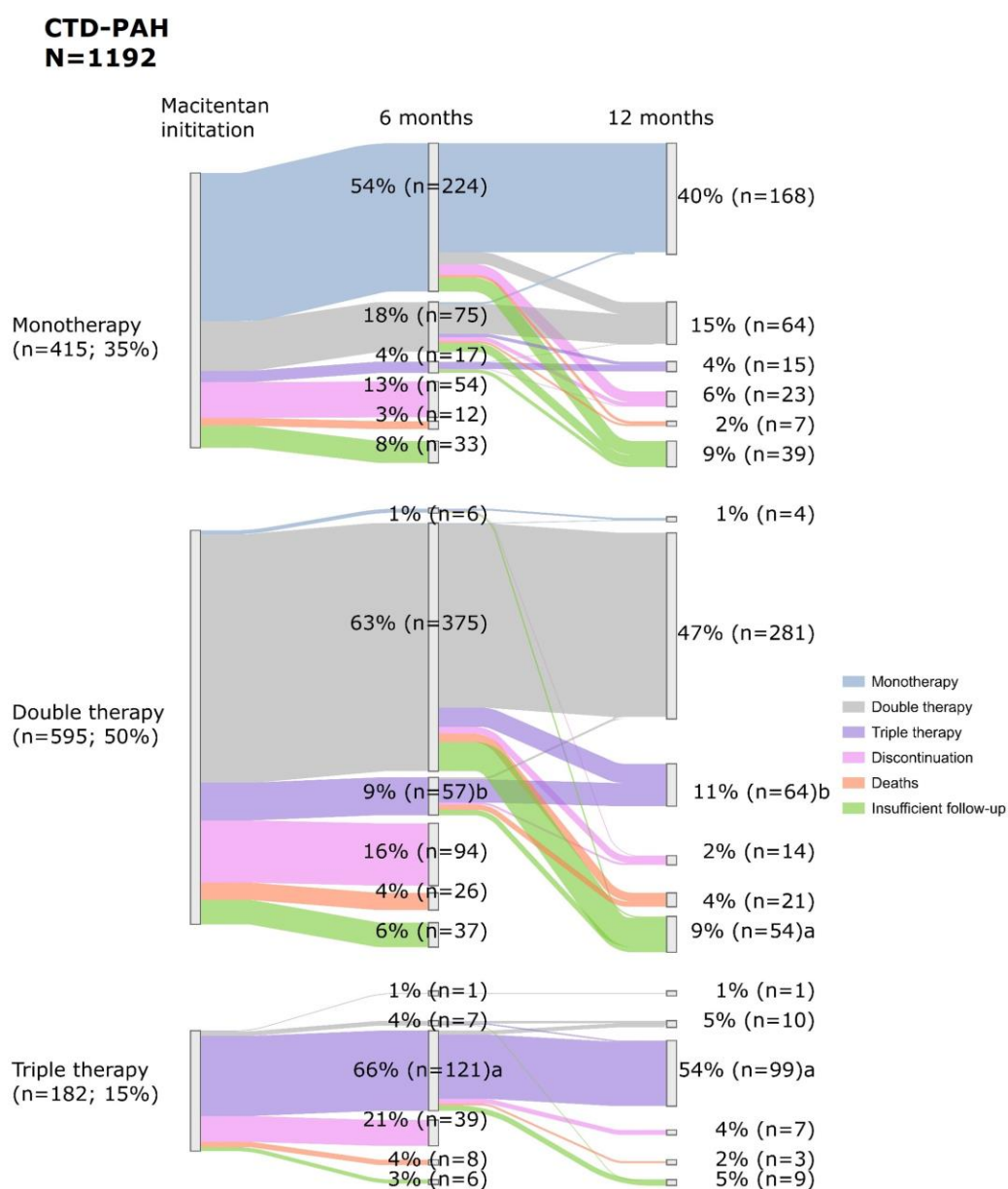


Patients receiving an ERA and macitentan at baseline were considered as monotherapy. Double therapy includes macitentan in combination with one other class of PAH therapy; triple therapy includes macitentan in combination with two other classes of PAH therapy. Classes of PAH therapy include PDE5i, prostanoids (oral, inhaled, or intravenous/subcutaneous) and/or sGCs. ^aIncludes 1 patient who was receiving 4 classes of PAH therapy; ^bIncludes 2 patients who were receiving 4 classes of PAH

therapy. Percentages are based on therapy at baseline and may not add up to 100% due to rounding.

ERA: endothelin receptor antagonist; I/HPAH: idiopathic/heritable PAH; PAH: pulmonary arterial hypertension; PDE5i: phosphodiesterase-5 inhibitor; sGCs: soluble guanylate cyclase stimulator.

Figure S2. Transition of patients through treatment regimens at macitentan initiation, 6 months and 12 months after macitentan initiation in the CTD-PAH population



Patients receiving an ERA and macitentan at baseline were considered as monotherapy. 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) and/or sGCS. ^aIncludes 1 patient who

was receiving 4 classes of PAH therapy; ^bIncludes 2 patients who were receiving 4 classes of PAH therapy. Percentages are based on therapy at baseline and may not add up to 100% due to rounding. CTD-PAH: PAH associated with connective tissue disease; ERA: endothelin receptor antagonist; PAH: pulmonary arterial hypertension; PDE5i: phosphodiesterase-5 inhibitor; sGCs: soluble guanylate cyclase stimulator.

1 **Table S1. Other relevant medical history at macitentan initiation**

	I/HPAH N = 2498	CTD-PAH N = 1192	SSc-PAH N = 708	SLE-PAH N = 159	MCTD-PAH N = 124
Relevant medical history – n (%)					
Hypertension	929 (37.2)	405 (34.0)	251 (35.5)	47 (29.6)	35 (28.2)
Autoimmune disease	122 (4.9)	275 (23.1)	143 (20.2)	61 (38.4)	21 (16.9)
Obesity (BMI ≥30 kg/m ²)	851 (34.1)	245 (20.6)	128 (18.1)	35 (22.0)	21 (16.9)
Anemia	223 (8.9)	166 (13.9)	101 (14.3)	27 (17.0)	17 (13.7)
Edema	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)
Other signs of right heart failure	222 (8.9)	124 (10.4)	81 (11.4)	16 (10.1)	8 (6.5)
Renal insufficiency	196 (7.8)	82 (6.9)	54 (7.6)	4 (2.5)	12 (9.7)
Permanent AF or episodes of AF	51 (2.0)	12 (1.0)	6 (0.8)	1 (0.6)	3 (2.4)
Gynecological disorder	28 (1.1)	10 (0.8)	2 (0.3)	4 (2.5)	3 (2.4)
Blood transfusion	4 (0.2)	8 (0.7)	5 (0.7)	2 (1.3)	0
Permanent AF	24 (1.0)	7 (0.6)	3 (0.4)	1 (0.6)	1 (0.8)
Hypotension	7 (0.3)	5 (0.4)	4 (0.6)	0	1 (0.8)
Drug abuse	14 (0.6)	1 (0.1)	1 (0.1)	0	0

2 Hypotension, encephalopathy, sepsis, other biliary disease, splenomegaly, jaundice, hepatic malignancy, ascites, and other liver condition available for

- 3 OrPHeUS only. Other infections available for OPUS only. AF: atrial fibrillation; BMI: body mass index; CTD-PAH: PAH associated with connective tissue disease;
- 4 I/HPAH: idiopathic/heritable PAH; MCTD-PAH: PAH associated with mixed connective tissue disease; PAH: pulmonary arterial hypertension; SLE-PAH: PAH
- 5 associated with systemic lupus erythematosus; SSc-PAH: PAH associated with systemic sclerosis.