SUPPLEMENTARY MATERIAL

Title: Macitentan and tadalafil combination therapy in patients with pulmonary arterial hypertension and cardiovascular comorbidities: Real-world evidence from OPUS and OrPHeUS

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Appendix I. List of investigators and sites including local ethical committees that enrolled patients in OPUS and OrPHeUS (included in these analyses)

PI Name	Site Name	PI City	PI State	PI Country
Allen, Samuel	Beaumont Medical Center	Troy	MI	UNITED STATES
Alnuaimat, Hassan	University of Florida	Gainesville	FL	UNITED STATES
Amin, Rohit	Sacred Heart Hospital	Pensacola	FL	UNITED STATES
Aranda, Alvaro	CardioPulmonary Research Center	San Juan		PUERTO RICO
Argula, Rahul Gupta	Medical University of South Carolina	Charleston	SC	UNITED STATES
Awdish, Rana	Henry Ford Health System	Detroit	MI	UNITED STATES
Badesch, David	University of Colorado	Aurora	CO	UNITED STATES
Bajwa, Abubakr	Saint Vincent's Medical Center	Jacksonville	FL	UNITED STATES
Bakshi, Sahil	Baylor Regional Medical Center at Plano	Plano	TX	UNITED STATES
Baratz, David	Pulmonary Associates	Phoenix	AZ	UNITED STATES
Bassetti, Dennis	Bassetti Medical Research Inc	Sebring	FL	UNITED STATES
Bensimhon, Daniel	LeBauer HeartCare	Greensboro	NC	UNITED STATES
Booth, David	University of Kentucky	Lexington	KY	UNITED STATES
Cabuay, Barry	Minneapolis Heart Institute	Minneapolis	MN	UNITED STATES
Cadaret, Linda	University of Iowa Hospitals and Clinics	Iowa City	IA	UNITED STATES
Carstens, Donna; Scharf, Michael	Asthma, Allergy and Pulmonary Associates	Philadelphia	PA	UNITED STATES
Cauthen, Carlton	Midlands Pulmonary, Critical Care & Sleep Medicine	Columbia	SC	UNITED STATES
Champion, Hunter	Southeastern Cardiology Associates	Columbus	GA	UNITED STATES
Chin, Kelly	University of Texas Southwestern Medical Center at Dallas	Dallas	TX	UNITED STATES
Costanzo, Maria Rosa	Midwest Heart Specialists	Naperville	IL	UNITED STATES

PI Name	Site Name	PI City	PI State	PI Country
Cuttica, Michael	Northwestern University	Chicago	IL	UNITED STATES
Daniels, Curt	Ohio State University, Wexner Medical Center	Columbus	OH	UNITED STATES
De La Zerda, David	University of Miami	Miami	FL	UNITED STATES
Deaton, Paul	Mid-South Pulmonary Specialists	Memphis	TN	UNITED STATES
DeSouza, Shilpa	Winthrop University Hospital, Clinical Trials Center	Mineola	NY	UNITED STATES
Dewhurst, Robert	Bay Area Cardiology Associates	Brandon	FL	UNITED STATES
Dia, Muhyaldeen	Advocate Health and Hospitals Corporation	Oakbrook	IL	UNITED STATES
Dong, Lin-Wang	Banner Health Research Institute	Greenley	CO	UNITED STATES
DuBrock, Hilary	Mayo Clinic	Rochester	MN	UNITED STATES
Eggert, Michael	Sentara Cardiovascular Research Institute	Norfolk	VA	UNITED STATES
El Bayadi, Sherif	Pulmonary Health Physicians	Fayetteville	NY	UNITED STATES
Elmaghraby, Zaki	Independent Lung Associates	Melbourne	FL	UNITED STATES
Elwing, Jean	University of Cincinnati	Cincinnati	OH	UNITED STATES
Engel, Peter	The Christ Hospital	Cincinnati	OH	UNITED STATES
Escolar, Esteban	Mount Sinai Comprehensive Cancer Center	Miami Beach	FL	UNITED STATES
Ford, Hubert	University of North Carolina Hospitals	Chapel Hill	NC	UNITED STATES
Friedenheim, Richard	Abington Pulmonary and Critical Care Associates	Abington	PA	UNITED STATES
Ganesh, Sivagini	University of Southern California	Los Angeles	CA	UNITED STATES
George, Marjorie Patricia	National Jewish Health	Denver	CO	UNITED STATES
Giri, Paresh	Loma Linda University Medical Center	Loma Linda	CA	UNITED STATES
Gorbett, Daniel	Mount Carmel Medical Group	Columbus	OH	UNITED STATES
Goyal, Anuj	Midwest Pulmonary & Sleep Research	Dayton	OH	UNITED STATES

PI Name	Site Name	PI City	PI State	PI Country
Guha, Ashrith; Goodarzi, Ahmad	Houston Methodist Hospital	Houston	TX	UNITED STATES
Guichard, Paul	Wellstar Marietta Pulmonary Medicine	Marietta	GA	UNITED STATES
Gupta, Ashish	Cardiovascular Consultants	Phoenix	AZ	UNITED STATES
Hage, Antoine	California Heart Center	Los Angeles	CA	UNITED STATES
Harvey, William L. F.	IU Health Physicians Pulmonary & Critical Care	Carmel	IN	UNITED STATES
Hull, Frank	Frank Hull, MD, PA	Fort Lauderdale	FL	UNITED STATES
Jacobs, Myron	Pulmonary Consultants Inc-St. Louis	St. Louis	MO	UNITED STATES
Jimenez, Javier	Cardiovascular Medicine Associates	South Miami	FL	UNITED STATES
Johnson, William	Nebraska Pulmonary Specialties, LLC	Lincoln	NE	UNITED STATES
Kable, Sanober	Premier Pulmonary CC and Sleep Medicine, PA	Denison	TX	UNITED STATES
Kamm, Richard; Desai, Himanshu	Pulmonary & Critical Care Specialists	Shreveport	LA	UNITED STATES
Kaplan, Adolfo	Pulmonary & Sleep Center of the Valley	Weslaco	TX	UNITED STATES
Khan, Akram	Oregon Health and Science University	Portland	OR	UNITED STATES
Khouri, Samer	The University of Toledo Medical Center	Toledo	OH	UNITED STATES
Kingrey, John	INTEGRIS Baptist Medical Center	Oklahoma City	OK	UNITED STATES
Kukreja, Sandeep	Indiana Internal Medicine Consultants	Greenwood	IN	UNITED STATES
Kunavarapu, Chandra	Texas Transplant Physician Group – Advanced Heart Failure & Transplant	San Antonio	TX	UNITED STATES
Kuru, Tunay	MedStar Georgetown University Hospital	Washington	DC	UNITED STATES
Lammi, Matthew	LSU Health Sciences Center	New Orleans	LA	UNITED STATES
Leary, Peter	University of Washington	Seattle	WA	UNITED STATES
Link, Chad	Sparrow Clinical Research Institute	Lansing	MI	UNITED STATES

PI Name	Site Name	PI City	PI State	PI Country
Malhotra, Vinay	Pulse Heart Institute Cardiology and Electrophysiology Services - Tacoma	Tacoma	WA	UNITED STATES
Mandras, Stacy	Ochsner Medical Center	New Orleans	LA	UNITED STATES
Markin, Catherine	Legacy Research Institute	Portland	OR	UNITED STATES
Marshall, Peter; Singh, Inderjit	Yale University	New Haven	CT	UNITED STATES
Mattson, Scott	Lutheran Hospital	Fort Wayne	IN	UNITED STATES
Matuschak, George	Mercy Hospital Saint Louis	St. Louis	MO	UNITED STATES
Mauriello, Daniel	All Children's Hospital	St. Petersburg	FL	UNITED STATES
McConnell, John	Kentuckiana Pulmonary Associates - Main Office	Louisville	KY	UNITED STATES
McLaughlin, Vallerie	University of Michigan Medical Center	Ann Arbor	MI	UNITED STATES
Medarov, Boris	Albany Medical Center	Albany	NY	UNITED STATES
Melendres-Groves, Lana	University of New Mexico	Albuquerque	NM	UNITED STATES
Miller, Chad	Piedmont Healthcare	Austell	GA	UNITED STATES
Mobin, Syed; Go, Jean	Central Florida Pulmonary Group, P.A. - Downtown Orlando Office	Orlando	FL	UNITED STATES
Mwangi, John	Saint Louis University	Saint Louis	MO	UNITED STATES
Pascual, Jose	West Pasco Pulmonary Associates	Hudson	FL	UNITED STATES
Patel, Bela	University of Texas Health Science Center at Houston	Houston	TX	UNITED STATES
Patel, Pratik; Migliore, Christina	Barnabas Health Ambulatory Care Center	Newark	NJ	UNITED STATES
Poch, David	University of California San Diego	La Jolla	CA	UNITED STATES
Presberg, Kenneth	Froedtert Hospital	Milwaukee	WI	UNITED STATES
Preston, Ioana	Tufts Medical Center	Boston	MA	UNITED STATES
Pritchett, Michael	Pinehurst Medical Clinic, Inc.	Pinehurst	NC	UNITED STATES

PI Name	Site Name	PI City	PI State	PI Country
Pulido, Juan	EMED RESEARCH, PA	Jacksonville	FL	UNITED STATES
Rahaghi, Franck	Cleveland Clinic Florida Hospital	Weston	FL	UNITED STATES
Raina, Amresh	Allegheny General Hospital	Pittsburgh	PA	UNITED STATES
Rajagopal, Sudarshan	Duke University Medical Center	Durham	NC	UNITED STATES
Ramani, Gautam	University of Maryland	Baltimore	MD	UNITED STATES
Raval, Abhijit	AnMed Health Medical Center	Anderson	SC	UNITED STATES
Ravichandran, Ashwin	St. Vincent Medical Group, Inc.	Indianapolis	IN	UNITED STATES
Restrepo Jaramillo, Ricardo	University of South Florida/USF Health	Tampa	FL	UNITED STATES
Robinson, Jeffrey	The Oregon Clinic	Portland	OR	UNITED STATES
Rodriguez-Lopez, Josanna	Massachusetts General Hospital	Boston	MA	UNITED STATES
Ross, David	David Geffen School of Medicine at University of California Los Angeles	Los Angeles	CA	UNITED STATES
Rovzar, Michael	Paloma Medical Group	San Juan Capistrano	CA	UNITED STATES
Runo, James	University of Wisconsin Hospital and Clinics	Madison	WI	UNITED STATES
Safdar, Zeenat	Houston Methodist Hospital	Houston	TX	UNITED STATES
Sager, Jeff	Santa Barbara Pulmonary Associates	Santa Barbara	CA	UNITED STATES
Samuel, Vinny Oommen	Coastal Pulmonary and Critical Care	St. Petersburg	FL	UNITED STATES
Scharf, Michael	Thomas Jefferson University	Philadelphia	PA	UNITED STATES
Scott, Robert	Mayo Clinic - Arizona	Phoenix	AZ	UNITED STATES
Segal, Ilia	Pulmonary and Critical Care Associates	Union	NJ	UNITED STATES
Selby, Van	UCSF School of Medicine	San Francisco	CA	UNITED STATES
Sharif, Irtza	Florida Lung, Asthma and Sleep Specialists	Celebration	FL	UNITED STATES
Sheatt, Mohammad	TriHealth Hatton Research Institute	Cincinnati	OH	UNITED STATES

PI Name	Site Name	PI City	PI State	PI Country
Shlobin, Oksana	Inova Fairfax Hospital	Falls Church	VA	UNITED STATES
Shrader, David	Bingham Memorial Hospital	Shelley	ID	UNITED STATES
Sikes, David	Florida Medical Clinic	Zephyrhills	FL	UNITED STATES
Simms, Robert	Boston University Medical Center	Boston	MA	UNITED STATES
Smith, A. Kerri	University of Pennsylvania Health System	Philadelphia	PA	UNITED STATES
Spikes, Leslie	The University of Kansas Physicians	Kansas City	KS	UNITED STATES
Stevenson, Joe	St Mary's Hospital	Reno	NV	UNITED STATES
Stewart, Jeffrey	Temple University Hospital	Philadelphia	PA	UNITED STATES
Strachan, Paul	Stony Brook University Hospital	Hauppauge	NY	UNITED STATES
Swift, Irene	Christiana Care Health Services	Newark	DE	UNITED STATES
Taghizadeh, Touraj	Southwest General Health Center	Middleburg Heights	OH	UNITED STATES
Talwar, Arunabh	Northwell Health	New Hyde Park	NY	UNITED STATES
Thompson, Austin	University of Nebraska Medical Center	Omaha	NE	UNITED STATES
Trivieri, Maria Giovanna	Mount Sinai	New York	NY	UNITED STATES
Tumuluri, Ramagopal	Aurora Health Care - Saint Luke's Medical Center	Milwaukee	WI	UNITED STATES
Vaska, Kevin	Sioux Falls Cardiovascular PC	Sioux Falls	SD	UNITED STATES
Walter, Robert	Louisiana State University Health Sciences Center in Shreveport	Shreveport	LA	UNITED STATES
Wells, Richard	University of Mississippi Medical Center	Jackson	MS	UNITED STATES
Wirth, Joel	Chest Medicine Associates	South Portland	ME	UNITED STATES
Yau, Peter	Scott and White Memorial Hospital	Temple	TX	UNITED STATES
Zaidi, Ali; Murthy, Sandhya	Montefiore Medical Center - Bronx	Bronx	NY	UNITED STATES
Zamanian, Roham	Stanford University Medical Center	Stanford	CA	UNITED STATES

PI Name	Site Name	PI City	PI State	PI Country
Zubkus, Dmitriy	Wellspan Health	York	PA	UNITED STATES

Ethical approval for OPUS/OrPHeUS was gained by the local ethical committee at each of the listed sites. 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:

- **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
- **Kelly M Chin,** MD, Associate Professor of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA.
- **Vallerie V McLaughlin,** MD (chairperson), Professor of Medicine and Director Pulmonary Hypertension Program, University of Michigan, Ann Arbor, MI, USA
- **Richard Channick,** MD, Department of Medicine, University of California at Los Angeles School of Medicine, Los Angeles, CA, USA

Appendix 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.

Appendix III. Supplementary Methods

Adverse Events of Special Interest (AESI) definitions

Hepatic AESI included: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5 x upper limit of normal (ULN); ALT or AST ≥3 x ULN and total bilirubin (TBIL) ≥2 x ULN; TBIL ≥2 x ULN; any events with a Preferred Term (PT) under the MedDRA system organ class 'Hepatobiliary Disorders' and having fatal outcome or under the MedDRA high-level Group Term 'Hepatobiliary Investigations' and having fatal outcome; or any event with a PT denoting hepatic failure, hepatic encephalopathy, hepatic cirrhosis or fibrosis, liver injury or liver transplant, non-infectious hepatitis or jaundice. The full list of PTs has been previously described [1].

AESI related to edema included: events with PTs included in the Standardized MedDRA query (SMQ) "Hemodynamic edema, effusions and fluid overload"; or any of the following PTs: eye edema, eyelid edema, face edema, orbital edema, periorbital edema, swelling face.

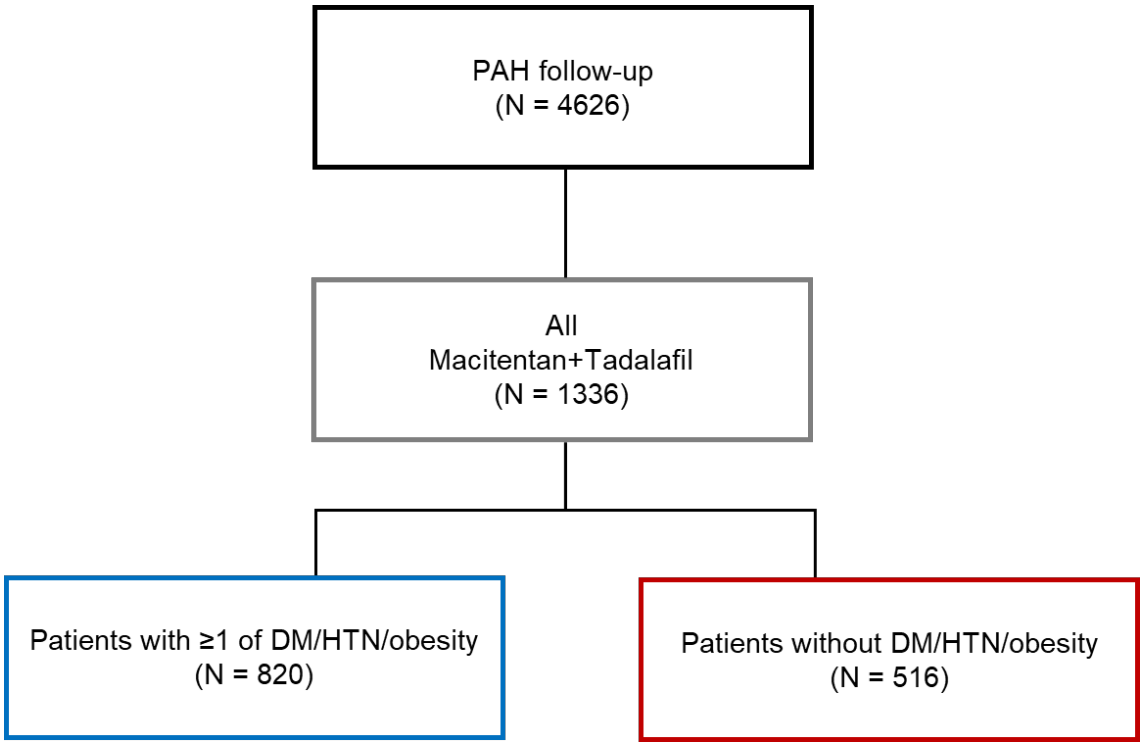
AESI related to anemia/hemoglobin decrease included: events with PTs included in the SMQs of 'Hematopoietic erythropenia' or 'Hematopoietic cytopenias affecting more than one type of blood cell', or are included in the following list of PTs: anemia hemolytic autoimmune, anemia megaloblastic, hemolytic anemia, iron deficiency anemia.

Imputation rules

Incomplete dates for macitentan start or discontinuation were imputed if the month and 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, the date of disposition was used. If only the year of macitentan discontinuation was available, the discontinuation date was imputed with 31 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 adverse events (OPUS only), hepatic adverse events, AESIs, laboratory abnormalities, hospitalization, and 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 76 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.

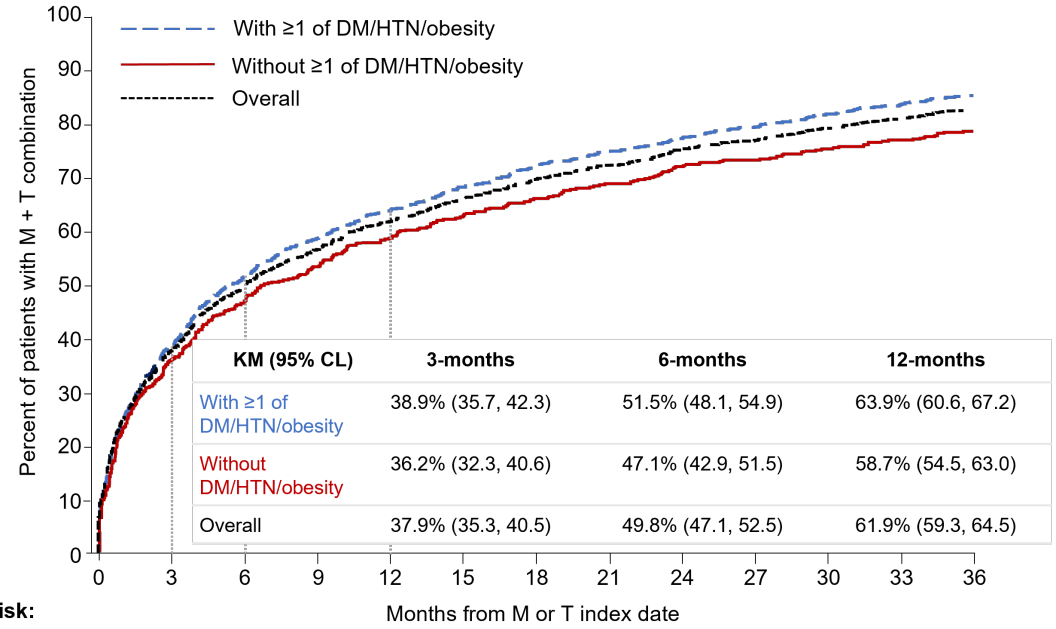
Figure S1. Patient disposition



155 sites contributed to the combined OPUS and OrPHeUS database which contained N=5654 patients at closure. DM: diabetes mellitus; HTN: hypertension; PAH: pulmonary arterial hypertension.

Figure S2. Kaplan-Meier estimates of time to escalation from first to second drug of the macitentan plus tadalafil combination (A) and macitentan plus tadalafil combination therapy to additional PAH therapy (B)

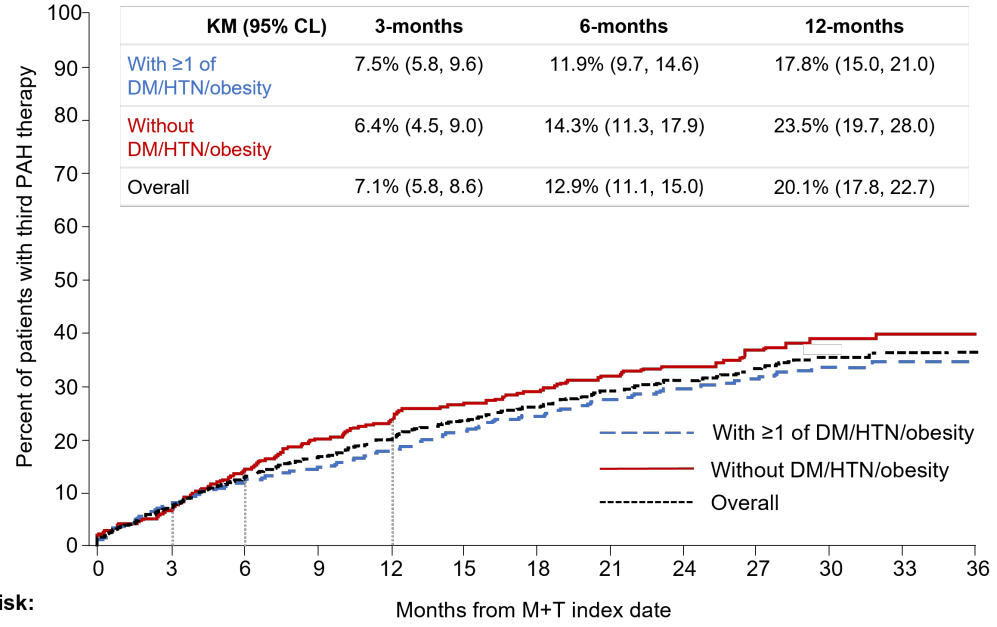
A)



KM (95% CL)	3-months	6-months	12-months
With ≥1 of DM/HTN/obesity	38.9% (35.7, 42.3)	51.5% (48.1, 54.9)	63.9% (60.6, 67.2)
Without DM/HTN/obesity	36.2% (32.3, 40.6)	47.1% (42.9, 51.5)	58.7% (54.5, 63.0)
Overall	37.9% (35.3, 40.5)	49.8% (47.1, 52.5)	61.9% (59.3, 64.5)

Patients at risk:

With ≥1 of DM/HTN/obesity	820	501	398	339	296	261	228	207	186	169	149	135	121
Without DM/HTN/obesity	516	329	273	240	213	191	175	161	144	138	127	119	110
Overall	1336	830	671	579	509	452	403	368	330	307	276	254	231



Patients at risk:

With ≥1 of DM/HTN/obesity	820	611	517	456	387	324	281	236	203	170	134	104	81
Without DM/HTN/obesity	516	409	339	292	247	211	185	152	125	101	75	66	52
Overall	1336	1020	856	748	634	535	466	388	328	271	209	170	133

CL: confidence limits; DM diabetes mellitus; HTN: hypertension; KM: Kaplan-Meier; M+T: macitentan plus tadalafil combination; PAH: pulmonary arterial hypertension.

Table S1. Sequence and time to macitentan and tadalafil combination

	Patients with PAH treated with macitentan + tadalafil		
	Patients with ≥1 of DM/HTN/obesity N = 820	**Patients without DM/HTN/obesity N = 516**	**Overall cohort N = 1336**
Sequence of macitentan and tadalafil initiation			
Macitentan first – n (%)	**194 (23.7)**	**109 (21.1)**	**303 (22.7)**
Time from macitentan to tadalafil initiation – months; median (Q1, Q3)	4.0 (1.1, 10.8)	3.7 (0.9, 11.7)	3.9 (1.0, 11.6)
Tadalafil first – n (%)	**573 (69.9)**	**373 (72.3)**	**946 (70.8)**
Time from tadalafil to macitentan initiation – months; median (Q1, Q3)	8.4 (1.7, 29.9)	12.0 (2.6, 39.1)	9.5 (1.9, 34.0)
Missing – n (%)	**53 (6.5)**	**34 (6.6)**	**87 (6.5)**

DM: diabetes mellitus; HTN: hypertension; Q1,Q3: interquartile range.

Table S2. PAH-specific therapy at index date

	Patients with PAH treated with macitentan + tadalafil		
	Patients with ≥1 of DM/HTN/obesity N = 820	**Patients without DM/HTN/obesity N = 516**	**Overall cohort N = 1336**
Two classes of therapy – n (%)	**820 (100)**	**516 (100)**	**1366 (100)**
Macitentan + tadalafil double therapy only	814 (99.3)	509 (98.6)	1323 (99.0)
Macitentan + tadalafil + sildenafil	6 (0.7)	7 (1.4)	13 (1.0)
Three classes of therapy – n (%)	**169 (20.6)**	**132 (25.6)**	**301 (22.5)**
Macitentan + tadalafil + PPA	167 (20.4)	131 (25.4)	298 (22.3)
Macitentan + tadalafil + sGC stimulator	1 (0.1)	0	1 (0.1)
Macitentan + tadalafil + investigational drug[a]	1 (0.1)	1 (0.2)	2 (0.1)
Four classes of therapy – n (%)	**1 (0.1)**	**1 (0.2)**	**2 (0.1)**
Macitentan + tadalafil + PPA + sGC stimulator	1 (0.1)	1 (0.2)	2 (0.1)

[a]Only in OrPHeUS. DM: diabetes mellitus; HTN: hypertension; PAH: pulmonary arterial hypertension; PPA: prostacyclin pathway agent; sGC: soluble guanylate cyclase.

Table S3. Patients discontinuing macitentan

	Patients with PAH treated with macitentan + tadalafil		
	Patients with ≥1 of DM/HTN/obesity N = 820	**Patients without DM/HTN/obesity N = 516**	**Overall cohort N = 1336**
Patients discontinuing combination therapy – n (%)	**387 (47.2)**	**243 (47.1)**	**630 (47.2)**
Macitentan and tadalafil[a]	130 (15.9)	83 (16.1)	213 (15.9)
Macitentan only	158 (19.3)	105 (20.3)	263 (19.7)
Tadalafil only	99 (12.1)	55 (10.7)	154 (11.5)
Reasons for macitentan discontinuation[b] – n (%)	**233 (80.9)**	**148 (78.7)**	**381 (80.0)**
Due to an AE	116 (14.1)	73 (14.1)	189 (14.1)
Not due to an AE	117 (14.3)	75 (14.5)	192 (14.4)
Missing reason	55 (6.7)	40 (7.8)	95 (7.1)

[a]Discontinued both therapies within 30 days. [b]Reasons for tadalafil discontinuation were not collected during the study. AE: adverse event; DM: diabetes mellitus; HTN: hypertension; PAH: pulmonary arterial hypertension.

REFERENCES

1. McLaughlin VV, Channick R, Kim NH, Frantz RP, McConnell J, Melendres-Groves L, et al. Safety of macitentan for the treatment of pulmonary hypertension: Real-world experience from the OPsumit® USers Registry (OPUS) and OPsumit® Historical USers cohort (OrPHeUS). Pulm Circ. 2022;12:e12150. doi:10.1002/pul2.12150.