

SUPPLEMENTAL MATERIAL

Integrating data from randomized controlled trials and observational studies to assess survival in rare diseases: Insights from pulmonary arterial hypertension

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Supplemental Table I. SERAPHIN – List of Independent Ethics Committees and Institutional Review

Boards

Study Center	Independent Ethics Committee/Institutional Review Board
Argentina	
8001	Comité Independiente de Etica para Ensayos en Farmacologia Clinic
8005	
8007	
8008	
8009	
8010	
8001	Comité de Revision Institucional - Sanatoria de la Trinidad Mitr
8002	Comité de Bioética de la Fundacion Favaloro (Bioethics Comité)
8004	Comité de Revision Institucional del Hospital Británico
8005	Comité de Docencia e Investigacion del Hospital Italiano Garibaldi
8007	Comité de Docencia e Investigacion del Instituto de Cardiologia Corrientes
8008	Comité de Revision de Interna del Hospital Privado Centro
8009	Comité de Etica en Investigaciones Biomedicas - Sanatorio Otamendi y Miroli S.A.
8010	Comite de Docencia e Investigacion del Hospital Italiano de Cordoba
Australia	
5001	The Alfred Hospital Research & Ethics Unit
5002	St. Vincent's Hospital Human Research Ethics Committee
5003	Sydney Local Health District
5004	Redcliffe-Caboolture Health Service District Ethics Committee
Austria	
1001	Ethikkommission der Medizinischen Universität Wien und des Allgemeinen Krankenhauses der Stadt Wien
Belarus	
3101	Minsk Regional Clinical Hospital
3102	Vitebsk Regional Clinical Hospital
3104	LEC of the Republican Scientific-Practical Center "Cardiology"
Belgium	
1101	Faculteit Geneeskunde Commissie voor Medische Ethiek/Klinisch Onderzoek
Bulgaria	
All sites	Ethics Committee for multi-centric trials
Canada	
9001	Conjoint Health Research Ethics Board - Office of Medical Bioethics
9002	University Health Network, Research Ethics Board
9002	Mount Sinai Hospital Research Ethics Board
9003	University of Western Ontario Office of Research Ethics
9004	IRB - Comite d'Ethique de la recherche
9005	University of British Columbia, Clinical Research Ethics Board Office
Chile	
8201	Comite Etica - Científico del Servicio de Salud Metropolitano Central
8201	Comite de Etica de la Direccion de Investigacion de la Escuela de Medicina de la Pontificia Universidad Catolica de Chile
8202	Comité de Etica Científico del Servicio de Salud Metropolitano Occidente

Study Center	Independent Ethics Committee/Institutional Review Board
8203	Comitè De Etica Cientifico del Servicio de Salud Metropolitano Oriente
China	
5101	Ethics Committee of Shanghai Pulmonary Hospital
5102, 5103	Ethics Committee, Renji Hospital, School of Medicine, Shanghai Jiao Tong University
5104	Ethics Committee of Zhongshan Hospital Fudan University
5105	Ethic Committee of Peking Union Medical College Hospital for Clinical Trials
5106	IEC of Beijing Anzhen Hospital of the Capital University of Medical Sciences
5107	IEC of Chinese PLA General Hospital
5108	Ethic Committee of Guangdong General Hospital
5109	IEC of The First Affiliated Hospital with Nanjing Medical University
Colombia	
8302	Comité de Ética e Investigaciones Fundación Clínica Shaio
8303	Comite de Etica en Investigacion Fundacion Cardiovascular de Colombia
Croatia	
3002	Središnje etičko povjerenstvo, Agencija za lijekove i medicinske proizvode (Central ethics committee, Agency for medicinal products and medical devices)
Denmark	
1201	Den Videnskabsetiske Komité for Region Midtjylland
Finland	
All sites	Etiska Kommitteerna
France	
All sites	CPP Ile-de-France VII
Germany	
All sites - 1401	Ethik-Kommission Fachbereich Medizin, Justus-Liebig- Universität
1403	Ethikkommission an der Medizinischen Fakultät Leipzig Institut für klinische Pharmakologie
1404	Landesamt für Gesundheit und Soziales, Geschäftsstelle der Ethik-Kommission des Landes Berlin
1406	Ethik-Kommission der Medizinischen Fakultät der Universität zu Köln
1408	Ethikkommission Ärztekammer Hamburg, Körperschaft des Öffentlichen Rechts
1409	Ethikkommission der Medizinischen Fakultät der TU Dresden
1410	Ethikkommission an der Medizinischen Fakultät, Ernst-Moritz-Arndt-Universität Greifswald, Institut für Pharmakologie
1411	Ethik-Kommission der Medizinische Fakultät der Ludwigs-Maximilians Universität
1412	Ethikkommission der Medizinischen Fakultät Heidelberg
1413	Ethikkommission der Medizinischen Fakultät der Universität Regensburg
1415	Ethik-Kommission bei der Ärztekammer des Saarlandes
Hong Kong	
5201	Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster
5202	Chinese University of Hong Kong - New Territories Ethics Committee
Hungary	
All sites	Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottság (Medical Research Council Ethics Committee for Clinical Pharmacology)
3401	Szegedi Tudományegyetem, Szent-Györgyi Albert Klinikai Központ Regionális és Intézményi Humán Orvosbiológiai Kutatásetikai Bizottsága

Study Center	Independent Ethics Committee/Institutional Review Board
3404	University of Pécs, Faculty of Medicine, Medical Microbiology and Immunity Institute, Regional Research Ethics Committee of the Medical Center
3405	Gottsegen György Országos Kardiologiai Intézet Etikai Bizottsága
3406	Semmelweis Egyetem Intézeti Tudományos és Kutatásetikai Bizottság
India	
5301	Ethics Committee Apollo Hospitals International Ltd
5302	Institutional Ethics Committee- Deenanath Mangeshkar Hospital & Research Centre
5303	Clinical Research & Ethics Committee, National Health & Education Society
5304	Institutional Ethics Committee, Care Foundation
5305	Ethical Research Committee-Narayana Hrudayalaya Institute of Medical Sciences
5306	Institutional Ethics Committee, Maulana Azad Medical College, New Dehli
5307	Ethics Committee For Research On Human Subjects
Israel	
7101	Helsinki Committee Carmel Medical Center
7102	Helsinki Committee Rabin Medical Center
7103	Prof. Amichai Rubin / Prof. Moshe Berant
7104	The Helsinki Committee Chaim Sheba Medical Center
7105	Helsinki Committee Kaplan Medical Center
7106	The Helsinki Committee Tel Aviv Sourasky Medical Center
Italy	
1501	Comitato Etico dell'Azienda Policlinico Umberto I di Roma - c/o Servizio Amministrativo Area Scientifica e di Ricerca
1502	Fondazione IRCCS, Policlinico "San Matteo" Comitato de Bioetico
Malaysia	
5401	Ethics Committee Institut Jantung Negara
Mexico	
8401	Ethics Committee Instituto Nacional de Cardiología Ignacio Chavez Comision de Investigacion del Instituto Nacional de Cardiología Igancio Chavez
8402	Comité de Ética e Investigación de la Unidad de Investigación Clínica en Medicina.
Netherlands	
All sites	Verenigde Commissies Mensgebonden Onderzoek
Norway	
1701	Regional komité for medisinsk og helsefaglig forskningsetikk, Sør-Øst-Norge
Peru	
All sites	Comite Institucional de Etica en Investigacion de la Universidad de San Martin de Porres - Clinical cada mujer
8501	EC Facultad de Medicina Humana Uni de San Martin de Porres
8502	Comision Reguladora De Estudios Clinicos Del Completo Hospitalario San Pablo
8503	Comite de Bioetica De La Red Asistencial Sabogal-Essalud Hospital Nacional Alberto Sabogal Sologuren, Essalud
Poland	
All sites	Komisja ds. Etyki Badań Naukowych przy Instytucie Gruźlicy i Chorób Płuc

Study Center	Independent Ethics Committee/Institutional Review Board
Romania	
All sites	Comisia Nationala de Etica pentru Studiu Clinic al Medicamentului
Russian Federation	
All sites	Ethics Council at Minzdravsocrazvitiya
3801	The Joint Local Ethics Committee of the Municipal Budgetary Healthcare Institution “Kemerovo Cardiology Dispensary”
3802	Committee on the Ethics issues in clinical cardiology of the Federal State Institution “Russian Cardiology Scientific and Production complex of Minzdravsotsrazvitiya of Russia”
3803	Biomedical Ethics Committee at Federal State Budgetary Institution “Scientific Research Institute of Cardiology” Siberian branch of RAMS
3804	Ethics Committee of the Regional Budgetary State Health Care Institution “Tomsk Regional Clinical Hospital”
3805	Committee on the Ethics of clinical trials of Sverdlovsk Regional Clinical Hospital #1
3806	Ethics Committee at the “Scientific Research Institute of Pulmonology” of Federal Medical and Biological Agency of Russia
3807	Ethics Committee of the Municipal Health Care Institution of Yaroslavl Region "Clinical Hospital of Emergency Care named after N.V. Solovyov"
3808	Local Independent Ethic Committee of National Research Centre for Preventive Medicine
3809	Ethics committee on clinical trials of the City Clinical Hospital #1 N.I. Pirogov
3810	Ethics committee of St. Petersburg Medical Academy of Postgraduate Education
3811	Ethics Committee at the Federal State Budgetary Institution “Federal Center of heart, blood and endocrinology named after V.A.Almazov” of the Ministry of Health Care and Social Development of the Russian Federation
3812	Ethics Committee of St. Petersburg State Medical University n.a. Pavlov
Serbia	
3901	Univerzitetska dečja klinika, Etički odbor
3902	Kliničko Bolnički Centar Zemun, Etički Komitet
3903	Klinički Centar Srbije, Etički Odbor
Singapore	
5501	Singapore General Hospital Ethics Committee
5501	Singapore Health Services Pte Ltd. Domain C
5502	National Healthcare Group Domain Specific Review Board, Domain C
Slovakia	
All sites	Etická komisia NÚSCH
South Africa	
6001, 6002	University of the Witwatersrand Human Research Ethics Committee
6003	Pharma Ethics (Pty) Ltd
6004	University of Stellenbosch Committee for Clinical Trials
Spain	
All sites	Hospital Vall d' Hebrón, Fundacio per la Recerca
1902	Comité Etico de Investigacion Clinica
1904	Comité Etico de Investigacion Clinica
1907	Comité Etico de Investigacion Clinica

Study Center	Independent Ethics Committee/Institutional Review Board
Sweden	
All sites	Regionala Etikprövningsnämnden i Uppsala
Taiwan	
5601	Research Ethics Committee National Taiwan University Hospital
5602	The Institutional Review Board of Taichung Veterans General Hospital
5602 - central	Joint Institutional Review Board
Thailand	
5701	Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects Faculty of Medicine, Ramathibodi Hospital, Mahidol University
5702	Ethics Committee Faculty of Medicine Siriraj Hospital, Mahidol University
5703	Research Ethics Committee, Faculty of Medicine, Chiang Mai University
5704	The Khon Kaen University Ethics Committee for Human Research
Turkey	
All sites	Hacettepe Üniversitesi Tıp Fakültesi Tibbi, Cerrahi ve Ilac Arastirmalari Etik Kurulu
Ukraine	
All sites	Central Ethics Committee of the Health Ministry of Ukraine
4101	Bioethics Committee affiliated to Dnepropetrovsk State Medical Academy
4102	Local Ethic Committee of Lviv Regional Clinical Hospital
United Kingdom	
2101	London – Hampstead (Formerly: EC Royal Free Hospital & Medical School Research Ethics Committee)
USA	
9101	Colorado Multiple IRB
9102	IRB - Columbia University Medical Center
9103	IRB - Western
9104	IRB - Western
9105	IRB - Mayo Clinic Foundation
9106	IRB - Western
9107	IRB - Louisiana State University Health Sciences Center
9108	IRB - Intermountain Healthcare Urban Central Region
9109	IRB - Western
9110	IRB - Boston University Medical Center
9111	IRB - Western
9112	IRB - Western
9114	IRB – Western
9115	IRB - The University of Michigan Medical School
9116	IRB - Western
9118	IRB – Western
9119	IRB - UTHSC-Committee for the Protection of Human Subjects
9121	IRB - Wayne State University - Human Investigation Committee
9123	IRB - University of California San Diego Human Research Protections Program
9125	IRB - University of Kansas Medical Center - Human Subjects Committee
9126	IRB - Washington University School of Medicine - Human Research Protect. Office
9127	IRB - Western
9128	IRB - Baylor College of Medicine
9129	IRB - The University of Chicago - Section of Regulatory Compliance

Study Center	Independent Ethics Committee/Institutional Review Board
9130	IRB - University of Maryland School of Medicine - Human Research Protection Office
9131	IRB - Cottage Health System
9132	IRB - Western
9133	IRB – Duke
9134	IRB - Partners Human Research Committee (Boston)
9135	IRB - Maine Medical Center - Office of Research Affairs
9136	IRB – Aurora
9137	IRB – Western
9138	IRB - Vanderbilt University
9139	IRB - Veterans Affairs Greater Los Angeles Healthcare System - 151
9140	IRB - University of Texas Southwestern Medical Center at Dallas
9142	IRB - Allegheny General Hosp
9143	IRB - Western

IEC, Independent Ethics Committee; IRB, Institutional Review Board

Supplemental Table II. REVEAL – List of Institutional Review Boards

Study Center	Institutional Review Board
Intermountain Medical Center	Intermountain Healthcare Urban Central Region IRB
Allegheny General Hospital	ASRI- WPAHS IRB
University of Pittsburgh Medical Center Cardiovascular Institute	WIRB
Oregon Health and Science University (up to 06Jun2008)	Oregon Health and Science University IRB
Legacy Good Samaritan Hospital and Health Center (after 06 Jun 2008)	WIRB
Inova Fairfax Hospital	WIRB
Kalamazoo Center for Medical Studies	Spectrum Health IRB
University of Colorado Health Sciences Center	Colorado Multiple IRB
Mayo Clinic Rochester	Mayo Clinic Office for Human Research IRB
Baylor College of Medicine	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals
Midwest Heart Specialists	WIRB
Georgia Health Sciences University	Human Assurance Committee
Aurora St. Luke's Medical Center	Aurora IRB
University of Alabama at Birmingham	WIRB
The University of Texas Health Science Center at San Antonio	The University of Texas Health Science Center IRB
University of Iowa Hospital and Clinics	Human Subjects Office/ IRB/ Hawk IRB
University of Colorado School of Medicine	Colorado Multiple IRB
University of California, San Diego	UCSD Human Research Protections Programs
Ochsner Clinic Foundation	Ochsner Clinic Foundation IRB
Rhode Island Hospital	Lifespan Rhode Island IRB
University of Maryland	University of Maryland IRB
Temple University	Temple University IRB
Brigham and Women's Hospital	Brigham Women's Hospital IRB
Mayo Clinic Florida	Mayo Clinic Office for Human Research IRB
University of California, San Francisco	Human Research Protection Program
North Shore-Long Island Jewish Health Systems	BRANY IRB
VA Greater Los Angeles Healthcare System	VA Greater Los Angeles Healthcare Systems IRB
University of Rochester	University of Rochester Research Subjects Review Board
Washington University in St. Louis	Washington University Human Research Protection Office
Suncoast Lung Center	WIRB
Wayne State University	Wayne State University IRB
Duke University Medical Center	Duke University Health System IRB
University of Pennsylvania	University of Pennsylvania IRB
University of Arizona	University of Arizona Human Subjects Protection Program

Study Center	Institutional Review Board
University of Minnesota Medical Center	University of Minnesota Research Subjects' Protection Programs IRB
Boston University Medical Center	WIRB
Nationwide Children's Hospital	Nationwide Children's Hospital IRB
Johns Hopkins University	WIRB
Cleveland Clinic	Cleveland Clinic Foundation IRB
Columbia University Medical Center	Columbia University Medical Center IRB
University of Chicago	The University of Chicago AURA IRB
Medical University of South Carolina	The Medical University of South Carolina IRB for Human Research
Texas Children's Hospital	IRB for Baylor College of Medicine and Affiliated Hospitals
Tufts-New England Medical Center Hospital	Tufts Health Sciences Campus Institutional Review Board
Lexington Pulmonary and Critical Care	WIRB
Stanford University Medical Center	Stanford University IRB
Monroe Carell Jr. Children's Hospital	Vanderbilt University IRB
Vanderbilt Medical Center	Vanderbilt University IRB
Ohio State University	Ohio State University Biomedical Sciences IRB
Kentuckiana Pulmonary Associates	WIRB
University of California, Los Angeles	UCLA Medical IRB
University Hospitals of Cleveland	University Hospitals Case Medical Center (UHCMC) IRB for Human Investigation
Beth Israel Medical Center	Beth Israel Medical Center IRB
Harbor UCLA Medical Center	Los Angeles Biomedical Research Institution
Seattle Children's Hospital	Children's Hospital and Regional Medical Center Seattle, Washington IRB
Virginia Commonwealth University	WIRB
University of Florida	WIRB

IRB, Institutional Review Board; WIRB, Western Institutional Review Board

Supplemental Table III. SERAPHIN eligibility criteria used for selection of the RAC

SERAPHIN eligibility criteria ¹	Collected in REVEAL at baseline	Eligibility criteria used for selection of RAC
	Yes/No	Yes/No
Inclusion criteria		
Males and females aged ≥ 12 years at enrollment	Yes	Yes
WHO FC II-IV at enrollment	Yes	No: Controlled via the prediction model
PAH belonging to Groups 1.1 to 1.3 of the Venice classification: Idiopathic, Familial, related to CTD, simple congenital systemic-to-pulmonary shunts, HIV infection, or Drugs and toxins	Yes	Yes
mPAP >25 mmHg (within 1 year of enrollment)	Yes	Yes
PAWP ≤ 15 mmHg (within 1 year of enrollment)	Yes	Yes
PVR at rest >320 dyn \cdot sec \cdot cm ⁻⁵	Yes	Yes
6MWD ≥ 50 m at enrollment	Yes	Yes
Exclusion criteria		
PAH associated with portal hypertension thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, or splenectomy	Yes	Yes
PAH associated with non-corrected simple congenital systemic-to-pulmonary shunts and, combined and complex systemic-to-pulmonary shunts, corrected or non-corrected	Yes	Yes
PAH associated with significant venous or capillary involvement (PAWP >15 mmHg), known pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis	Yes	Yes
Persistent pulmonary hypertension of the newborn	Yes	Yes
Pulmonary hypertension belonging to Groups 2 to 5 of the Venice classification	Yes	Yes
Moderate to severe obstructive lung disease: forced expiratory volume in 1 second/forced vital capacity (FEV ₁ /FVC) $<70\%$ and FEV ₁ $<65\%$ of predicted value after bronchodilator administration	Yes	Yes
Moderate to severe restrictive lung disease: total lung capacity $<60\%$ of normal predicted value	No	No: Not collected in REVEAL
Moderate to severe hepatic impairment, e.g. Child-Pugh Class B or C	Yes	No; Related to the safety profile of ERAs known at the start of SERAPHIN*
Estimated creatinine clearance <30 mL/min	Yes	Yes

Serum aspartate aminotransferase and/or alanine aminotransferase > 1.5 times the upper limit of normal	No	No: Not collected in REVEAL
Haemoglobin <75 % of the lower limit of the normal range	No	No: Not collected in REVEAL
Systolic blood pressure <100 mmHg	Yes	Yes
Acute or chronic impairment (other than dyspnea), limiting the ability to comply with the study requirements	Yes	No: Considered too subjective
Pregnant or breast-feeding	No	No: Not collected in REVEAL
Known concomitant life-threatening disease with a life expectancy <12 months	Yes	No: Considered too subjective
Body weight <40 kg	Yes	Yes
Any condition that prevented compliance with the protocol or adherence to therapy	Yes	No: Considered too subjective
Recently started (<8 weeks prior to randomization) or planned cardio-pulmonary rehabilitation program based on exercise	No	No: Not collected in REVEAL
Treatment with ERAs within 3 months prior to randomization	Yes	No: Use of background PAH therapies not considered for selection of the RAC
Systemic treatment within 4 weeks prior to randomization with immunosuppressants: calcineurin, or mTOR inhibitors (e.g. cyclosporine A and tacrolimus, everolimus, sirolimus)	Yes	No: Related to potential DDIs with macitentan that were unknown at the start of SERAPHIN
Treatment with CYP3A inducers within 4 weeks prior to randomization	Yes	No: Related to known DDIs with macitentan
Known hypersensitivity to drugs of the same class as the study drug, or any of their excipients	Yes	No: Considered too subjective
Planned treatment or treatment with another investigational drug within 1 month prior to randomization	No	No: Not collected in REVEAL

*Macitentan must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal [$> 3 \times \text{ULN}$])². 6MWD, 6-minute walk distance; CTD, connective tissue disease; CYP3A, cytochrome P450 Family 3A; DDI, drug-drug interaction; ERA, endothelin receptor antagonist; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HIV, human immunodeficiency virus; mPAP, mean pulmonary arterial pressure; mTOR, mammalian target of rapamycin; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAC, REVEAL analysis cohort; SD, standard deviation; WHO FC, World Health Organization functional class.

Supplemental Table IV. SERAPHIN eligibility criteria adjusted for Sensitivity RAC-A

Parameter	SERAPHIN eligibility criteria	Adjusted criteria threshold
Inclusion criteria		
mPAP	>25 mmHg	>20 mmHg
PAWP	≤15 mmHg	≤23 mmHg
PVR	>320 dyn·sec·cm ⁻⁵	>84.8 dyn·sec·cm ⁻⁵
Exclusion criteria		
SBP	<100 mmHg	<90 mmHg
Body weight	<40 kg	<36.5 kg

mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAC, REVEAL analysis cohort; SBP, systolic blood pressure.

Supplemental Table V. Baseline characteristics of the patients in the analysis cohorts of REVEAL

Variable	REVEAL RAC	REVEAL Ex-RAC	REVEAL Sensitivity RAC-A	REVEAL Ex-Sensitivity RAC-A	REVEAL Sensitivity RAC-B	REVEAL Ex-Sensitivity RAC-B
	n = 734	n = 2781	n = 1013	n = 2502	n = 391	n = 343
Female, n (%)	595 (81.1)	2132 (76.7)	829 (81.8)	1898 (75.9)	311 (79.5)	284 (82.8)
Age, years, mean±SD	52.3±14.7	50.8±17.3	52.4±14.9	50.6±17.5	51.9±15.1	52.7±14.4
SBP, mmHg, mean±SD	120.3±14.9	115.8±18.2	118.1±16.6	116.2±18.1	121.0±14.7	119.4±15.0
Heart rate, bpm, mean±SD	84.0±14.7	83.0±15.3	83.8±14.8	82.9±15.3	84.8±15.4	83.2±13.8
BMI, kg/m ² , mean±SD	28.8±6.4	27.8±7.5	28.9±6.7	27.6±7.5	28.5±6.1	29.1±6.7
SvO ₂ , %, mean±SD	62.8±9.5	64.6±9.9	63.4±9.6	64.5±10.0	62.2±10.0	63.4±9.1
PVR, dyn·sec·cm ⁻⁵ , mean±SD	888±520	797±579	816±507	820±588.2	911±517	861±478
mRAP, mmHg, mean±SD	9.1±5.5	9.1±5.5	9.1±5.5	9.0±5.4	9.2±5.4	8.9±5.5
Borg Index, mean±SD	3.1±2.0	3.1±2.1	3.2±2.1	3.0±2.0	3.1±2.0	3.1±2.0
6MWD, m, mean±SD	359±125.2	361±129.1	362±123.5	350±130.7	354.1±127.8	365.4±122.2
WHO FC, n (%)						
I	56 (7.6)	182 (7.5)	79 (7.8)	159 (7.4)	31 (7.9)	25 (7.3)
II	263 (35.8)	846 (34.9)	375 (37.0)	734 (34.2)	129 (33.0)	134 (39.1)
III	377 (51.4)	1216 (50.2)	504 (49.8)	1089 (50.8)	206 (52.7)	171 (49.9)
IV	38 (5.2)	180 (7.4)	55 (5.4)	163 (7.6)	25 (6.4)	13 (3.8)
Missing	0	357	0	357	0	0
Use of medications for PAH, n (%)						
Yes	644 (87.7)	2181 (78.4)	891 (88.0)	1934 (77.3)	301 (77)	343 (100)
PAH classification, n (%)						
Idiopathic	382 (52.0)	1263 (45.4)	515 (50.8)	1130 (45.2)	215 (55.0)	167 (48.7)

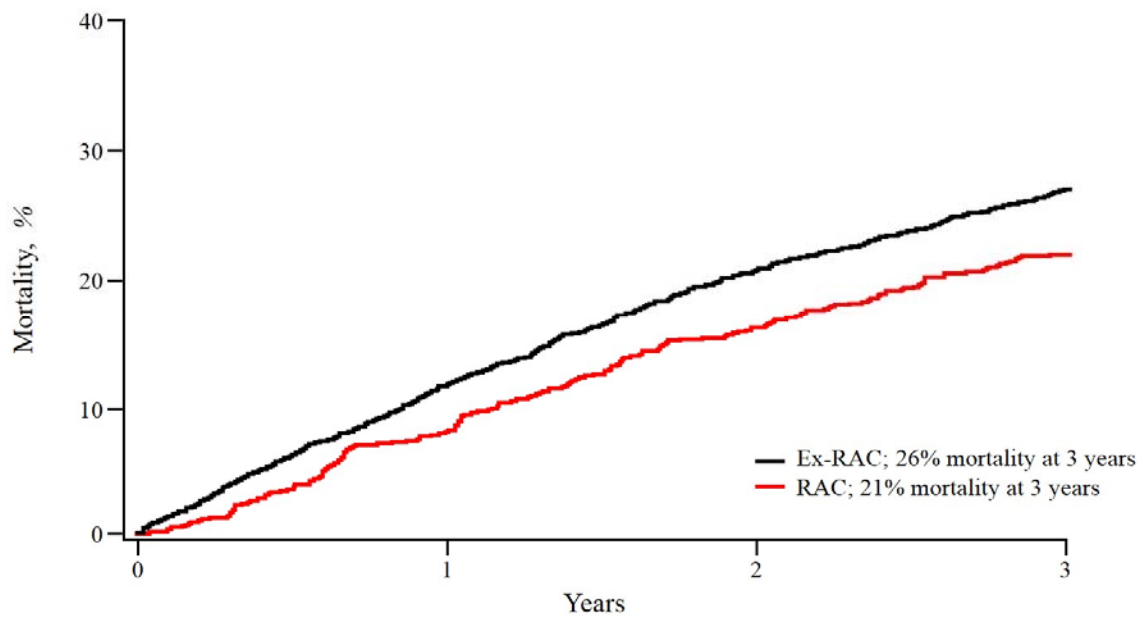
Heritable	32 (4.4)	65 (2.3)	41 (4.1)	56 (2.2)	13 (3.3)	19 (5.5)
Associated with CTD	220 (30.0)	670 (24.1)	314 (31.0)	576 (23.0)	117 (29.9)	103 (30.0)
Associated with congenital shunts	42 (5.7)	332 (11.9)	58 (5.7)	316 (12.6)	18 (4.6)	24 (7.0)
Associated with HIV infection	10 (1.4)	50 (1.8)	14 (1.4)	46 (1.8)	3 (0.8)	7 (2.0)
Associated with drug use/toxin exposure	48 (6.5)	128 (4.6)	71 (7.0)	105 (4.2)	25 (6.4)	23 (6.7)
Other	0	273 (9.8)	0	273 (10.9)	0	0
Geographical region, n (%)						
North America (inc. Canada)	734 (100)	2781 (100)	1013 (100)	2502 (100)	391 (100)	343 (100)
Rest of World	0	0	0	0	0	0

6MWD, 6-minute walk distance; BMI, body mass index; bpm, beats per minute; CTD, connective tissue disease; ex-RAC, patients excluded from the REVEAL analysis cohort; ex-Sensitivity RAC-A, patients excluded from the REVEAL sensitivity analysis cohort A; ex-Sensitivity RAC-B, patients excluded from the REVEAL sensitivity analysis cohort B; HIV, human immunodeficiency virus; mRAP, mean right atrial pressure; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; RAC, REVEAL analysis cohort; Sensitivity RAC, REVEAL sensitivity analysis cohort; SBP, systolic blood pressure; SvO₂, mixed venous oxygen saturation; WHO FC, World Health Organization functional class.

Supplemental Table VI. Sensitivity analyses of observed vs predicted mortality in SERAPHIN

Sensitivity Analyses	Placebo vs predicted HR (95% CI)	Macitentan 10 mg vs predicted HR (95% CI)
1) Baseline PAH therapy included as a covariate in the survival prediction model	0.89 (0.64, 1.17)	0.65 (0.46, 0.91)
2) Sensitivity RAC-A used to develop survival prediction model	0.90 (0.67, 1.22)	0.69 (0.50, 0.97)
3) Sensitivity RAC-B used to develop survival prediction model	0.88 (0.66, 1.19)	0.68 (0.48, 0.95)

Sensitivity analyses of observed mortality for patients receiving placebo or macitentan 10 mg in SERAPHIN compared with predicted mortality for the overall SERAPHIN patient population had they received real-world treatment. Sensitivity analysis performed using: 1) RAC ($n = 734$) to develop the survival prediction model with baseline PAH therapy included as a covariate, 2) Sensitivity RAC-A ($n = 1013$), comprising the 734 RAC patients and an additional 279 REVEAL patients who were included after the thresholds for some criteria were adjusted to reflect the enrolled SERAPHIN population, to develop the survival prediction model, or 3) Sensitivity RAC-B comprising the 391 RAC patients who were not receiving ERA therapy at baseline to develop the survival prediction model. CI, confidence interval; ERA, endothelin receptor antagonist; HR, hazard ratio; RAC, REVEAL analysis cohort.



Supplemental Figure I. Observed mortality comparisons between REVEAL patients included in the RAC and those excluded from the RAC

RAC: $n = 734$; Ex-RAC: $n = 2781$.

Ex-RAC, Patients excluded from the REVEAL analysis cohort; RAC, REVEAL analysis cohort.

SUPPLEMENTAL REFERENCES

1. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, Mittelholzer CM, Perchenet L, Sastry BK, Sitbon O, Souza R, Torbicki A, Zeng X, Rubin LJ, Simonneau G and Investigators S. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med.* 2013;369:809-18. doi: 10.1056/NEJMoa1213917
2. Opsumit® (macitentan). *US Prescribing Information, March.* 2017. doi: <https://opsumit.com/opsumit-prescribing-information.pdf>. Date last accessed March 2018