

Relationship Between Time From Diagnosis and Morbidity/Mortality in Pulmonary Arterial Hypertension

Results From the Phase III GRIPHON Study

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e-Table 1: Prognostic value of time from diagnosis for long-term outcome in adjusted and unadjusted Cox models

	Time from diagnosis	Age*time from diagnosis interaction	PAH background therapy*time from diagnosis interaction	Number of baseline low risk criteria*time from diagnosis interaction
Base model (unadjusted) [§] p value	0.0005	-	0.0485	-
Model 1 (adjusted) [†] p value	0.0053	0.3660	0.0798	-
Model 2a (unadjusted) [¶] p value	0.0077	-	-	0.9948
Model 2b (adjusted) [‡] p value	0.0082	-	0.0941	0.9703

[§]Base model includes treatment group, time from diagnosis, PAH background therapy as covariates plus the interaction terms treatment*time from diagnosis, and time from diagnosis*PAH background therapy. [†]Model 1 individual severity measures: base model plus sex, race, etiology, age, geographical region, individual severity measures of baseline WHO FC, baseline 6MWD, baseline NT-proBNP, and the interaction terms treatment*time from diagnosis, time from diagnosis*PAH background therapy and age*time from diagnosis. [¶]Model 2a: low risk criteria, treatment group, time from diagnosis and number of baseline low-risk criteria¹ as covariates plus the interaction term time from diagnosis*number of low risk criteria. Low risk criteria were defined as WHO FC I-II, 6MWD > 440 m, or NT-proBNP of < 300 ng/L. WHO FC: World Health Organization functional class; 6MWD: 6-minute walk distance. [‡]Model 2b: low risk criteria expanded - base model plus sex, race, etiology, age, geographical region, and the number of baseline low-risk criteria¹. The interaction terms treatment*time from diagnosis, treatment*PAH background therapy, time from diagnosis*PAH background therapy, treatment*time from diagnosis*PAH background therapy, and time from diagnosis*number of low risk criteria were included.

e-Table 2: Comparison of the treatment effect of selexipag versus placebo (time to morbidity/mortality event) by time from diagnosis in adjusted and unadjusted Cox models

	Time from diagnosis ≤ 6 months	Time from diagnosis > 6 months	Treatment*time from diagnosis interaction p-value
Adjusted model* HR (95% CI)	0.45 (0.33–0.63)	0.74 (0.57–0.96)	0.0219
Unadjusted model [†] HR (95% CI)	0.45 (0.33–0.63)	0.70 (0.54–0.91)	0.0391

*Model adjusted for treatment group, time from diagnosis, sex, race, etiology, age, geographical region, baseline WHO FC, baseline 6MWD and baseline NT-proBNP as covariates and age*time from diagnosis and treatment*time from diagnosis as interaction terms. [†]The model included treatment group and time from diagnosis as covariates and the interaction term treatment*time from diagnosis. 6MWD: 6-minute walk distance; CI: confidence interval; HR: hazard ratio; NT-proBNP: N-terminal pro brain natriuretic peptide; PAH: pulmonary arterial hypertension; WHO FC: World Health Organization functional class.

e-Table 3: Comparison of the effect of PAH therapy at baseline and time from diagnosis on the treatment effect of selexipag versus placebo (time to morbidity/mortality event) in unadjusted and adjusted Cox models

	Time from diagnosis \leq 6 months		Time from diagnosis $>$ 6 months		Treatment*time from diagnosis interaction p-value
	No PAH therapy at baseline	PAH therapy at baseline	No PAH therapy at baseline	PAH therapy at baseline	
Adjusted model* HR (95% CI)	0.47 (0.28–0.79)	0.44 (0.29–0.68)	0.99 (0.38–2.56)	0.73 (0.56–0.96)	0.1805
Unadjusted model [†] HR (95% CI)	0.48 (0.29–0.81)	0.44 (0.29–0.66)	0.89 (0.35–2.24)	0.69 (0.53–0.91)	0.2547

*Model adjusted for treatment group, time from diagnosis, PAH therapy at baseline, sex, race, etiology, age, geographical region, baseline WHO FC, baseline 6MWD, baseline NT-proBNP, and the interaction terms treatment*time from diagnosis, treatment*PAH background therapy, time from diagnosis*PAH background therapy, age*time from diagnosis and treatment*time from diagnosis*PAH background therapy. [†]The model included treatment group, time from diagnosis and PAH background therapy as covariates and the interaction terms treatment*time from diagnosis, treatment*PAH background therapy, time from diagnosis*PAH background therapy and treatment*time from diagnosis*PAH background therapy. 6MWD: 6-minute walk distance; CI: confidence interval; HR: hazard ratio; NT-proBNP: N-terminal pro brain natriuretic peptide; WHO FC: World Health Organization functional class.

e-Table 4: Individualized maintenance dose according to time from diagnosis

		Time from diagnosis \leq 6 months	Time from diagnosis $>$ 6 months
Dose groups	Twice-daily dose	Selexipag N = 207 n (%)	Selexipag N = 368 n (%)
	0	5 (2.4)	10 (2.7)
Low-dose group (200–400 μ g)	200	23 (11.1)	45 (12.2)
	400	25 (12.1)	40 (10.9)
Medium-dose group (600–1000 μ g)	600	21 (10.1)	41 (11.1)
	800	31 (15.0)	51 (13.9)
	1000	12 (5.8)	23 (6.3)
High-dose group (1200–1600 μ g)	1200	15 (7.2)	27 (7.3)
	1400	12 (5.8)	29 (7.9)
	1600	62 (30.0)	101 (27.4)
Other than per-protocol dosing	N/A	1 (0.5)	1 (0.3)

Safety analysis set. The individualized maintenance dose is defined as the selexipag b.i.d. dose to which the patient was exposed for the longest duration in the maintenance period or, for patients who did not enter the maintenance period, as the highest tolerated selexipag b.i.d. dose to which the patient was exposed during the titration period. b.i.d: twice daily; N/A: not applicable.

e-Appendix 1: List of Independent Ethics Committees and Institutional Review Boards

Center	Independent Ethics Committee/Institutional Review Board (Chairperson)	Approval number
Argentina		
6004 6007 (Central)	Comité Independiente de Ética para Ensayos en Farmacología Clínica (FEFYM) (Luis Zieher)	N/A
6001	Comité Institucional de Ética de Investigación en Salud (CIEIS) (Adrián Kahn)	N/A
6004	Comité de Docencia e Investigación del Instituto de Cardiología de Corrientes (María del Carmen Bangher)	N/A
6005	Comité de Ética en Investigación Clínica de la Federación Círculo Católico de Obreros y Fundación CIDEA (CEIFyC) (Fernando A. Díaz Couselo)	N/A
6006	Comité de Revisión Institucional del Hospital Británico (Federico Bottaro)	372
6007	Comité de Ética en Investigaciones Biomédicas – Sanatorio Otamendi y Miroli S.A. (Myriam Edith Levi)	N/A
6008	Comité Independiente de Ética para Ensayos en Farmacología Clínica (FEFYM) (Julio César Figal)	N/A
Australia		
1008 1009 (Central)	St Vincent’s Hospital (Melbourne) Human Research Ethics Committee (D) (Rosalba Drummond)	10/SVH/20
1001	Tasmania Health & Medical Human Research Ethics Committee (Peter Mudge)	H11139
1002	Royal Adelaide Hospital Research Ethics Committee (Andrew Thornton)	100616
1003	Southern Adelaide Clinical Human Research Ethics Committee (David Gordon)	218.10
1004 (Central)	St. Vincent’s Hospital Human Research Ethics Committee (Sarah Charlton)	09/SVH/150
1005 (Central)	St. Vincent’s Hospital Human Research Ethics Committee (Sarah Charlton)	09/SVH/150
1006	Royal Perth Hospital Human Research Ethics Committee (Prof. Frank Van Bockxmeer)	2010/054
1007	The Prince Charles Hospital - Human Research Ethics Committee (Denman Russell)	09/QPCH/173
1008 (Central)	St Vincent’s Hospital (Melbourne) Human Research Ethics Committee (D) (Rosalba Drummond)	10/SVH/20
1009	Melbourne Health Research Directorate (Jessica Turner / Angela Watt)	10/SVH/20
1010 ^a (Central)	St. Vincent’s Hospital Human Research Ethics Committee (Sarah Charlton)	09/SVH/150
Austria		

1101 1102 (Central)	Ethikkommission der Medizinischen Universität Wien und des Allgemeinen Krankenhauses der Stadt Wien (Ernst Singer)	395/2010
Belarus		
6101	LEC of Minsk Regional Clinical Hospital (Viacheslav Solodukho)	02040/2585
6102	LEC of Health Institution "9th City Clinical Hospital" (Tatiana Anatolievna Kamenetskaya)	01-11-14/8736
6103	LEC of the Republican Scientific-Practical Center "Cardiology" (Natalia Anatolyevna Kazaeva)	32/10.10
Belgium		
1201 1202 (Central)	Faculteit Geneeskunde Commissie voor Medische Ethiek/Klinisch Onderzoek (Walter Van den Bogaert)	P2010/118
1201	Comité d'Éthique CUB Hôpital Erasme (Christian Melot)	P2010/118
1202	Faculteit Geneeskunde Commissie voor Medische Ethiek/Klinisch Onderzoek (Walter Van den Bogaert)	
Canada		
1301	IRB - Comite d'Éthique de la Recherche UCPQ (Frank Molin)	20532
1302	IIRB - University of Manitoba School of Medicine Biomedical Research Ethics Board (Lindsay Nicole)	B2010:020
1303	University Health Network Research Ethics Board Office (Alan Barolet)	10-0087B
1304	Research Ethics Office - University of Saskatchewan BioMedical Research Ethics Board (Jim Blackburn)	10-14
1305	University of Ottawa Heart Institute Human Research Ethics Board Ottawa Hospital, Civic Campus (James Robblee)	2010612-01H
1306	University of British Columbia Clinical Research Ethics Board Office (Peter Loewen)	H10-00053
1307	University of Alberta Health Research Ethics Board - PAH / PULM (Shane Kimber)	00011835
1308	Research Ethics Committee Hopital General Juif - Jewish General Hospital (Vasiliki Bessy Bitzas)	10-138
Chile		
6201 (Central)	Comite De Etica Cientifico Servicio De Salud Metropolitano Central (Emiliano Soto Romo)	N/A
6201	Comité de Ética en Investigacion de la Escuela de Medicina de la Pontificia Universidad Católica de Chile (Beatriz Shand Klagges)	10-142
6202	Comité de Ética Cientifico Servicio de Salud Metropolitano Oriente (Andres Stuardo)	N/A
6203	Comité de Ética Cientifico Servicio de Salud Metropolitano Oriente (Andres Stuardo)	N/A

China		
1401	Ethics Committee of Peking Union Medical College Hospital for Clinical Trials (Yuangong Shan)	N/A
1402	Ethics Committee of Shanghai Pulmonary Hospital (Wei Ding)	2011L00082
1403	Ethics Committee of Cardiovascular Institute & Fuwai Hospital for Clinical Trials (Xiansheng Cheng)	2011L00082
1404	Ethics Committee of Guangdong General Hospital (Nianqiao Zhang)	2011L00082
1405	Ethics Committee, Renji Hospital, School of Medicine, Shanghai Jiao Tong University (Xianming Kong)	2011L00082
1406	Ethics Committee, Renji Hospital, School of Medicine, Shanghai Jiao Tong University (Xianming Kong)	36B
1407	Ethics Committee of Beijing Shijitan Hospital, CMU (Janli Xu)	2011L00082
Colombia		
6303	Comité de Ética e Investigaciones, Fundación Clínica Shaio (Jorge Alberto Aldas Gracia)	N/A
6304	Comité de Ética en Investigación Clínica (Sinay Arevalo)	00007736
Czech Republic		
1601 (Central)	Ethics Committee - General Faculty Hospital of Prague (Josef Šedivý)	N/A
Denmark		
1701 1702 (Central)	Den Videnskabetiske Komité for Region Midtjylland (Marianne Kleis Møller)	N/A
France		
1901 1902 ^a 1903 1904 1905 1906 (Central)	CPP Ile-de-France VII (Françoise Boissy)	N/A
Germany		
2001	Ethikkommission der Medizinischen Fakultät an der Ernst-Moritz-Arndt-Universität Greifswald, Institut für Pharmakologie (Werner Siegmund)	LV 16/10
2002	Ethikkommission der Medizinischen Fakultät "Carl Gustav Carus" der TU Dresden (Wilhelm Kirch)	EK 205072010

2003	Landesamt für Gesundheit und Soziales, Geschäftsstelle der Ethik-Kommission des Landes Berlin (K. Thomas Moesta)	ZS EK 11 213/10
2004	Ethik-Kommission bei der Landesärztekammer Baden-Württemberg (Georg Hook)	B-AM-2010-073
2005	Ethikkommission der Medizinischen Fakultät, Universitätsklinikum (Christian Stroszczyński)	AFmu-225/210
2006	Ethik-Kommission des Medizinischen Hochschule Hannover (H. Tröger)	N/A
2007	Ethik-Kommission des Fachbereichs Medizin, Justus-Liebig-Universität Giessen (H. Tillmanns)	65/11
2008	Ethikkommission der Medizinischen Fakultät Heidelberg (Thomas Strowitzki)	AFmu – 225/2010
2009	Sächsische Landesärztekammer, Ethikkommission (Anke Schmieder)	EK-AMG-MCB-65/10-1
2010	Ethik-Kommission der Medizinischen Fakultät der Universität zu Köln (Walter Lehmacher)	10-306
Greece		
6401 6402 ^a 6403 ^a (Central)	National Ethics Committee (Athanasios Papavasileiou)	431/04.08.10
6401	Committee of Medical Deontology and Clinical Research Ethics (Eleni Binou)	431/04.08.10
6402 ^a	EC University Hospital of Alexandroupolis, Cardiology Clinic (Vasilios Vargemezis)	431/04.08.10
6403 ^a	EC AHEPA Universtiy General Hospital of Thessaloniki (Vaso Kalampoka)	431/04.08.10
Hungary		
3901 3902 3903 3904 3905 (Central)	Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottság (Medical Research Council Ethics Committee for Clinical Pharmacology) (Zsuzsanna Fürst)	OGYI/22031-6/2010
India		
6501	Central Ethics Committee, Apollo Hospital Group (Rao Ranga)	N/A
6502	Central Ethics Committee, Apollo Hospital Group (Rao Ranga)	N/A
6503	Care Hospital Care Convergence Centre (Ethics Committee - Care Hospitals) (Justice N Subba Raju)	A-CH2011-52939
6504	Sanjivani Hospital Ethics Committee, Sanjivani Hospital (Supriya Malhotra)	A-CH2011-46084
6505	Institutional Ethics Committee, Frontier Lifeline - Dr. K.M. Cherian Heart Foundation, International Centre for Cardio-Thoracic and Vascular Diseases (V. Chokalingam)	A-CH2011-46094
Ireland		
5001 (Central)	Mater Misericordiae University Hospital and Mater Private Hospital Research Ethics Committee (Malcolm Kell)	CT-1478/2/1

Israel		
4001	The Helsinki Committee Hadassah Medical Organization (Tova Chajeck)	1734/2090
4002	The Helsinki Committee Chaim Sheba Medical Center (Dror Harats)	7431-09-SMC
4003 ^a	The Helsinki Committee Tel Aviv Sourasky Medical Center (Marcel Topilsky)	0558-09-TLV
4004	Helsinki Committee Kaplan Medical Center (Lidia Arcabi)	20090689
4005	Helsinki Committee Rabin Medical Center (Meir Lahav)	20120978
4006	Helsinki Committee Carmel Medical Center (Ruth Kitzis)	021-21712/.21-29087
Italy		
2301 2302 2303 ^a 2304 (Central)	Comitato Etico Indipendente dell'Azienda Ospedaliero-Universitaria Policlinico S. Orsola-Malpighi di Bologna_PADIGLIONE 3 (Nicola Montanaro)	N/A
2301	Comitato Etico dell'Azienda Ospedaliera Universitaria della Seconda Università degli Studi di Napoli - dell'Azienda Ospedaliera dei Colli (Liberato Berrino)	CE/64/2010
2302	Comitato Etico Indipendente dell'Azienda Ospedaliero-Universitaria Policlinico S. Orsola-Malpighi di Bologna PADIGLIONE 3 (Nicola Montanaro)	N/A
2303 ^a	Comitato Etico dell'Azienda Ospedaliera Universitaria della Seconda Università degli Studi di Napoli - dell'Azienda Ospedaliera dei Colli (Liberato Berrino)	RIF CE /49/2010
2304	Comitato Etico dell'Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione di Palermo (Mario Palazzo Adriano)	IRRB /26/2010
Republic of Korea (South)		
7101	Yonsei University Health System Institutional Review Board (Seung Min Kim)	4-2010-0141
7102	Gachon University Gil Hospital Institutional Review Board (Suk Young Kim)	GIRBA2279
7103	The Catholic University of Korea, Seoul St. Mary's Hospital Institutional Review Board (Seung-Kew Hoon)	KC10MGGT0233
7105	Seoul National University Hospital Institutional Review Board (Jae-Seung Paick)	H-1004-067-316
7106	Samsung Medical Center Institutional Review Board (Suk Koo Lee)	N/A
Malaysia		
6601	Ethics Committee Institute Jantung Negara (Thiru Kumar Namasiwayam)	I JNEC 7 02/10 (3)
Mexico		

6701	Comision de Bioetica del Instituto Nacional de Cardiologia "Ignacio Chávez" (Angel Buenaventura Romero Cardenas)	INC/CEI/333/2014
6703	Comite Institucional de Investigacion Biomeica en Humanos (Arturo Galindo Fraga)	N/A
Netherlands		
4102 4103 4105 4106 (Central)	EC-VU Medisch Centrum, Amsterdam (J. A. Rauwerda)	
4102	Medisch Ethische Toetsings commissie, Academisch Ziekenhuis Maastricht (R. van Gils)	4430/CB/fh
4103	EC-VU Medisch Centrum, Amsterdam (J. A. Rauwerda)	N/A
4105	Medisch Ethische Toetsing Commisie, Erasmus MC-kamer Z 504 (C.P. Bron-van Vliet)	RvB/metc/120722
4106	Verenigde Commissies Mensgebonden Onderzoek (VCMO) (V.H.M. Deneer)	NL30641.029
Peru		
6802 (Central)	Comité de ética Asociación Benéfica Prisma (Salomon Zavala Sarrio)	114-2010-CIEI-HNCH
6802	Comisión Reguladora de Estudios Clinicos del Complejo Hospitalario San Pablo (Agustin Iza Stoll)	N/A
6803	Comite de etica del Hospital Nacional Edgardo Rebagliati Martins (Julio Alfaro Mantilla)	00003285
Poland		
2601 2602 2603 2604 (Central)	Komisja ds. Etyki Badań Naukowych przy Instytucie GruŹlicy i Chorób P ³ uc (Jan Kuœ)	116/2011
Romania		
6901 6902 (Central)	National Bioethics Committee for Medicines and Medical Devices (Dinu Antonescu)	N/A
Russian Federation		
7001 7002 7003 7004 7005 7006 7007 7008 7009 7010 (Central)	Ethics Council at Minzdravsocrazvitiya (Alexander Chuchalin)	N/A

7001	Ethics Committee of the Federal State Budgetary Institution "Federal Medical Scientific Center named after V.A. Almazov" of the Ministry of Health Care of the Russian Federation (Edvard Bergard)	66 21 June 2010
7002	Ethics Committee of the Federal State Budgetary Institution "Scientific Research Institute of Rheumatology named after V.A.Nasonova" of RAMS (Boris Sergeevich Belov)	20 17 September 2010
7003	Local Ethics Committee of Federal State Budgetary Institution "Russian Cardiology Scientific and Production Complex" (Mikhail Ruda)	157 04 October 2010
7004	Ethics Committee at the Federal State Budgetary Institution "Scientific Research Institute of Pulmonology" of the Federal Medical and Biological Agency (Andrey Chernyaev)	01 October 2010
7005	Biomedical Ethics Committee of Tomsk Research Institute of Cardiology (Georgy Chernogoryuk)	15SEP10
7006	Local Ethics Committee at GBUZ SO "Sverdlovsk Regional Clinical Hospital #1" (Vladimir Viktorovich Bazarnyy)	28.01.2010
7007	Local Ethics Committee of Federal State Budgetary Institution "Scientific Research Institute of Systemic Problems of Cardiovascular Diseases" (Evgeniy Grigoriev)	16 September 2010
7008	Local Ethics Committee of Tomsk Regional Clinical Hospital (Galina Vladimirovna Semke)	EP 30/07/14
7009	Local Ethics Committee at Municipal Health Care Institution "City Hospital #5" (Svetlana Vladimirovna Kovchina)	50 02.08.2010
7010	Local Committee at Limited Liability Company, Consultative Diagnostic centre "Healthy joints" (Alexandra Sergeevna Mikhaylova)	06 FEB13
Serbia		
3801	Klinički Centar Srbije, Etički Odbor (Zivan Maksimoviæ and Branislav Stefanovic)	605/2010/4000
3802	Kliničko Bolnički Centar Zemun, Etički Komitet (Biljana Putnikoviæ)	605/2010/4000
Singapore		
2901 ^a 2903 (Central)	SingHealth Centralised Institutional Review Board, Domain C (Jagadesan Raghuram)	2009/973/C
Slovakia		
2701 2702 (Central)	Etická komisia NÚSCH (Dagmar Kuèerová)	N/A
2701	Etická komisia VÚSCH (Stanislav Juhás)	16/12/2009
2702	Etická komisia NÚSCH (Dagmar Kuèerová)	N/A

Spain		
3201 3202 3204 (Central)	Hospital Vall d' Hebrón, Fundacio per la Recerca (Soledad Gallego)	8 enero 2010
3201	Comite Etico de Investigacion Clinica, Hospital Clinic I Provincial de Barcelona (Xavier Carné)	26 de enero de 2010
3202	Hospital Vall d' Hebrón, Fundacio per la Recerca (Soledad Gallego)	ESP.A 13/10/2009
3204	Comité Etico de Investigacion Clinica, Hospital Universitario "12 de Octubre" (María del Puy Goyache Goñi)	09/274
Sweden		
3301 3302 3303 3305 (Central)	Regionala Etiksprövningsnämnden i Göteborg (Marika Estreen)	N/A
Switzerland		
3401	Ethikkommission Nordwest- und Zentralschweiz (EKNZ) (André Perruchoud)	109/10
3402	Commission Centrale d'Ethique de la Recherche (CCER) du Canton de Genève (Bernard Hirschel)	10/145
3403 ^a	Commission cantonale (VD) d'éthique de la recherche sur l'être humain / Lausanne (Patrick Francioli)	210/10
3404 ^a	Kantonale Ethikkommission Bern (KEK) (Christian Seiler)	104/10
3406	Kantonale Ethikkommission St.Gallen (EKSG) (Susanne Driessen)	EKSG 10/063
Taiwan		
4501	Research Ethics Committee National Taiwan University Hospital (Hong-Nerng Ho)	No. 1033705197
4502	IRB Kaohsiung Veterans General Hospital (Jin-Shiung Cheng)	No.0990014515
Thailand		
7202	The Khon Kaen University Ethics Committee in Human Research (Polasak Jeeravipoolvarn)	IRB/IEC No. HE 531179
Turkey		
4901 4902 4903 4904 (Central)	Istanbul Universitesi Týp Fakóltesi Etik Kurulu başkanlýđý (Üresin Yađiz)	N/A
Ukraine		

7301 7302 7303 7304 (Central)	Central Ethics Committee of the Health Ministry of Ukraine (Vasyl Kornatskiy)	N/A
7301	Local Ethic Committee of Lviv Regional Clinical Hospital (Igor Stepanovych Zakalyuzhnyi)	EC/539-1
7302	LEC of Municipal Institution "Dnipropetrovsk Regional Clinical Centre of Cardiology and Cardiosurgery" (Oleksandr Novichikhin)	EC/539-2
7303	Local Ethics Committee of Public Institution "F.H. Yanovskyi Physiology and Pulmonology National Institute under the Ukrainian Academy of Medical Sciences" (Vasyl Mykhaylovych Melnyk)	EC/539-4
7304	Local Ethics Committee of Health Care Municipal Institution "City Clinical Hospital #13" (Viktoria Danylivna Reznikova)	EC/539-3
United Kingdom		
3501 3503 3505 (Central)	London – West London & GTAC, Health Research Authority, National Research Ethics Service (Catherine Urch)	09/H0707/95
USA		
(Central)	IRB - Western Institutional Review Board (Theodore D. Schultz)	12-154
3101	IRB - The University of Michigan Medical School (Alan Sugar)	IRB00001995
3102	IRB - University of Texas Southwestern Medical Center - PAH (NA – IRB does not disclose any member names)	CR00006273/00000083
3103 ^s	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-680054-1
3106	Christiana Care Institutional Review Board (Gary Johnson Steven Kushner)	32071
3107 ^a	IRB - Mercy Hospital (James Hopson)	IRB00004814
3108	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-837583-1
3109	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-620222-1
3111	IRB - University of California - Davis Medical Center (John Anderson)	235847
3112	IRB - Cedars-Sinai Medical Center (Stephen Lim)	CR00008779/Pro00022187
3113	IRB - University of Texas Health Science Center - The Committee for the Protection of Human Subjects (Catherine Thompson)	HSC-MS-10-0257
3114	IRB - Columbia University Medical Center (Marilyn Morris)	AAAE8349

3115	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-838660-1
3118	IRB - Henry Ford Health System IRB (Human Rights Committee) (Timothy Roehrs)	6244
3120	IRB - Johns Hopkins (Joseph Carrese)	JHM-IRB5
3123 ^s	IRB - Mayo Clinic Foundation (Rita Basu)	10-004626
3124	IRB - Louisiana State University Health Sciences Center (Kenneth Kratz)	7568
3125	IRB - Vanderbilt University (James A.S. Muldowney III)	101569
3126	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-837583-1
3127	IRB - University of California - San Diego - Human Research Protection Program (Michael Caligiuri)	110982
3128 ^a	IRB - KUMC Human Subjects Committee (Valerie Schroeder)	12506
3129	IRB - University of Pennsylvania, Office of Regulatory Affairs (Emma Meagher)	813199
3152	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-856007-1
3154 ^a	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-649949-1
3155	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-806245-1
3156	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-626739-1
3157 ^a	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-609472-1
3158	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-837583-1
3159 ^a	IRB - Chesapeake Center for IRB Intelligence (Jeffrey Wendel)	00005534
3160	IRB - Washington University School of Medicine - Human Research Protect. Office (Jonathan M. Green)	201106080
3161 ^a	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-649949-1
3162 ^a	IRB - Wake Forest University Health Sciences (Ross Holmes)	00012022
3163 ^a	IRB - St. Luke's Medical Group (John Buettner)	00002453
3164	IRB - Human Assurance Committee OHRP (Ivy Tilman)	HAC1005221
3165	IRB - Barnabas Health Newark Beth Israel Institutional Review Board (Victor Parsonnet)	2010.02
3166	IRB - William Beaumont Human Investigation Committee (John M. Koerber)	2010-089
3167 ^a	IRB - Wellspan Health (Jonathan E. Rhoads, Jr.)	0910020
3168	IRB - Baylor College of Medicine - Office of Research (David Schlueter)	H-26937
3169	IRB - Indiana University Purdue University at Indianapolis Human Subjects Office (John Baumann)	1010002211
3171	IRB - Duke University Health System Institutional Review Board (John Falletta)	00028861

3172	IRB - Aurora (Brian Weir)	10-114; 104.504
3173 ^a	IRB - Partners Human Research Committee (Elizabeth Hohmann)	2010P002434
3174	IRB - Tufts New England Medical Center & Tufts University Health Sciences (Andreas Klein)	9798
3175	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-786712-1
3176	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-856007-1
3177	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-837583-1
3178	Veterans Affairs Greater Los Angeles Healthcare System - 151 IRB (Jacob Fleischmann)	2014-080925
3180	IRB - Biomedical Research Alliance Of New York (Ira Leviton Mark J. Sinnett)	12-02-230-01
3182 ^a	University of South Alabama IRB (W. Kevin Green)	12-154
3183	IRB - Thomas Jefferson University School of Medicine, Office of Human Research, Division of Human Subject Protection (J. Bruce Smith)	12C.468
3185	IRB - University Hospitals Case Medical Center (Sri Madan Mohan)	09-12-21
3187	IRB - Western Institutional Review Board (Theodore D. Schultz)	1-837583-1

^aSites that were initiated but did not enroll any subjects. N/A = not available.

e-Appendix 2: Methods for statistical analyses

Cox proportional hazard models included treatment group as a covariate and were either unadjusted or adjusted for sex (male, female), race (Caucasian/Hispanic, Asian, Black or Other), age (continuous variable), PAH etiology (idiopathic, heritable, drug- or toxin-induced, associated with connective tissue disease, congenital heart disease, HIV [human immunodeficiency virus] infection), geographical region (Asia, Eastern Europe [including Turkey], Latin America, North America, Western Europe and Australia [including Israel]), World Health Organization functional class (WHO FC; I–II, III–IV), 6-minute walk distance (6MWD; continuous variable) and N-terminal pro brain natriuretic peptide (NT-proBNP; low [< 300 ng/L], medium [300–1400 ng/L], high [> 1400 ng/L]) at baseline.

To assess the effect of time from diagnosis, the first adjusted Cox model additionally included time from diagnosis as a covariate, and treatment*time from diagnosis and age*time from diagnosis as interaction terms. A subsequent model was adjusted to assess the effect of PAH background therapy by additionally including PAH background therapy (yes/no) as a covariate and PAH background therapy*time from diagnosis as an interaction term. In a consecutive step, a further model added the interaction terms treatment*PAH background therapy, and treatment*time from diagnosis*PAH background therapy.

The influence of the number of low risk criteria (WHO FC I–II; 6MWD > 440 m; NT-proBNP level of < 300 ng/L¹) at baseline on the prognostic relevance of time from diagnosis was assessed by an adjusted Cox model that included time from diagnosis, number of low risk criteria, PAH background therapy, sex, race, etiology, age, and geographical region as covariates and time from diagnosis*number of low risk criteria, treatment*time from diagnosis, treatment*PAH background therapy, time from diagnosis*PAH background therapy and treatment*time from diagnosis*PAH background therapy as interaction terms. WHO FC, 6MWD and NT-pro-BNP were not included as covariates as the number of low risk criteria comprises these variables.

REFERENCES

- 1 Boucly, A, Weatherald, J, Savale, L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J* 2017; 50:1700889.