SUPPLEMENTARY MATERIAL

Title: Real-world management of PAH patients: Insights from EXPOSURE

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EXPOSURE Incident Prevalent manuscript

Supplementary Appendix

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Supplementary Methods

1. EXPOSURE Study design

EXPOSURE (EUPAS19085) is a post-authorisation safety study (PASS) to further characterise the safety profile of selexipag. The EXPOSURE study consists of two patient cohorts: the Selexipag cohort that includes patients initiating selexipag within 1 month of enrolment, at enrolment, or during observation, and the Other pulmonary arterial hypertension (PAH)-specific therapy cohort that includes patients initiating any other PAH-specific therapy (excluding calcium channel blockers) less than 1 month prior to enrolment or at enrolment and who were never treated with selexipag. Patients in the Other PAH-specific therapy cohort may initiate selexipag during the study; from the time of selexipag initiation they contribute to the Selexipag cohort and no longer to the Other PAH-specific therapy cohort. To minimise selection bias during patient recruitment, participating sites were requested to invite consecutive patients with PAH who meet the eligibility criteria for either cohort.

2. Cardiovascular comorbidities

Cardiovascular comorbidities included diabetes, systemic hypertension, body mass index (BMI) >30 kg/m^2, and historical evidence of reported significant coronary artery disease (defined as coronary arteriosclerosis, myocardial ischaemia [overall or myocardial infarction or unstable angina] or coronary revascularisation procedure).

3. Observations and assessments

Data were collected for each patient at the initiation of new PAH-specific therapy/throughout observation period as per routine clinical practice. The planned observation period for each patient enrolled in the study is at least 18 months or until the earliest of death, date of study discontinuation or study end. The following variables were collected: Study specifics, demographics, clinical characteristics, laboratory data, medical history, medication, outcomes, adverse events/serious adverse events (for Market Authorisation Holder products only, i.e., Sponsor products). Data on PAH-specific therapies taken within 12 months prior to, at, or after baseline were collected. Study outcomes were PAH-specific treatment patterns over time, all-cause or PAH-related hospitalisations, including start/end dates and reason for hospitalisation, and all-cause or PAH-related deaths, including date and cause of death.

4. Assessment of 1-year mortality risk

3-strata risk assessment

- One-year mortality risk category (low, intermediate, and high) was assessed using the COMPERA method[8] and determined based on availability of ≥2 baseline components (WHO functional class [WHO FC], 6-minute walk distance [6MWD], brain natriuretic peptide [BNP]/N-terminal [NT]-proBNP, mean right atrial pressure, cardiac index and/or mixed venous oxygen saturation). Only right heart catheterisation data ≤3 months prior to baseline were considered.

4-strata risk assessment

- For assessment of one-year mortality risk category (low, intermediate-low, intermediate-high, and high), baseline data for a minimum of two parameters were required, including BNP/ NT-proBNP and either WHO FC and/or 6MWD[3,4].

5. Definitions of PAH-specific therapy status

PAH-specific treatment status at baseline was classified as follows:

- Monotherapy if patients were untreated within 7 days prior to new PAH-specific therapy initiation, and did not initiate another PAH-specific therapy within the next 30 days,
- Double combination therapy if patients were untreated or on monotherapy within 7 days prior to new PAH-specific therapy initiation, and did not initiate another PAH-specific therapy within the next 30 days,
- Triple combination therapy if patients were untreated or on monotherapy/double combination therapy within 7 days prior to new PAH-specific therapy initiation, and did not initiate another PAH-specific therapy within the next 30 days.

6. Time to treatment escalation analysis

Only patients escalating treatment were included in this analysis; patients with more than three treatments at new PAH-specific therapy initiation were excluded. The follow-up time started on the day when the last component of the baseline PAH-specific combination therapy started. The follow-up

ended when treatment was escalated with the addition of a PAH-specific therapy during the observation period.

Supplementary tables

Table S1: Imputation rules for missing dates

Type of Date	If date is incomplete:
Start date of hospitalisation	Year missing: • No replacement Year present, month missing: • No replacement. Year and month present, day missing: • Impute day with 1st of the month. Missing dates before the new PAH-specific therapy initiation will be left as missing.
End date of hospitalisation	Year missing: • No replacement Year present, month missing: • No replacement Year and month present, day missing: • Impute the missing day with earliest of: last day of the month or the latest date among dates used for end date of hospitalisation imputation* during the respective year and month. Missing dates before the new PAH-specific therapy initiation will be left as missing.
Date of discontinuation of new PAH-specific therapy	In case a missing value occurs during the titration or dose adjustment period (e.g. for selexipag) and a start date for the next dose level is available, end date will be imputed as start date of next dose level – 1 day. In case during titration the exact start date of new dose level and end date of previous dose level are not known, but month and year of both are available and equal, then: • 14th of the month will be used for end date of first dose level and 15th the month for start date of the second dose level in case the start month of first dose level treatment differs from the end month of the first dose level. • In case start month and year and end month and year of first dose level are the same, last day of the month – 1 will be used for end date of first dose level and last day of the month will be used for the start date of the second dose level. • In case start month and year and end month and year of second dose level are the same, first day of the month + 1 will be used for start date of second dose level and first day of the month will be used for the end date of the first dose level. Otherwise, Year missing: • No replacement Year present, month missing: • If year is the same as year of at least one of the dates used for new PAH-specific therapy discontinuation date imputation*, impute with latest of the dates used for new PAH-specific therapy discontinuation* during the respective year. • If year is after the year of all of the dates used for new PAH-specific therapy discontinuation date imputation*, impute with 1st of January.

	Year and month present, day missing: • If year and month is after the year and month of all of the dates used for new PAH-specific therapy discontinuation date imputation*, impute with 1st day of the month. • If year and month is the same as the year and month of at least one of the dates used for the new PAH-specific therapy discontinuation date imputation*, impute with maximum of the dates used for new PAH-specific therapy discontinuation date imputation* during the respective year and month. • If year and month is before the year and month of all the dates used for new PAH-specific therapy discontinuation date imputation*, impute with the last day of the month.
Start date of the new PAH-specific therapy (excluding selexipag start date for late initiators)	1) In case no missing date on medication eCRF page, use the date from the medication eCRF page. 2) In case partial date available on the medication eCRF page, but no missing date on the baseline eCRF page, use the date from the baseline eCRF page. 3) In case the same date is missing on both the medication and the baseline eCRF pages: Year missing: • No replacement Year present, month missing: • No replacement Year and month present, day missing: • Impute day with 1st of the month.
Start date of selexipag (for those initiating during the observation period)	Year missing: • No replacement Year present, month missing: • No replacement Year and month present, day missing: • Impute day with 1st of the month.
PAH diagnosis date†	Year missing: • No replacement Year present, month missing: • No replacement Year and month present, day missing: • Impute day with 1st of the month.
Death date	Year missing: • No replacement Year present, month missing: • If year is the same as the year of at least one of the dates used for death date imputation*, impute with latest of the dates used for death date imputation + 1 day. • If year is after the year of all the dates used for death date imputation*, impute with the 1st day of the year. Year and month present, day missing: • If year and month is after the year and month of all the dates used for death date imputation*, impute with 1st day of the month.

	• If year and month is the same as the year and month of at least one of the dates used for death date imputation*, impute with minimum (end of the month; maximum of the dates used for death date imputation* during the respective year and month + 1 day). Missing dates before the new PAH-specific therapy initiation will be left as missing.

*****Dates used for end date of hospitalisation imputation, new PAH-specific therapy discontinuation date imputation and death date imputation: date of death (for end date of hospitalisation and new PAH-specific therapy discontinuation date imputations), date of study discontinuation, date of last visit before data cut (or visit date for death date imputation, excluding the date of the visit where death was recorded), date of hospitalisation (in case patient has several hospitalisations, some of which have non-missing/non-partial start dates), hospital end date (in case patient has several hospitalisations, some of which have non-missing/non-partial end dates), start date of treatment (PAH-specific therapy, other concomitant medications), date treatment interrupted (or discontinued for dates used for death date imputation) (PAH-specific therapy, other concomitant medications), date treatment dose changed (PAH-specific therapy), date of informed consent. Initiation will be left (new PAH-specific therapy discontinuation date imputation). †Patients with partial missing diagnosis date (i.e., day and/or month missing, but year always available) were allocated to the prevalent group. eCRF: electronic case report form; PAH: pulmonary arterial hypertension.

Table S2. List of Institutional Review Boards and Ethics Committees

Country	Site	Ethics Committee	Address	Central or Local
Denmark	01-001	Data Protection Agency (Datatilsynet)	Borgergade 28, 5.1300 København K	n/a
Sweden	02-001	Etikprövningsmyndigheten	Box 2110750 02 Uppsala Sweden	Local
	02-002	Etikprövningsmyndigheten	Box 2110 750 02 Uppsala Sweden	Central
	02-003	Etikprövningsmyndigheten	Box 2110 750 02 Uppsala Sweden Visiting address: Guldhedsgatan 5 A, hus 2, plan 4, 413 20 Göteborg Sweden	Central
Austria	03-001	EC of the medical university of Vienna	Borschkegasse 8b/6 1090 Wien, Österreich	Central
	03-002	EC of the medical university of Vienna	Borschkegasse 8b/6 1090 Wien, Österreich	Central
	03-003	EC of the medical university of Vienna	Borschkegasse 8b/6 1090 Wien, Österreich	Central
	03-004	EC of the medical university of Vienna	Borschkegasse 8b/6 1090 Wien, Österreich	Central
Germany	04-001	Ethikkommission der Charité - Universitätsmedizin Berlin	Landesamt für Gesundheit und Soziales Berlin Geschäftsstelle der Ethik-Kommission des Landes Berlin Fehrbelliner Platz 1 10707 Berlin	Central
	04-002	Ethikkommission der Charité - Universitätsmedizin Berlin	Landesamt für Gesundheit und Soziales Berlin Geschäftsstelle der Ethik-Kommission des Landes Berlin Fehrbelliner Platz 1 10707 Berlin	Central
	04-003	Ethik-Kommission der Friedrich-Schiller-Universität Jena an der Medizinischen Fakultät	Ethik-Kommission der Friedrich-Schiller-Universität Jena Postfach Bachstraße 18 07740 Jena	Local
	04-004	Ethikkommission der Medizinischen Fakultät Heidelberg	Alte Glockengießerei 11/1 69115 Heidelberg	Local
	04-005	Ethik-Kommission der Medizinischen Fakultät der Christian-Albrechts-Universität zu Kiel	Universitäts-Kinderklinik Schwanenweg 20 / 2. Stock / Zimmer: 13 und 53 D - 24105 Kiel	Local
	04-006	Ethik-Kommission der Otto-von-Guericke-Universität Magdeburg	Otto-von-Guericke-Universität Ethikkommission Leipziger Str. 44 39120 Magdeburg	Local
	04-007	Ethik-Kommission bei der Landesärztekammer Baden-Württemberg	Jahnstraße 40 70597 Stuttgart	Local
	04-008	Ethikkommission der Fakultät für Medizin der Technischen Universität München	Ismaninger Straße 22 81675 München	Local
	04-009	Ethik-Kommission der Medizinischen Hochschule Hannover	Ethik-Kommission der MHH - OE 9515 - Carl-Neuberg-Str. 1 30625 Hannover	Local

	04-010	Ethikkommission der Medizinischen Fakultät der Universität zu Köln	Gebäude 55, Kerpener Str. 62 50937 Köln	Local
	04-011	Ethik-Kommission an der Medizinischen Fakultät der Universität Leipzig	Käthe-Kollwitz-Straße 82, 04109 Leipzig	Local
	04-012	Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster	Gartenstr. 210 – 214 D-48147 Münster	Local
	04-013	Ethikkommission an der TU Dresden	Haus 101 Fiedlerstraße 33 01307 Dresden	Local
	04-014	Ethik-Kommission des Fachbereichs Medizin der Justus-Liebig-Universität Gießen	Klinikstraße 29 35392 Gießen	Local
	04-015	Ethikkommission der Charité - Universitätsmedizin Berlin	Landesamt für Gesundheit und Soziales Berlin Geschäftsstelle der Ethik-Kommission des Landes Berlin Fehrbelliner Platz 1 10707 Berlin	Central
	04-016	Ethikkommission der Charité - Universitätsmedizin Berlin	Landesamt für Gesundheit und Soziales Berlin Geschäftsstelle der Ethik-Kommission des Landes Berlin Fehrbelliner Platz 1 10707 Berlin	Central
	04-017	Ethik-Kommission der Ärztekammer Hamburg	Ärztekammer Hamburg Weidestr. 122 b 22083 Hamburg	Local
	04-018	Ethik-Kommission bei der Ärztekammer des Saarlandes	Faktoreistraße 4 66111 Saarbrücken	Local
	04-019	Ethik-Kommission an der Universitätsmedizin Greifswald Institut für Pharmakologie	Institut für Pharmakologie Felix-Hausdorff-Str. 3 17487 Greifswald	Local
	04-020	Ethikkommission der Charité - Universitätsmedizin Berlin	Landesamt für Gesundheit und Soziales Berlin Geschäftsstelle der Ethik-Kommission des Landes Berlin Fehrbelliner Platz 1 10707 Berlin	Central
	04-021	Ethik-Kommission - Landesärztekammer Rheinland-Pfalz	Deutschhausplatz 3 55116 Mainz	Local
	04-022	Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn	Biomedizinisches Zentrum Sigmund-Freud-Str. 25 53105 Bonn	Local
	04-023	Ethikkommission der Charité - Universitätsmedizin Berlin	Landesamt für Gesundheit und Soziales Berlin Geschäftsstelle der Ethik-Kommission des Landes Berlin Fehrbelliner Platz 1 10707 Berlin	Central
	04-024	Ethikkommission der Charité - Universitätsmedizin Berlin	Landesamt für Gesundheit und Soziales Berlin Geschäftsstelle der Ethik-Kommission des Landes Berlin Fehrbelliner Platz 1 10707 Berlin	Central
	04-025	Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster	Gartenstr. 210 – 214 D-48147 Münster	Local

	04-026	Ethik-Kommission an der Medizinischen Fakultät der RWTH Aachen	Templergraben 55, 52056 Aachen	Local
	04-027	Ethik-Kommission bei der Landesärztekammer Baden-Württemberg	Liebknechtstr. 33 70656 Stuttgart Germany	Local
Spain	05-001	CEIC Área 11 - Hospital 12 de Octubre	Centro de Actividades Ambulatorias, Bloque D, Planta 6ª, Unidad Admtva Address: Glorieta de Málaga, S/N Location: Madrid CP: 28041	Central
	05-002	CEIC Área 6 - Hospital Universitario Puerta de Hierro de Majadahonda	Dirección: C/ Joaquin Rodrigo, 2 Majadahonda Localidad: Madrid CP: 28222	Local
	05-003	Comité Autonómico de Ética de la Investigación de Galicia	Unidad: Secretaria Xeral. Conselleria de Sanidade Dirección: C/ San Lázaro, s/n Localidad: Santiago de Compostela CP: 15781	Local
	05-004	CEIC Area 1 - Hospital General Universitario Gregorio Maranon	Dirección: C/ Doctor Esquerdo, 46 Localidad: Madrid CP: 28007	Local
	05-005	CEIC Hospital Universitari i Politècnic La Fe	Dirección: Avenida de Fernando Abril Martorell, n.106 Localidad: Valencia CP: 46026	Local
	05-006	Comité Etico de Investigacion Clínica de Cantabria	Unidad: IDIVAL Instituto de Investigación Marqués de Valdecilla Dirección: Edificio IFIMAV 3ª Planta Avda Cardenal Herrera Oria s/n Localidad: Santander CP: 39011	Local
	05-007	Comité Autonómico de Ética de la Investigación de Galicia	Unidad: Secretaria Xeral. Conselleria de Sanidade Dirección: C/ San Lázaro, s/n Localidad: Santiago de Compostela CP: 15781	Local
	05-008	CEIC Área 4 - Hospital Universitario Ramón y Cajal	Dirección: Ctra. De Colmenar Viejo, km. 9,1 Localidad: Madrid CP: 28034	Local
	05-009	CEIC Hospital Universitari i Politècnic La Fe	Dirección: Avenida de Fernando Abril Martorell, n.106 Localidad: Valencia CP: 46026	Local
	05-010	CEIC Hospital Universitari de Bellvitge	Dirección: Feixa Llarga, s/n - Antiguo Módulo Banco de Santander Localidad: Hospitalet de Llobregat CP: 08907	Local
	05-011	CEIC HOSPITAL DE ALCOY	PAGINA WEB- CEIC HOSPITAL DE ALCOY	Local
	05-012	Comité de Ética de la Investigación de las Illes Balears	Unit: Consejería de Salud Address: C/ Jesús, 38A Localidad: Palma CP: 07010	Local
	05-013	CEI Provincial de Málaga	Unidad: Hospital Regional Universitario de Málaga Dirección: Avda. Carlos Haya, s/n Pabellón A 7ª Planta Localidad: Málaga CP: 29010	Local
	05-014	CEI Provincial de Málaga	Unidad: Hospital Regional Universitario de Málaga Dirección: Avda. Carlos Haya, s/n Pabellón A	Local

			7ª Planta Localidad: Málaga CP: 29010	
	05-015	CEIC Hospital Universitari Vall d Hebron	Dirección: Passeig de la Vall d.Hebron, 119-129 - Edificio Materno-Infantil, planta 13 Localidad: Barcelona CP: 08035	Local
	05-016	CEIC Area de Salud de Salamanca	Unidad: COMPLEJO ASISTENCIAL UNIVERSITARIO DE SALAMANCA Dirección: 10ª planta Hospital Virgen de la Vega Pº San Vicente, nº 55-182 Localidad: Salamanca CP: 37007	Local
	05-017	CEIC Hospital Universitari Vall d Hebron	Dirección: Passeig de la Vall d.Hebron, 119-129 - Edificio Materno-Infantil, planta 13 Localidad: Barcelona CP: 08035	Local
	05-018	Comité Etico de Investigacion Clínica de Aragon - CEICA	Unidad: Centro de Investigación Biomédica de Aragón Dirección: Avda. San Juan Bosco, 13, planta 1 Localidad: Zaragoza CP: 50009	Local
	05-019	Comité Ético de Investigación Clínica de Asturias	C/ Avda. Roma, s/n. N - 1, S 3.19 Location: Oviedo CP: 33011	Local
	05-020	CEIm de los Hospitales Universitarios Virgen Macarena-Virgen del Rocío	Unidad de Gestión de Ensayos Clínicos Hospital Universitario Virgen del Rocío Edificio de Laboratorios – 6ª Planta (a la izquierda) Hospital Universitario Virgen del Rocío Avda. Manuel Siurot	Local
	05-021	CEIm Área de Salud Valladolid Este	Hospital Clínico Valladolid Facultad de Medicina, Farmacología, C/ Ramón y Cajal, 7 47005 Valladolid, España	Local
	05-022	CEIm Provincial de Las Palmas	Bco. de la Ballena, s/n Edf. Anexo al Hospital Univ. de Gran Canaria "Dr. Negrín"	Local
	05-023	CEIC del Hospital Universitari Germans Trias i Pujol	Ctra. Canyet s/n 08916, Edifici General 1ª Planta, Mòduls Urgències 1ª Planta, Badalona, Barcelona, Spain	Local
	05-024	CEIC del Institut Hospital del Mar d'Investigacions Mediques	Doctor Aiguader, 88. 08003 Barcelona	Local
	05-025	CEIC Hospital Clinic de Barcelona	Dirección: Villarroel, 170 - Planta 0 - Puerta 6b Localidad: Barcelona CP: 08036	Local
	05-026	CEIC del Parc Tauli	Parc Taulí, 1, 08208 Sabadell, Barcelona	Local
	05-027	Comité Ético de Investigación Clínica de Aragón (CEICA)	Calle de San Juan Bosco, 13, 50009 Zaragoza	Local
Netherlands	06-001	CCMO (central committee for research involving human subjects)	PO Box 16302 2500 BH The Hague The Netherlands	Central
	06-002	CCMO (central committee for research involving human subjects)	PO Box 16302 2500 BH The Hague The Netherlands	Central
	06-003	CCMO (central committee for research involving human subjects)	PO Box 16302 2500 BH The Hague The Netherlands	Central

Greece	07-001	Scientific Council (within the Hospital)	114, Vas. Sofias Av.	Local
	07-002	Scientific Council (within the Hospital)	Stavros Niarchou Av., 45500	Local
	07-003	Scientific Council (within the Hospital)	356 Syggrou Avenue, 17674	Local
	07-004	Scientific Council (within the Hospital)	Exohi, 57010	Local
	07-005	Scientific Council (within the hospital)	356 Syggrou Avenue, 17674	Local
	07-006	Scientific Council (within the Hospital)	Stavrakia & Voutes	Local
	07-007	Scientific Council (within the Hospital)	1 Kiriakidi St., 54637	Local
	07-008	Scientific Council (within the Hospital)	Viopolis 41110	Local
	07-009	Scientific Council (within the Hospital)	1 Rimini street, 12462	Local
Finland	08-001	EETTINEN TOIMIKUNTA	Kiinamyllynkatu 4-8 PO Box 52 FI-20521 TURKU	Central
	08-002	EETTINEN TOIMIKUNTA	Kiinamyllynkatu 4-8 PO Box 52 FI-20521 TURKU	Central
Switzerland	09-001	University Hospital Zürich, Department of Pulmonology	GeschaftsfUhrer Stampfenbachstrasse 121 Postfach 8090 Zurich	Central
	09-002	CHUV Centre hospitalier universitaire vaudois	Kantonale Ethikkomission, Stampfenbachstrasse 121, Postfach, 8090 Zurich	Central
Slovakia	10-001	Eticka komisia/Ethics Committee Stredoslovensky ustav srdcovych a cievnych chorob, a.s.	Cesta k nemocnici 622/1 974 01 Banska Bystrica Slovenska republika /Slovak republic	Local
	10-002	Etická komisia pri spol. Východoslovenský ústav srdcových a cievnych chorôb, a.s.	Ondavská č.8, 040 11 Košice, Company ID : 36 601 284	Local
	10-003	Etická komisia Národný ústav srdcových a cievnych chorôb, a.s.	Pod Krásnou hôrkou 1, 833 48 Bratislava 37 Slovenská republika	Central
	10-004	Etická komisia Národný ústav srdcových a cievnych chorôb, a.s.	Pod Krásnou hôrkou 1, 833 48 Bratislava 37 Slovenská republika	Central
Italy	11-001	Comitato Etico AVEC c/o segreteria locale AOU di Bologna Policlinico S.Orsola-Malpighi	Via Albertoni 15 40138 BOLOGNA	Central
	11-002	Comitato Etico ATS Sardegna	Via Enrico Costa 57 07100 Sassari	Local
	11-003	Comitato etico azienda sanitaria della provincia autonoma di Bolzano	Via Lorenz Böhler, 5 39100 Bolzano	Local
	11-004	Comitato etico Area Vasta Centro-Segreteria del Comitato Etico, Pad. 3 - Nuovo Ingresso Careggi (NIC) - Didattica –	Largo Brambilla, 3 50134 Firenze	Local
	11-005	Comitato Etico IRCCS MulitMedica Sezione del	Via Milanese 300, 20099 Sesto San Giovanni (Milano)	Local

		Comitato Etico Centrale IRCCS Lombardia.		
	11-006	COMITATO ETICO IRCCS OSPEDALE SAN RAFFAELE	Via Olgettina 60 20123 MILANO	Local
	11-007	Comitato Etico di Brescia	Piazzale Spedali Civili, 1 - 25123 Brescia	Local
	11-008	Comitato Etico Regionale IRCCS AOU S. Martino	Largo Benzi, 10 - 16132 Genova	Local
	11-009	Comitato Etico Regionale (C.E.R.) delle Marche	Via Conca, 71 - 60126 Ancona	Local
	11-010	Comitato Etico Regionale (C.E.R.) delle Marche	Via Conca, 71 - 60126 Ancona	Local
	11-011	Comitato etico interaziendale presso AOU Maggiore della Carità di Novara	Corso G. Mazzini, 18 28100 Novara	Local
	11-012	Comitato Etico Regionale Calabria Area Centro	Via T. Campanella 115 - 88100 CATANZARO	Local
	11-013	Comitato Etico per le sperimentazioni cliniche (CESC) della provincia di Vicenza	Viaole Rodolfi, 37 - 36100 Vicenza	Local
	11-014	Comitato Etico Catania 1	Via Santa Sofia 78 – 95125 CATANIA	Local
	11-015	Comitato Etico Milano Area 2	Via Francesco Sforza 28 20122 MILANO	Local
	11-016	Comitato Etico Unico Regionale (C.E.U.R.) c/o Direzione Scientifica centro di riferimento oncologico Istituto di ricovero e cura a carattere scientifico	Via Franco Gallini, 2 33081 Aviano (PN)	Local
	11-017	Comitato Etico Milano Area 2	Via Francesco Sforza 28 – 20122 MILANO	Local
	11-019	Comitato Etico Regionale (C.E.R.) delle Marche	Via Conca, 71 - 60126 Ancona	Local
	11-020	ENTE ECCLES OSP GENERALE MIULLI	Comitato Etico di AREA Vasta Emilia Centro della Regione Emilia-Romagna, Via Albertoni, 15, 40138 Bologna	Central
	11-021	Ospedale Universitario Padova	Comitato Etico di AREA Vasta Emilia Centro della Regione Emilia-Romagna, Via Albertoni, 15, 40138 Bologna	Central
Canada	12-001	Conjoint Health Research Ethics Board (CHREB)	University of Calgary 2500 University Dr. NW Calgary, Alberta, Canada T2N 1N4	Local
	12-002	Ottawa Health Science Network Research Ethics Board (OHSNREB)	Ottawa Health Science Network Research Ethics Board (OHSN-REB) Ottawa Hospital, Civic Campus 725 Parkdale Avenue LOEB Building Ottawa, Ontario, Canada K1Y 4E9	Local
	12-003	Hamilton Integrated Research Ethics Board (HiREB)	293 Wellington Street North, Suite 102 Hamilton, Ontario, Canada L8L 8E7	Local

	12-004	Western University office of Research Ethics	Office of Human Research Ethics Room 5150, Support Services Building Western University London, Ontario, Canada N6G 1G9	Local
	12-005	Jewish General Hospital Research Ethics Board	Jewish General Hospital, A-925 3755 Côte Sainte-Catherine West Montreal, Quebec, Canada H3T 1E2	Local
	12-006	Vancouver General Hospital, The Lung Centre	Clinical Research Ethics Board, 10th Avenue, Vancouver BC V5Z 1L8	Central
	12-007	University of Alberta	Health Research Ethics Board, 2-01 North Power Plant, 11312-89 Ave NW, Edmonton, Alberta, Canada T6G 2N2	Central
United Kingdom	13-001	Yorkshire & The Humber - Leeds East Research Ethics Committee	NHSBT Newcastle Blood Donor Centre Holland Drive Newcastle upon Tyne NE2 4NQ	Central
	13-002	Yorkshire & The Humber - Leeds East Research Ethics Committee	NHSBT Newcastle Blood Donor Centre Holland Drive Newcastle upon Tyne NE2 4NQ	Central
	13-003	Yorkshire & The Humber - Leeds East Research Ethics Committee	NHSBT Newcastle Blood Donor Centre Holland Drive Newcastle upon Tyne NE2 4NQ	Central
	13-004	Yorkshire & The Humber - Leeds East Research Ethics Committee	NHSBT Newcastle Blood Donor Centre Holland Drive Newcastle upon Tyne NE2 4NQ	Central
	13-005	Yorkshire & The Humber - Leeds East Research Ethics Committee	NHSBT Newcastle Blood Donor Centre Holland Drive Newcastle upon Tyne NE2 4NQ	Central
	13-006	Yorkshire & The Humber - Leeds East Research Ethics Committee	NHSBT Newcastle Blood Donor Centre Holland Drive Newcastle upon Tyne NE2 4NQ	Central
Czech Rep	14-001	Eticka komise Vseobecne fakultni nemocnice v Praze	Na Bojisti 1, 128 08 Praha 2. Czech Republic	Central
Portugal	16-001	Comitê Local de Hospital de Santa Maria e o Hospital de Pulido Valente	Alameda das Linhas de Torres, 117 1769-001 Lisboa	Local
	16-002	Comitê Local de Centro Hospitalar e Universitário de Coimbra	Praceta Prof. Mota Pinto, 3000-075 Coimbra	Local
Belgium	17-001	Ethische Commissie Onderzoek KU/UZ Leuven	Herestraat 49, 3000 Leuven, Belgium	Central
	17-002	Ethische Commissie Onderzoek KU/UZ Leuven	Herestraat 49, 3000 Leuven, Belgium	Central
France	18-001	CPP Ile de France IV	Hôpital Saint-Louis Porte 5 du carré Historique 1 avenue Claude Vellefaux 75475 Paris Cedex 10 France	Central
	18-002	CPP Ile de France IV	Hôpital Saint-Louis Porte 5 du carré Historique 1 avenue Claude Vellefaux 75475 Paris Cedex 10 France	Central
	18-003	CPP Ile de France IV	Hôpital Saint-Louis Porte 5 du carré Historique 1 avenue Claude Vellefaux 75475 Paris Cedex 10 France	Central

	18-004	CPP Ile de France IV	Hôpital Saint-Louis Porte 5 du carré Historique 1 avenue Claude Vellefaux 75475 Paris Cedex 10 France	Central
	18-005	CPP Ile de France IV	Hôpital Saint-Louis Porte 5 du carré Historique 1 avenue Claude Vellefaux 75475 Paris Cedex 10 France	Central
	18-006	CPP Ile de France IV	Hôpital Saint-Louis Porte 5 du carré Historique 1 avenue Claude Vellefaux 75475 Paris Cedex 10 France	Central
	18-007	CPP Ile de France IV	Hôpital Saint-Louis Porte 5 du carré Historique 1 avenue Claude Vellefaux 75475 Paris Cedex 10 France	Central
Russia	19-002	LEC at FSBEI HE RyazSMU MOH Russia	9, Vysokovoltnaya ul.,Ryazan, 390026, Russia	Local
	19-003	Independent Interdisciplinary Committee on Ethics Evaluation of Clinical Trials	Legal address: 51, Leningradsky prospect, Moscow, 125468, Russia; Actual address: 20, bld 1, Delegatskaya ul., Moscow, 127472, Russia;	Local
	19-004	Independent Interdisciplinary Committee on Ethics Evaluation of Clinical Trials	Legal address: 51, Leningradsky prospect, Moscow, 125468, Russia; Actual address: 20, bld 1, Delegatskaya ul., Moscow, 127472, Russia;	Local
	19-005	IEC atSBHI MR "MRRCI n.a. M.F. Vladimirsky"	61/2, Schepkina ul., Moscow, 129110, Russia	Local
	19-006	Independent Interdisciplinary Committee on Ethics Evaluation of Clinical Trials	Legal address: 51, Leningradsky prospect, Moscow, 125468, Russia; Actual address: 20, bld 1, Delegatskaya ul., Moscow, 127472, Russia;	Local
	19-007	Independent Interdisciplinary Committee on Ethics Evaluation of Clinical Trials	Legal address: 51, Leningradsky prospect, Moscow, 125468, Russia; Actual address: 20, bld 1, Delegatskaya ul., Moscow, 127472, Russia;	Local
	19-008	LEC at SBHI NSR NRCCD	6 bld 8, Zalesskogo ul., Novosibirsk, 630047, Russia	Local
	19-009	EC at SBHI RH	3, Pirogova ul., Petrozavodsk, 185019, Russia	Local
	19-010	LEC at SAHI "ICDC"	12a, Karbysheva ul., Kazan, 420101, Russia	Local
	19-011	Independent Interdisciplinary Committee on Ethics Evaluation of Clinical Trials	Legal address: 51, Leningradsky prospect, Moscow, 125468, Russia; Actual address: 20, bld 1, Delegatskaya ul., Moscow, 127472, Russia;	Local
	19-012	EC at SBHI RCC	96, Stepana Kuvykina ul., Ufa, 450106, Russia	Local

	19-013	Independent Interdisciplinary Committee on Ethics Evaluation of Clinical Trials	Legal address: 51, Leningradsky prospect, Moscow, 125468, Russia; Actual address: 20, bld 1, Delegatskaya ul., Moscow, 127472, Russia	Local
Lithuania	20-001	Lithuanian University of Health Sciences Kauno Klinikos	Eiveniu str.2, Kaunas, LT-50161	Local
	20-002	Vilnius University Hospital Santaros Klinikos	Santariskiu str.2, Vilnius, LT-08661	Local
Poland	21-001	Europejskie Centrum Zdrowia – Otwock TNP/CTEPH	Centrum Medyczne Ksztalcenia Podyplomowego, Ul. Marymoncka 99/103, 01-813 Warszawa	Central
	21-002	Uniwersyteckie Centrum Kliniczne PAH/CTEPH Kliniczne Centrum Kardiologii, Klinika Kardiologii i Elektroterapii Serca	Centrum Medyczne Ksztalcenia Podyplomowego, Ul. Marymoncka 99/103, 01-813 Warszawa	Central
	21-003	SPSK 2 PUM	Centrum Medyczne Ksztalcenia Podyplomowego, Ul. Marymoncka 99/103, 01-813 Warszawa	Central
	21-004	Gornoslaskie Centrum Medyczne SUM	Centrum Medyczne Ksztalcenia Podyplomowego, Ul. Marymoncka 99/103, 01-813 Warszawa	Central
	21-005	Uniwersytecki Szpital Kliniczny	Centrum Medyczne Ksztalcenia Podyplomowego, Ul. Marymoncka 99/103, 01-813 Warszawa	Central
	21-006	II Katedra Kardiologii CM	Centrum Medyczne Ksztalcenia Podyplomowego, Ul. Marymoncka 99/103, 01-813 Warszawa	Central
	21-007	Śląskie Centrum Chorób Serca *TNP/CTEPH* *III Katedra i Oddział Kliniczny Kardiologii SUM*	Centrum Medyczne Ksztalcenia Podyplomowego, Ul. Marymoncka 99/103, 01-813 Warszawa	Central
Estonia	22-001	North Estonian Medical Center	J. Sutiste tee 19, 13416 Tallinn	Local

Table S3. Proportion of patients enrolled by country

	Incident **N = 1110**	**Prevalent** **N = 834**	**Overall** **N = 1944**
Country – n (%)			
Austria	22 (2)	13 (2)	35 (2)
Belgium	25 (2)	14 (2)	39 (2)
Canada	147 (13)	100 (12)	247 (13)
Czech Republic	7 (1)	5 (1)	12 (1)
Denmark	3 (<1)	4 (<1)	7 (<1)
Finland	10 (1)	5 (1)	15 (1)
France	8 (1)	9 (1)	17 (1)
Germany	361 (33)	248 (30)	609 (31)
Greece	70 (6)	67 (8)	137 (7)
Italy	54 (5)	42 (5)	96 (5)
Lithuania	6 (1)	3 (<1)	9 (<1)
Netherlands	11 (1)	10 (1)	21 (1)
Poland	5 (<1)	6 (1)	11 (1)
Russia*	3 (<1)	4 (<1)	7 (<1)
Slovakia	10 (1)	20 (2)	30 (2)
Spain	190 (17)	173 (21)	363 (19)
Sweden	74 (7)	26 (3)	100 (5)
Switzerland	4 (<1)	1 (<1)	5 (<1)
United Kingdom	100 (9)	84 (10)	184 (9)

*Study discontinued from Russia due to Sponsor decision.

Table S4. Treatment escalation during the observation period

Time to first treatment escalation	**Incident** **N = 1110**
Observation period – median (Q1, Q3), months	17.0 (7.5, 29.9)
Monotherapy at baseline – *n*	*532*
Monotherapy (oral/inhaled) to double therapy (oral/inhaled) – n/N (%)	199/530 (38)
Median (Q1, Q3), months	3.4 (1.9, 6.6)
Monotherapy (oral/inhaled) to a combination therapy incl. i.v./s.c. prostacyclin – n/N (%)	2/530 (≤1)
Median (Q1, Q3), months	1.8 (0.4, 3.2)
Double therapy at baseline – *n*	*457*
Double therapy (oral/inhaled) to triple therapy (oral/inhaled) – n/N (%)	78/455 (17)
Median (Q1, Q3), months	7.0 (3.4, 12.7)
Double or triple therapy at baseline – *n*	*513*
Double or triple therapy (oral/inhaled) to a combination therapy incl. i.v./s.c. prostacyclin – n/N (%)	13/510 (3)
Median (Q1, Q3), months	5.8 (3.5, 8.9)

i.v./s.c.: intravenous/subcutaneous; Q1, Q3: interquartile range.

Table S5. Hospitalisations after baseline and survival during the observation period for the overall population

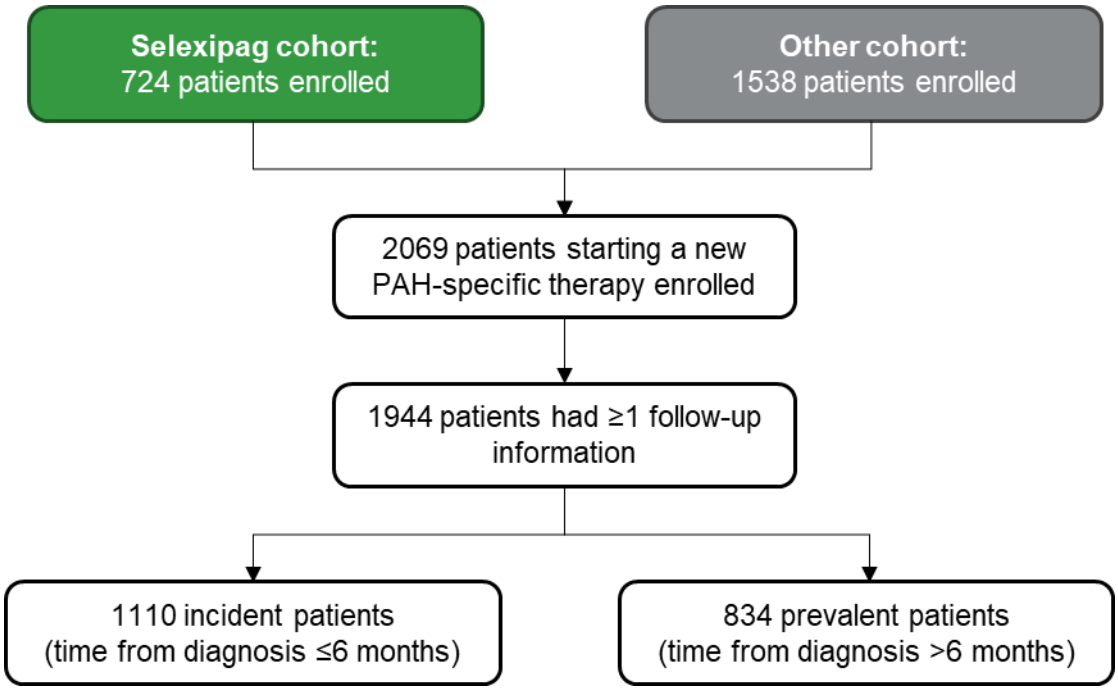
	Overall **N = 1944**
Observation period – median (Q1, Q3), months	17.9 (8.6, 31.1)
Hospitalisation	
Patients hospitalised – n (%)	706 (36)
Time to first hospitalisation – median (Q1, Q3), days	175 (74, 428)
Patients with PAH-related hospitalisation – n (%)	439 (23)
Time to first PAH-related hospitalisation – median (Q1, Q3), days	212 (91, 459)
Total number of hospitalisations* – *n*	*1619*
Hospitalisations post-baseline – n (%)	1471 (91)
PAH-related hospitalisations – n/N† (%)	724/1389 (52)
Incidence rate – per 100 person-years (95% CI) – *n*	*1939*
All hospitalisations	28.9 (26.3, 31.6)
PAH-related hospitalisations	15.7 (14.2, 17.4)
Survival	
Total all-cause deaths – n (%)	368 (19)
PAH-related deaths as per physician judgement – *n*	*275*
Yes – n (%)	165 (60)
No – n (%)	110 (40)
Unknown – n	93
Main cause of death – *n*	*368*
Disease progression / PAH worsening – n (%)	87 (24)
Right heart failure – n (%)	48 (13)
Sudden death / sudden cardiac arrest – n (%)	36 (10)
Myocardial infarction – n (%)	4 (1)
Stroke – n (%)	2 (1)
Arrythmia – n (%)	1 (<1)

Other causes (occurring in <5% of patients) – n (%)	190 (52)
Unknown cause of death – n (%)	60 (16)
Mortality rate – per 100 person-years (95% CI)	11.2 (10.1, 12.4)

*Patients could have been hospitalised multiple times. †Excludes 82 hospitalisations in the overall group where the reason for hospitalisation was unknown. CI: confidence interval; PAH: pulmonary arterial hypertension; Q1, Q3: interquartile range.

Supplementary Figures

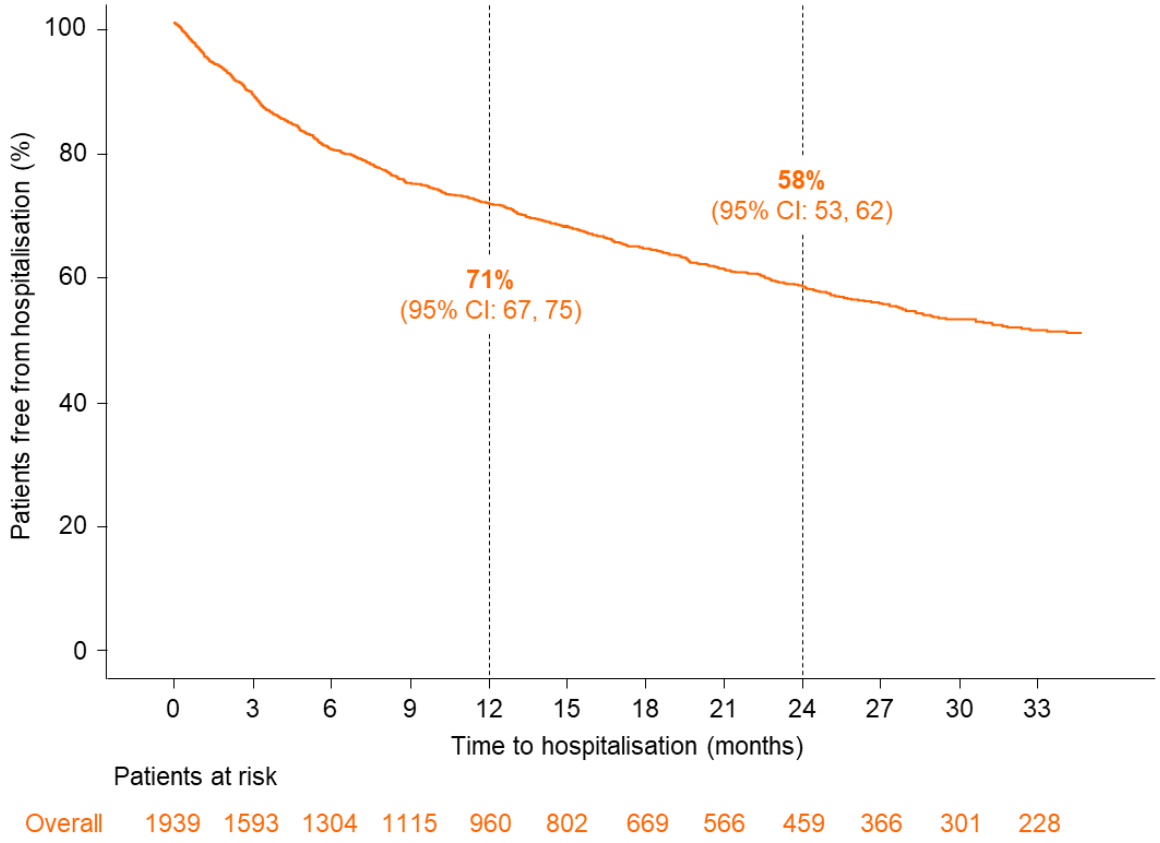
Figure S1. Patient disposition



PAH: pulmonary arterial hypertension.

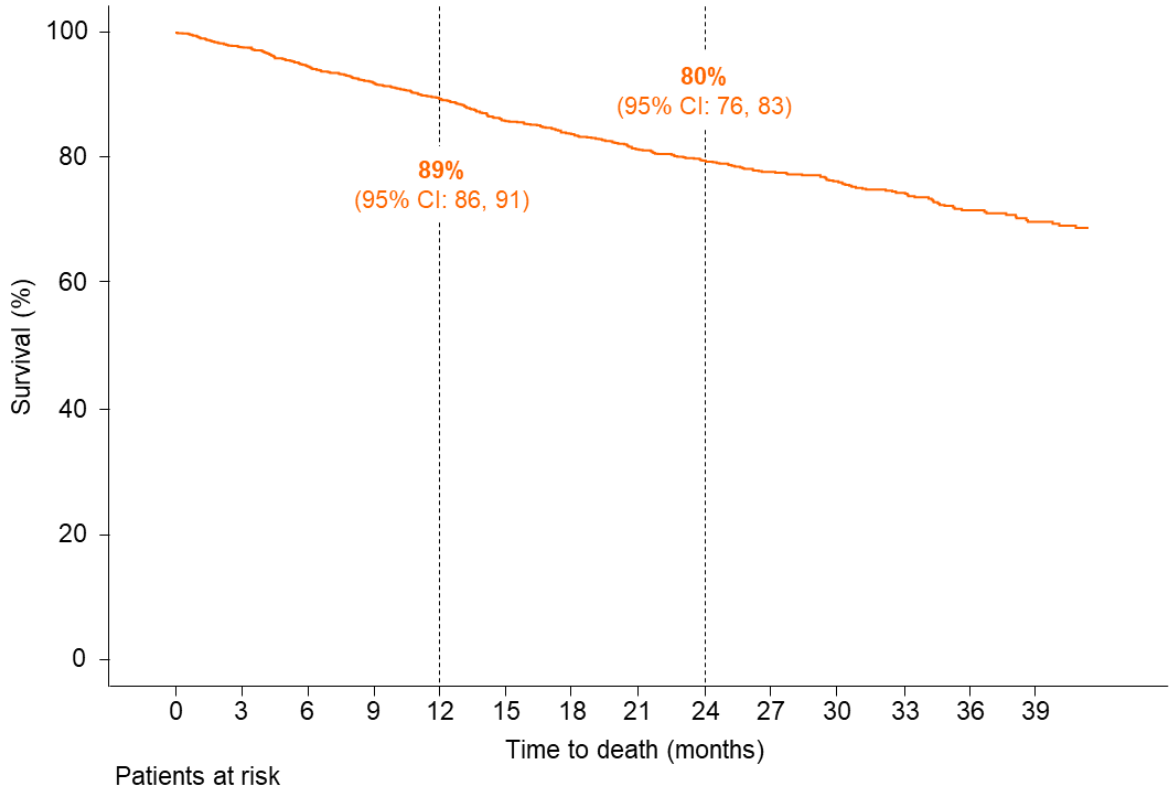
Figure S2. Time to A) first all-cause hospitalisation and B) all-cause death during the observation period for the overall patient population

A)



Kaplan-Meier curves illustrating time to first all-cause hospitalisation for the overall population during the observation period. Kaplan-Meier estimates (95% CI) shown at 12 and 24 months. CI: confidence interval.

B)



Kaplan-Meier curves illustrating time to all-cause death for the overall population during the observation period. Kaplan-Meier estimates (95% CI) shown at 12 and 24 months. CI: confidence interval.