10-year data on oral selexipag: long-term survival, safety, and dosing insights in pulmonary arterial hypertension (PAH) from the GRIPHON study and its open-label extension (OLE)

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Relevant Financial Relationship Disclosure Statement

[Vallerie V. McLaughlin]

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I **will not** discuss off-label use and/or investigational use of any drugs or devices.

Introduction

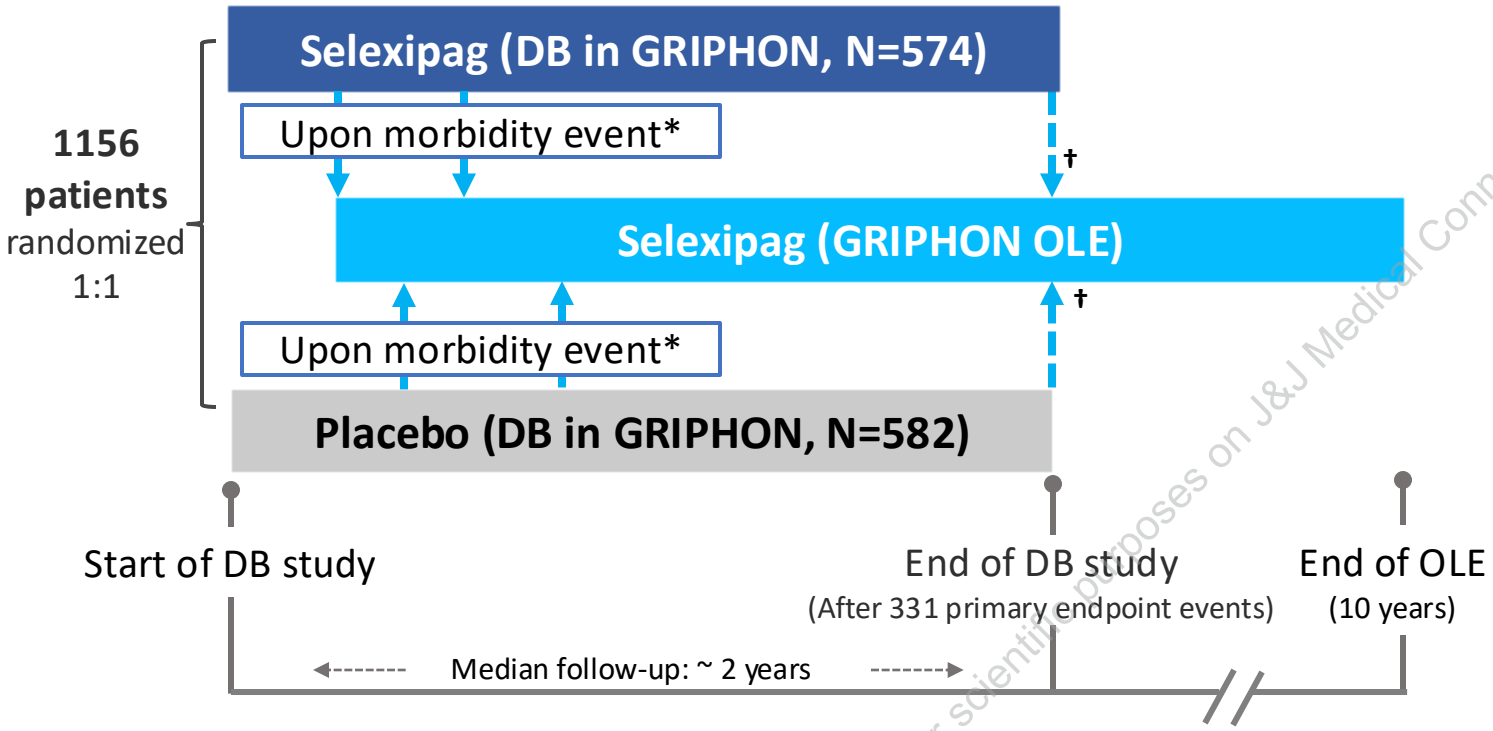
- Selexipag, an oral selective IP prostacyclin receptor agonist, significantly reduced morbidity/mortality risk by 40% versus placebo in the pivotal GRIPHON study[1]
  - The treatment effect of selexipag was consistent whether used as monotherapy, as part of double combination therapy or as part of triple therapy[1] and across different risk categories[2-4]
- Results from GRIPHON and its OLE[5] have guided the use of selexipag in PAH clinical practice[6,7]

These analyses from GRIPHON and its OLE report survival among patients treated with selexipag for up to 10 years, including post-hoc survival assessments by individual maintenance dose, risk category, background therapy and time from diagnosis

1. Sitbon O, et al. *N Engl J Med*. 2015; 373:2522–33; 2. Sitbon O, et al. *J Heart Lung Transplant*. 2020; 39:300–309; 3. Benza R, et al. *CHEST*. 2021; 160:A2318–A2321; 4. Benza RL, et al. *J Heart Lung Transplant*. 2024; 43:1998–2007; 5. Galiè N, et al. *Adv Ther*. 2022; 39:796–810; 6. Humbert M, et al. *Eur Heart J*. 2022; 43:3618-3731; 7. Humbert M, et al. *Eur Respir J*. 2023; 61:2200879. OLE: open label extension; PAH: pulmonary arterial hypertension.

Study design and analyses

GRIPHON (NCT01106014) AND ITS OLE (NCT01112306)



ITT-selexipag population

- Patient characteristics
- KM survival estimates
  - Overall population
  - By individual maintenance dose
  - By risk category
  - By background therapy and time from diagnosis
- Safety and tolerability

All analyses, including subgroups, are descriptive only:

- Survival analyses were post hoc, and baseline characteristics were not balanced
- Subgroups were based on characteristics at selexipag initiation or start of individualized maintenance dose
- Changes in patient characteristics over the long-term follow up could not be accounted for

*After a morbidity event prior to entering GRIPHON OLE, patients started selexipag on lowest dose (200 µg b.i.d), and up-titrated to an individualized dose (in order to maintain integrity of DB study). †At end of GRIPHON DB, patients randomized to selexipag entered GRIPHON OLE at the same dose received at end of study and patients randomized to placebo started selexipag at the lowest dose (200 µg b.i.d) and up-titrated to their individualized dose. Individualized maintenance dose corresponds to the individual maximum tolerated dose. DB: double-blind; b.i.d: twice-daily; ITT: intention-to-treat; KM: Kaplan-Meier.

Demographics and baseline characteristics (1)

Characteristic	ITT-selexipag population (N = 574)
Female, n (%)	457 (80)
Age, years, mean ± SD	48 ± 15
Time from PAH diagnosis*, years, median (Q1, Q3)	0.9 (0.3, 2.9)
PAH classification, n (%)	
Idiopathic PAH	312 (54)
Heritable PAH	13 (2)
Associated with connective tissue disease	167 (29)
Associated with congenital heart disease	60 (10)
Associated with HIV	5 (1)
Drug- or toxin-induced	17 (3)

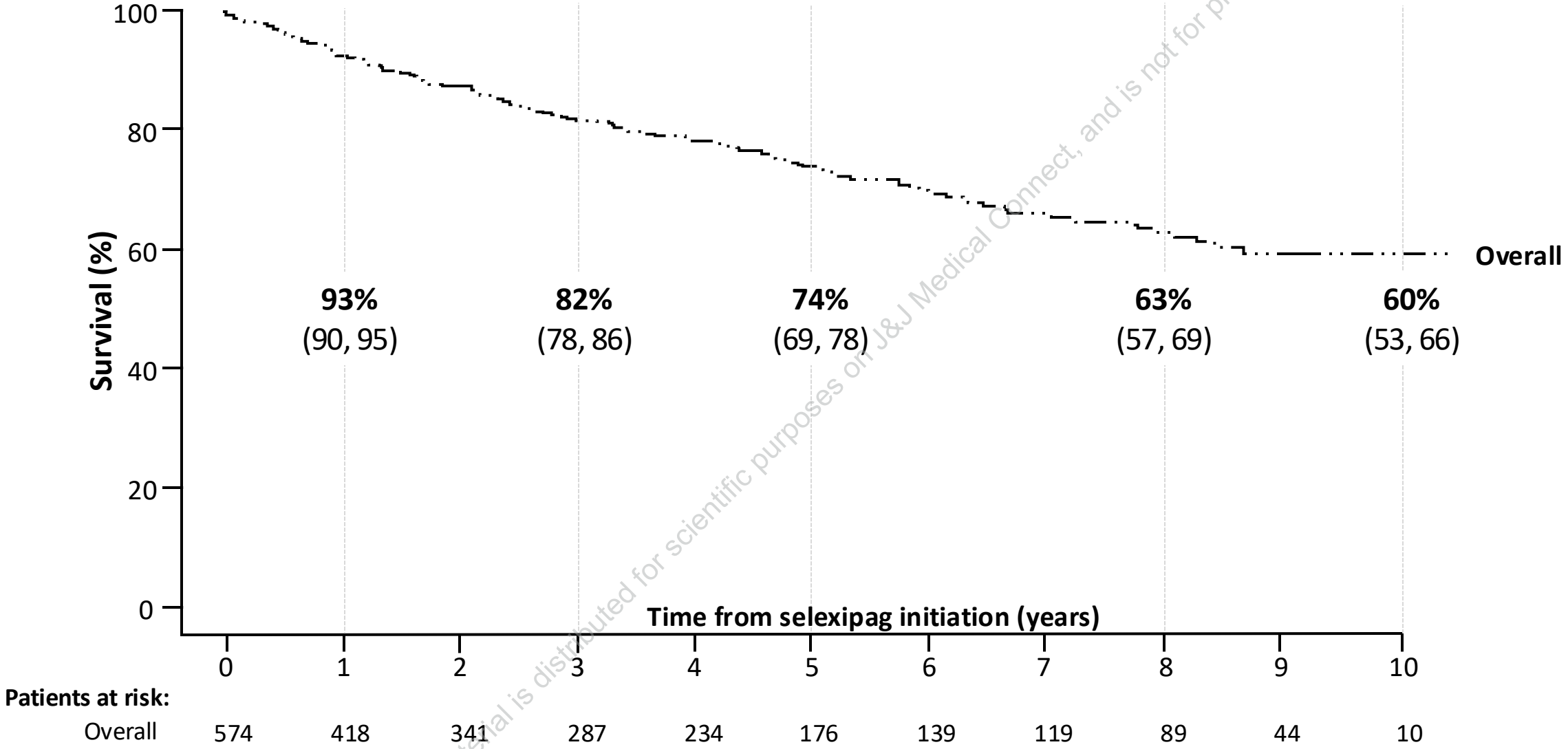
Values are rounded and may not add up to 100%.*PAH diagnosis confirmed by right heart catheterization.
HIV: human immunodeficiency virus; SD: standard deviation; Q1, Q3: interquartile range.

Demographics and baseline characteristics (2)

Characteristic	ITT-selexipag population (N = 574)
6MWD, m, mean ± SD	359 ± 76
WHO FC, n (%)	
I	4 (1)
II	273 (48)
III	294 (51)
IV	3 (1)
4-strata risk category*, n (%)	
Low	118 (21)
Intermediate-low	266 (46)
Intermediate-high	177 (31)
High	7 (1)
Background PAH therapy, n (%)	
ERA and PDE5i combination therapy	179 (31)
ERA monotherapy	94 (16)
PDE5i monotherapy	189 (33)
None	112 (20)

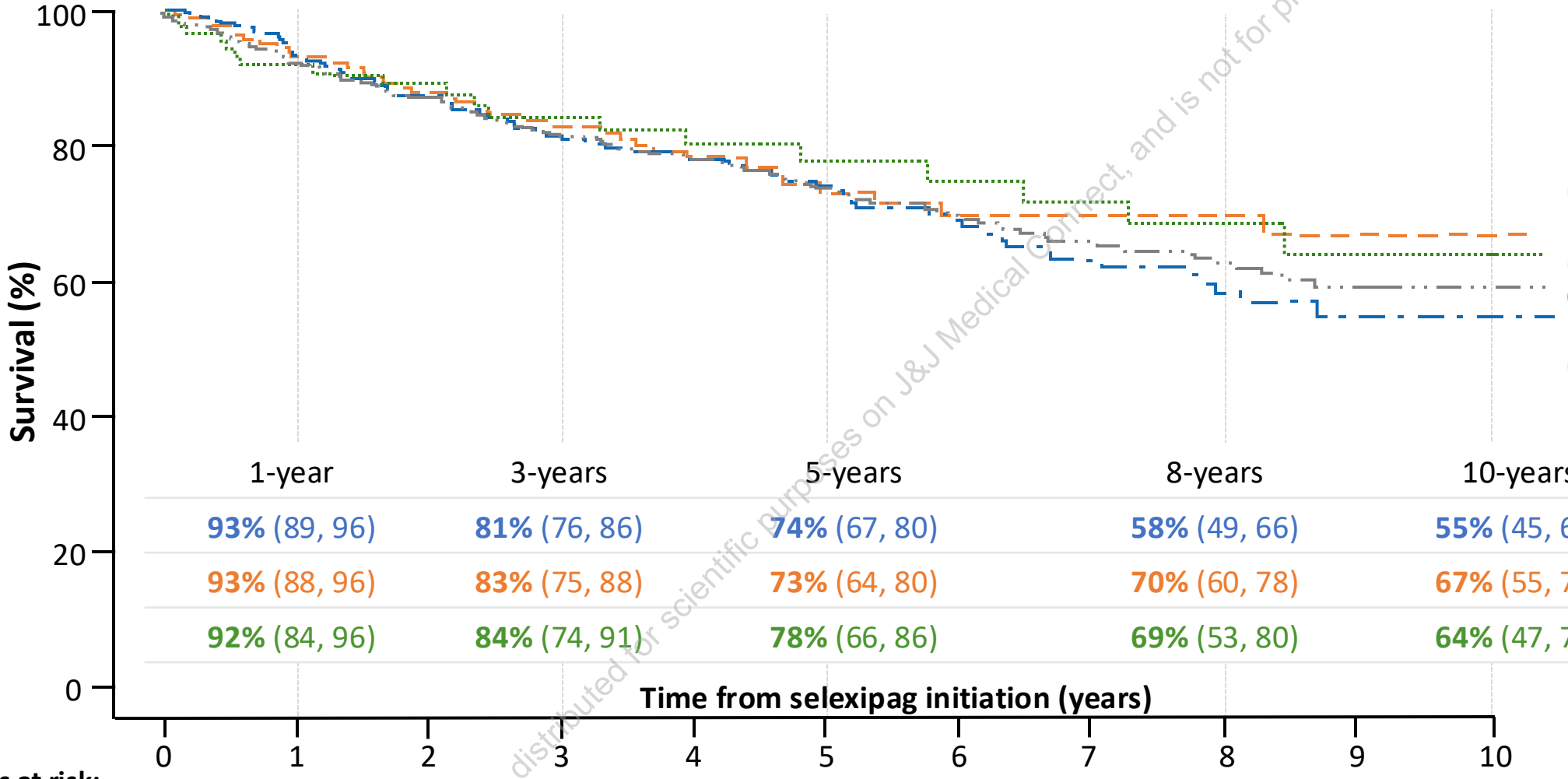
Values are rounded and may not add up to 100%.*Risk of 1-year mortality calculated according to the 4-strata risk score recommended by the 2022 ESC/ERS guidelines[1,2], based on at least two of 6MWD, BNP/NT-proBNP or WHO FC at GRIPHON DB baseline; 6 patients did not have data available for risk assessment. 6MWD: six-minute walk distance; BNP/NT-proBNP: brain natriuretic peptide/N-terminal pro-BNP; ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase 5 inhibitor; WHO FC: World Health Organization functional class. 1. Humbert M, et al. *Eur Heart J*. 2022; 43:3618-3731; 2. Humbert M, et al. *Eur Respir J*. 2023; 61:2200879.

Overall survival



Kaplan-Meier curve for time from selexipag initiation to death up to end of treatment + 30 days. Kaplan-Meier survival estimates (95% CI) are shown. CI: confidence interval.

Individualized maintenance dose by dose stratum



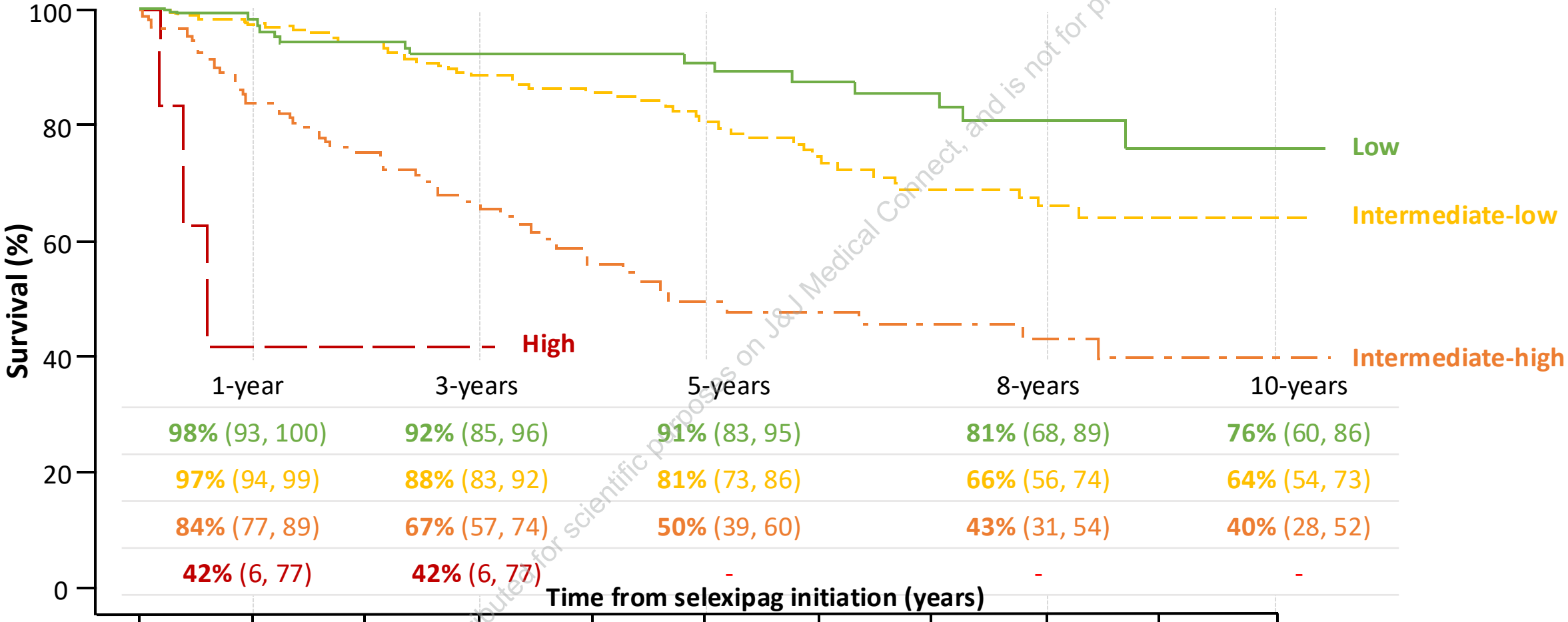
	1-year	3-years	5-years	8-years	10-years
High dose	**93%** (89, 96)	**81%** (76, 86)	**74%** (67, 80)	**58%** (49, 66)	**55%** (45, 64)
Medium dose	**93%** (88, 96)	**83%** (75, 88)	**73%** (64, 80)	**70%** (60, 78)	**67%** (55, 76)
Low dose	**92%** (84, 96)	**84%** (74, 91)	**78%** (66, 86)	**69%** (53, 80)	**64%** (47, 77)

Time from selexipag initiation (years)

Patients at risk:	0	1	2	3	4	5	6	7	8	9	10
High dose	261	213	173	141	117	93	74	62	44	22	6
Medium dose	175	133	110	95	77	51	40	33	27	12	1
Low dose	129	70	57	50	39	31	24	23	18	10	3

Kaplan-Meier curve for time from selexipag initiation to death up to end of treatment + 30 days. Kaplan-Meier survival estimates (95% CI) are shown. Does not include 8 patients in the overall population who were on an individualized maintenance dose of selexipag < 200 µg b.i.d. and 1 patient whose individualized maintenance dose of selexipag (700/900 µg b.i.d.) did not meet the criteria for "medium" dose.

4-strata risk category at selexipag initiation

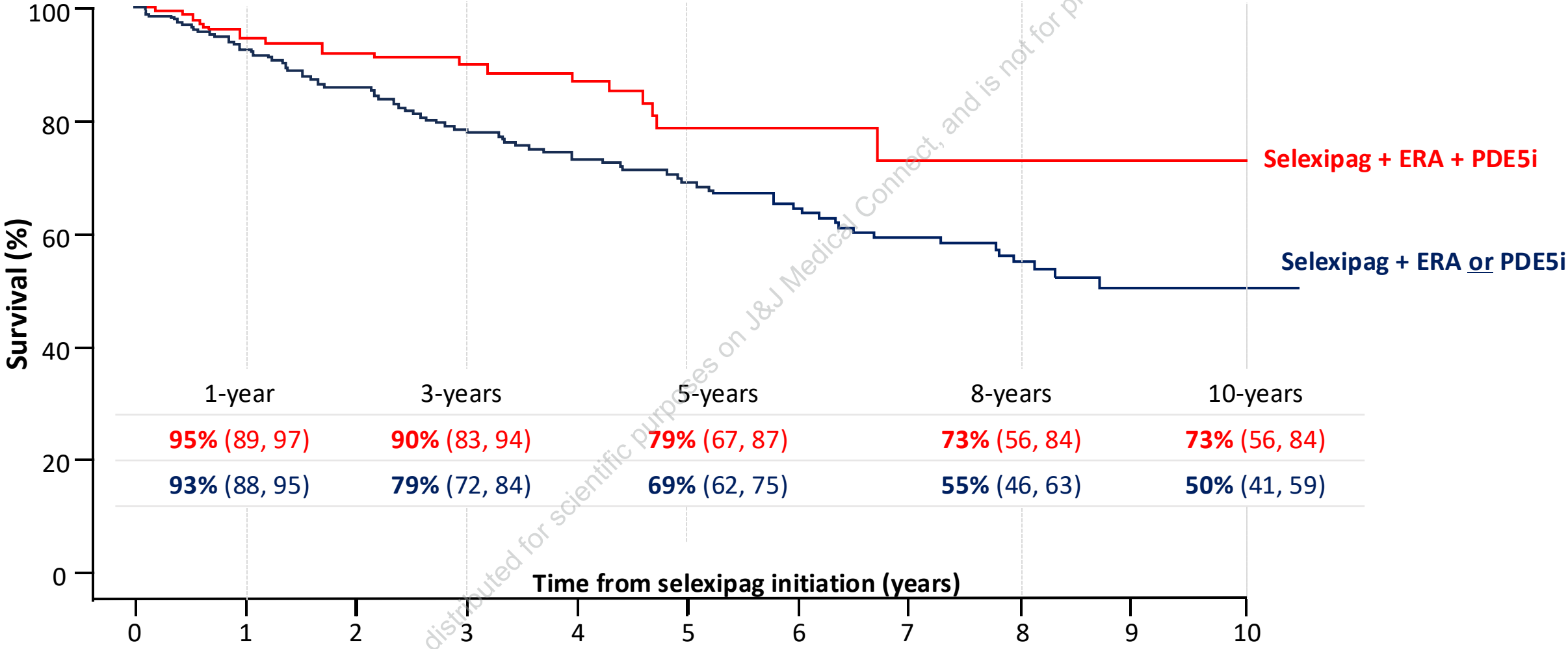


	1-year	3-years	5-years	8-years	10-years
Low	**98%** (93, 100)	**92%** (85, 96)	**91%** (83, 95)	**81%** (68, 89)	**76%** (60, 86)
Intermediate-low	**97%** (94, 99)	**88%** (83, 92)	**81%** (73, 86)	**66%** (56, 74)	**64%** (54, 73)
Intermediate-high	**84%** (77, 89)	**67%** (57, 74)	**50%** (39, 60)	**43%** (31, 54)	**40%** (28, 52)
High	**42%** (6, 77)	**42%** (6, 77)	-	-	-

Patients at risk:	0	1	2	3	4	5	6	7	8	9	10
Low	118	100	89	84	75	63	47	39	28	13	3
Intermediate-low	266	205	168	146	116	85	68	58	43	24	4
Intermediate-high	177	106	79	53	40	27	23	21	17	7	3
High	7	2	2	1	0	0	0	0	0	0	0

Kaplan-Meier curve for time from selexipag initiation to death up to end of treatment + 30 days. Kaplan-Meier survival estimates (95% CI) are shown. Does not include 6 patients in the overall population who did not have data available for risk assessment.

PAH-specific combination therapy regimen at selexipag initiation



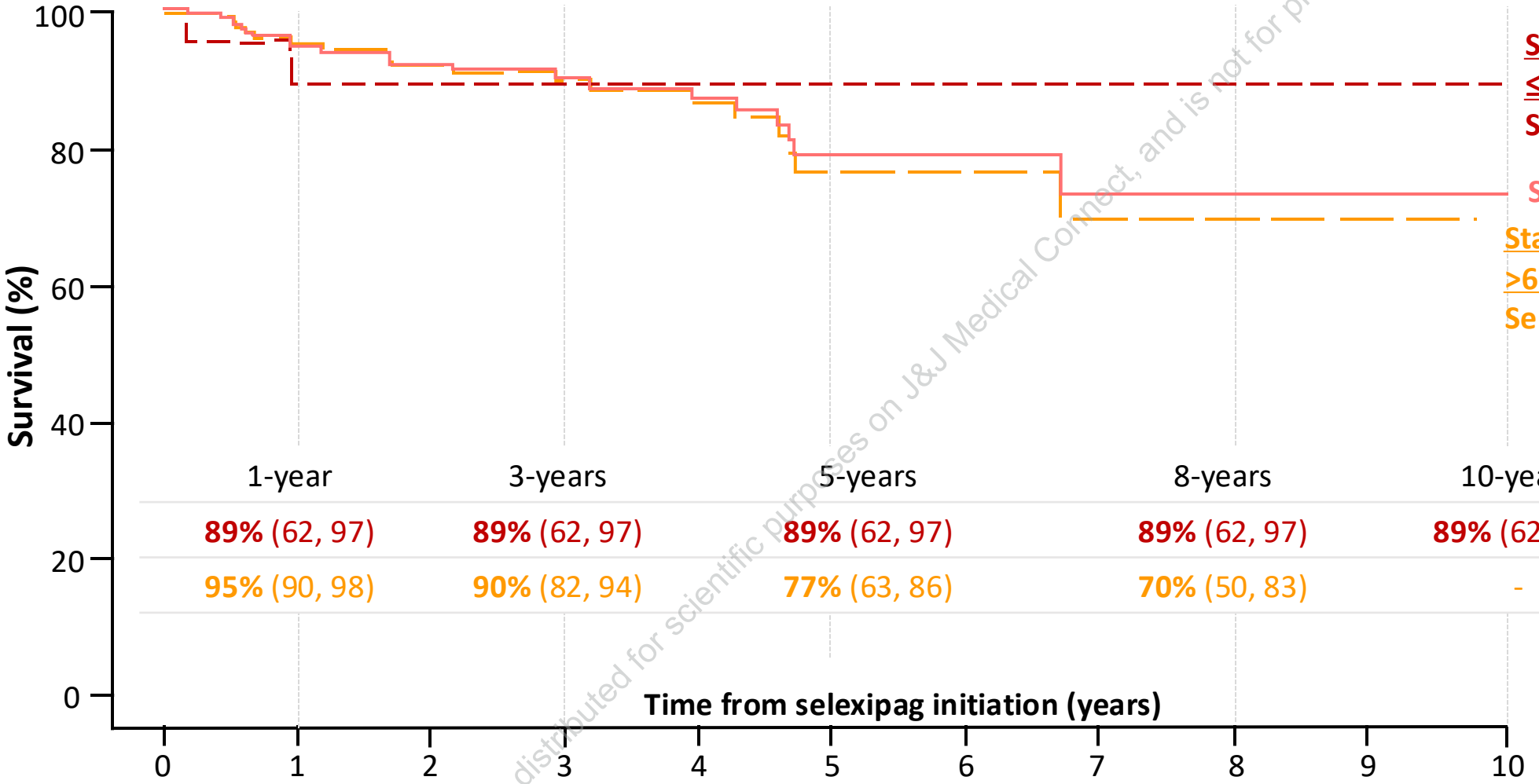
	1-year	3-years	5-years	8-years	10-years
Selexipag + ERA + PDE5i	**95%** (89, 97)	**90%** (83, 94)	**79%** (67, 87)	**73%** (56, 84)	**73%** (56, 84)
Selexipag + ERA or PDE5i	**93%** (88, 95)	**79%** (72, 84)	**69%** (62, 75)	**55%** (46, 63)	**50%** (41, 59)

Patients at risk:

Triple	179	123	95	78	57	26	17	12	11	4	1
Double	283	202	170	140	117	96	76	64	47	22	5

Kaplan-Meier curve for time from selexipag initiation to death up to end of treatment + 30 days. Kaplan-Meier survival estimates (95% CI) are shown. Does not include 112 patients in the overall population who did not have a PAH-specific background therapy at baseline.

Triple combination therapy and time from diagnosis



	1-year	3-years	5-years	8-years	10-years
	89% (62, 97)	**89%** (62, 97)	**89%** (62, 97)	**89%** (62, 97)	**89%** (62, 97)
	95% (90, 98)	**90%** (82, 94)	**77%** (63, 86)	**70%** (50, 83)	-

Patients at risk:

≤6 months	23	14	12	11	10	4	4	3	2	1	1
>6 months	156	109	83	67	47	22	13	9	9	3	0

Kaplan-Meier curve for time from selexipag initiation to death up to end of treatment + 30 days. Kaplan-Meier survival estimates (95% CI) are shown. Does not include 112 patients in the overall population who did not have a PAH-specific background therapy at baseline.

Safety and exposure

	ITT-selexipag population (N = 574)
Selexipag exposure, months, median (range)	35.8 (0.0–126)
Total selexipag exposure, patient-years	2105.5
Adverse events, n (%)	
Patients with ≥ 1 adverse event	572 (100)
Patients with ≥ 1 serious adverse event	368 (64)
Patients with ≥ 1 adverse event leading to selexipag discontinuation*	223 (39)
Patients with ≥ 1 prostacyclin-associated adverse event leading to selexipag discontinuation	47 (8)
Most frequent adverse events†, n (%)	
Headache	390 (68)
Diarrhea	265 (46)
Nausea	209 (36)
Pulmonary arterial hypertension worsening	203 (35)
Pain in jaw	156 (27)
Deaths‡, n (%)	126 (22)

- **Median follow-up time** from selexipag initiation in GRIPHON: **54 months**
  - **176 (31%)** patients had been receiving selexipag for **≥5 years**
  - **10 (2%)** patients had been receiving selexipag for **≥10 years**

*All adverse events leading to discontinuation of selexipag are reported here and not only those considered the primary reason for discontinuation. †Occurring in ≥ 25% of patients. ‡Up to end of treatment + 30 days; Most common (> 1%) reasons for death were: PAH worsening (6%), right ventricular failure (4%), sudden death (2%) and cardiac arrest (1%).

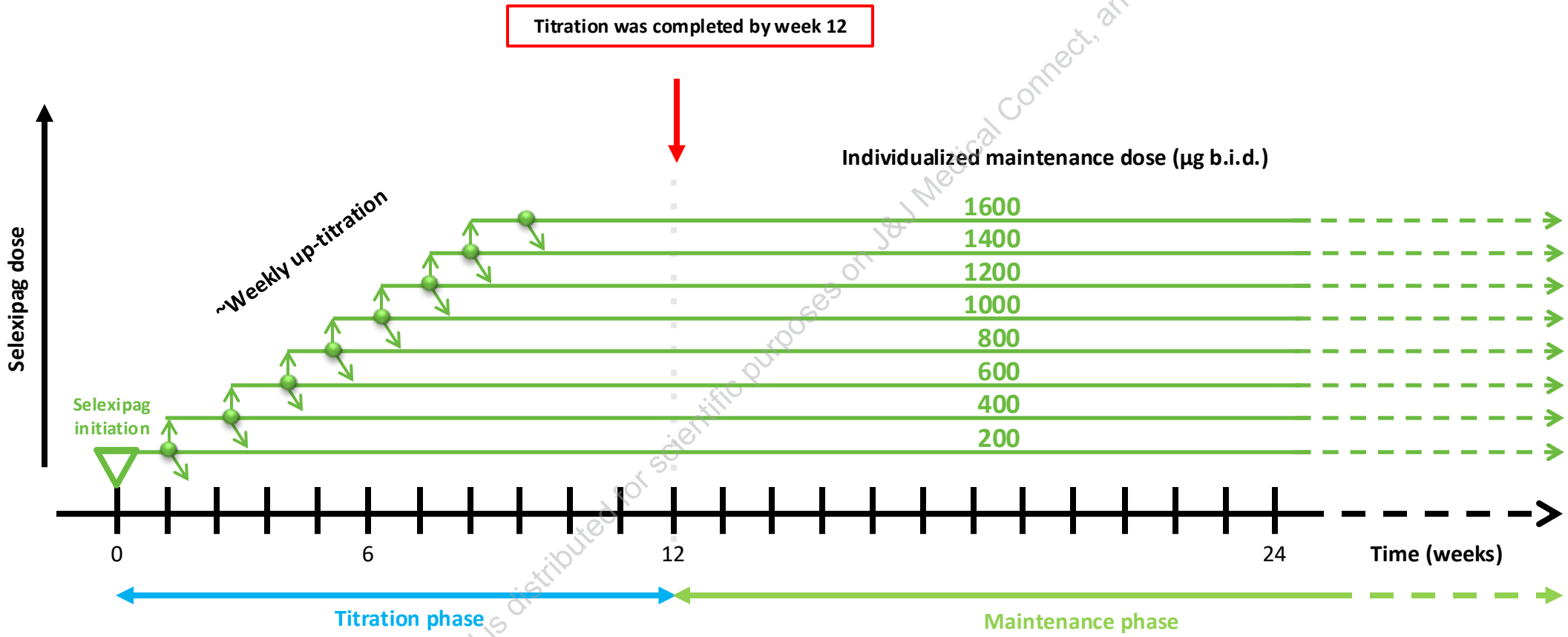
Conclusions

- In the overall population treated with selexipag, 10-year survival was 60%, and was consistent across dose groups
- These 10-year data provide valuable insights, while earlier timepoints facilitate their contextualization with other datasets[1,2]. We observed 5-year survival of 74% including:
  - >80% survival when selexipag was initiated in patients at low and intermediate-low risk and ~50% survival when initiated in intermediate-high risk patients
  - ~80% survival when selexipag was initiated as part of triple therapy with and ERA and PDE5i, and ~90% survival when this triple therapy regimen was initiated within 6 months of diagnosis
- The safety profile of selexipag over this extended period was consistent with previous observations
- Despite limitations inherent to long-term, open-label studies, these findings represent the most comprehensive safety, tolerability, and survival data for selexipag and the longest follow-up in a clinical study of any PAH therapy

1. Benza RL, et al. *CHEST*. 2012; 142:448-456; 2. Boucly A, et al. *Am J Respir Crit Care Med*. 2021; 204:842-854.

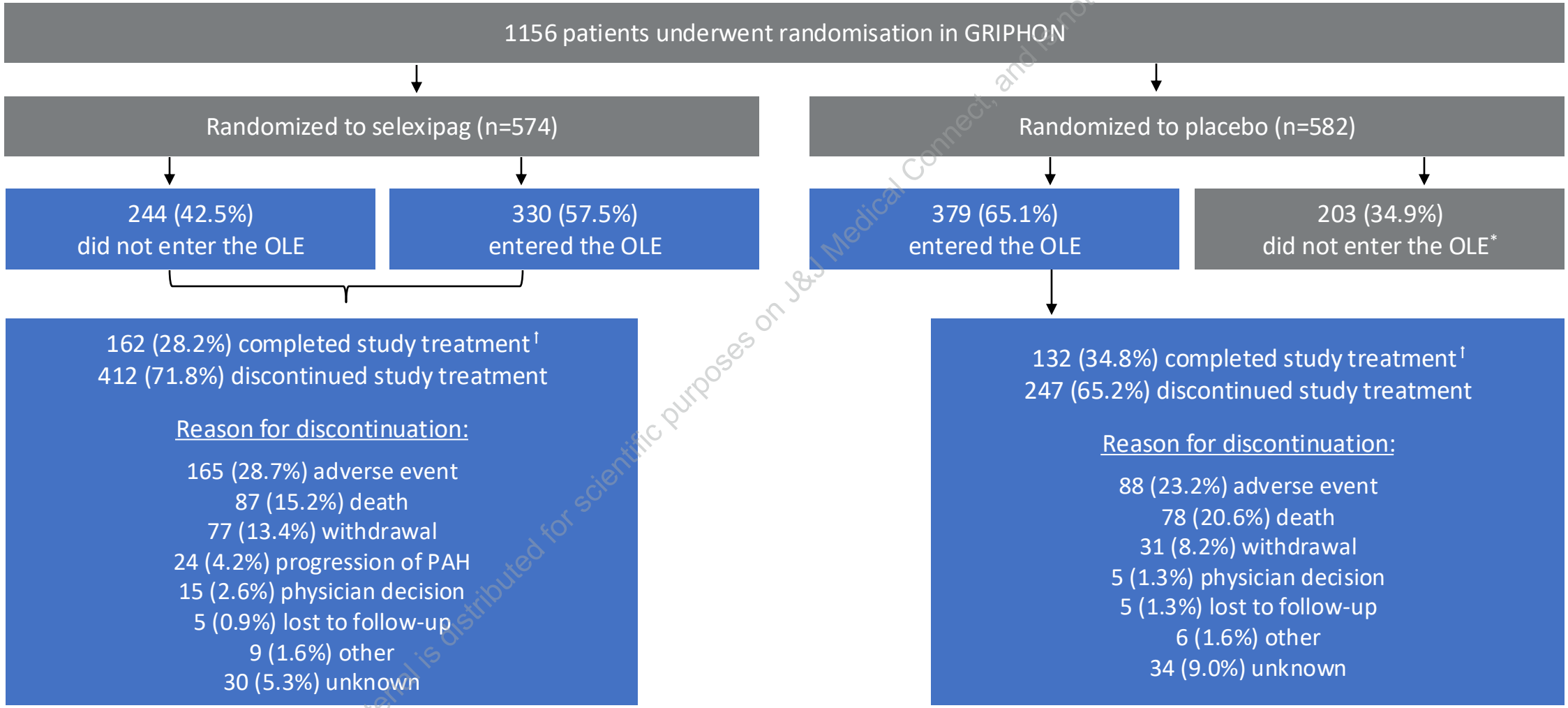
Backup slides

Selexipag titration scheme in GRIPHON DB



1. Sitbon O, *et al. N Engl J Med* 2015; 373:2522-2533.

Patient Disposition



* patients did not receive placebo as assigned. †Completed study treatment in GRIPHON DB or GRIPHON OLE: Patients who performed the end of study assessment. Blue shading indicates patients who received selexipag.

Safety and exposure (2)

	ITT-selexipag population (N = 574)
Most frequent adverse events*, n (%)	
Dyspnea	131 (23)
Peripheral edema	118 (21)
Vomiting	115 (20)
Pain in extremity	110 (19)
Dizziness	106 (19)
Nasopharyngitis	100 (17)
Myalgia	96 (17)
Upper respiratory tract infection	94 (16)
Cough	90 (16)
Right ventricular failure	84 (15)
Flushing	79 (14)
Anemia	77 (13)
Arthralgia	75 (13)
Bronchitis	64 (11)
Pneumonia	63 (11)
Fatigue	58 (10)

*Occurring in ≥ 10% of patients.