PNEUMOMEDICINA 2020

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Ipertensione Polmonare

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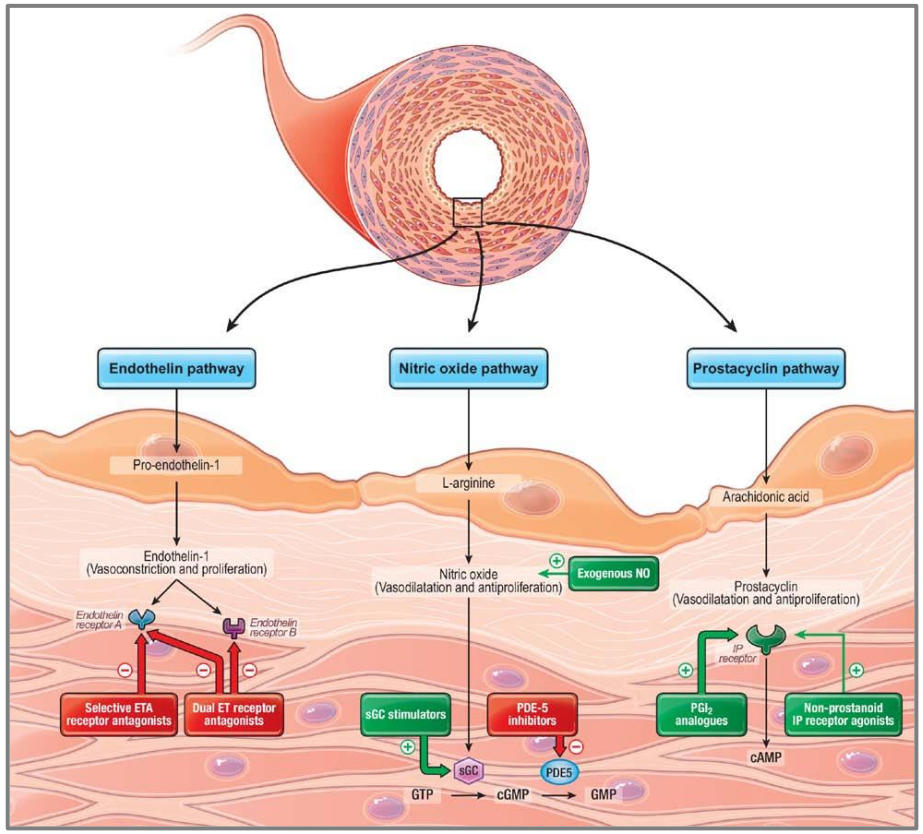
Current PAH-targeted medications:
Targeting 3 major pathways of endothelial dysfunction

Advances in Therapeutic Interventions for Patients With Pulmonary Arterial Hypertension

Marc Humbert, MD, PhD; Edmund M.T. Lau, MD, PhD; David Montani, MD, PhD; Xavier Jaïs, MD; Oliver Sitbon, MD, PhD; Gérald Simonneau, MD



Endothelin pathway

Endothelin receptor antagonists (ERAs)

- Ambrisentan
- Bosentan
- Macitentan

NO–cGMP pathway

PDE5 inhibitors

- Sildenafil
- Tadalafil

sGC stimulators
Riociguat

Prostacyclin pathway

Prostanoids

- Epoprostenol iv
- Iloprost inhaled, iv
- Treprostinil sc, iv, (inhaled, oral)*
- (Beraprost)**

Non prostanoids IP receptor agonist
Selexipag (oral)

*Only approved in the US; **Only approved in Japan and South Korea

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

Nazzareno Galiè[1] (ESC Chairperson), Marc Humbert[2] (ERS Chairperson), Jean-Luc Vachiery[3], Simon Gibbs[1], Irene Lang[1], Adam Torbicki[1], Gérald Simonneau[2], Andrew Peacock[2], Anton Vonk Noordegraaf[2], Maurice Beghetti[4], Ardeschir Ghofrani[2], Miguel Angel Gomez Sanchez[1], Georg Hansmann[4], Walter Klepetko[3], Patrizio Lancellotti[1], Marco Matucci[5], Theresa McDonagh[1], Luc A. Pierard[1], Pedro T. Trindade[1], Maurizio Zompatori[6] and Marius Hoeper[2]

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

Treatment Algorithm for Pulmonary Arterial Hypertension

30

Recommendations for PAH general treatment measures

	Class[a]	Level[b]
ents with PAH.	I	C
nza and pneumococcal		C
		C
		B
		C
		C
		C

32

Recommendations for calcium channel blocker therapy in patients who respond to the acute vasoreactivity test

Recomme
High doses c and DPAH re
Close follow therapy (inclu and DPAH tr
Continuation patients with haemodynam
Initiation of s FC III or IV (near normal
High doses o study or nor other indicat

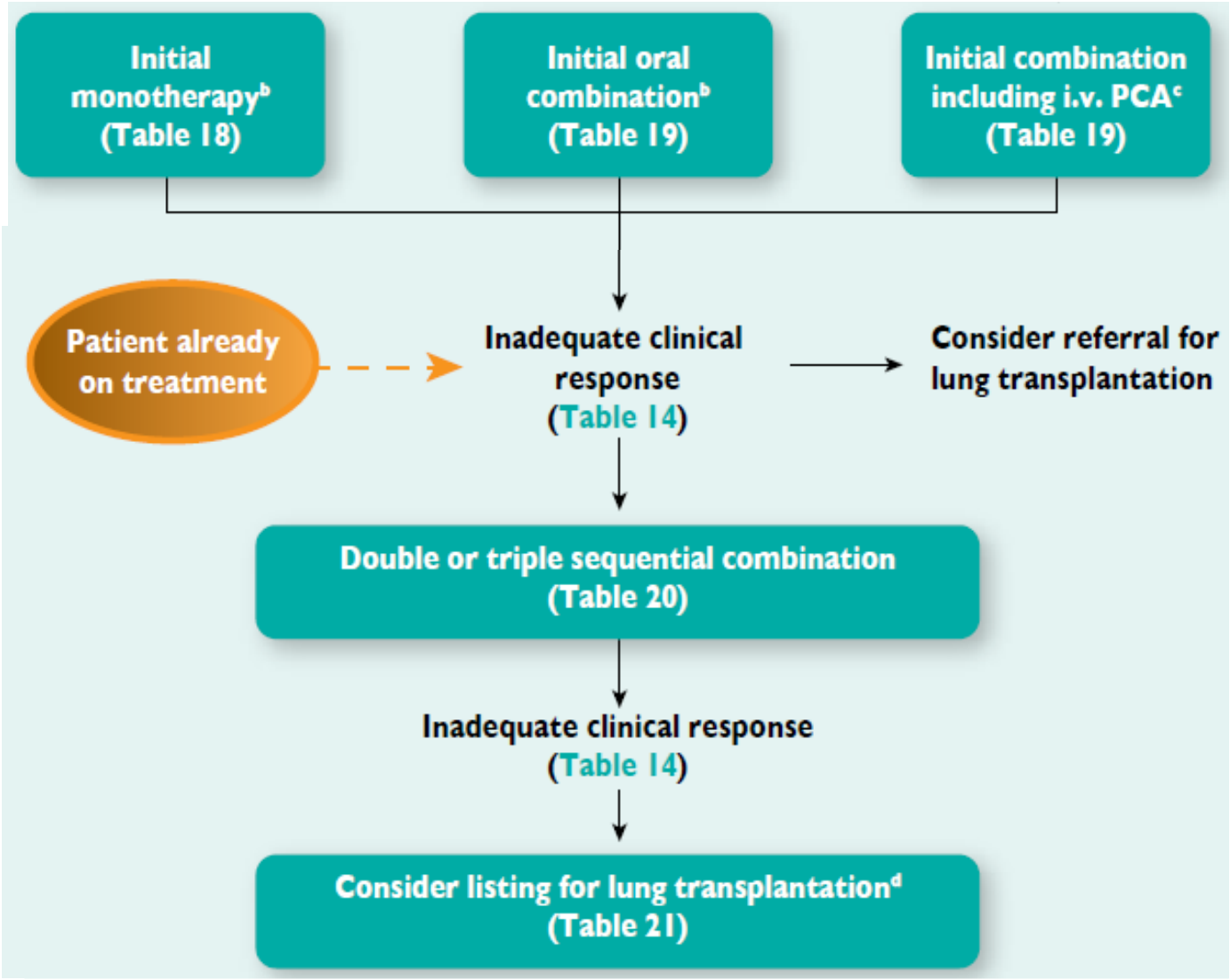
28

Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65 % pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35 % pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65 %	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60 %

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

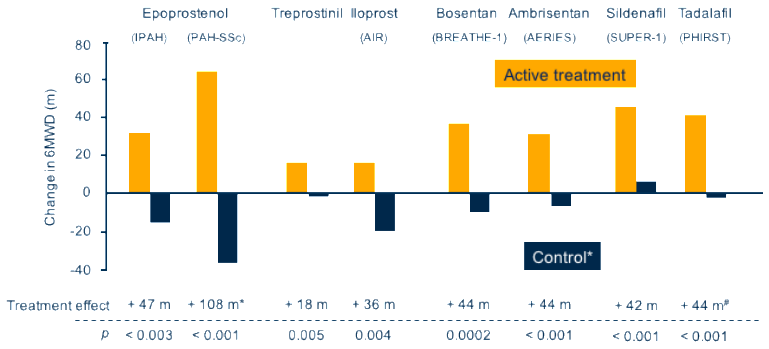
Treatment Algorithm for Pulmonary Arterial Hypertension

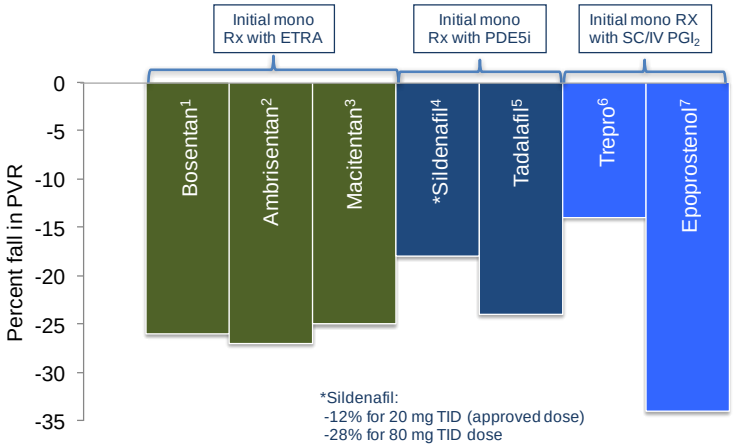


Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

Initial monotherapy in PAH

- Many RCTs with all drugs targeting the 3 dysfunctional pathways (PGI_2, ERA, PDE-5 inhibitors)
  - Improvement in exercise capacity (35-45 m) after 3-6 months[1-7]
  - Modest improvement in haemodynamics[1-7]
    - 25-35% decrease in PVR;
    - almost no change in PAP
  - Metanalysis[8]
    - 25 RCTs, 3839 patients, 14.3 weeks
    - 44% reduction in mortality (p=0.016)
- Huge experience worldwide



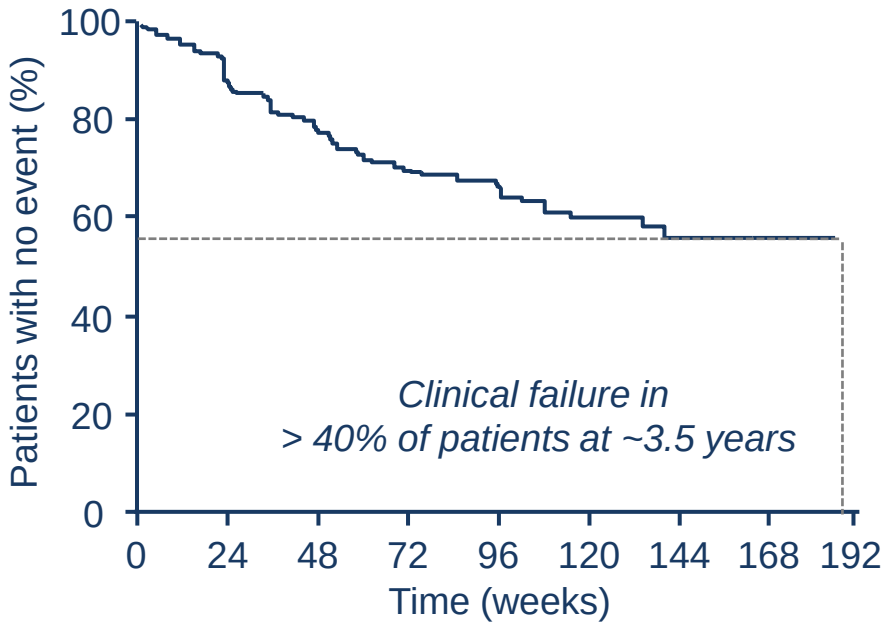


1. Channick RN. *Lancet* 2001; 2. Galiè N. *J Am Coll Cardiol* 2005; 3.Pulido T. *N Engl J Med* 2013; 4. Galiè N. *N Engl J Med* 2005; 5. Galiè N. *Circulation* 2009; 6. Simonneau G. *Am J Respir Crit Care Med* 2002; 7. Barst RJ. *N Engl J Med* 1996. 8. Galiè N. *Eur Heart J* 2010.

PAH progresses rapidly in patients on monotherapy

Pooled monotherapy arm from AMBITION

Time to first event of clinical failure* (primary endpoint)



Number at risk:								
Pooled monotherapy	247	209	155	108	77	49	25	5

*Clinical failure: the first occurrence of a composite endpoint of death, hospitalization for PAH worsening, disease progression, or unsatisfactory long-term clinical response.

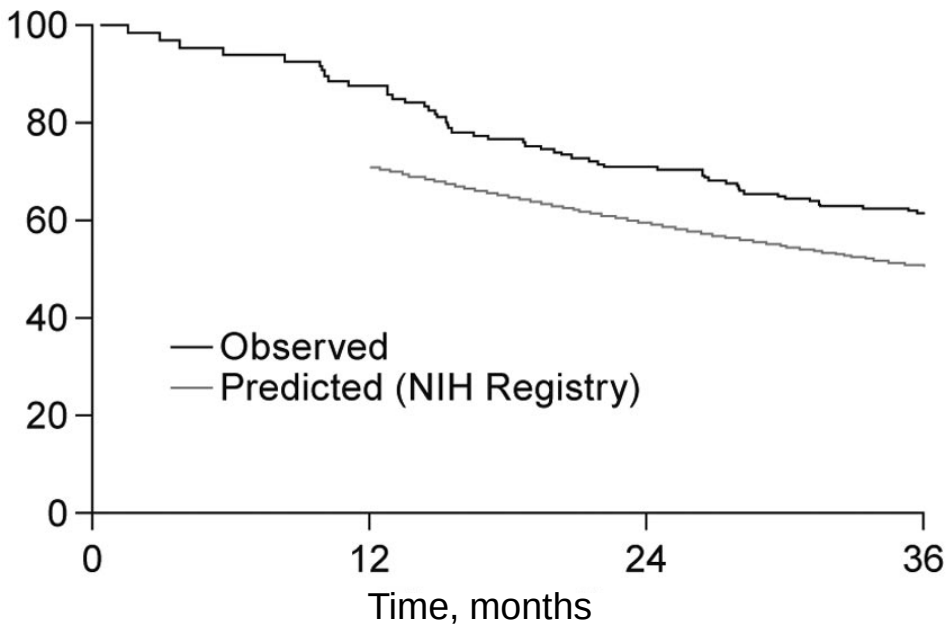
AMBITION, AMBrisentan and Tadalafil in patients with pulmonary arterial HypertensION.

Adapted from Galiè N *et al*. *N Engl J Med* 2015;373:834–44.

French cohort: Idiopathic, heritable and drug-induced PAH

2002-2003

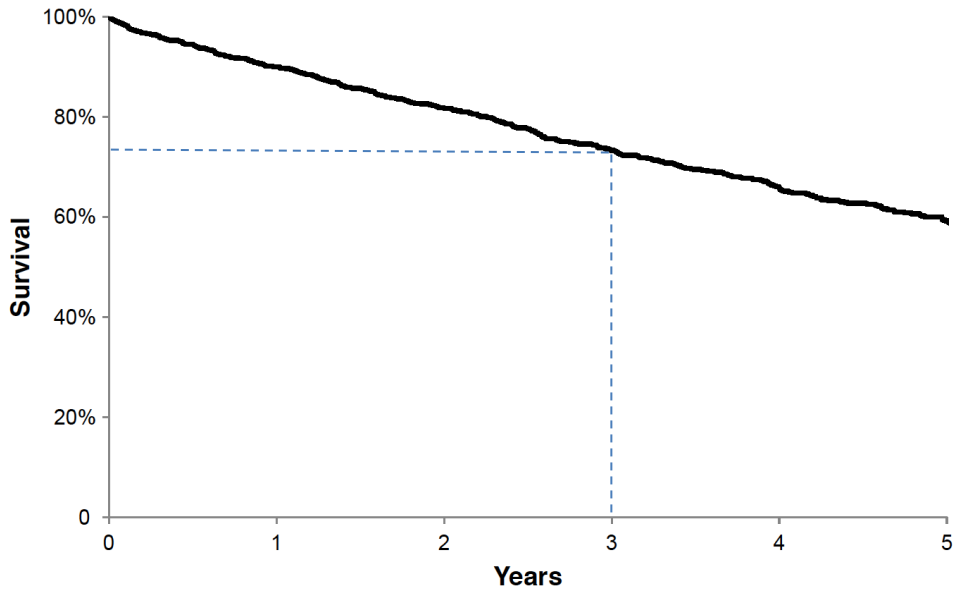
N=190 (incident)



3-year survival
58%

2006-2016

N=1592 (incident)

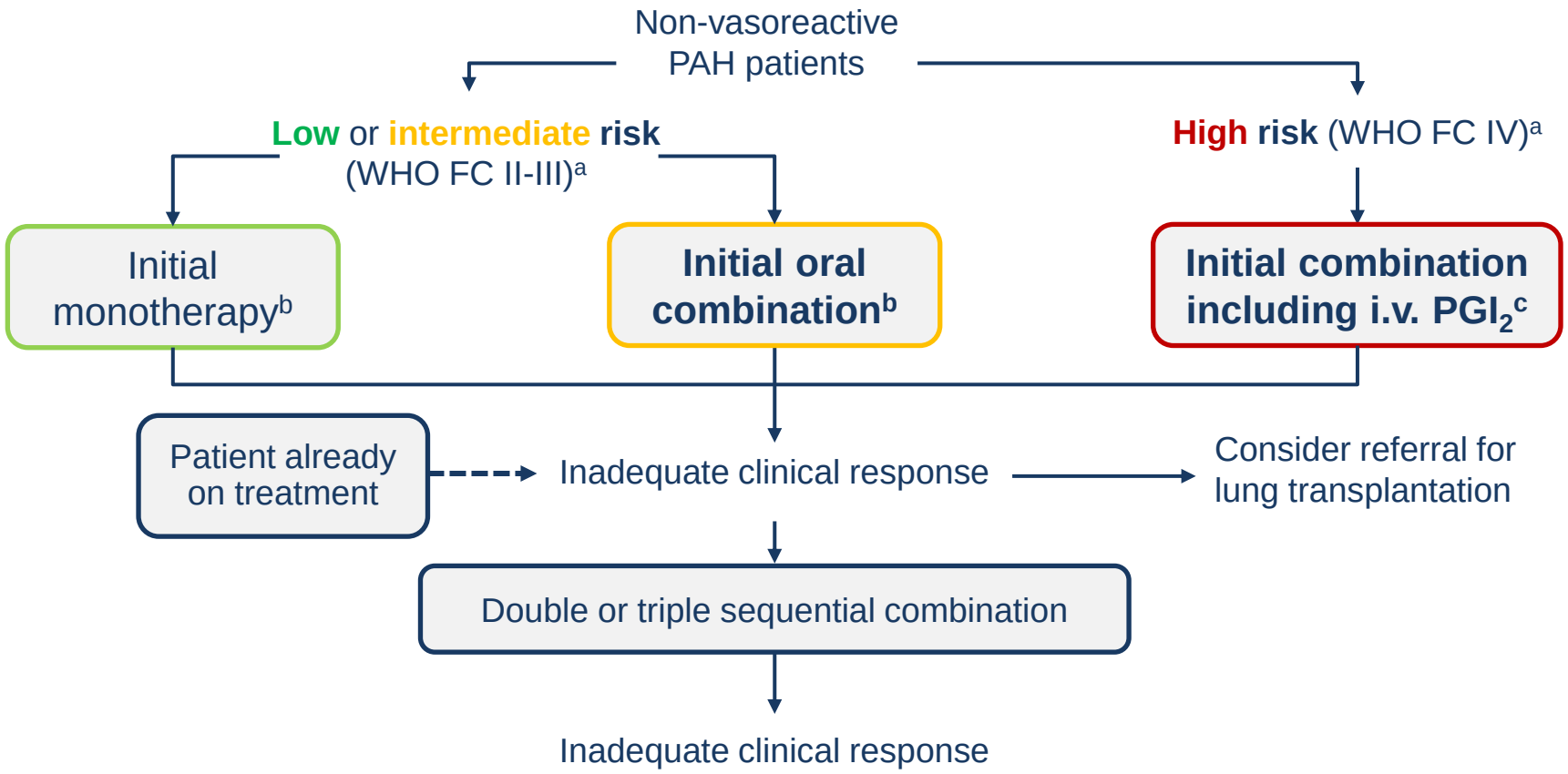


Patients at risk, n	1591	1063	823	605	417	285
Overall survival		90%				59%

3-year survival
73%

1. Humbert M, *et al. Circulation*. 2010;122:156-63.
2. Boucly A, *et al. Eur Respir J* 2017;50:1700889.

Initial combination therapy is recommended for patients at intermediate or high risk at the time of diagnosis



[a] Some WHO-FC III patients may be considered high-risk;
[b] Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure;
[c] Intravenous epoprostenol should be prioritized as it has reduced the 3 month rate for mortality in high-risk PAH patients also as monotherapy.

1. Galiè N, *et al. Eur Respir J* 2015; 46:903-75;
2. Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

Initial combination therapy: What is the evidence?

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C
Other ERA or PDE-5i + s.c. treprostinil			IIb	C	IIb	C
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C	IIb	C

- 2 **RCTs** + 1 ongoing

- 2 open-label studies
- Small observational studies

AMBITION: Galiè N, *et al. N Engl J Med* 2015.
Hassoun P, *et al. Am J Respir Crit Care Med* 2015.

Sitbon O, *et al. Eur Respir J* 2016.
Joint-INTENTION; OPTIMA

Sitbon O, *et al. Eur Respir J.* 2014.

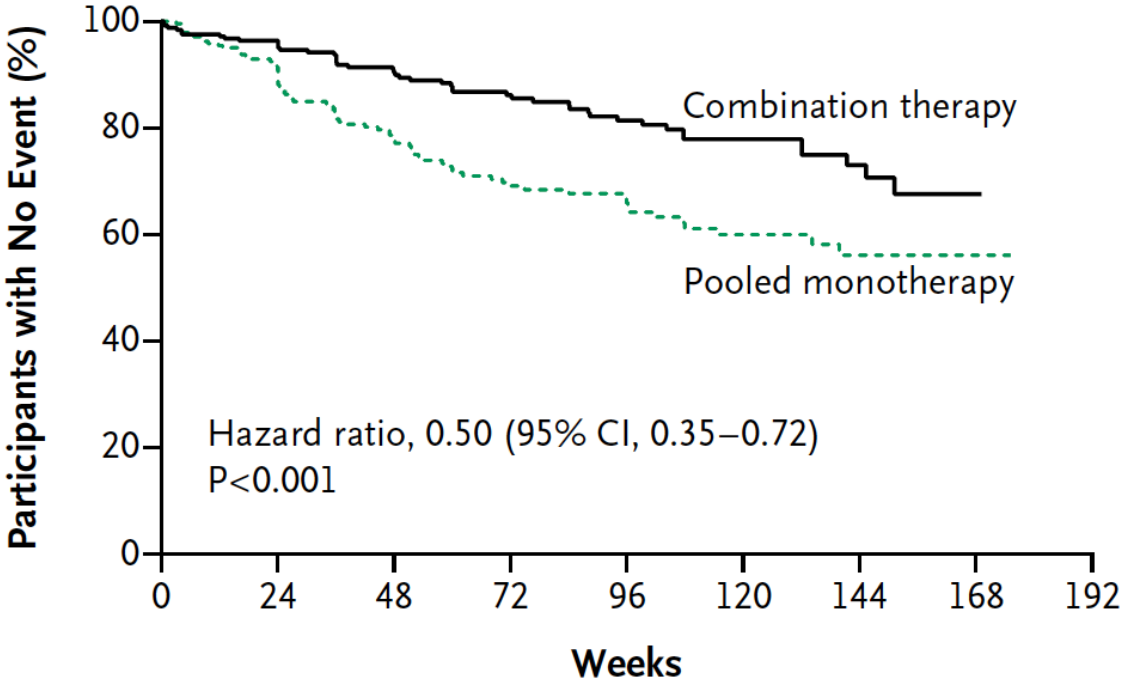
BREATHE-2: Humbert M, *et al. Eur Respir J.* 2004.
Kemp K, *et al. J Heart Lung Transplant* 2012.

TRITON study (macitentan, tadalafil, ± selexipag) ongoing

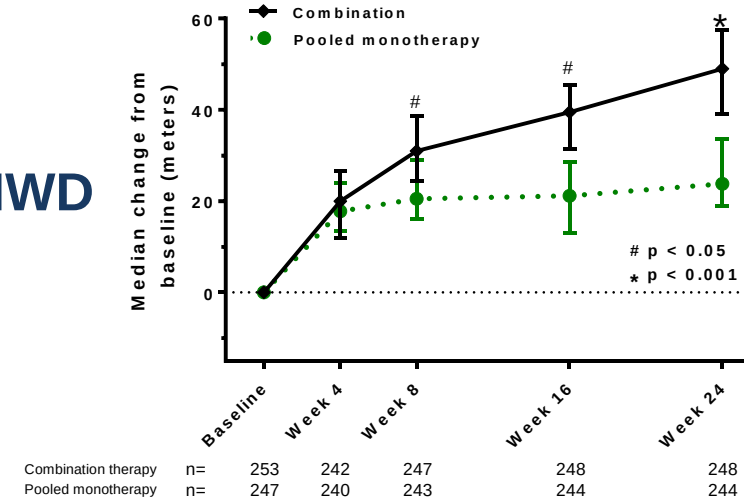
Galiè N, Humbert M, *et al. Eur Respir J* 2015;46:903–75; *Eur Heart J* 2016;37:67–119.

AMBITION: Initial combo of ambrisentan AND tadalafil is superior to monotherapy with ambrisentan OR tadalafil

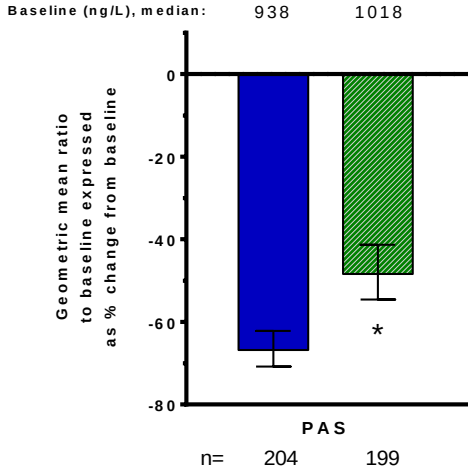
- N=500 treatment-naïve patients with PAH (31% FC II)
- **Primary endpoint**: Time to the first occurrence of a composite endpoint of death, hospitalization for PAH worsening, disease progression, or unsatisfactory long-term clinical response



6MWD



NT-ProBNP



Hospitalisation for PAH worsening was the main component of the primary endpoint

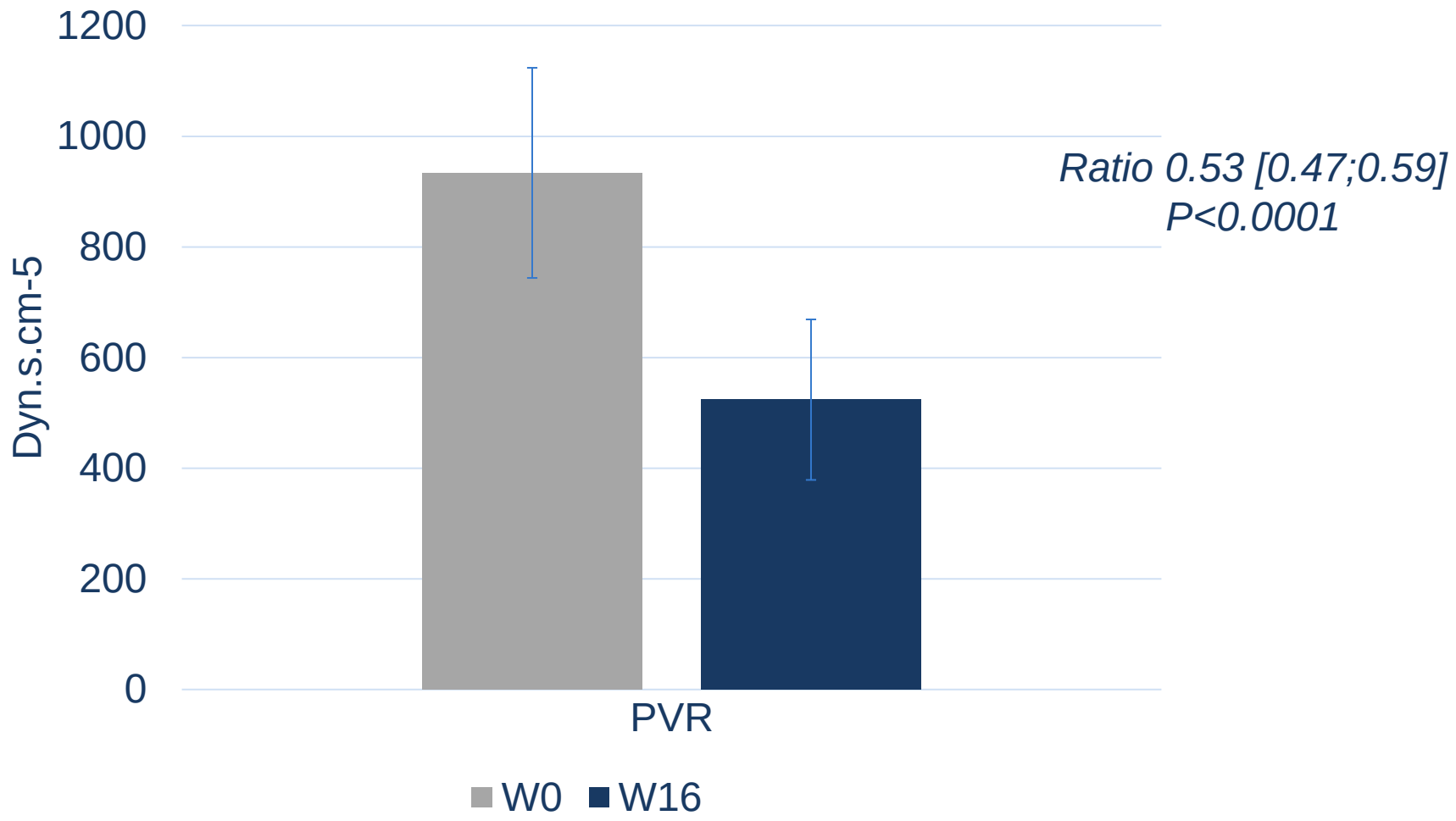
Galiè N, et al. N Engl J Med 2015;273:834:44.

OPTIMA study

- Prospective, multicenter, open-label study evaluating the effects of first-line oral c**O**mbination thera**P**y of maci**T**entan and tadalaf**I**l in patients with newly diagnosed pul**M**onary **A**rterial Hypertension
- Primary objective: change in PVR at week 16
- Treatment naive PAH patients with 6MWD ≥ 50 m at screening
- 15 centres in France; 50 patients screened / 46 enrolled

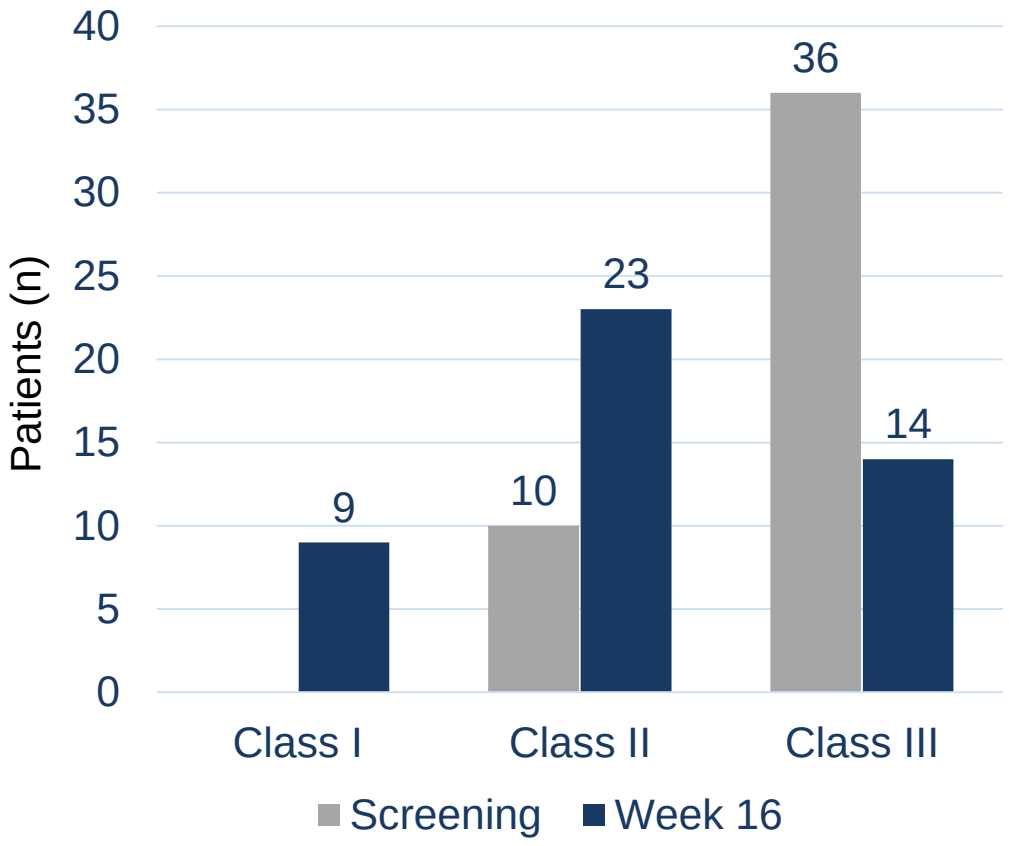
  - Mean age: 57 ± 15 years
  - 65% female
  - 70% idiopathic/heritable PAH
  - 78% FC III / 22% FC II
  - 6MWD 352 ± 135 m
  - PVR 934 ± 379 dyn.s/cm^5

OPTIMA study: Change in PVR after 16 weeks



OPTIMA study: Change in other variables

	Baseline	Week 16	P-value
RAP, mmHg	8.1 ± 4.7	7.8 ± 5.3	0.73
mPAP, mmHg	50.0 ± 12.3	42.2 ± 14.7	0.0002
CI, L/min/m^2	2.2 ± 0.6	3.1 ± 0.8	<0.0001
SvO_2, %	63.0 ± 7.1	68.2 ± 7.2	0.0003
NT-proBNP, ng/L	1457 (647 – 2119)	404 (147 – 874)	0.001
6MWD, m	352 ± 135	388 ± 142	0.0008



- No patient experienced a worsening of FC
- There was no missing data

Initial dual oral combination in PAH:
A matter of drugs or strategy?

	AMBITION–BONSAI* Ambrisentan + tadalafil (n=19)[1]	Joint–INTENTION# Bosentan + sildenafil (n=23)[2]	French Network Cohort ERA + PDE5i (n=97)[3]	OPTIMA Macitentan + tadalafil (n=46)
Δ RAP (%)	-17	- 36	-29	-4
Δ mPAP (%)	-33	- 21	-16 (-10 mmHg)	-16 (-8 mmHg)
Δ CI (%)	+56	+63	+46 (+1 L/min/m^2)	+41 (+0.9 L/min/m^2)
Δ PVR (%)	-61	-60	-43 (from 12.7 WU)	-47 (from 11.7 WU)
Δ 6MWD (%)	+25	+ 42	+22 (+71 m)	+10 (+36 m)

*BONSAI: BOlogNa Sub-study on hAemodynamIcs
#Joint Bologna and Calgary study on INiTial bosENTan plus sIldenafil in pulmonary arterial hypertension.

1. Bachetti C *et al. Am J Respir Crit Care Med* 2015;191:A479.
2. Palazzini M *et al. Am J Respir Crit Care Med* 2016;193:A6317.
3. Sitbon O *et al. Eur Respir J* 2016;47:1727–36.

PAH-specific therapies targeting the prostacyclin signalling pathway

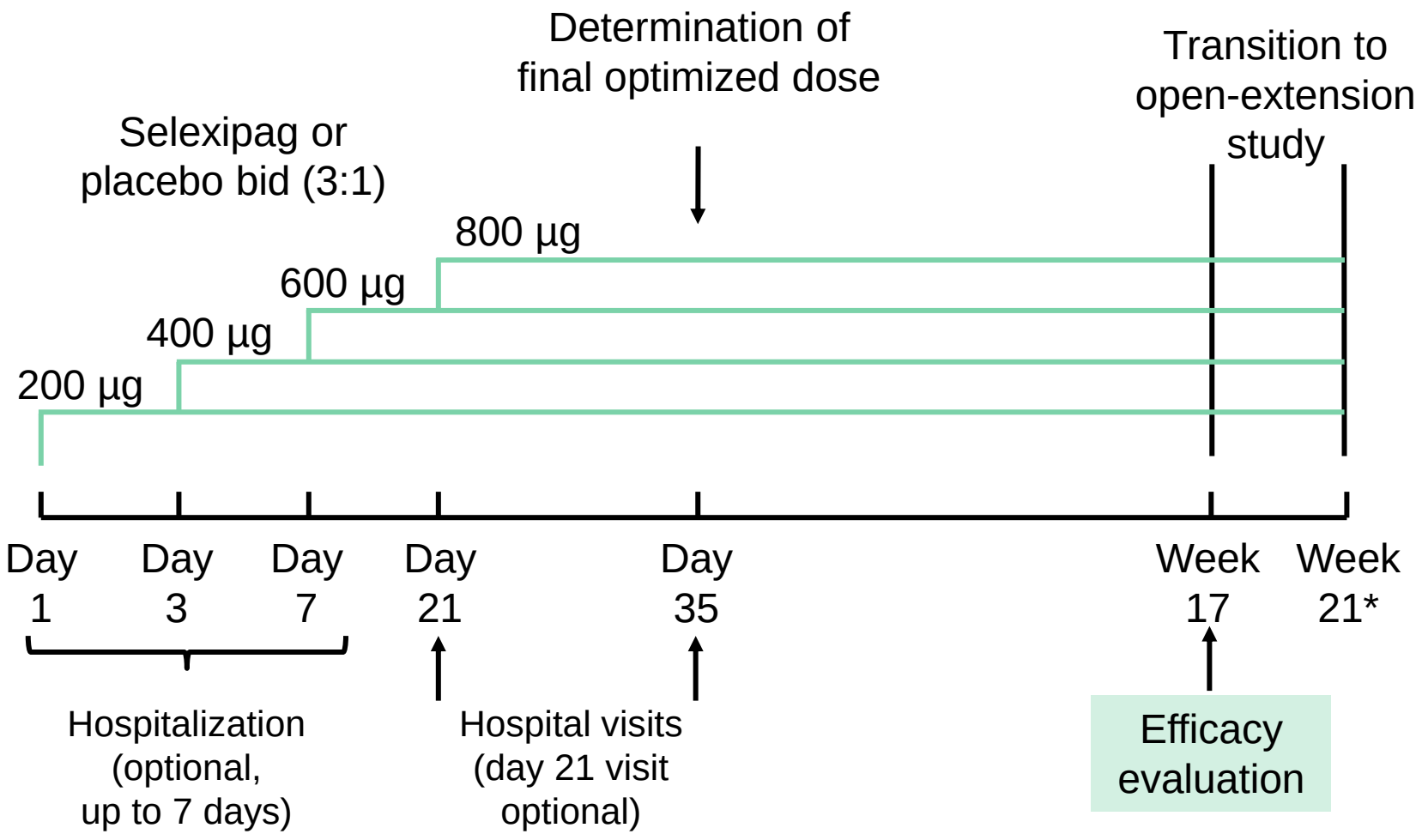
- **Prostacyclin**
  - Epoprostenol: i.v.

- **Prostacyclin analogues**
  - Iloprost: i.v., inhaled
  - Treprostinil: i.v., s.c., inhaled*, oral*
  - Beraprost: oral#

- **Non prostanoid IP receptor agonist**
  - Selexipag: oral

* only licensed in the US
# only licensed in Japan and South Korea

Phase II study with selexipag: Study design



- 43 patients
  - Selexipag (n = 33)
  - Placebo (n = 10)
- All on background treatment with ERA and/or PDE-5i

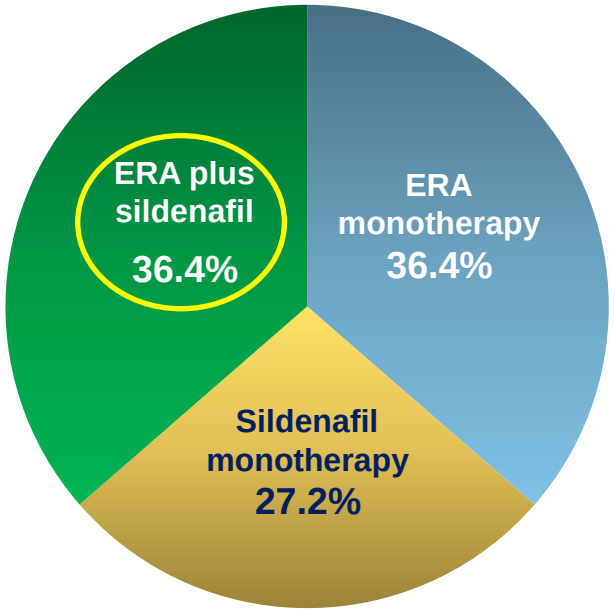
- Primary EP
  - % change in PVR
- Secondary EP
  - Change in 6MWD,
  - Change in other hemodynamic variables

Simonneau G, *et al. Eur Respir J* 2012; 40:874–80.

Phase II study with selexipag: Main baseline characteristics

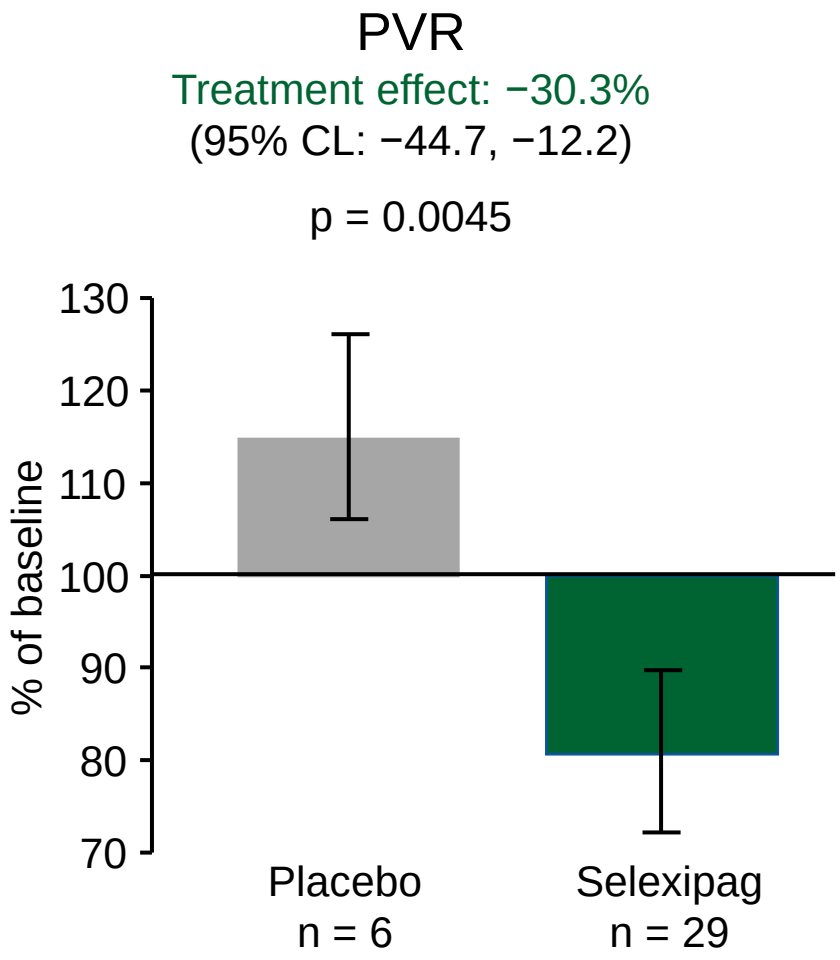
	Placebo	Selexipag
	n = 10	n = 33
FC II : III (n, %)	2 (20%) : 8 (80%)	15 (45%) : 18 (55%)
Mean 6MWD ± SD (m)	350 ± 123	396 ± 71
Mean PVR ± SD (dyn•s•cm^5)	867 ± 379	929 ± 437
Background therapy		
ERAs, *n* (%)	7 (70%)	24 (73%)
PDE-5 inhibitor, *n* (%)	6 (60%)	21 (64%)
Combination, *n* (%)		
ERA + PDE-5 inhibitor	3 (30%)	12 (36%)

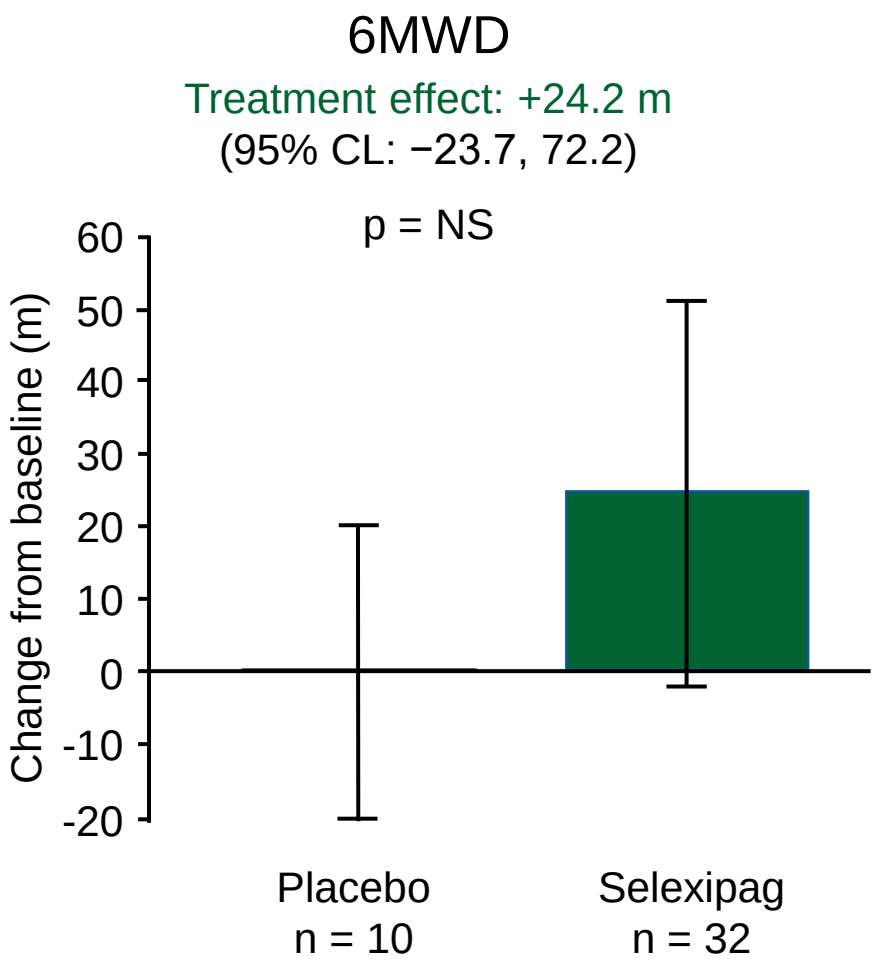
Selexipag Group
n = 33



Simonneau G, *et al. Eur Respir J* 2012; 40:874–80.

Phase II study with selexipag: Change in PVR and 6MWD



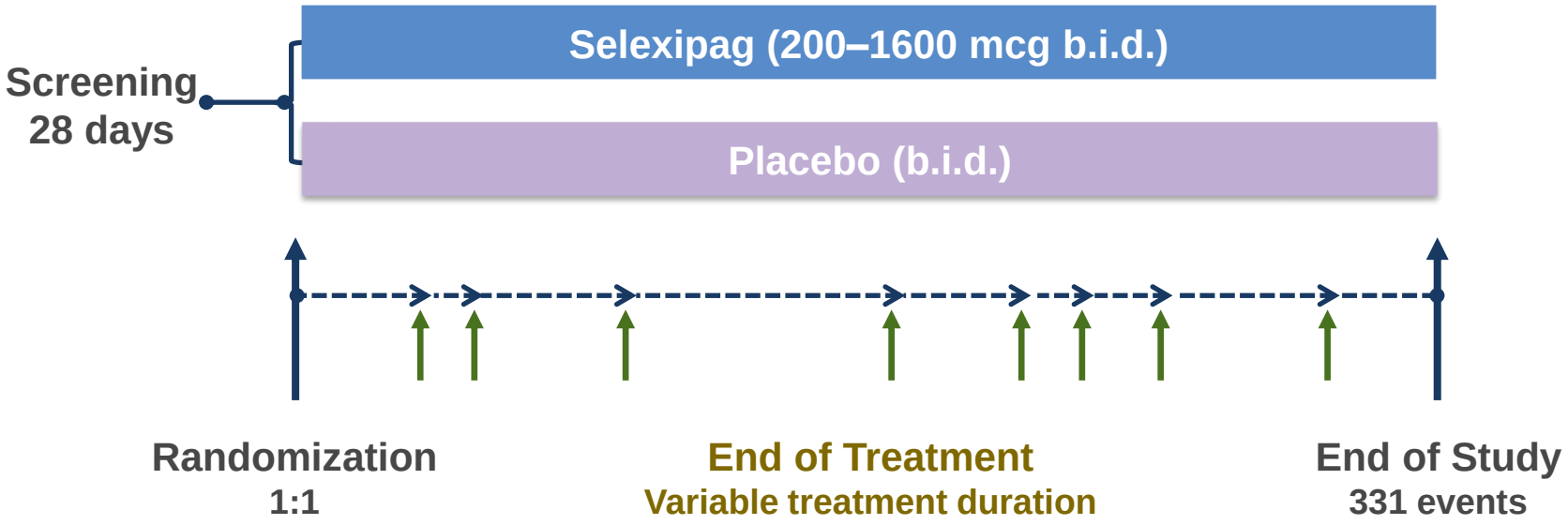


The beneficial effects with selexipag were observed despite patients receiving background therapy with an ERA and/or sildenafil

Simonneau G, *et al. Eur Respir J* 2012; 40:874–80.

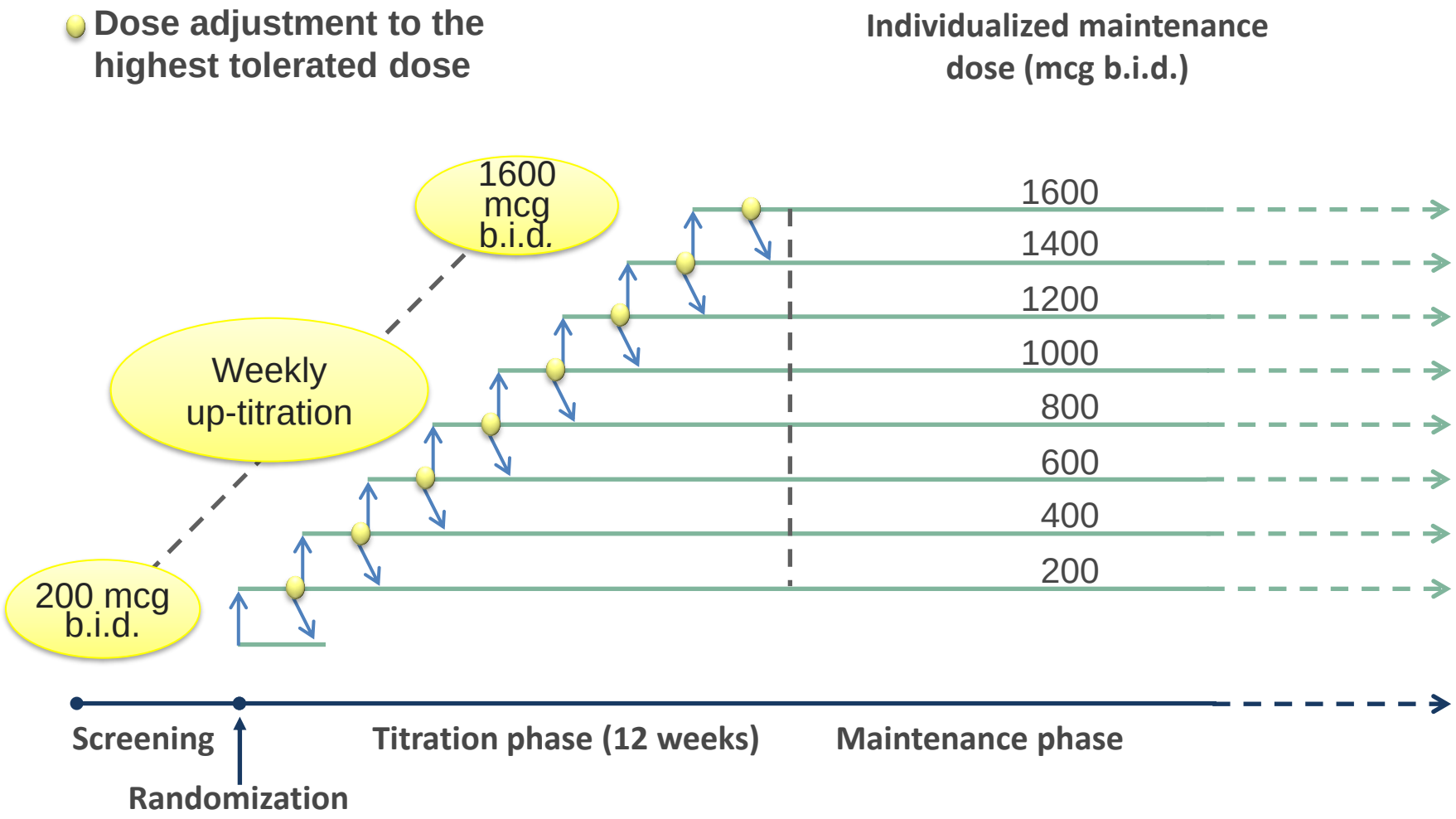
GRIPHON: Pivotal phase III study with selexipag

- Global, multicenter, double-blind, 1:1 randomized, parallel-group, placebo-controlled, event-driven, phase III study



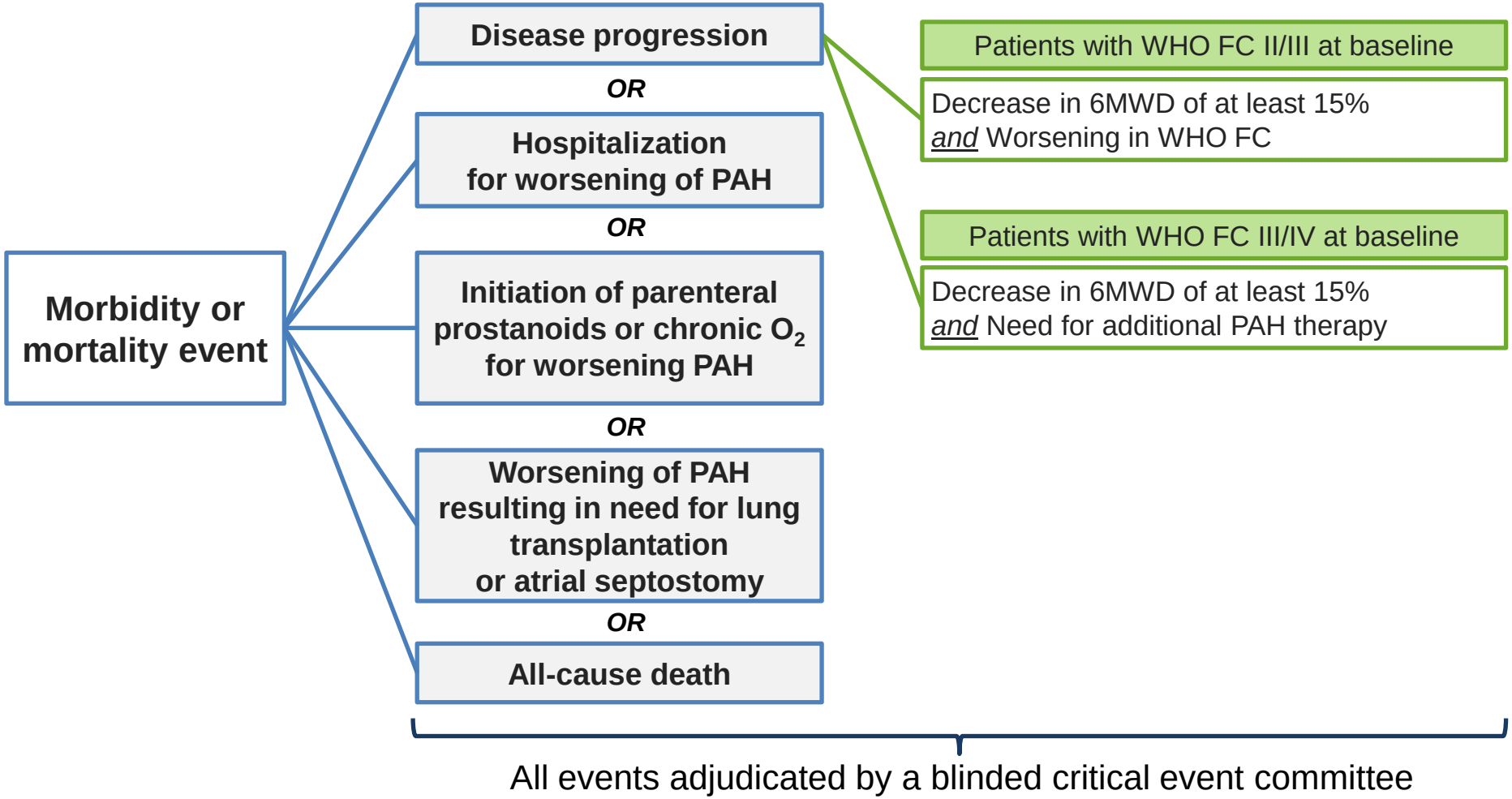
Sitbon O, *et al. N Engl J Med* 2015;373:2522–33.

GRIPHON study titration and dosing



Sitbon O, *et al. N Engl J Med* 2015;373:2522–33.

GRIPHON primary composite endpoint of death or morbidity due to PAH



Sitbon O, *et al. N Engl J Med* 2015;373:2522–33.

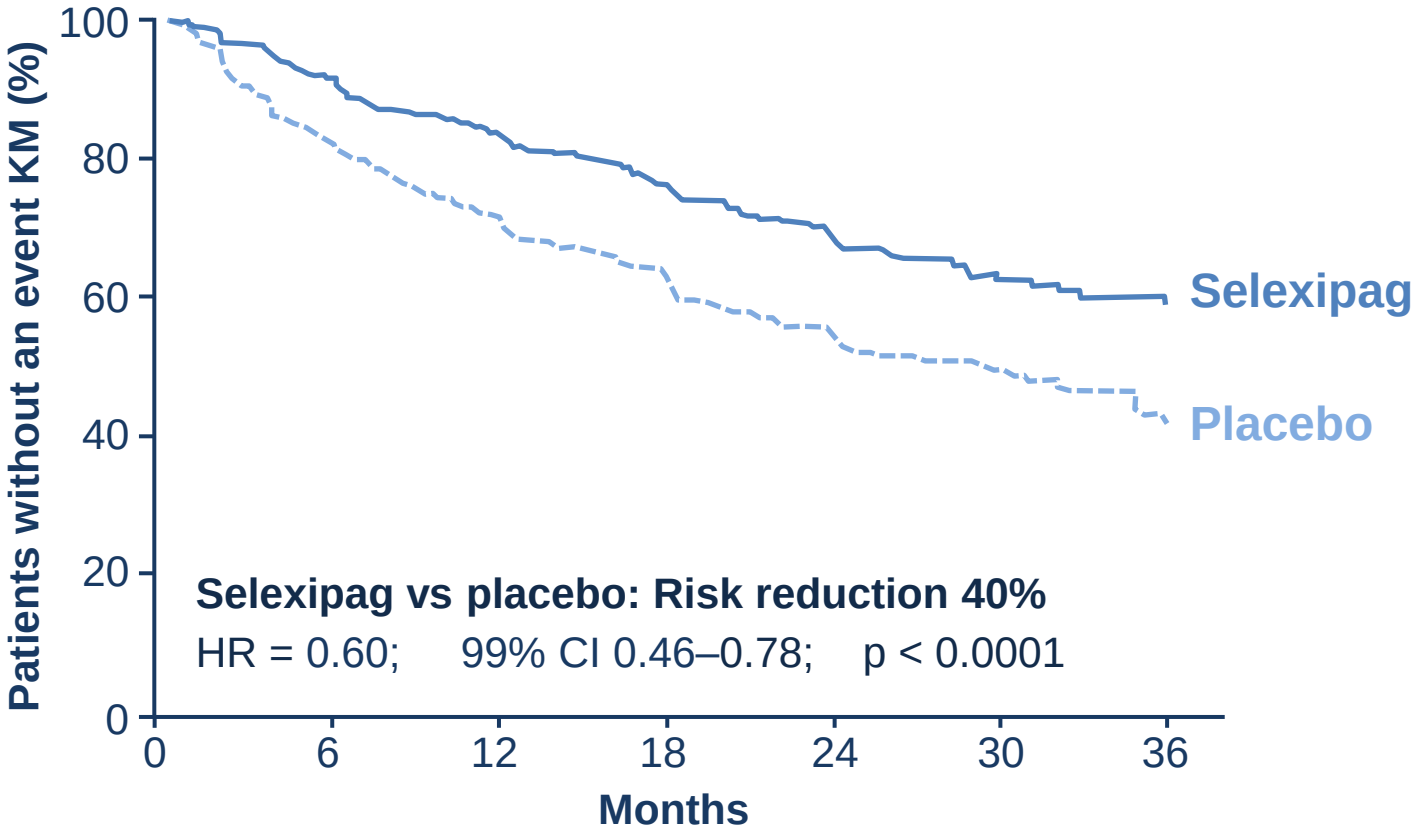
GRIPHON secondary efficacy endpoints

- Change from baseline to week 26 in 6MWD at trough
- Absence of worsening from baseline to week 26 in NYHA/WHO FC
- Time to death due to PAH or hospitalization due to PAH worsening up to EOT + 7 days
- Time to death of all causes up to study closure
- Change from baseline to week 26 in CAMPHOR breathlessness and symptoms score

EOT = end of double-blind treatment

Sitbon O, *et al. N Engl J Med* 2015;373:2522–33.

GRIPHON: Selexipag reduced the risk of the primary outcome composite of death or morbidity due to PAH



No. at Risk

Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

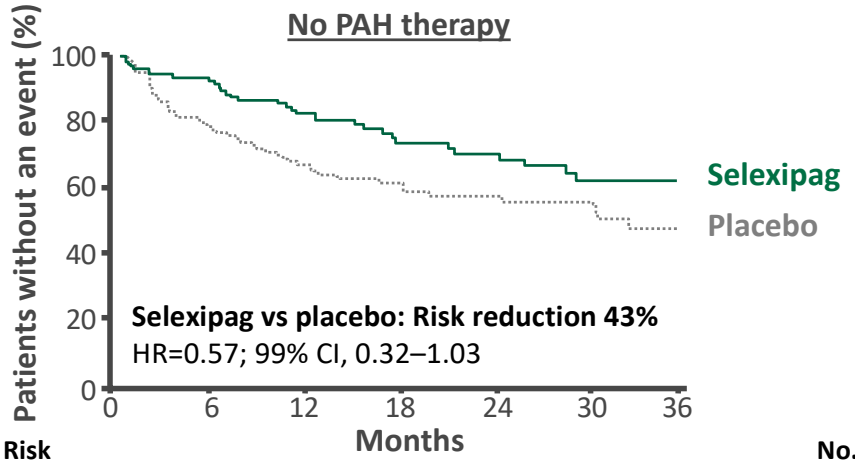
Sitbon O, *et al. N Engl J Med* 2015;373:2522–33.

GRIPHON: Events contributing to the primary endpoint up to EOT

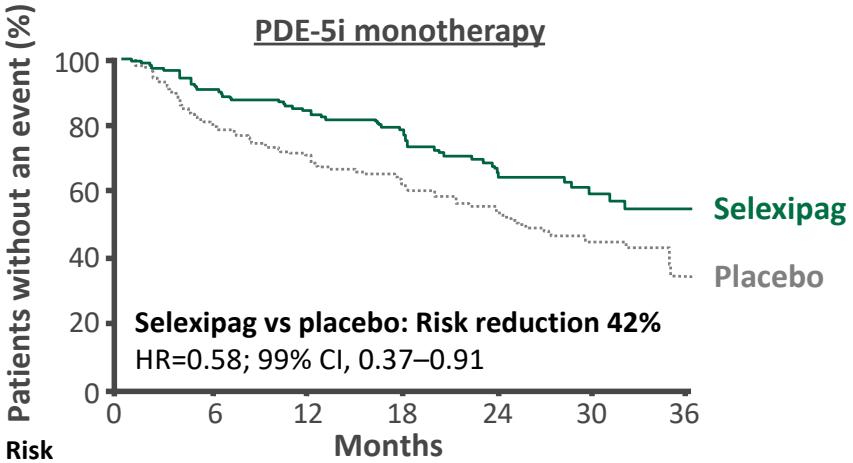
Primary endpoint events, n (%)	Placebo n = 582	Selexipag n = 574
All primary endpoint events	242 (41.6)	155 (27.0)
Hospitalization for PAH	109 (18.7)	78 (13.6)
Disease progression	100 (17.2)	38 (6.6)
Death (all causes)	18 (3.1)	28 (4.9)
Parenteral prostanoid or chronic O_2 therapy	13 (2.2)	10 (1.7)
PAH worsening resulting in need for lung transplantation or balloon atrial septostomy	2 (0.3)	1 (0.2)

Sitbon O, *et al. N Engl J Med* 2015;373:2522–33.

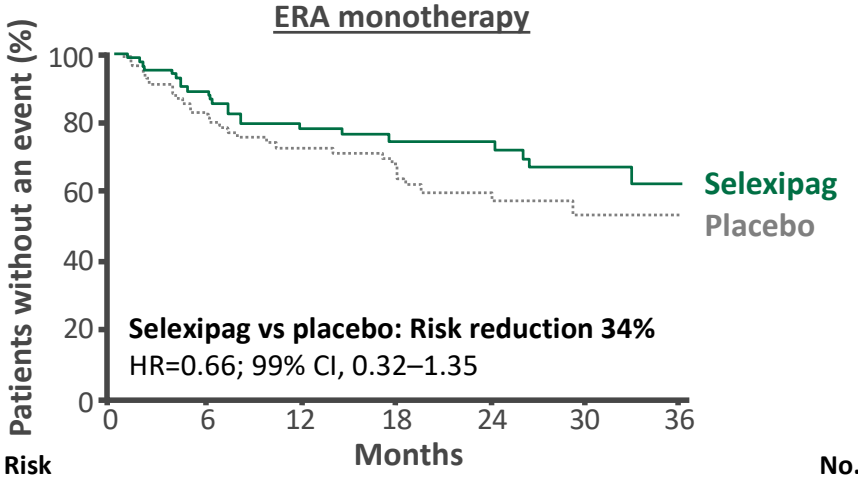
Primary endpoint according to background PAH therapy



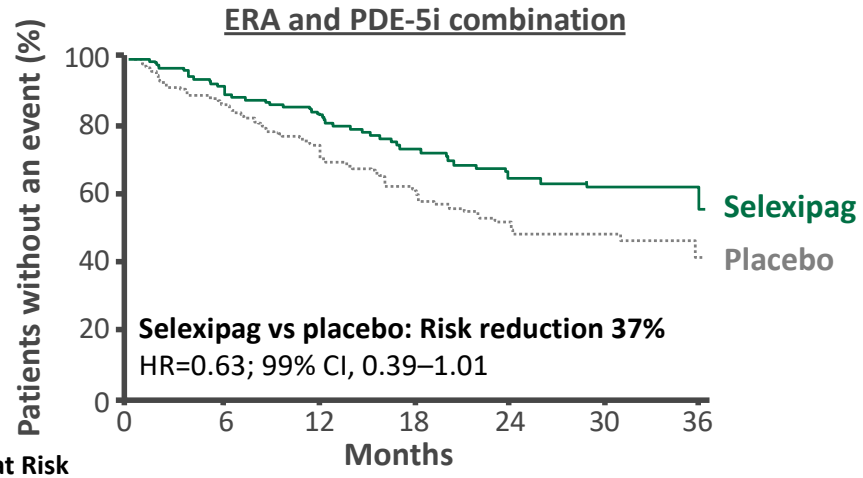
No. at Risk							
Placebo	124	84	67	45	33	23	8
Selexipag	112	97	81	49	40	23	12



No. at Risk							
Placebo	185	135	114	73	49	27	9
Selexipag	189	151	125	91	59	30	11



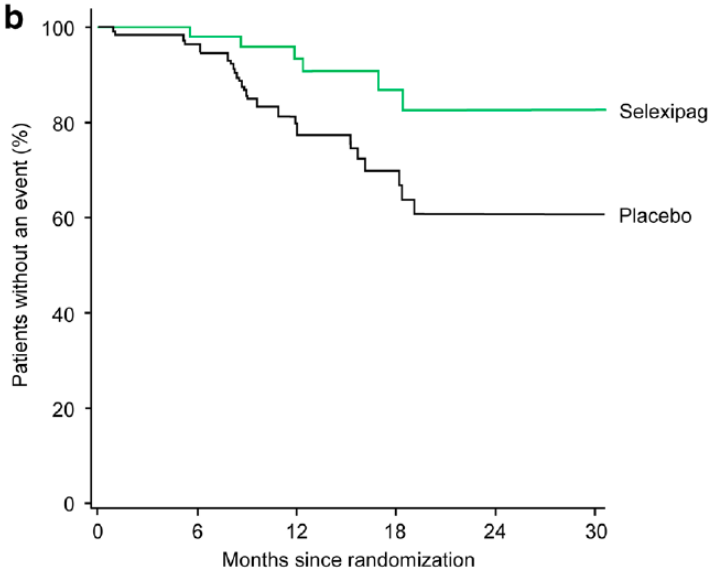
No. at Risk							
Placebo	76	56	47	32	23	11	4
Selexipag	94	67	50	36	29	17	9



No. at Risk							
Placebo	197	158	119	70	44	27	7
Selexipag	179	140	105	70	43	31	8

Effect of selexipag on primary composite endpoint in patients receiving dual combination therapy (ERA and PDE-5i)

FC II symptoms

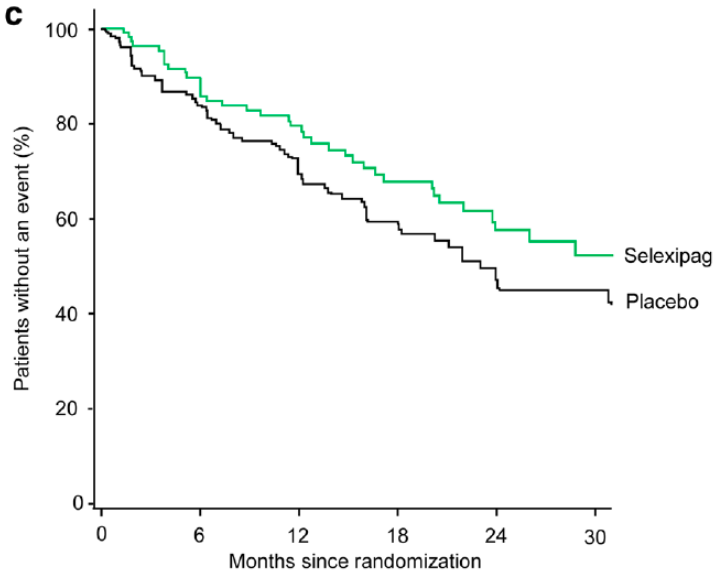


Patients at risk						
Selexipag	55	46	36	22	14	13
Placebo	60	52	40	23	12	7

HR 0.36
(95% CI 0.14 – 0.91)

Risk reduction
FC II patients 63%
FC III patients 26%

FC III symptoms

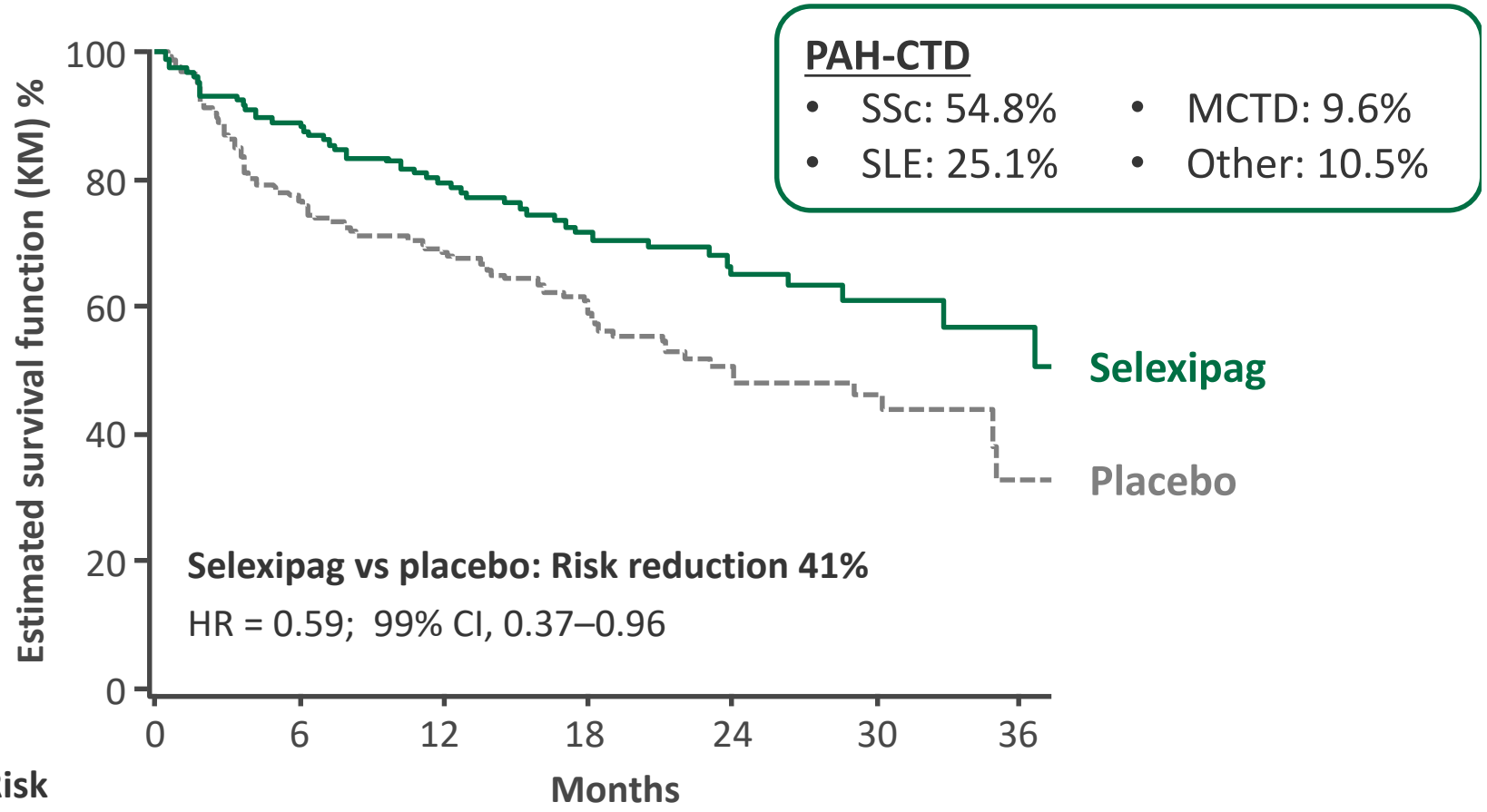


Patients at risk						
Selexipag	122	92	68	47	28	17
Placebo	133	104	77	46	31	19

HR 0.74
(95% CI 0.50 – 1.10)

Coghlan JG, *et al. Am J Cardiovasc Drugs* 2018;18:37–47.

Effect of selexipag on primary composite endpoint in patients with connective-tissue diseases



No. at Risk							
Placebo	167	114	92	57	38	21	3
Selexipag	167	129	102	70	44	21	10

Gaine S, *et al. Eur Respir J* 2017;50:1602493.

GRIPHON: Most frequent adverse events and abnormal laboratory results

Variable	Placebo (N=577)	Selexipag (N=575)	P Value
Adverse events — no.	3937	4607	
Patients with ≥1 adverse event — no. (%)	559 (96.9)	565 (98.3)	0.18
Patients with ≥1 serious adverse event — no. (%)†	272 (47.1)	252 (43.8)	0.26
Patients with adverse events leading to discontinuation of study agent — no. (%)	41 (7.1)	82 (14.3)	<0.001

Sitbon O, *et al. N Engl J Med* 2015;373:2522–33.

GRIPHON: Most frequent adverse events and abnormal laboratory results

Variable	Placebo (N=577)	Selexipag (N=575)	P Value
Adverse event — no. of patients (%)‡			
Headache	189 (32.8)	375 (65.2)	<0.001
Diarrhea	110 (19.1)	244 (42.4)	<0.001
Nausea	107 (18.5)	193 (33.6)	<0.001
Pain in jaw	36 (6.2)	148 (25.7)	<0.001
Worsening of PAH	206 (35.7)	126 (21.9)	<0.001
Vomiting	49 (8.5)	104 (18.1)	<0.001
Pain in extremity	46 (8.0)	97 (16.9)	<0.001
Dyspnea	121 (21.0)	92 (16.0)	0.03
Myalgia	34 (5.9)	92 (16.0)	<0.001
Dizziness	85 (14.7)	86 (15.0)	0.93
Peripheral edema	104 (18.0)	80 (13.9)	0.06
Upper respiratory tract infection	80 (13.9)	75 (13.0)	0.73
Nasopharyngitis	63 (10.9)	75 (13.0)	0.28
Flushing	29 (5.0)	70 (12.2)	<0.001
Arthralgia	44 (7.6)	62 (10.8)	0.07
Cough	67 (11.6)	56 (9.7)	0.34
Fatigue	59 (10.2)	46 (8.0)	0.22
Right ventricular failure	58 (10.1)	46 (8.0)	0.26

Selexipag in Pulmonary Arterial Hypertension

- In the GRIPHON study, selexipag significantly reduced the risk of a composite of death or first morbidity event by 40% compared with placebo
- The efficacy of selexipag was consistent across key subgroups, including patients receiving dual PAH combination therapy at baseline
- Individualised titration to the highest tolerated dose resulted in consistent efficacy across the high, medium and low dose groups
- The tolerability and safety of selexipag was consistent with what is known from prostacyclin therapies
- To analyse the effect of an initial triple oral combination therapy including selexipag is the next step (ongoing TRITON study)...

Conclusions

- Many drugs… but strategies are more important than drugs
- Initial dual oral combination therapy with ERA and PDE5i is superior to monotherapy in FC II-III patients and is becoming the “gold standard” for most patients having an intermediate risk at baseline
- Initial double/triple combination therapy including parenteral PGI_2 is notably effective and seems to be associated with an improved survival in the most severe patients (FC IV and some III with high risk profile)
- No direct comparison between initial combination and rapid (“aggressive”) sequential treatment escalation if treatment goals are not met