Selexipag for the Treatment of Pulmonary Arterial Hypertension

Richard Wells, MD

Objectives

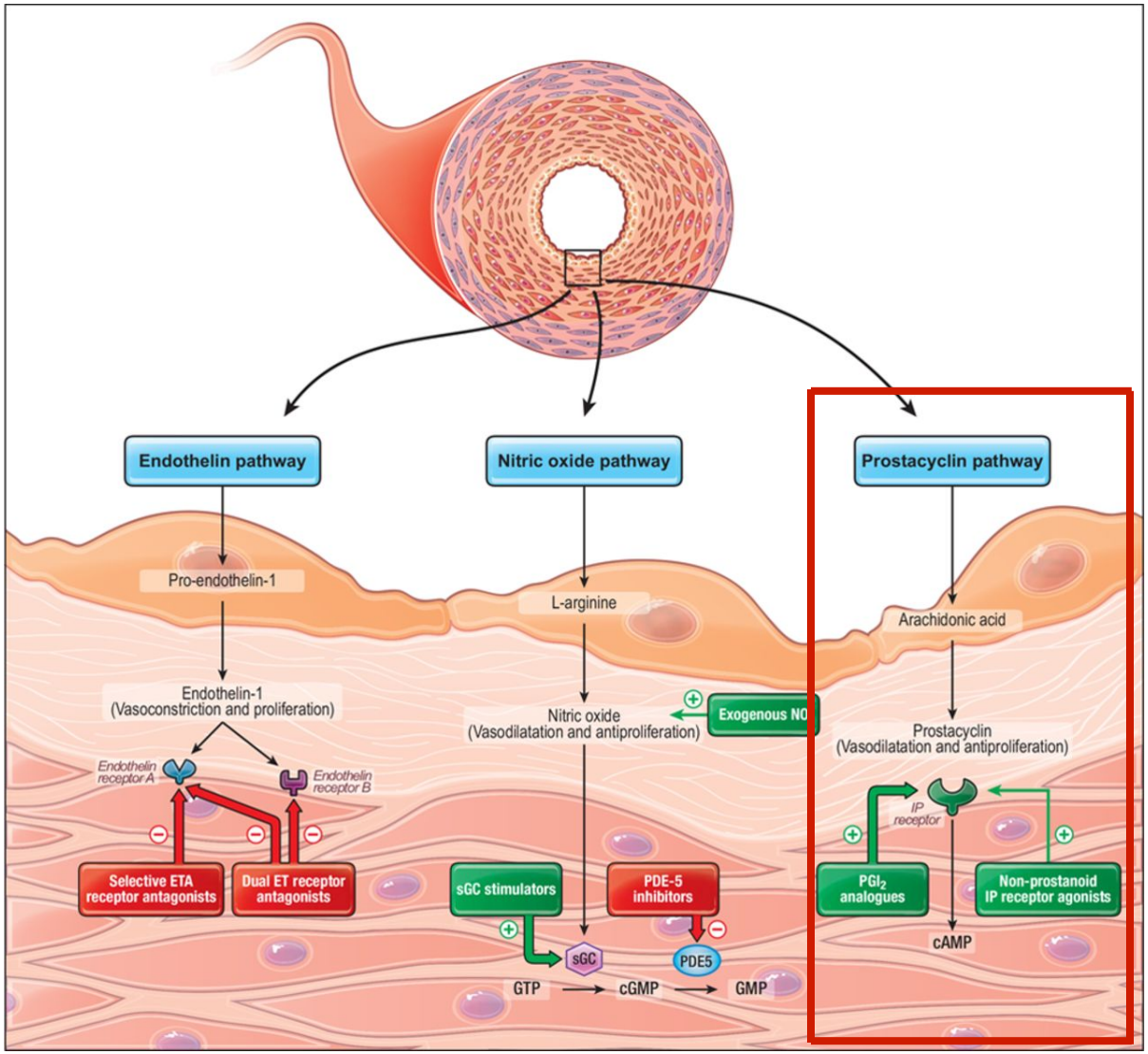
- Prostacyclin pathway in pulmonary arterial hypertension (PAH)
- Current guidelines for management of PAH with prostacyclin analogues (prostanoids)
- Pharmacology of prostanoids
- Evidenced based medicine for the use of selexipag

Background

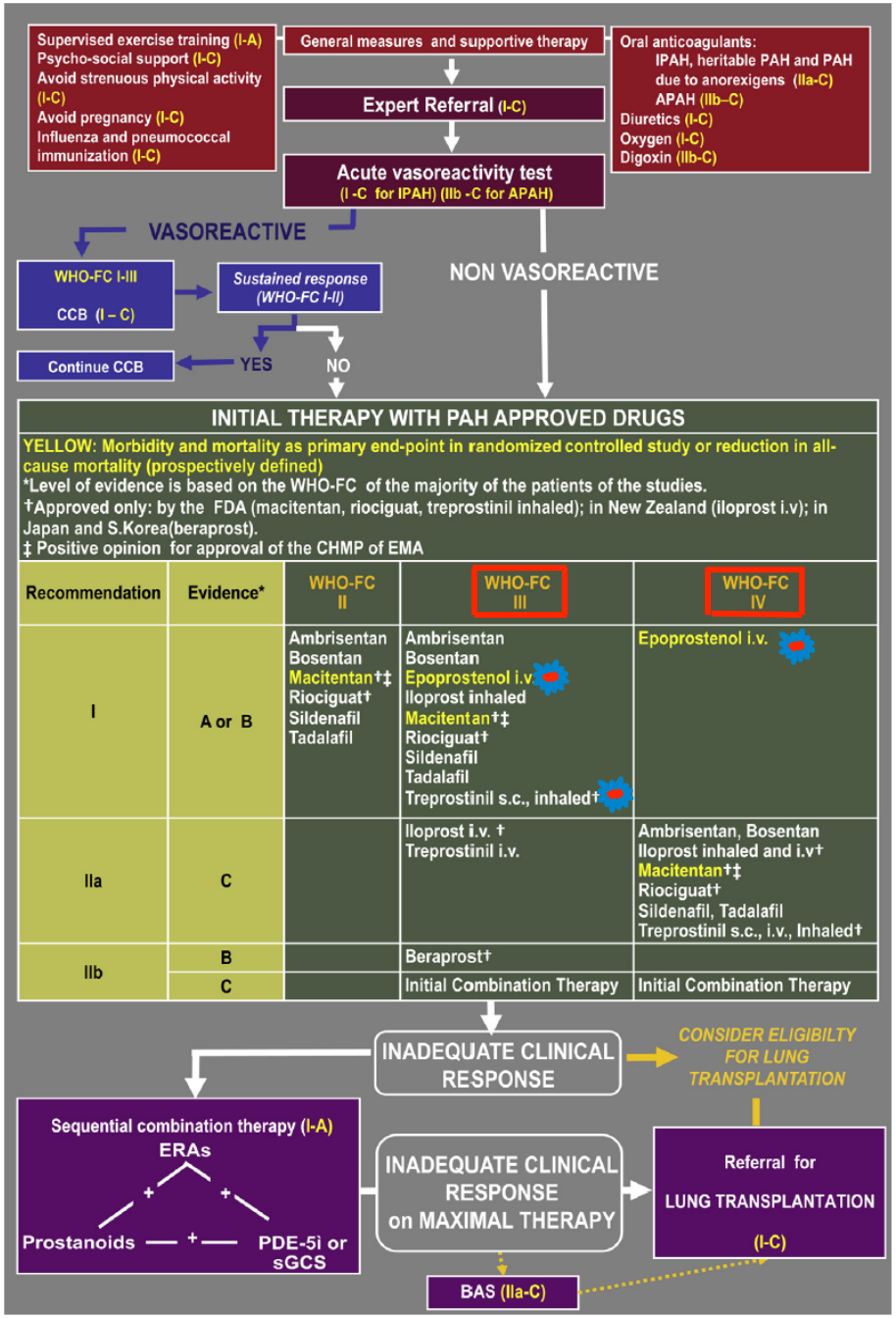
- Prostacyclin Pathway
  - Endothelial cells use arachidonic acid to produce prostacyclin (PGI2)
  - Effects mediated through increased cyclic AMP (cAMP) production
  - Potent vasodilator
  - Cyto-protective and anti-proliferative effects
  - PAH patients show reduction in prostacyclin synthase expression and reduction in metabolites of PGI2

Galiè N et al. Updated Treatment Algorithm of Pulmonary Arterial Hypertension. Journal Am Col Card 2013; 62(25 D)

Background


Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Pro-endothelin-1
L-arginine
Arachidonic acid
Endothelin-1
(Vasoconstriction and proliferation)
Nitric oxide
(Vasodilatation and antiproliferation)
Exogenous NO
Prostacyclin
(Vasodilatation and antiproliferation)
Endothelin receptor A
Endothelin receptor B
IP receptor
Selective ETA receptor antagonists
Dual ET receptor antagonists
sGC stimulators
PDE-5 inhibitors
PGI2 analogues
Non-prostanoid IP receptor agonists
sGC
PDE5
cAMP
GTP
cGMP
GMP

Pulmonary Arterial Hypertension Treatment



WSPH 2013

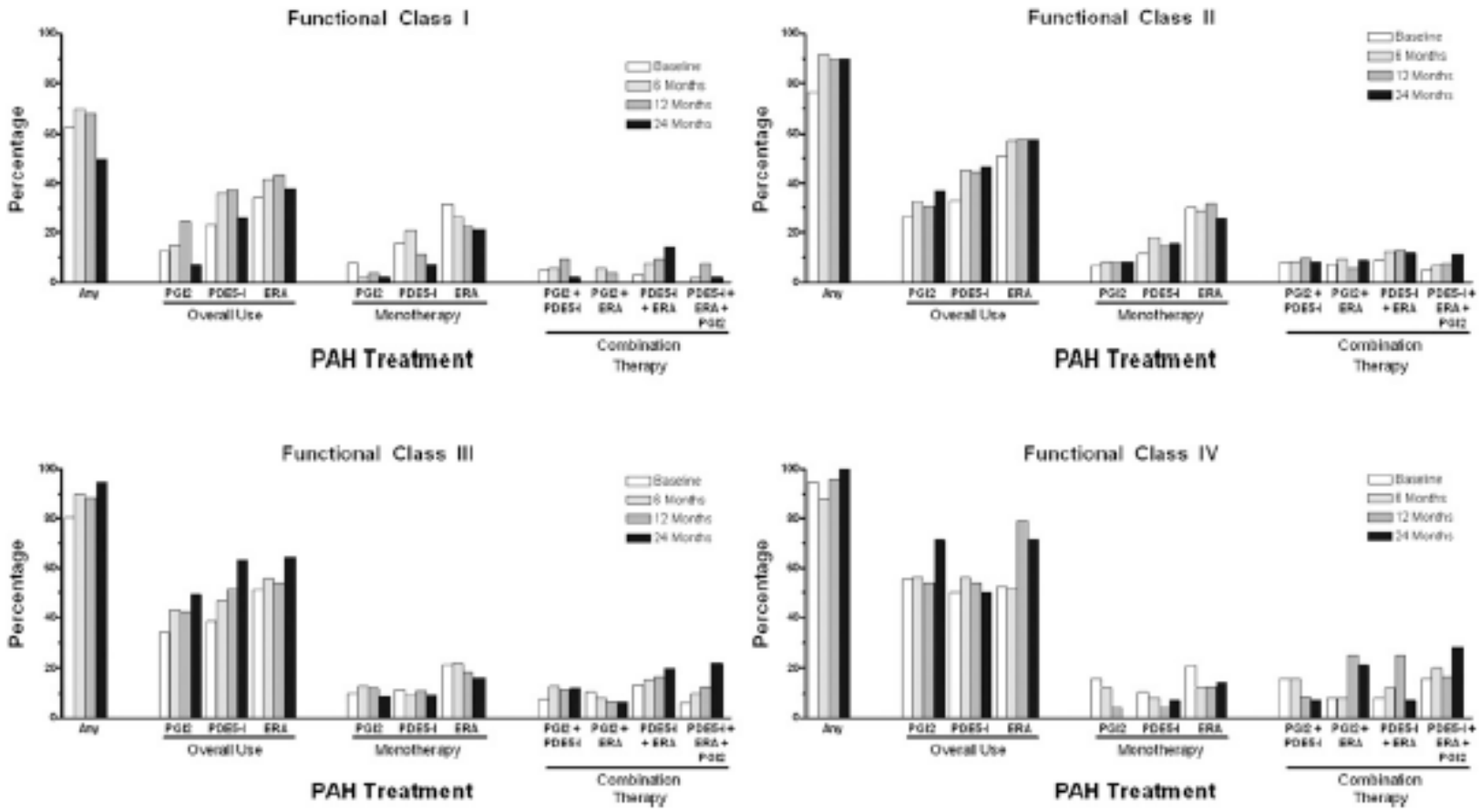
Prostanoids recommended for WHO group 1 PAH who are NYHA III and IV

Background

- Prostanoids
  - Transformed the care of patients with PAH
  - Epoprostenol (synthetic PGI2) remains one of the few PAH therapies shown to reduce mortality

Galiè N et al. Updated Treatment Algorithm of Pulmonary Arterial Hypertension. Journal Am Col Card 2013; 62(25 D)

PAH-Specific Treatments



McLaughlin VV et al. Contemporary Trends in the Diagnosis and Management of Pulmonary Arterial Hypertension: An Initiative to Close the Care Gap. Chest 2013; 143(2): 324-332

Prostanoids

- REVEAL study
  - Demonstrated that 40% of PAH patients who died did not receive a prostanoid at the time of death

Farber HW et al. Use f parenteral prostanoids at time of death in patients with pulmonary arterial hypertension in REVEAL. Chest 2011; 140: 903A

Background

- Prostacyclin therapy
  - Side effects
    - Headache
    - Nausea vomiting
    - Jaw pain
    - Flushing
    - Diarrhea
    - Hypotension
    - Paresthesia
    - Anxiety

Background

- Prostanoid
  - Relatively short *in vivo* half-lives
    - Administered by either continuous intravenous or subcutaneous infusion
  - Extreme inconvenience
  - CRBSI
  - Intractable site pain in the case subcutaneous infusion
  - Other line complications
    - Line falling out
    - Break in tubing
    - Lumen blockage

Bourge, RC et al. Rapid transition from inhaled iloprost to inhaled treprostinil in patients with pulmonary arterial hypertension. Cardiovasc Ther 2013; 31(1): 38-44

Background

- Inhaled prostanoids
  - Local effects and fewer side effects
  - Frequent dosing and inconvenience

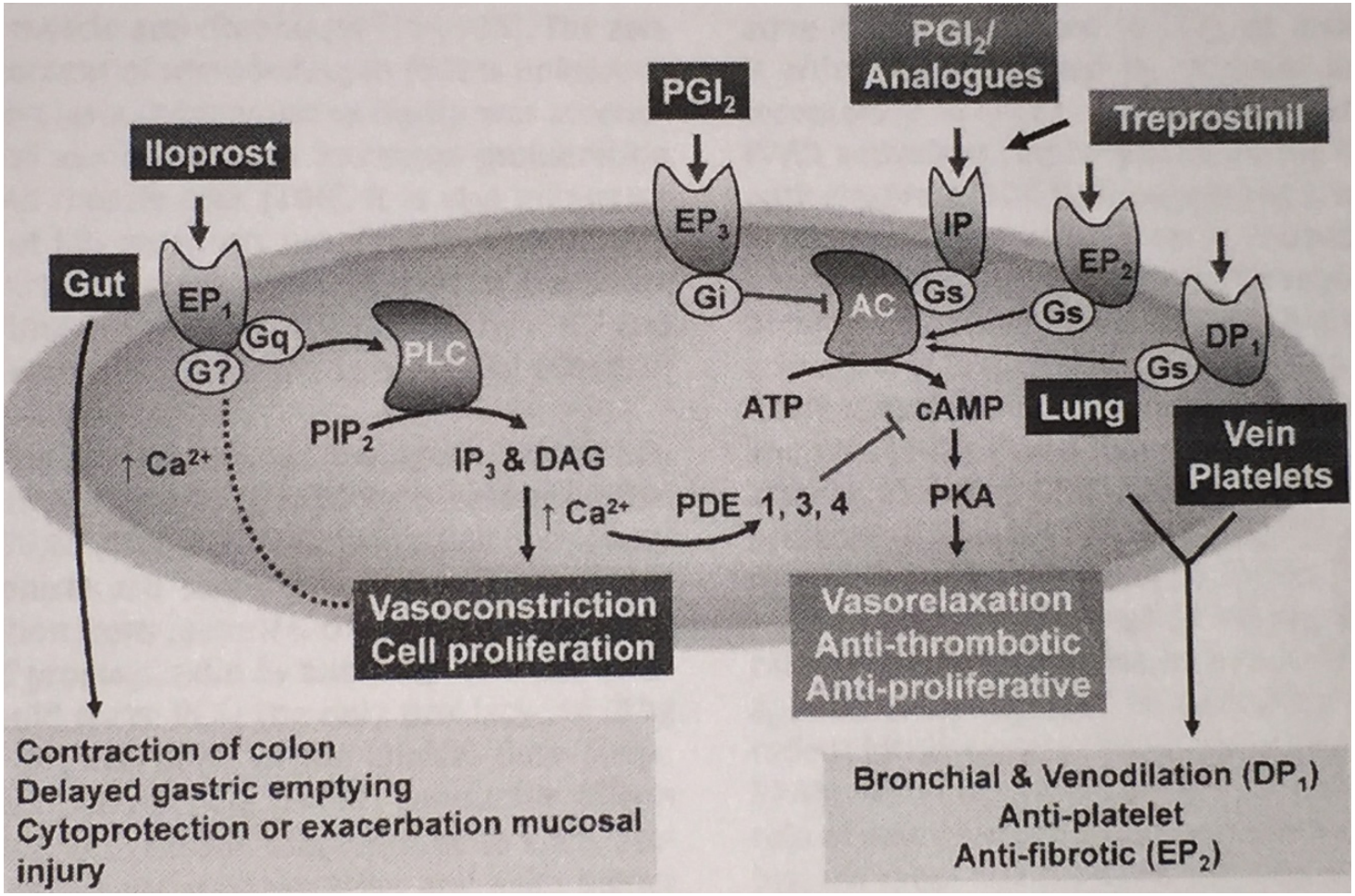
The Ideal Prostanoid

- Longer half life → Fewer dosages
- Oral formulation
- Effective
  - Improvement exercise tolerance
  - Improvement in hemodynamics
  - Reduction in morbidity and mortality

Prostanoid Pharmacology

Prostanoids

- Prostanoid receptors



Prostanoid

- Prostanoids have significant actions at other prostacyclin receptors which can contribute or mitigate their therapeutic action

- Polymorphisms in prostanoid receptors has also been reported and likely impacts variations disease susceptibility and drug response

Clapp LH and Gurung R. The mechanistic basis of prostacyclinc and its stable analogues in pulmonary arterial hypertension: role of membrane versus nuclear receptors. Prostaglandins and other lipid mediators 2015; 120: 56-71

Narumiya, S and Fitzgerald GA. Genetic and pharmacological analysis of prostanoid receptor function. J. Clin Invest. 2001; 108: 25-30

Selexipag

Selexipag

- Oral PGI2 receptor agonist
- Non-prostanoid pro-drug
- Metabolized rapidly to an active metabolite with high affinity for the classical human “IP receptor”
- Metabolite has a long plasma half-life of 8hrs
- Selexipag nor its metabolite binds to other prostacyclin receptors with significant affinity

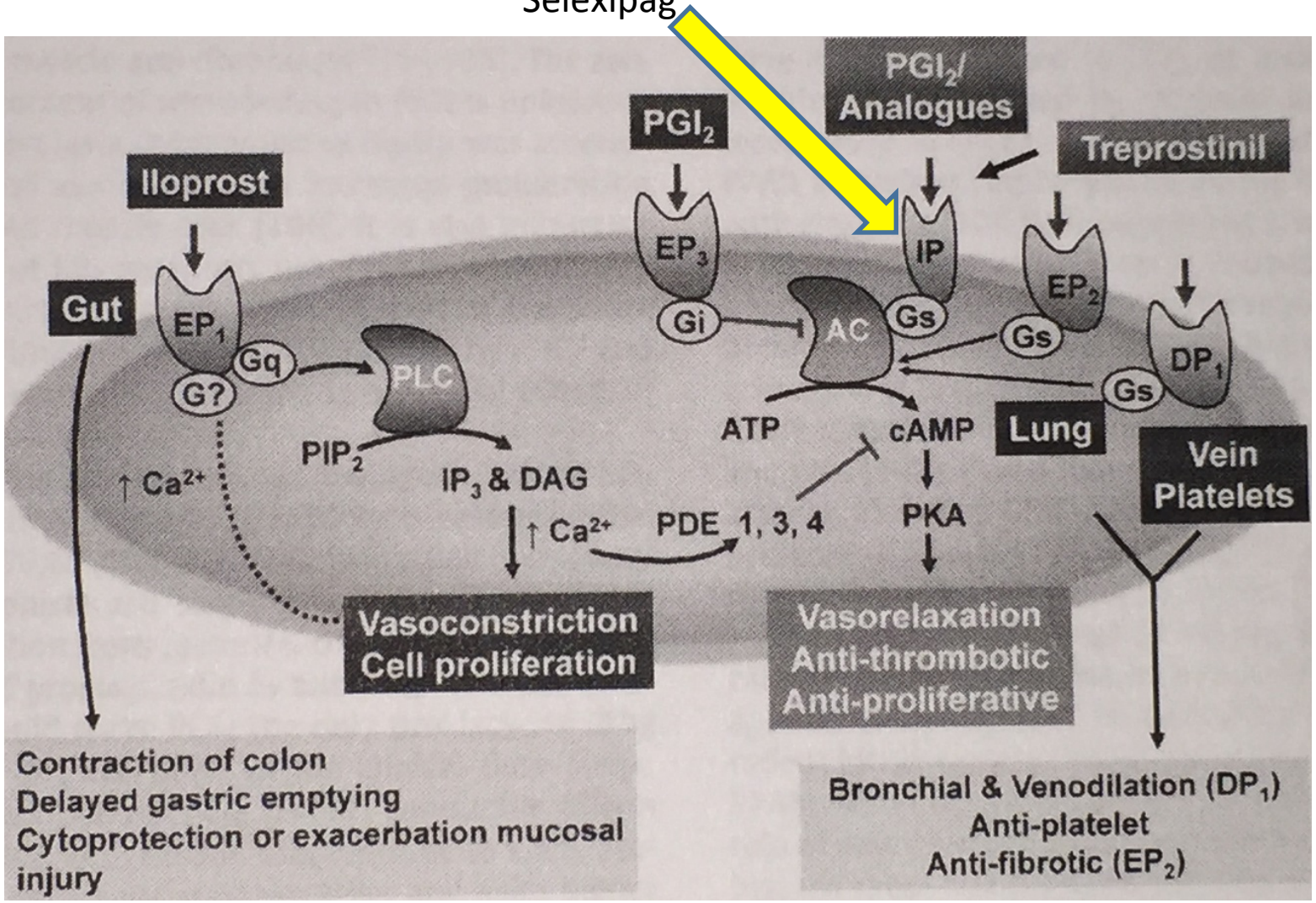
Clapp, LH and Gurung R. The mechanistic basis of prostacyclin and its stable analogues in pulmonary arterial hypertension: Role of membrane vs nuclear receptors. Prostaglandine and other Lipid Mediators 2015; 120: 56-71

Selexipag

Ligands		IP	DP	EP1	EP2	EP3	EP4	TP	FP
Cicaprost	Human	17	>1340	>1340	>1340	255	44	>1340	>1340
	Mouse	10		1300		170			
Iloprost	Human	4	1016	1	1172	203 (56)[a]	212		131
	Mouse	11		21	1600	27	2300		
Beraprost	Human	39				680			
	Mouse (rat)	16 (19)				110			
Treprostinil	Human	32	4.4	212	3.6	2505	826		
	Mouse	YES	ND	ND	YES	ND	ND	ND	ND
Selexipag	Human	260							
	Rat	2100							
MRE-269	Human	20	2600						
	Rat	220							
PGI_2	Human	2	ND	≥100	ND	10–40		~100	ND
	Mouse (GP)	17 (16)	ND	~200	ND	12–50	NO	~100	ND
PGE_2	Human		307	9.1	4.9	0.3	0.8		119
	Mouse			20	12	0.8	1.9		100
PGD_2	Human		2		2973	421	1483		7
	Mouse		21			280			47

[a] K_i value from Ref. [89] and GP = guinea-pig.

Selexipag


Selexipag
PGI2/ Analogues
PGI2
Treprostinil
Iloprost
EP3
IP
EP2
Gut
EP1
Gi
AC
Gs
Gs
DP1
Gq
PLC
G?
Gs
ATP
cAMP
Lung
Vein
Platelets
PIP2
IP3 & DAG
↑ Ca2+
↑ Ca2+
PDE 1, 3, 4
PKA
Vasoconstriction
Cell proliferation
Vasorelaxation
Anti-thrombotic
Anti-proliferative
Contraction of colon
Delayed gastric emptying
Cytoprotection or exacerbation mucosal injury
Bronchial & Venodilation (DP1)
Anti-platelet
Anti-fibrotic (EP2)

Selexipag

Eur Respir J 2012; 40: 874–880
DOI: 10.1183/09031936.00137511

Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension

Gérald Simonneau*, Adam Torbicki[#], Marius M. Hoeper[¶], Marion Delcroix[+], Kristóf Karlócai[§], Nazzareno Galiè[ƒ], Bruno Degano*, Diana Bonderman, Marcin Kurzyna[#], Michela Efficace[##], Ruben Giorgino[##] and Irene M. Lang****

Selexipag-Phase 2

- Proof of concept
  - Multicenter
  - Double blind
  - Placebo controlled
  - 17 weeks duration

Selexipag-Phase 2

- Inclusion
  - Age ≥18 yrs
  - Idiopathic or familial-, CTD related-, corrected congenital-, or anirexogen use related-PAH
  - 12 weeks of stable background therapy with PDE-5i +/- ERA
  - Baseline RHC showing PVR >400dyn·s·cm^{-5} and 6MWT 150-500m

Selexipag-Phase 2

- Randomization was 3:1 (selexipag:placebo)
- At week 17
  - Selexipag
    - 42.4% 800µg BID
    - 21.2% 600µg BID
    - 18.2% 400µg BID
    - 12.1% 200µg BID
  - Placebo
    - 90% 800µg BID

Selexipag-Phase 2

- Follow up
  - Until week 17 patients when RHC performed

- Primary Outcome
  - Change in PVR at week 17 expressed as a percentage of the baseline value

Selexipag-Phase 2

TABLE 1 Demographics and aetiology of pulmonary arterial hypertension (PAH) (all-treated set)

	Placebo	Selexipag
Subjects n	10	33
Demographics		
Male/female	2/8 (20.0/80.0)	6/27 (18.2/81.8)
Age yrs	53.8±16.3	54.8±16.8
Weight kg	70.6±13.9	68.7±12.4
Caucasian/other	9/1 (90.0/10.0)	29/4 (88.0/12.0)
Aetiology of PAH		
Idiopathic PAH	7 (70.0)	24 (72.7)
Hereditary PAH	1 (10.0)	1 (3.0)
Anorexigen-induced PAH		2 (6.1)
PAH-CTD	2 (20.0)	4 (12.1)
PAH associated with congenial heart disease		2 (6.1)

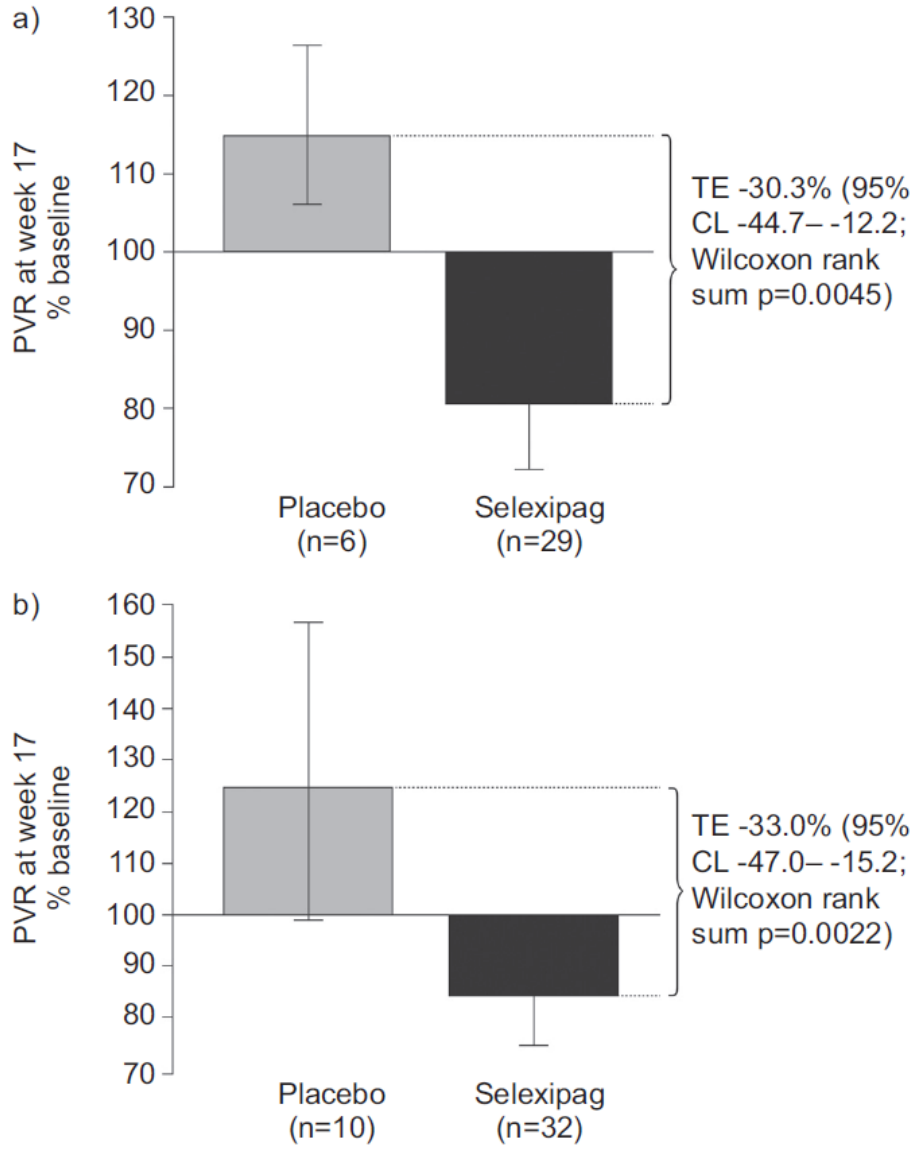
Data are presented as n (%) or mean±SD, unless otherwise stated. CTD: connective tissue disease.

TABLE 2 Disease characteristics and pulmonary arterial hypertension (PAH) background therapy (all-treated set)

	Placebo	Selexipag
Subjects n	10	33
Time from diagnosis yrs	4.0±3.1	5.5±6.1
PVR dyn·s·cm^{-5}	867.2±379.3	928.6±436.6
6-min walk distance m	350.3±123.5	396.2±71.4
WHO FC		
I		
II	2 (20.0)	15 (45.5)
III	8 (80.0)	18 (54.5)
IV		
Borg dyspnoea score	4.1±2.6	3.3±2.1^{+}
NT-proBNP pg·mL^{-1} $^{\#}$	2400.9±1269.8¶	1601.4±2443.0§
Background PAH therapy		
ERA monotherapy	4 (40.0)	12 (36.4)
Sildenafil monotherapy	3 (30.0)	9 (27.2)
ERA plus sildenafil	3 (30.0)	12 (36.4)

Data are presented as mean±SD or n (%), unless otherwise stated. PVR: pulmonary vascular resistance; WHO FC: World Health Organization functional class; NT-proBNP: N-terminal pro-brain natriuretic peptide; ERA: endothelin receptor antagonist. $^{\#}$: Upper reference values are 100 pg·mL^{-1} and 172 pg·mL^{-1} for males aged 45–59 and ⩾60 yrs, respectively, and 164 pg·mL^{-1} and 225 pg·mL^{-1} for females aged 45–59 and ⩾60 yrs, respectively [18]; ¶: n=8; $^{+}$: n=32; §: n=27.

Selexipag-Phase 2



Primary End Point

- Treatment Effect: -30.3%

Selexipag-Phase 2

- Demonstration of the hemodynamic effects of selexipag on PVR through agonism of the IP receptor

- Can only postulate that this hemodynamic improvement translates into long term PAH outcomes

Selexipag-Phase 3

ORIGINAL ARTICLE

Selexipag for the Treatment of Pulmonary Arterial Hypertension

Olivier Sitbon, M.D., Richard Channick, M.D., Kelly M. Chin, M.D., Aline Frey, Pharm.D., Sean Gaine, M.D., Nazzareno Galiè, M.D., Hossein-Ardeschir Ghofrani, M.D., Marius M. Hoeper, M.D., Irene M. Lang, M.D., Ralph Preiss, M.D., Lewis J. Rubin, M.D., Lilla Di Scala, Ph.D., Victor Tapson, M.D., Igor Adzerikho, M.D., Jinming Liu, M.D., Olga Moiseeva, M.D., Xiaofeng Zeng, M.D., Gérald Simonneau, M.D., and Vallerie V. McLaughlin, M.D., for the GRIPHON Investigators*

ABSTRACT

Selexipag-Phase 3

- GRIPHON, (Prostacyclin (P**G**I2) **R**eceptor agonist In **P**ulmonary arterial **H**ypertensi**ON**)
- Randomized (1:1)
- Placebo-controlled trial
- Multicenter
- Double-blind
- Collaboration between steering committee and Actelion

Selexipag-Phase 3

- Inclusion
  - 18-75 yrs
  - Idiopathic, Familial, HIV, CTD, Drugs and toxins- and CHD with repaired shunts
  - RHC confirmed PAH with PVR at least 400 $dyn \cdot s \cdot cm^{-5}$ and 6MWD 50-450m
  - 12 weeks of stable medication regimen excluding prostanoids

Selexipag-Phase 3

- Dose adjustment phase – 12 weeks

Randomization to selexipag or placebo

↓

Started with 200µg BID of study drug

↓

Weekly 200µg BID increase

↓

Weekly increases of 200µg BID until unmanageable PGI2 side effects occurred

↓

Decrease by 200µg BID – determined the maximum tolerated dose for the patient

↓

Entered the maintenance phase (max dose of 1600µg BID)

Selexipag-Phase 3

- Follow up
  - Baseline, 8 weeks, 16 weeks, 26 weeks, every 6 months thereafter until the end of the trial
  - Continued until a pre-specified number of primary end points occurred which was defined as the end of the study

Selexipag-Phase 3

- Primary Outcome
  - Composite of all cause-death or complication related to PAH
    - Complication related to PAH included:
      - Worsening of PAH that caused hospitalization, initiation of parenterals, long term O2 or need for lung txp or balloon atrial septostomy
      - Disease progression: ≥15% drop in 6MWD with worsening NYHA FC or need for additional PAH therapy

- Independent blinded critical event committee adjudicated all events including death

Selexipag-Phase 3

- Secondary Outcomes
  - 6MWD up to 26 weeks
  - Absence of worsening NYHA FC up to 26 weeks
  - Time to event analysis of death from PAH or hospitalization from PAH
  - Time to event analysis of all cause death over entire study period

Selexipag-Phase 3

- To achieve 90% power to detect HR of 0.65 determined that 331 primary outcome events would have to be observed → 1150 patients needed
- For primary end point analysis patients, who discontinued without having a nonfatal primary end point were censored at time of discontinuation
- KM method to estimate end points and log rank test for comparison
- 99% CI for primary and most secondary end points

Selexipag-Phase 3

Table 1. **Characteristics of the Patients at Baseline.***

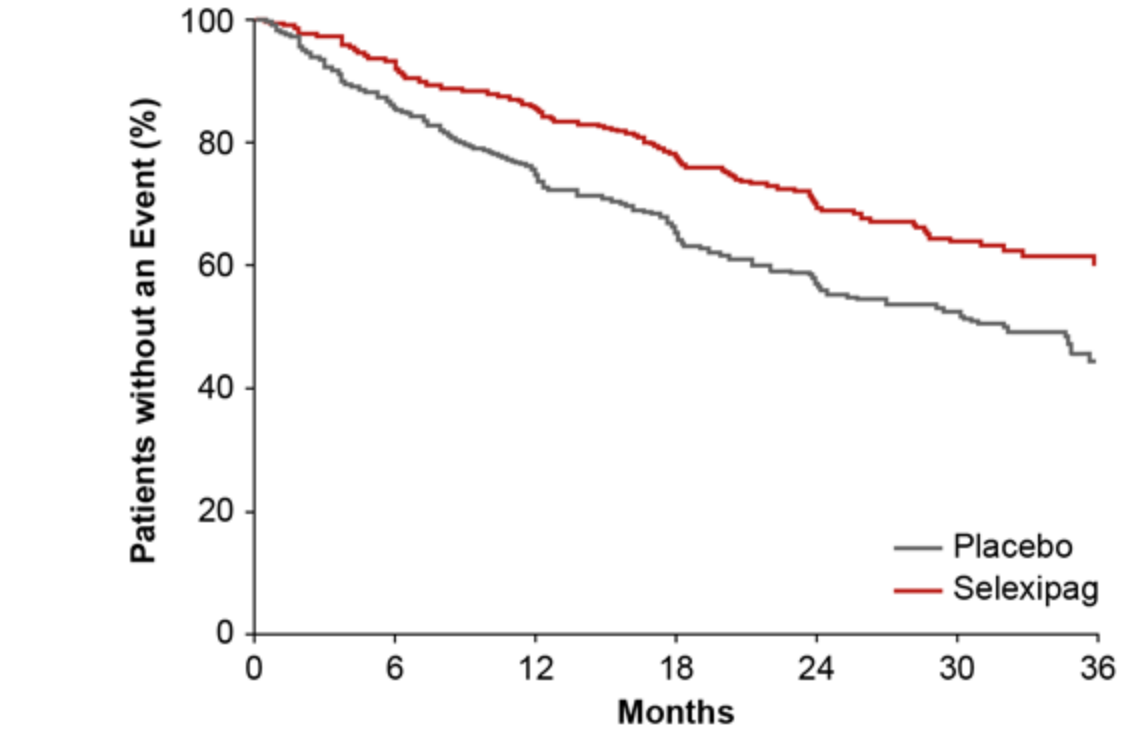
Characteristic	Placebo (N=582)	Selexipag (N=574)	All Patients (N=1156)
Female sex — no. (%)	466 (80.1)	457 (79.6)	923 (79.8)
Age			
Mean — yr	47.9±15.55	48.2±15.19	48.1±15.37
Distribution — no. (%)			
<65 yr	474 (81.4)	475 (82.8)	949 (82.1)
≥65 yr	108 (18.6)	99 (17.2)	207 (17.9)
Geographic region — no. (%)			
Asia	113 (19.4)	115 (20.0)	228 (19.7)
Eastern Europe	155 (26.6)	149 (26.0)	304 (26.3)
Latin America	56 (9.6)	54 (9.4)	110 (9.5)
North America	98 (16.8)	95 (16.6)	193 (16.7)
Western Europe and Australia	160 (27.5)	161 (28.0)	321 (27.8)
Time since diagnosis of PAH — yr†	2.5±3.75	2.3±3.49	2.4±3.62
PAH classification — no. (%)			
Idiopathic	337 (57.9)	312 (54.4)	649 (56.1)
Heritable	13 (2.2)	13 (2.3)	26 (2.2)
Associated with connective tissue disease	167 (28.7)	167 (29.1)	334 (28.9)
Associated with corrected-congenital shunts	50 (8.6)	60 (10.5)	110 (9.5)
Associated with HIV infection	5 (0.9)	5 (0.9)	10 (0.9)
Associated with drug or toxin exposure	10 (1.7)	17 (3.0)	27 (2.3)
WHO functional class — no. (%)‡			
I	5 (0.9)	4 (0.7)	9 (0.8)
II	255 (43.8)	274 (47.7)	529 (45.8)
III	314 (54.0)	293 (51.0)	607 (52.5)
IV	8 (1.4)	3 (0.5)	11 (1.0)
6-Minute walk distance — m	348.0±83.23	358.5±76.31	353.2±80.01
Use of medications for PAH — no. (%)			
None	124 (21.3)	112 (19.5)	236 (20.4)
Endothelin-receptor antagonists	76 (13.1)	94 (16.4)	170 (14.7)
Phosphodiesterase type 5 inhibitors	185 (31.8)	189 (32.9)	374 (32.4)
Endothelin-receptor antagonists plus phosphodiesterase type 5 inhibitors	197 (33.8)	179 (31.2)	376 (32.5)

Selexipag-Phase 3

Table 1. **Characteristics of the Patients at Baseline.***

Characteristic	Placebo (N=582)	Selexipag (N=574)	All Patients (N=1156)
Female sex — no. (%)	466 (80.1)	457 (79.6)	923 (79.8)
Age			
Mean — yr	47.9±15.55	48.2±15.19	48.1±15.37
Distribution — no. (%)			
<65 yr	474 (81.4)	475 (82.8)	949 (82.1)
≥65 yr	108 (18.6)	99 (17.2)	207 (17.9)
Geographic region — no. (%)			
Asia	113 (19.4)	115 (20.0)	228 (19.7)
Eastern Europe	155 (26.6)	149 (26.0)	304 (26.3)
Latin America	56 (9.6)	54 (9.4)	110 (9.5)
North America	98 (16.8)	95 (16.6)	193 (16.7)
Western Europe and Australia	160 (27.5)	161 (28.0)	321 (27.8)
Time since diagnosis of PAH — yr†	2.5±3.75	2.3±3.49	2.4±3.62
PAH classification — no. (%)			
Idiopathic	337 (57.9)	312 (54.4)	649 (56.1)
Heritable	13 (2.2)	13 (2.3)	26 (2.2)
Associated with connective tissue disease	167 (28.7)	167 (29.1)	334 (28.9)
Associated with corrected-congenital shunts	50 (8.6)	60 (10.5)	110 (9.5)
Associated with HIV infection	5 (0.9)	5 (0.9)	10 (0.9)
Associated with drug or toxin exposure	10 (1.7)	17 (3.0)	27 (2.3)
WHO functional class — no. (%)‡			
I	5 (0.9)	4 (0.7)	9 (0.8)
II	255 (43.8)	274 (47.7)	529 (45.8)
III	314 (54.0)	293 (51.0)	607 (52.5)
IV	8 (1.4)	3 (0.5)	11 (1.0)
6-Minute walk distance — m	348.0±83.23	358.5±76.31	353.2±80.01
Use of medications for PAH — no. (%)			
None	124 (21.3)	112 (19.5)	236 (20.4)
Endothelin-receptor antagonists	76 (13.1)	94 (16.4)	170 (14.7)
Phosphodiesterase type 5 inhibitors	185 (31.8)	189 (32.9)	374 (32.4)
Endothelin-receptor antagonists plus phosphodiesterase type 5 inhibitors	197 (33.8)	179 (31.2)	376 (32.5)

Selexipag-Phase 3



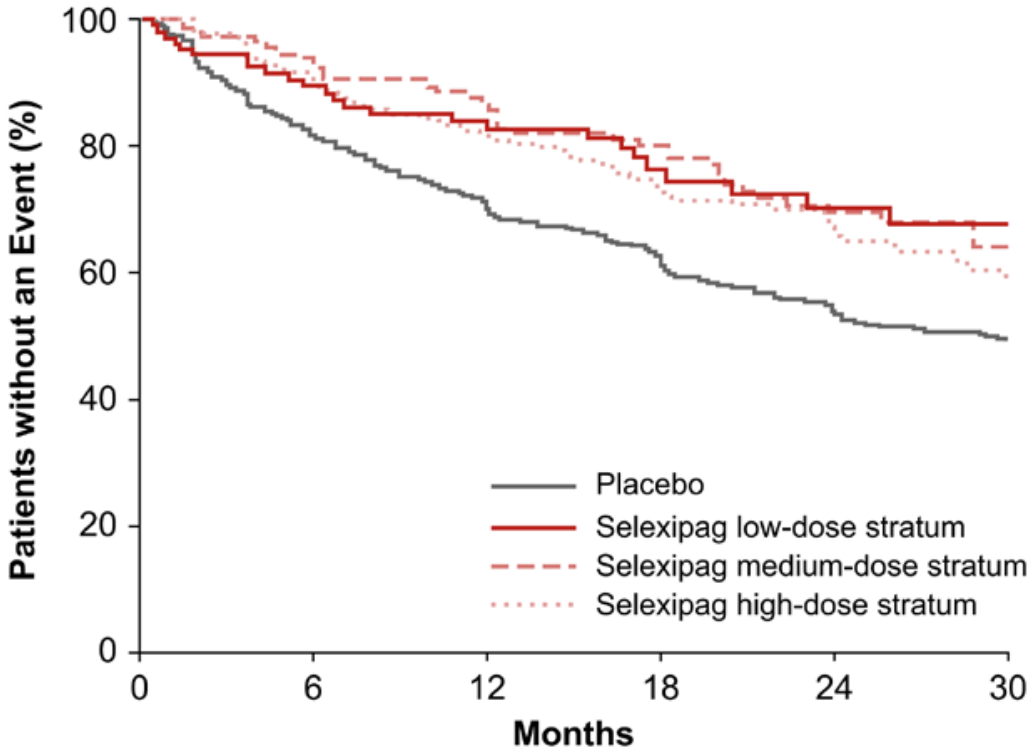
No. at Risk:							
Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

HR, 0.6; 99% CI 0.46 to 0.78; p<0.001

Selexipag-Phase 3

	Hazard ratio (CI)	p Value
Primary analysis	0.6 (99%, 0.46-0.78)	<0.001
Sensitivity analysis (a)	0.65 (95%, 0.54-0.78)	<0.001
Sensitivity analysis (b)	0.82 (95%, 0.70-0.96)	0.007

Selexipag-Phase 3

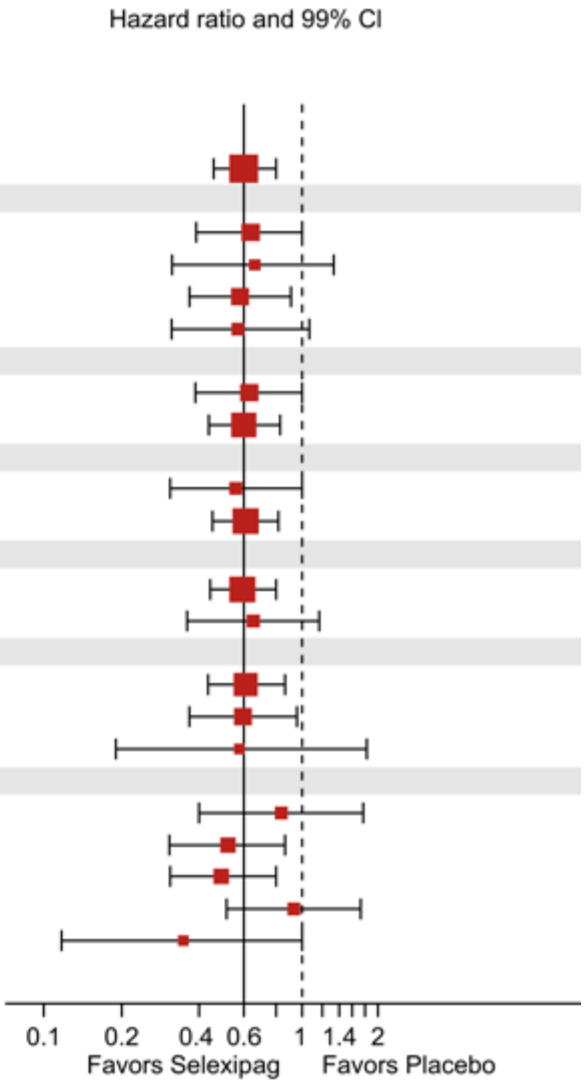


Low 200-400 µg BID
Medium 600-1000 µg BID
High 1200-1600 µg BID

No. at Risk:						
Placebo	582	433	347	220	149	88
Selexipag low-dose stratum	133	84	68	41	29	19
Selexipag medium-dose stratum	180	152	116	84	52	28
Selexipag high-dose stratum	246	219	177	121	90	54

Selexipag-Phase 3

Subgroup	P value for interaction	Placebo No. of patients/no. of events	Selexipag No. of patients/no. of events
All patients		582/242	574/155
PAH therapy at baseline	0.9518		
ERA and PDE5 inhibitors		197/80	179/47
ERA monotherapy		76/29	94/23
PDE5 inhibitor monotherapy		185/84	189/54
No PAH therapy		124/49	112/31
WHO functional class	0.7792		
I / II		260/74	278/52
III / IV		322/168	296/103
Sex	0.6578		
Males		116/48	117/31
Females		466/194	457/124
Age at screening	0.6783		
<65 years		474/190	475/124
≥65 years		108/52	99/31
PAH etiology	0.9765		
IPAH, HPAH, HIV, drug or toxin induced		365/156	347/98
Assoc. with connective tissue disease		167/73	167/48
Assoc. with corrected congenital shunts		50/13	60/9
Geographical region	0.0734		
North America		98/28	95/23
Western Europe / Australia		160/68	161/39
Eastern Europe		155/85	149/48
Asia		113/39	115/37
Latin America		56/22	54/8



Selexipag Phase 3

Table 2. **End Points Related to Pulmonary Arterial Hypertension and Death.***

End Point	Placebo (N=582)	Selexipag (N=574)	Hazard Ratio (99% or 95% CI)†	P Value‡
	no. of patients (%)			
Primary end point: composite of death or a complication related to PAH up to the end of the treatment period§				
All events	242 (41.6)	155 (27.0)	0.60 (0.46–0.78)	<0.001
Hospitalization for worsening of PAH	109 (18.7)	78 (13.6)		
Disease progression	100 (17.2)	38 (6.6)		
Death from any cause	18 (3.1)	28 (4.9)		
Initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH	13 (2.2)	10 (1.7)		
Need for lung transplantation or balloon atrial septostomy for worsening of PAH¶	2 (0.3)	1 (0.2)		
Secondary end point: death due to PAH or hospitalization for worsening of PAH up to the end of the treatment period§‖				
All events	137 (23.5)	102 (17.8)	0.70 (0.54–0.91)	0.003
Hospitalization for worsening of PAH	123 (21.1)	86 (15.0)		
Death due to PAH	14 (2.4)	16 (2.8)		
Secondary end point: death up to the end of the study‖**				
Death due to PAH	83 (14.3)	70 (12.2)	0.86 (0.63–1.18)	0.18
Death from any cause	105 (18.0)	100 (17.4)	0.97 (0.74–1.28)	0.42

Selexipag Phase 3

Table 2. **End Points Related to Pulmonary Arterial Hypertension and Death.***

End Point	Placebo (N=582)	Selexipag (N=574)	Hazard Ratio (99% or 95% CI)†	P Value‡
	no. of patients (%)			
Primary end point: composite of death or a complication related to PAH up to the end of the treatment period§				
All events	242 (41.6)	155 (27.0)	0.60 (0.46–0.78)	<0.001
Hospitalization for worsening of PAH	109 (18.7)	78 (13.6)		
Disease progression	100 (17.2)	38 (6.6)		
Death from any cause	18 (3.1)	28 (4.9)		
Initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH	13 (2.2)	10 (1.7)		
Need for lung transplantation or balloon atrial septostomy for worsening of PAH¶	2 (0.3)	1 (0.2)		
Secondary end point: death due to PAH or hospitalization for worsening of PAH up to the end of the treatment period§‖				
All events	137 (23.5)	102 (17.8)	0.70 (0.54–0.91)	0.003
Hospitalization for worsening of PAH	123 (21.1)	86 (15.0)		
Death due to PAH	14 (2.4)	16 (2.8)		
Secondary end point: death up to the end of the study‖**				
Death due to PAH	83 (14.3)	70 (12.2)	0.86 (0.63–1.18)	0.18
Death from any cause	105 (18.0)	100 (17.4)	0.97 (0.74–1.28)	0.42

Selexipag-Phase 3

- 6MWD – at week 26
  - Median loss of 9m from baseline in placebo
  - Median gain of 4m from baseline in selxipag
  - Treatment effect of 12m (99% CI, 1 to 24, p 0.003)
- NYHA FC – at week 26
  - There was no significant difference between placebo and selexipag in proportion of patients with no worsening functional class (74.9% and 77.8% respectively)

Selexipag-Phase 3

Table 3. 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
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
Other adverse events and laboratory findings of interest — no. of patients (%)§			
Hyperthyroidism	0	8 (1.4)	0.004
Hypotension	18 (3.1)	29 (5.0)	0.10
Anemia	31 (5.4)	48 (8.3)	0.05
Syncope	51 (8.8)	37 (6.4)	0.15
Major bleeding event¶	12 (2.1)	14 (2.4)	0.70
Hemoglobin <8 g/dl‖	4 (0.7)	7 (1.3)	0.38

Selexipag-Phase 3

Table 3. 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
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
Other adverse events and laboratory findings of interest — no. of patients (%)§			
Hyperthyroidism	0	8 (1.4)	0.004
Hypotension	18 (3.1)	29 (5.0)	0.10
Anemia	31 (5.4)	48 (8.3)	0.05
Syncope	51 (8.8)	37 (6.4)	0.15
Major bleeding event¶	12 (2.1)	14 (2.4)	0.70
Hemoglobin <8 g/dl‖	4 (0.7)	7 (1.3)	0.38

Selexipag-Phase 3

	Selexipag (n=577)	Oral treprostinil FREEDOM-C (n=174)	Oral treprostinil FREEDOM-C2 (n=157)
Headache	65.2	86	71
Nausea	33.6	64	46
Diarrhea	42.4	61	55
Vomiting	18.1	43	21
Jaw Pain	25.7	43	25
Flushing	12.2	49	35
Extremity pain	16.9	31	17

Take Home Points

- Selexipag is a non-prostanoid agonist selective for the IP receptor and mediates vasodilation of pulmonary vasculature
- Selxipag has a longer half life than other prostanoids
- In PAH selxipag led to an improvement in PVR and limited complications related to PAH in phase 2 and phase 3 trials respectively
- Selexipag causes side effects similar to other prostanoids
- Selexipag may have a better side effects profile than other oral prostanoids

Thank you