PNEUMOLOGIA 2016

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Ipertensione polmonare: cosa abbiamo imparato dagli studi clinici

Sergio Harari

U.O. di Pneumologia e Terapia Semi Intensiva

Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare

Osp. San Giuseppe - MultiMedica, Milano

Conflict of interests disclosures

Actelion

Boehringer Ingelheim

InterMune

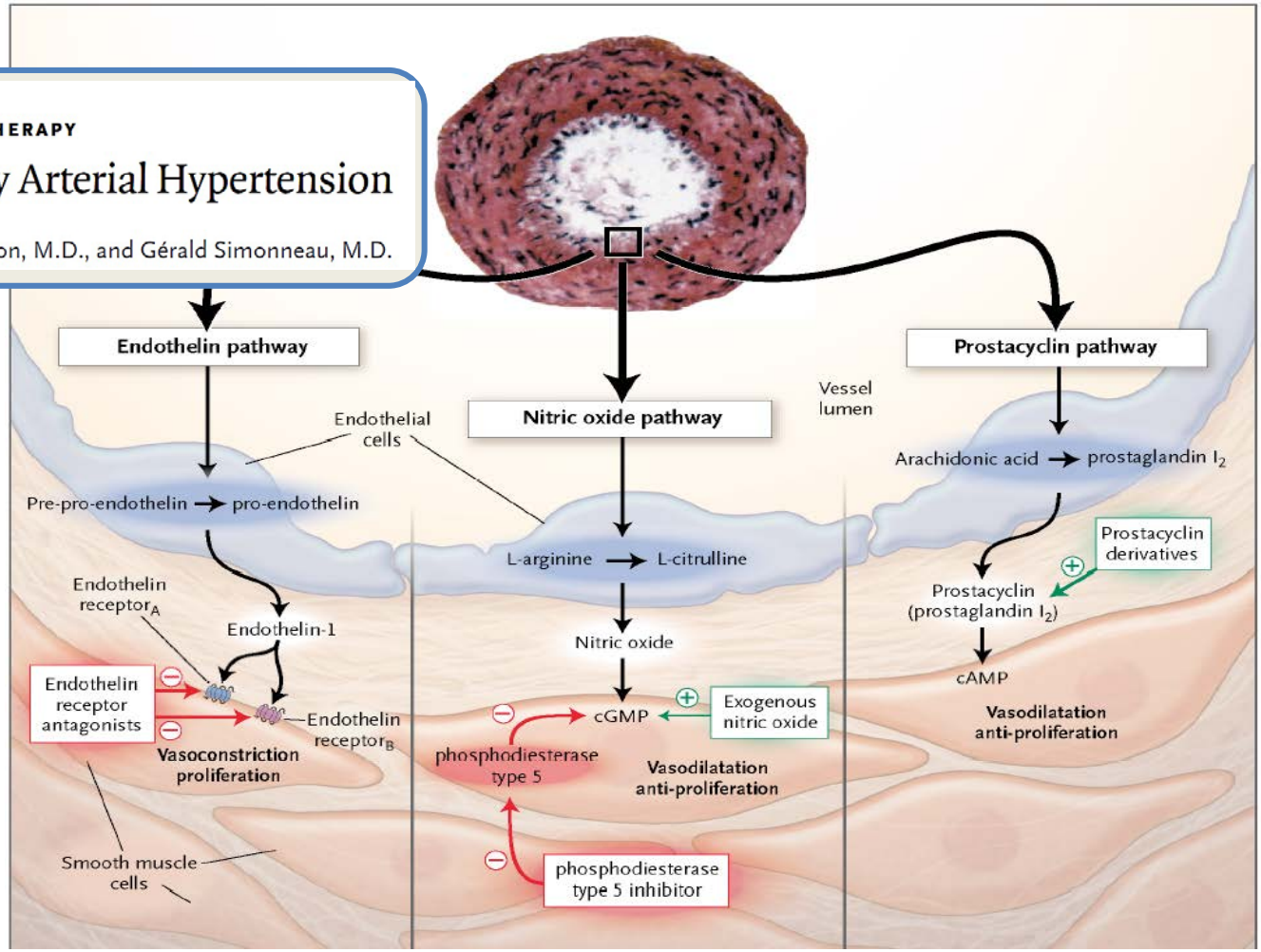
Roche

Targeting 3 major dysfunctional pathways in PAH (2004)

DRUG THERAPY

Treatment of Pulmonary Arterial Hypertension

Marc Humbert, M.D., Ph.D., Olivier Sitbon, M.D., and Gérald Simonneau, M.D.



cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate.

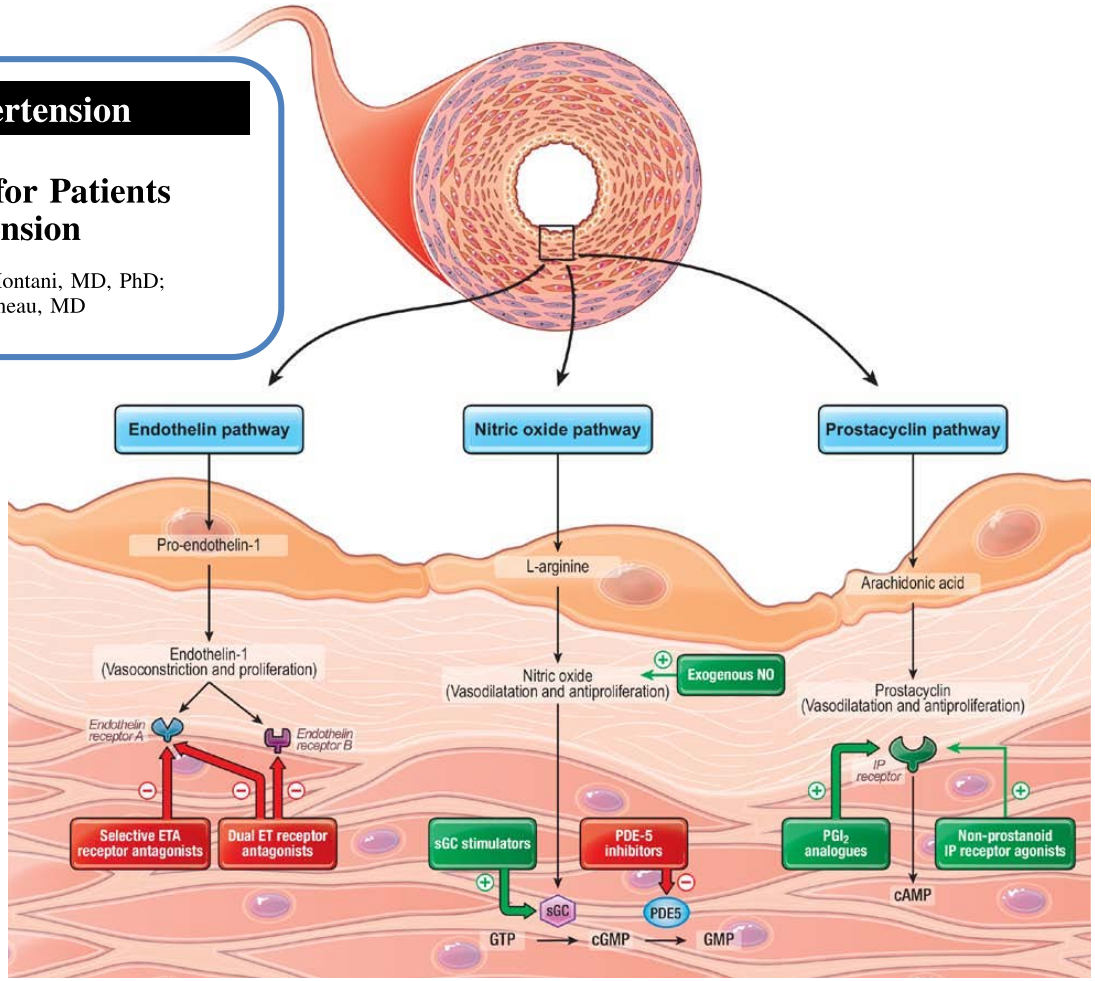
Humbert M *et al. N Engl J Med* 2004;351:1425–36.

Targeting 3 major dysfunctional pathways in PAH (2014)

Recent Advances in Pulmonary Hypertension

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



cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET, endothelin; ETA, endothelin receptor A; GTP, guanosine triphosphate; NO, nitric oxide; PGI_2, prostaglandin I_2; sGC, soluble guanylate cyclase.

Humbert M *et al. Circulation* 2014;130:2189–208.

Drugs approved for PAH in Europe

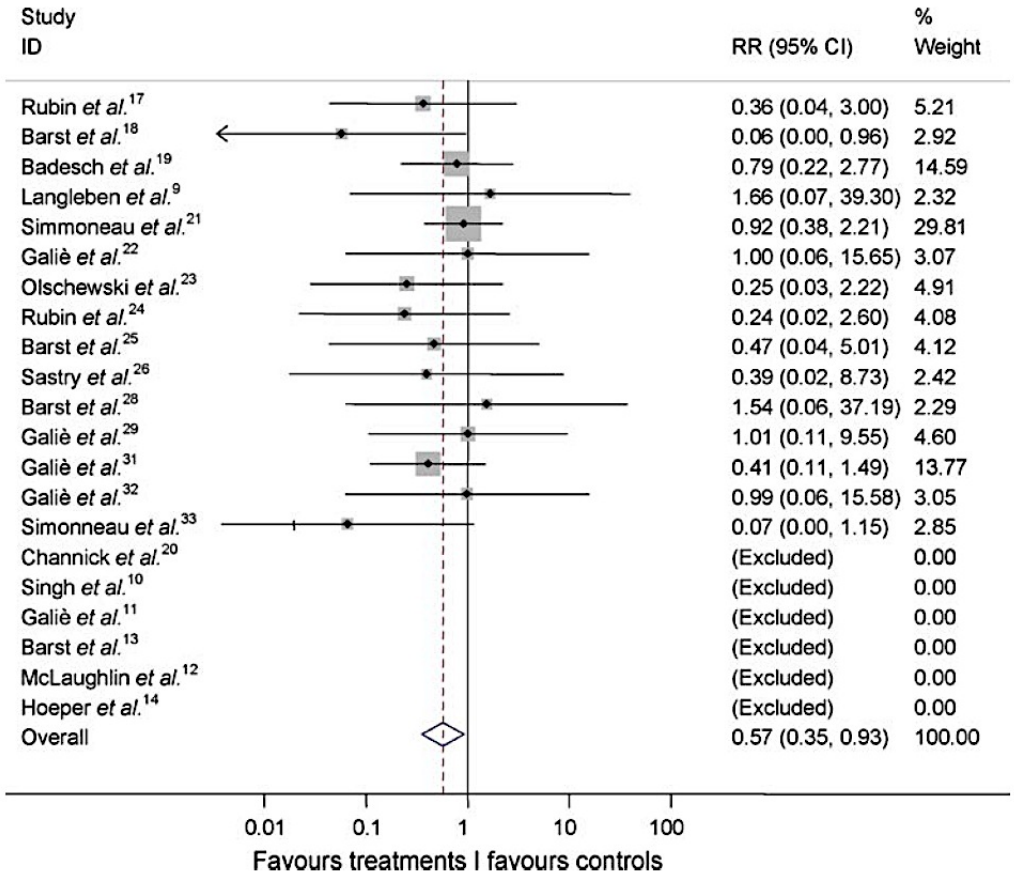
Endothelin pathway	Prostacyclin pathway	NO / cGMP pathway
▪ ERA dual (ET_A&ET_B) ▪ ERA selective(ET_A)	▪ Prostanoids ▪ IP receptors agonists	▪ PDE-5 inhibitor ▪ sGC stimulators
Bosentan	Epoprostenol IV Epo thermostable IV	Sildenafil
Ambrisentan	Iloprost inhaled	Tadalafil
Macitentan	Treprostinil SC (IV*)	Riociguat
	Oral Selexipag	

* IV Treprosinil as 2nd line Tx when SC not tolerated.

A meta-analysis of randomized controlled trials in pulmonary arterial hypertension

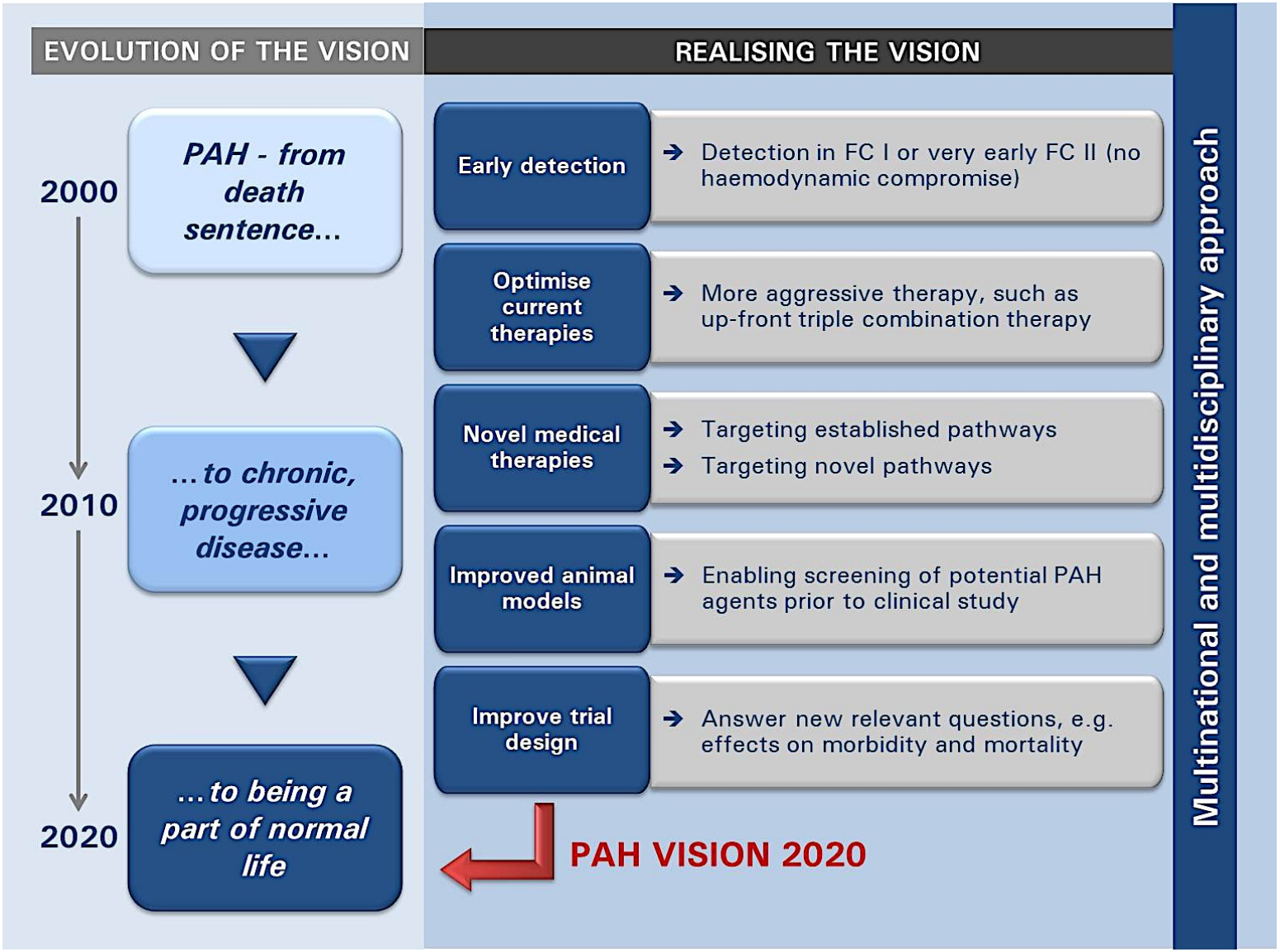
Nazzareno Galiè*, Alessandra Manes, Luca Negro, Massimiliano Palazzini, Maria Letizia Bacchi-Reggiani, and Angelo Branzi

European Heart Journal (2009) **30**, 394–403



- 23 RCTs
- Average duration 14.3 wks
- 3140 patients
- All-cause mortality rate in the control group = 3.8%
- Active treatments:
  - 43% reduction in mortality
  - RR 0.57 (95%CI 0.35–0.92)
  - P = 0.023

PAH management: How to do better?



Progress in PAH

- **Evolving Paradigm in the evaluation of novel therapies in PAH**

- New approach for the use of combination therapy

- Development of oral drugs targeting the Prostacyclin pathway

Until recently, most of RCTs have used 6'WD as the Primary E-P

	Primary End-point	Duration	Sample Size
Epoprostenol (1)	6-MWD	12 Wks	81
Bosentan (2)	6-MWD	16 Wks	213
Treprostinil s.c. (3)	6-MWD	12 Wks	470
Iloprost (4)	Combined E-P (6-MWD & FC)	16Wks	203
Sildenafil (5)	6-MWD	12 Wks	277
Ambrisentan (6)	6-MWD	12 Wks	202 & 192
Tadalafil (7)	6-MWD	16 Wks	405
Riociguat (8)	6-MWD	17 Wks	445

Evolving primary endpoints in PAH Trials

6-MWD
- A simple, reproducible and valid tool to assess exercise capacity
- **Initially thought ∆6-MWD** was a reliable surrogate of outcome
- Accepted by regulatory authorities for registration of PAH drugs

6-MWD
- Today, there is growing evidence that 6-WD is not a reliable surrogate of outcome
- In addition, short-term trials are not appropriate for evaluating new drugs in a chronic and severe disease

4th World Symposium on Pulmonary Hypertension

Expanding knowledge in PAH suggest to move from 6 MWD to more clinically relevant primary endpoints like morbidity and mortality in Phase III RCTs

McLaughlin VV, *et al*. *J Am Coll Cardiol* 2009

Relationship between 6MWD and long-term outcome Evidence from the SERAPHIN trial*

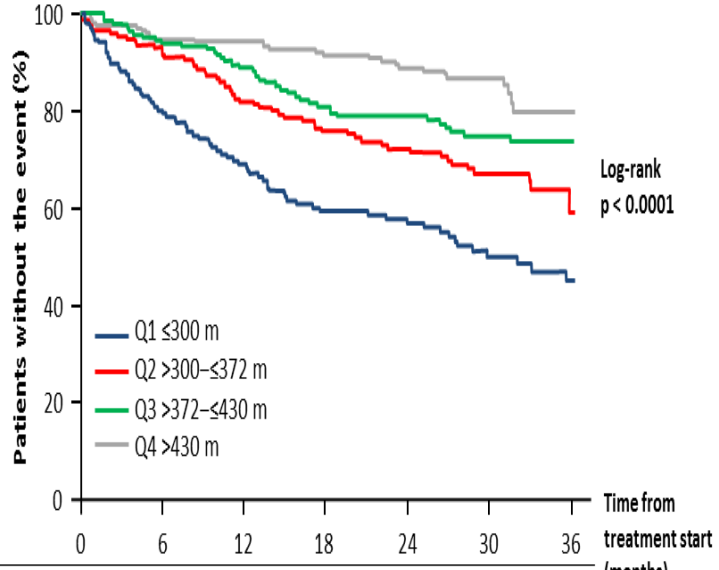
- The relationship between 6WMD,and long-term outcome was investigated in 595 patients with available data included in the Seraphin trial*

- Hazard ratios were calculated to determine the association between PAH-related Death or Hospitalisation at the EOT and between all cause death up to EOS with
  - Baseline 6MWD
  - Absolute 6MWD reached at month 6
  - Change in 6MWD from baseline to month 6

*Effect of Macitentan on Morbidity and Mortality in PAH

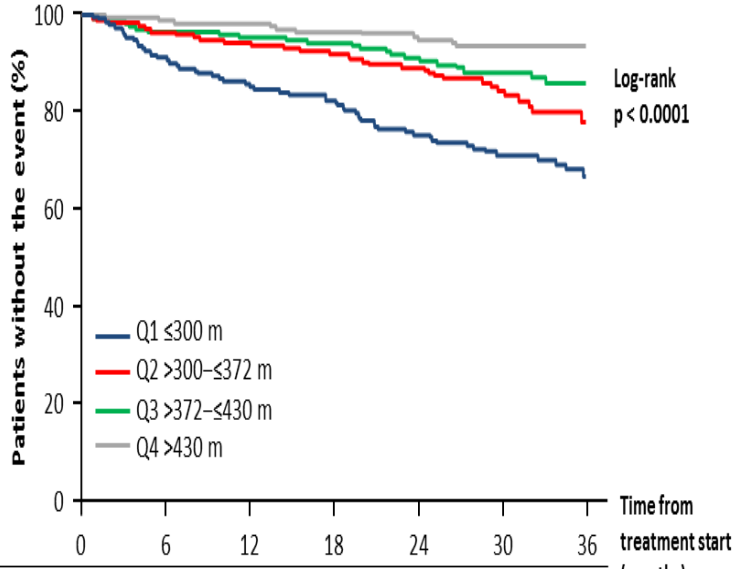
Association between baseline 6MWD and long-term outcome

PAH related death or hospitalization at EOT



Quartile	Patients at risk						
Q1 ≤300 m	197	130	102	82	72	43	22
Q2 >300–≤372 m	179	148	124	109	101	57	25
Q3 >372–≤430 m	182	157	139	120	109	64	26
Q4 >430 m	181	164	154	146	133	61	19

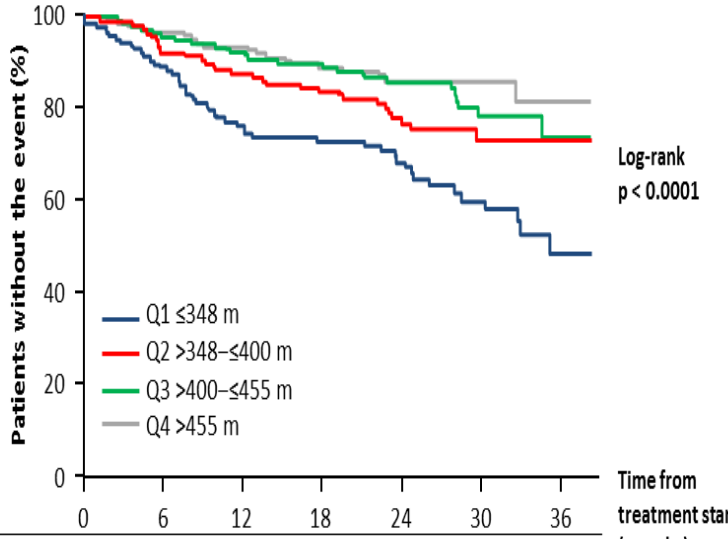
All cause death up to EOS



Quartile	Patients at risk						
Q1 ≤300 m	197	175	160	154	139	102	54
Q2 >300–≤372 m	179	172	168	164	159	94	39
Q3 >372–≤430 m	182	173	169	167	162	103	45
Q4 >430 m	181	178	175	172	167	81	33

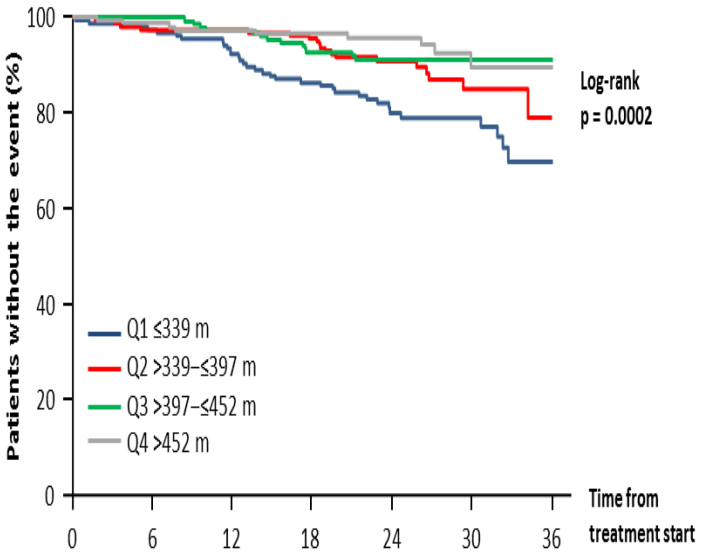
Association between absolute 6MWD at Month 6 and long-term outcomes

PAH related death or hospitalization at EOT



Quartile	Baseline 6MWD	Patients at risk						
Q1 ≤348 m	276 m	149	114	89	82	44	20	3
Q2 >348–≤400 m	354 m	149	127	113	99	48	25	1
Q3 >400–≤455 m	403 m	151	135	124	114	73	27	1
Q4 >455 m	459 m	146	137	127	115	55	21	1

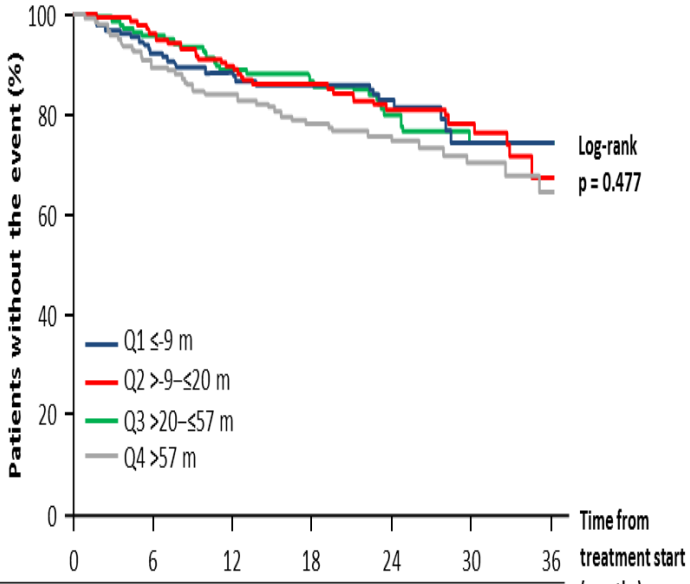
All cause death up to EOS



Quartile	Baseline 6MWD	Patients at risk						
Q1 ≤339m	272 m	157	150	144	131	82	45	5
Q2 >339–≤397 m	348 m	158	153	153	150	89	42	6
Q3 >397–≤452 m	400 m	154	153	148	141	90	41	2
Q4 >452 m	457 m	156	152	150	146	79	30	2

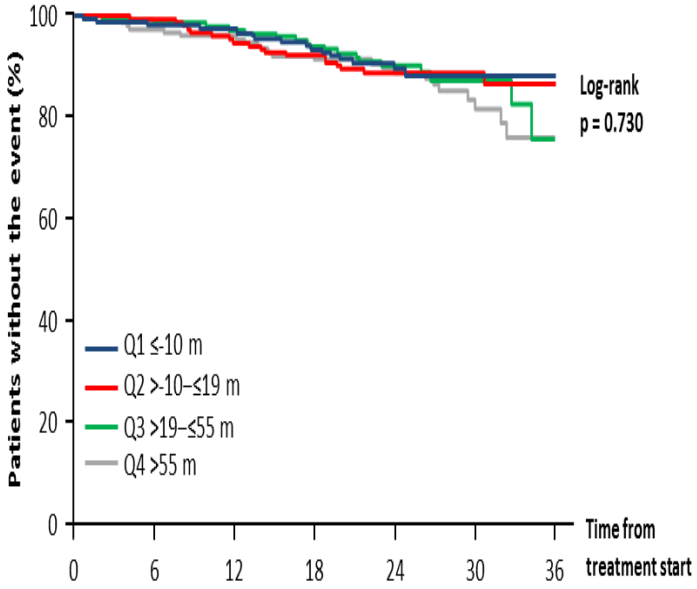
Association between change in 6MWD from baseline to Month 6 and long-term outcome

PAH related death or hospitalization at EOT



Quartile	Baseline 6MWD	Patients at risk						
Q1 ≤-9 m	403 m	153	118	103	94	43	10	0
Q2 >-9–≤20 m	390 m	156	139	120	111	63	31	3
Q3 >20–≤57 m	369m	141	130	116	108	56	22	2
Q4 >57 m	325 m	145	126	114	97	58	30	1

All cause death up to EOS



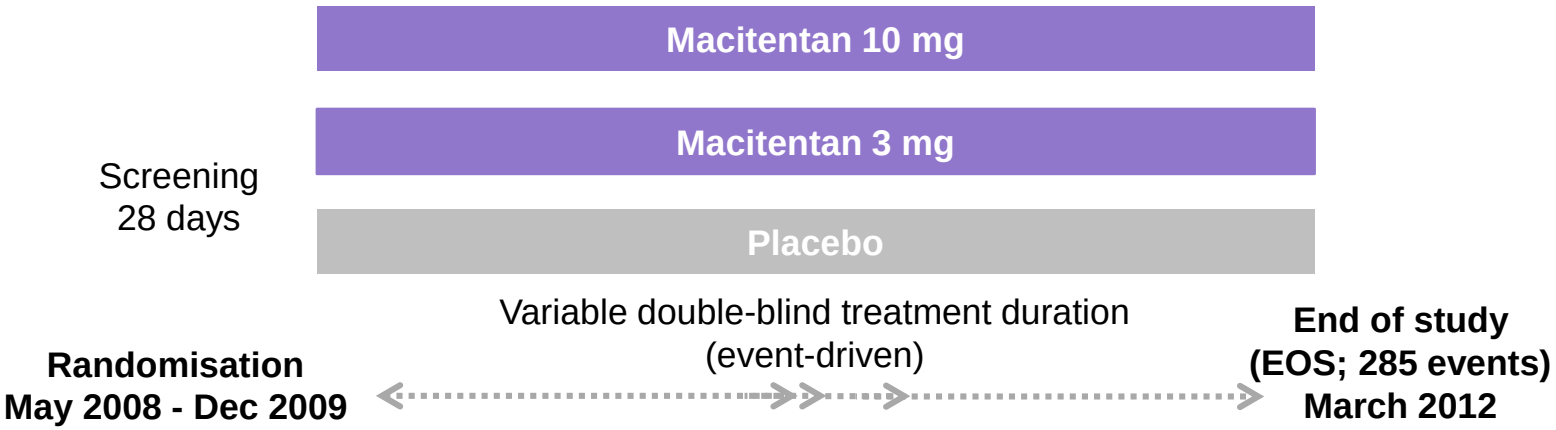
Quartile	Baseline 6MWD	Patients at risk						
Q1 ≤-10 m	393 m	160	154	152	145	75	33	4
Q2 >-10–≤19 m	389 m	157	154	147	141	86	43	5
Q3 >19–≤55 m	371 m	153	151	149	142	83	37	3
Q4 >55 m	322 m	155	149	147	140	96	45	3

Recent morbidity-mortality trials in PAH

TRIAL	Inclusion Period	Maximum Follow-up
Seraphin (n=742) : Primary end-point met Macitentan vs placebo 64% pre- treated with PDE5-inh or Prostanoids	1.5 year	3 years
Griphon (n=1156) : Primary end-point met Selexipag vs placebo 80% treated with PDE5-in and or ERA	3.5 years	3 years
Ambition (n=605) : Primary end-point met Ambrisentan+Tadalafil vs monotherapy	3.8 years	3 years

Seraphin: Study design

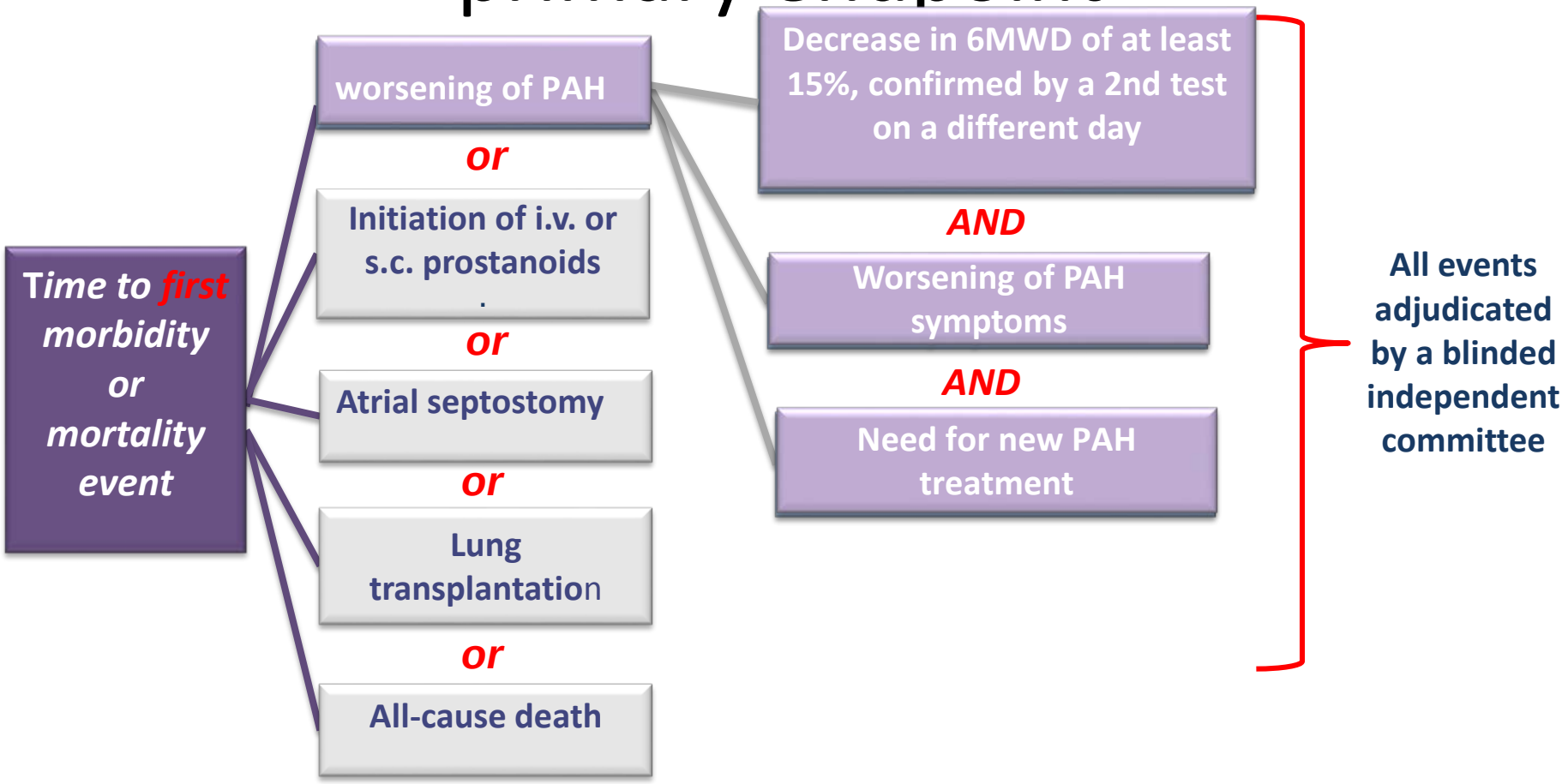
Multicentre, double-blind, randomised, placebo-controlled event-driven, phase III clinical trial



Investigating long-term benefits of macitentan in PAH patients with a novel and robust endpoint, measuring time to the first morbidity or mortality

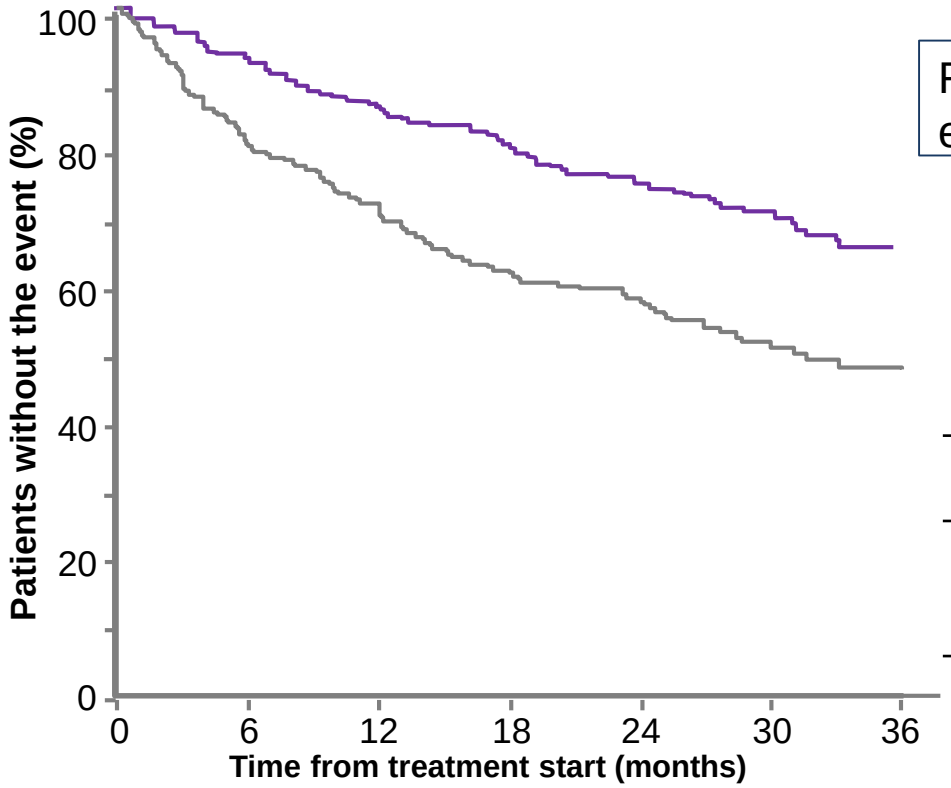
Pulido T, *et al. N Engl J Med* 2013; 369:809-18.

Seraphin : Morbidity and mortality primary endpoint



Pulido T, *et al. N Engl J Med* 2013; 369:809-18.

Primary endpoint: Time to the first morbidity and mortality event



Risk reduction of primary endpoint event vs placebo

Macitentan 10 mg: 45%

Placebo

Treatment difference	10 mg
Hazard ratio (HR)	0.55
Log-rank p-value	< 0.001

Patients at risk

242	208	187	171	155	91	41	Macitentan 10 mg
250	188	160	135	122	64	23	Placebo

SERAPHIN :Different components of the morbidity- mortality 1st end-point

	Placebo *n* = 250	Macitentan 10 mg *n* = 242
Patients with an event n (%)	**116 (46.4)**	**76 (31.4)**
Type of the 1st event, n (%)		
PAH worsening	**93 (37.2)**	**59 (24.4)**
Initiation of Prostanoids	**6 (2.4)**	**1 (0.4)**
Deaths All causes	**17 (6.8)**	**16 (6.6)**

Pulido T, *et al. N Engl J Med* 2013; 369:809-18.

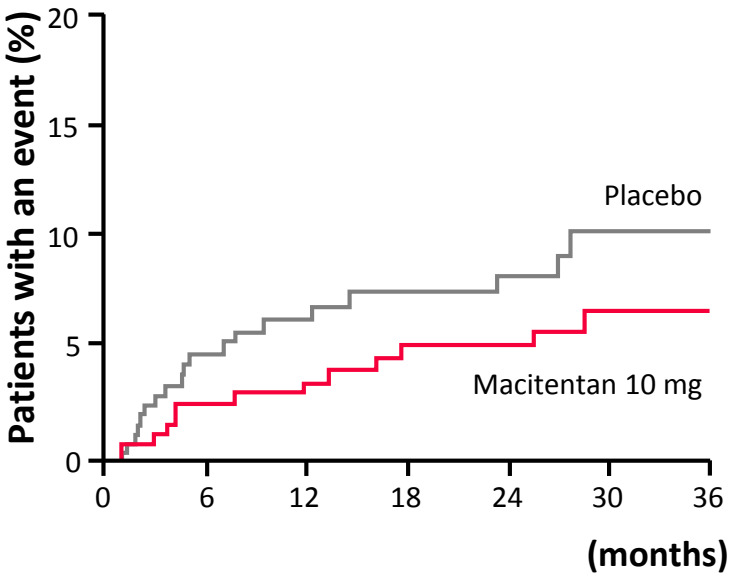
Death as first event in morbidity-mortality trials

- PAH is a progressive disease and death is generally preceded by a clinical deterioration
- Sudden death is rare especially in Functional Class II or III patients
- Sudden death is relatively more frequent in class IV unstable patients, but this population is excluded from current RCTs

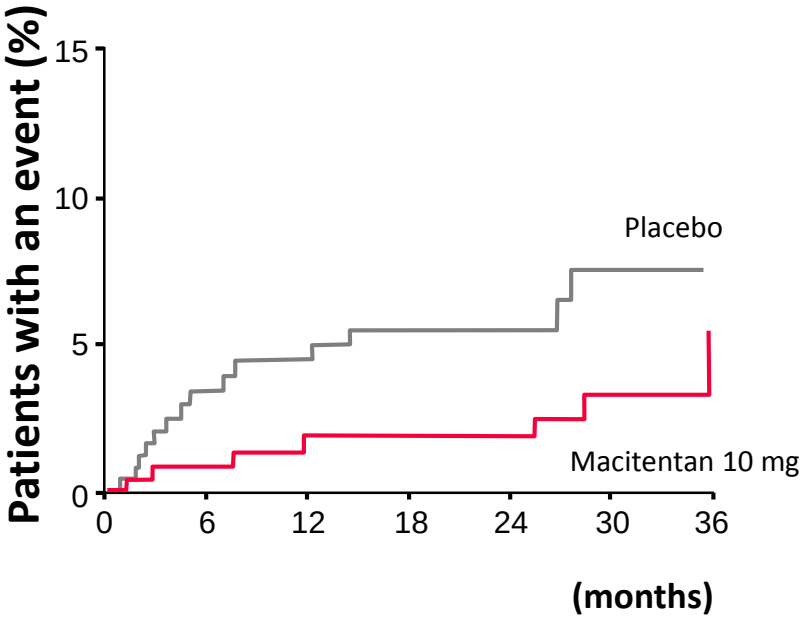
Pulido T, *et al. N Engl J Med* 2013; 369:809-18.

Seraphin : All causes of deaths at the EOT

All causes of deaths:
36% Risk Reduction (p = 0,20)



Deaths due to PAH
56% Risk Reduction (p = 0,07)



Pulido T, *et al. N Engl J Med* 2013; 369:809-18.

Summary (1)

- Until now, changes in 6MWD have served as primary E-P in pivotal RCTs of PAH
- Today, >10 drugs are currently approved in PAH. So, the level of requirement for the approval of new drugs need to be markedly increased
- PAH is a chronic life-threatening disease and recent proceedings and guidelines support the use of long-term outcome studies to assess the effects of novel therapies on disease progression

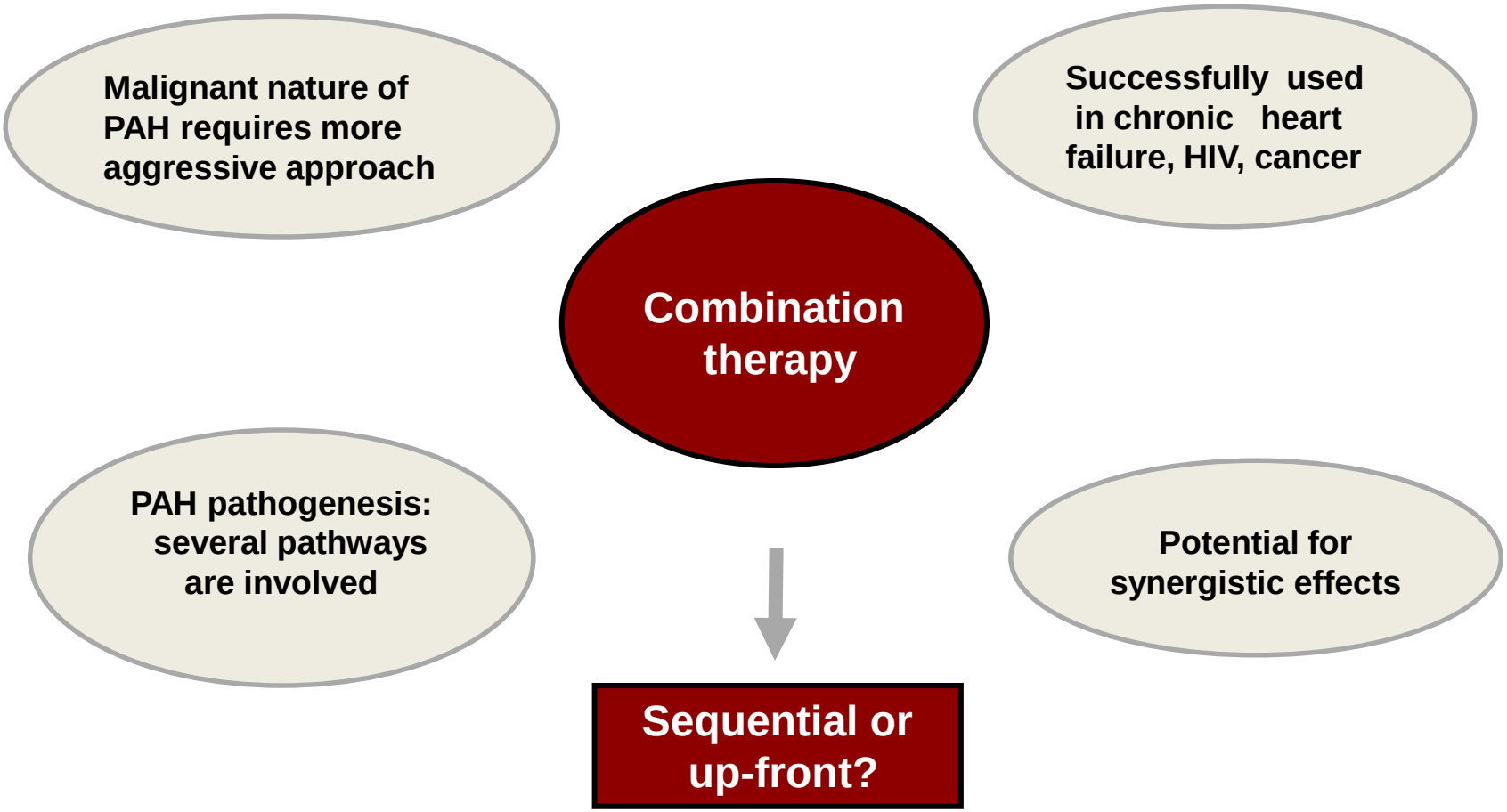
Summary (2)

- Since PAH is a progressive disease, death is rarely the first recorded event and generally preceded by a clinical deterioration
- In morbidity- mortality trials the treatment effect for the primary end-point is mainly driven by the rates of worsening events
- In Seraphin, when death is analyzed at the EOT or EOS there were trends toward risk reduction of deaths with macitentan 10 mg
- With Seraphin, Griphon and Ambition trials, we are entering a new era for drug evaluation in PAH

Progress in PAH

- Evolving Paradigm in the evaluation of novel therapies in PAH
- **New approach for the use of combination therapy**
- Development of oral drugs targeting the Prostacyclin pathway

Rationale for combination therapy

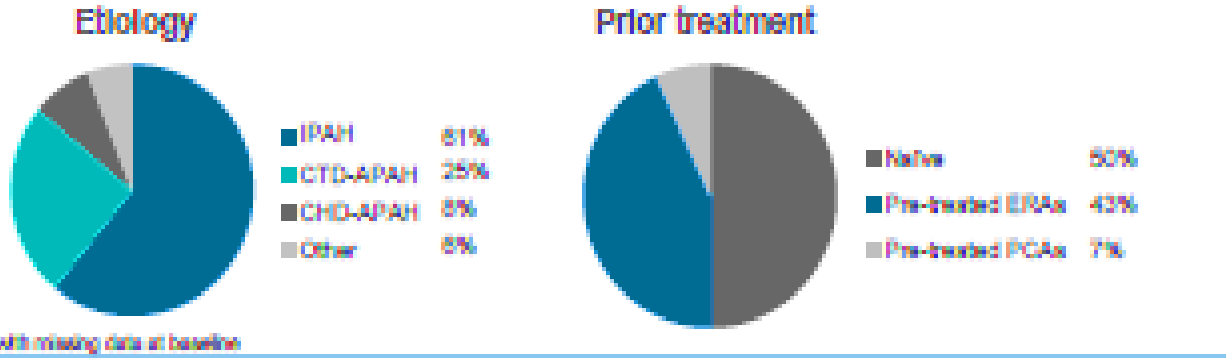


Sequential combination therapy in PAH

	Background therapy	Added therapy	Patients (n)	Study duration	Primary endpoint	Primary EP met
STEP[1]	Bosentan	Iloprost	67	12 weeks	6MWD	No
PACES[2]	Epoprostenol	Sildenafil	267	16 weeks	6MWD	Yes
PHIRST[3]	Naïve or bosentan	Tadalafil	405 (206)	16 weeks	6MWD	Yes NO
TRIUMPH-1[4]	Bosentan or sildenafil	Treprostinil (inhaled)	235	12 weeks	6MWD	Yes
FREEDOM-C[5]	Bosentan and/or sildenafil	Treprostinil (oral)	350	16 weeks	6MWD	No
FREEDOM-C2[6]	Bosentan and/or sildenafil	Treprostinil (oral)	310	16 weeks	6MWD	No
IMPRES[9]	≥ 2 drugs	Imatinib	202	24 weeks	6MWD	Yes
SERAPHIN[7]	**Naïve or sildenafil**	**Macitentan**	**742**	**115 weeks**	**Morbi-mortality**	**Yes (10 mg)**
PATENT[8]	**Naïve or ERA**	**Riociguat**	**443**	**12 weeks**	**6MWD**	**Yes**

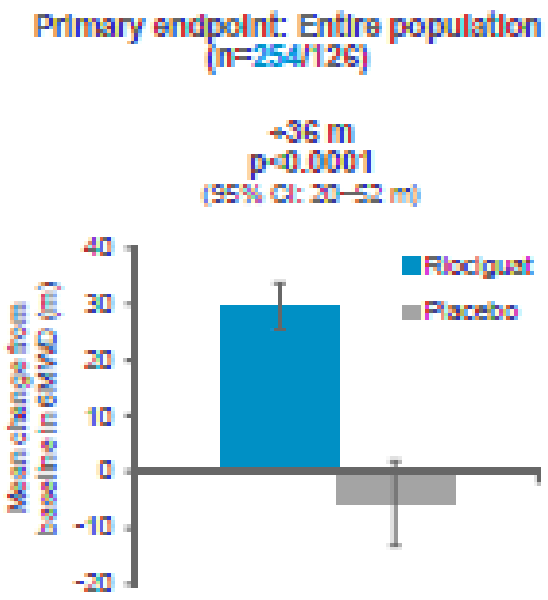
Patent Study:Patients characteristics

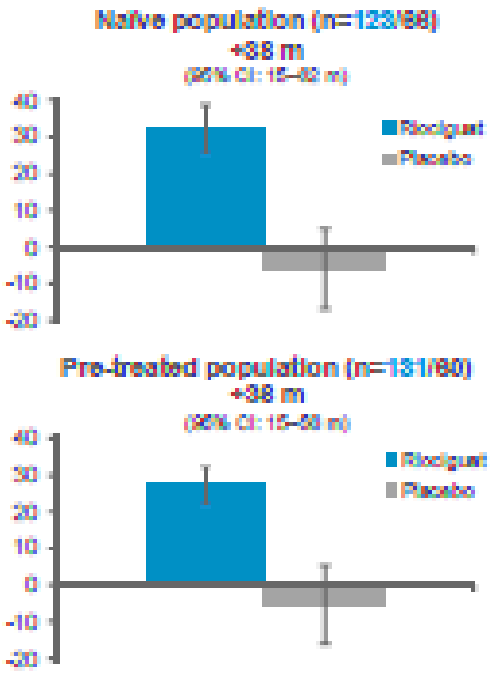
	Riociguat	Placebo
Age (years)	51	51
Female (%)	80	78
PVR (dyn·s·cm^{-5})	784	856
mPAP (mmHg)	46.9	48.9
6MWD (m)	361	368
WHO FC I/II/III/IV (%)	2/43/55/<1	3/48/46/2*



*1 patient with missing data at baseline

Patent Study:Primary endpoint (6MWD)

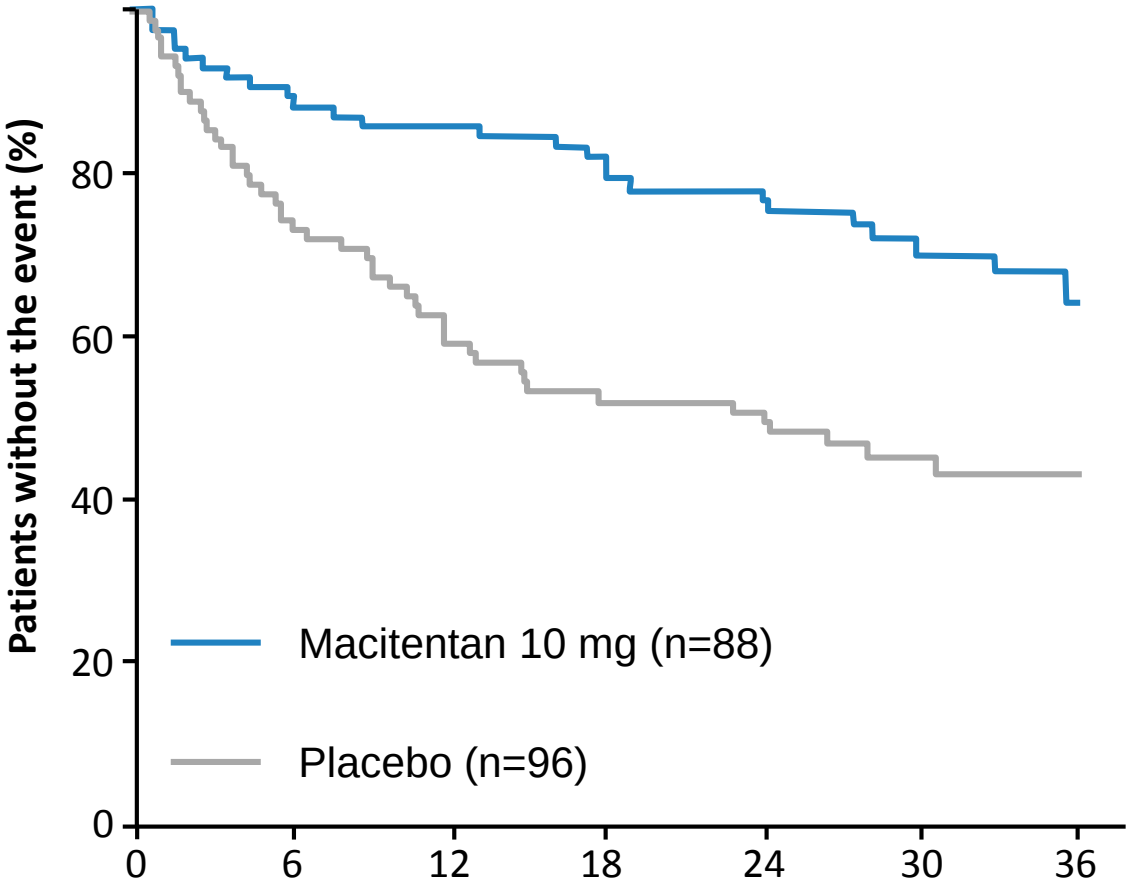




Seraphin Syudy:Demographics and baseline characteristics

	All patients n=742	Placebo n=250	Macitentan 3 mg n=250	Macitentan 10 mg n=242
Female sex, %	**77**	74	75	80
Age, years, mean ± SD	**45.6 ± 16.1**	46.7 ± 17.0	44.5 ± 16.3	45.5 ± 15.0
Time from diagnosis, years, mean ± SD	**2.7 ± 4.0**	2.6 ± 3.7	3.0 ± 4.5	2.6 ± 3.6
6MWD, m, mean ± SD	**360 ± 100**	352 ± 111	364 ± 96	363 ± 93
WHO FC, %				
I/II	**53**	52	56	50
III/IV	**47**	48	44	50
Background PAH therapy, %	**64**	62	66	64
PDE-5 inhibitors	**61**	60	62	62
Oral/inhaled prostanoids	**5**	3	7	6

Morbidity and mortality in patients <u>not on</u> background PAH therapy

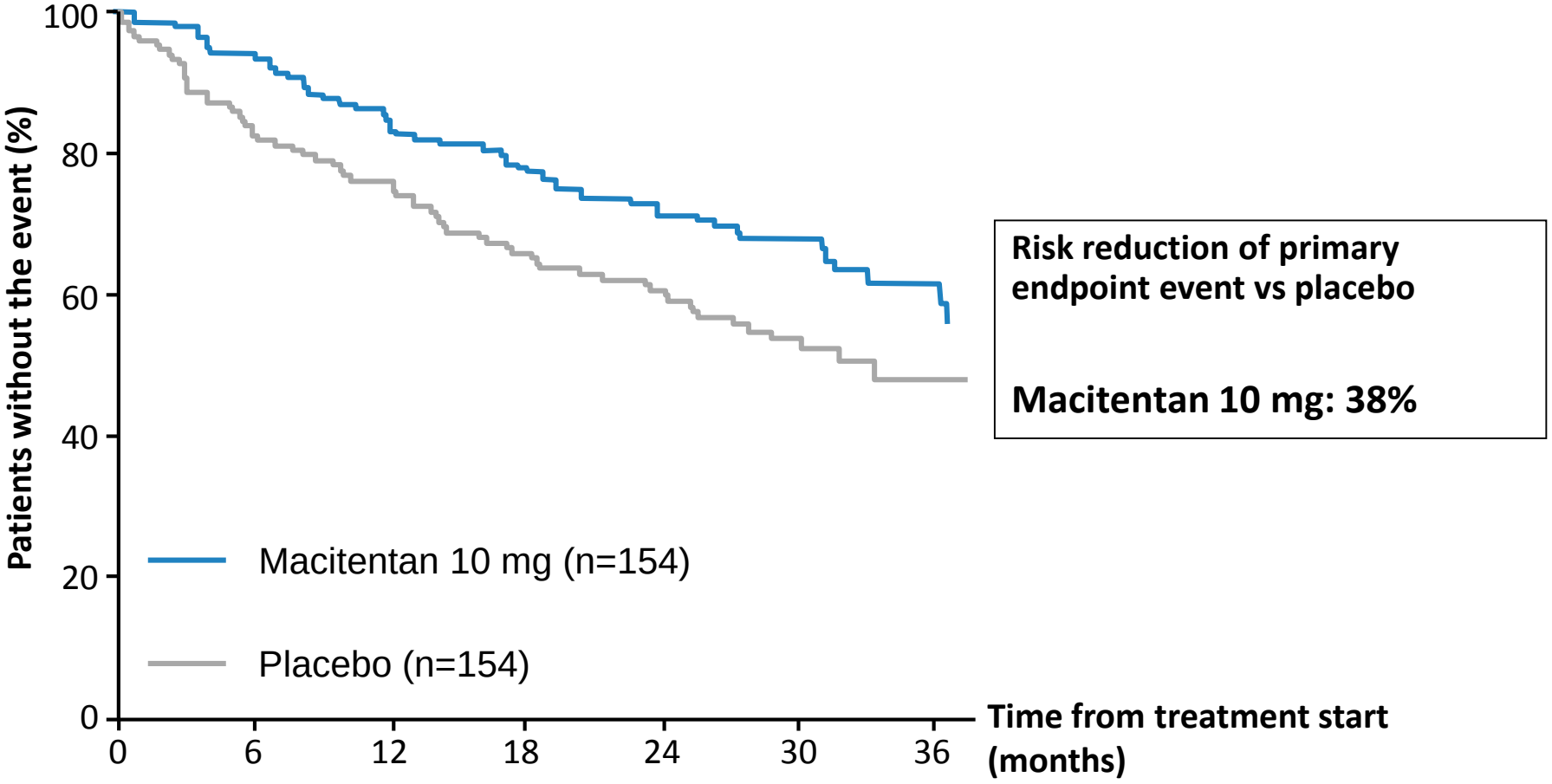


Risk reduction of primary endpoint event vs placebo

Macitentan 10 mg: 55%

Macitentan 10 mg: **Hazard ratio = 0.45; log-rank p = 0.0007**

Morbidity and mortality in patients on background PAH therapy



Risk reduction of primary endpoint event vs placebo

Macitentan 10 mg: 38%

Macitentan 10 mg: Hazard ratio=0.62; log-rank p=0.0094

PAH paradigm – the next regimen?

Current Dogma

- 2 drugs regimen
- Sequential approach

Alternative Approach

- Upfront combination
- combining 2 or 3 Drugs

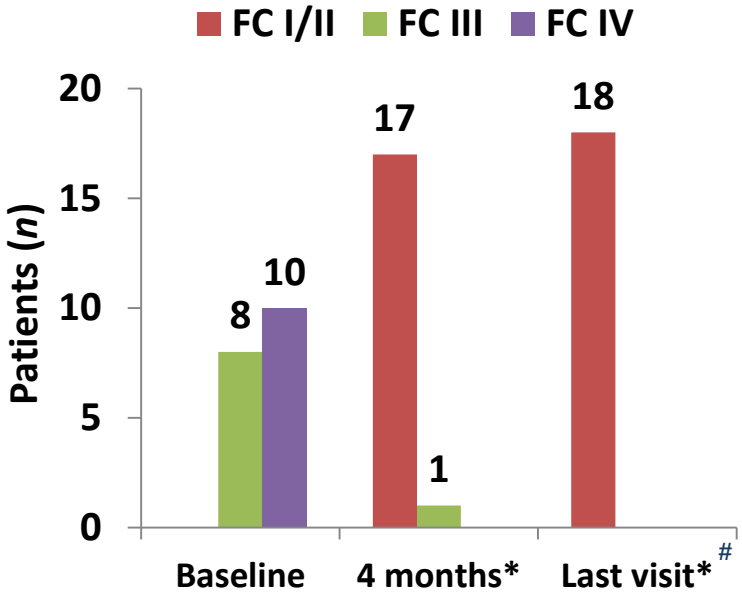
Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study

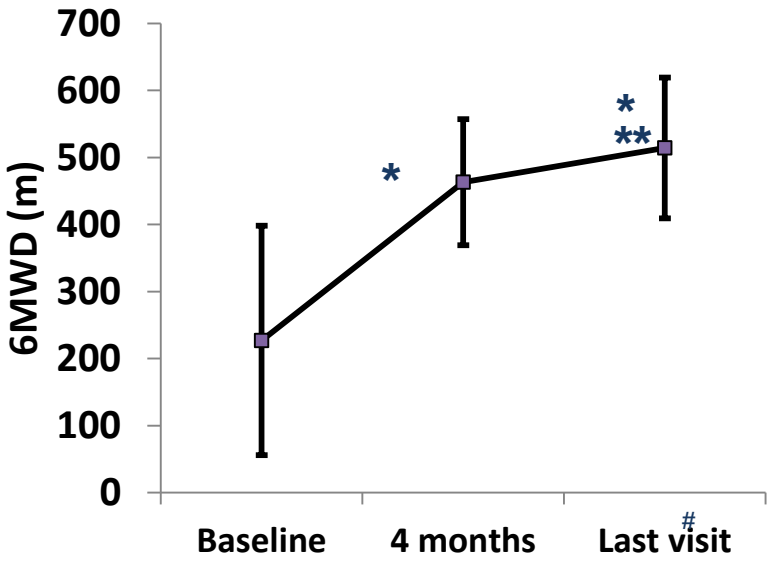
Olivier Sitbon[1,2,3], Xavier Jaïs[1,2,3], Laurent Savale[1,2,3], Vincent Cottin[4], Emmanuel Bergot[5], Elise Artaud Macari[1,2,3], Hélène Bouvaist[6], Claire Dauphin[7], François Picard[8], Sophie Bulifon[1,2,3], David Montani[1,2,3], Marc Humbert[1,2,3] and Gérald Simonneau[1,2,3]

- Upfront triple combo therapy: i.v. epoprostenol + bosentan + sildenafil
- 19 incident (i.e. newly diagnosed) patients with Idiopathic (n=9) or Heritable (n=10) PAH
- Mean age 39 ± 14 years (18 – 63)
- NYHA FC III (n=8) or IV (n=11)
- Severe haemodynamics: CI < 2.0 L/min/m^2 or PVR > 1000 d.s.cm^{-5}

Upfront triple combination therapy: Effect on FC and 6MWD

Prospective, observational analysis of idiopathic or heritable PAH patients (n = 19) treated with upfront combination therapy (epoprostenol, bosentan and sildenafil)



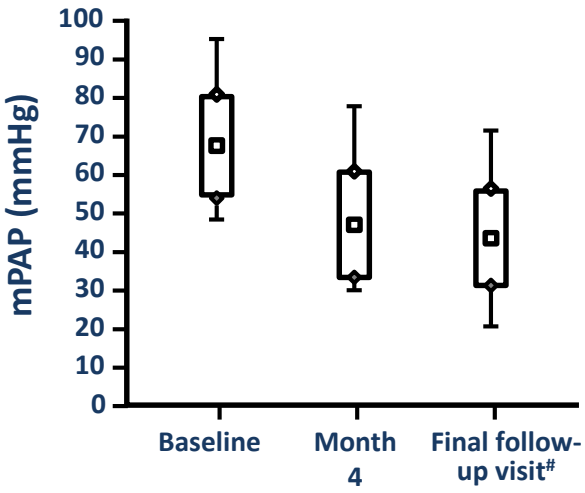


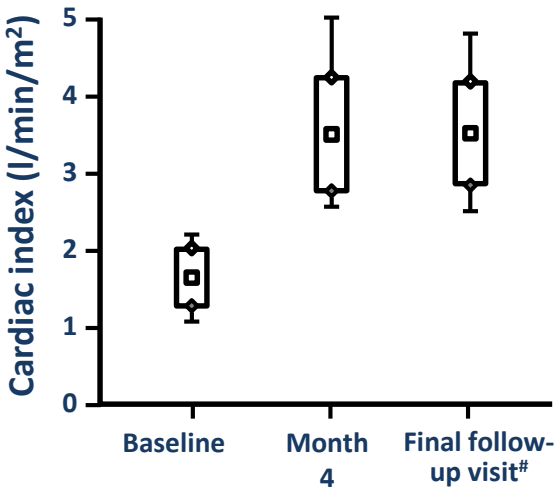
#32 ± 19 months

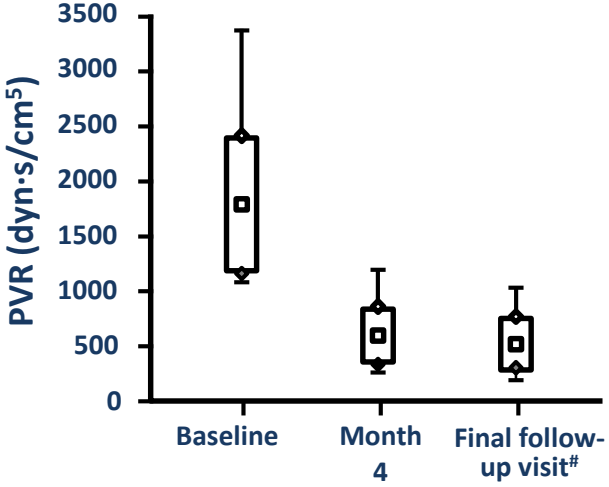
*p < 0.01 versus baseline; ** p < 0.01 versus 4 months

Sitbon O, et al. Eur Respir J. 2014;43:1691–7

Upfront triple combination therapy: Effect on haemodynamics







	Baseline	Month 4	Final follow-up#
RAP (mmHg)	11.9 ± 5.2	4.9 ± 4.9*	5.2 ± 3.5*
mPAP (mmHg)	65.8 ± 13.7	45.7 ± 14.0*	44.4 ± 13.4*
CI (l/min/m^2)	1.66 ± 0.35	3.49 ± 0.69*	3.64 ± 0.65*
PVR (d.s.cm^{-5})	1718 ± 627	564 ± 260*	492 ± 209*

Sitbon O, et al. Eur Respir J. 2014;43:1691–7

Upfront triple combination therapy: Long-term outcome / survival

- Long-term follow-up (n=18)
  - Median follow-up: 39.2 months (range: 13.7 – 73.3 months)
  - All patients well and alive in NYHA FC I-II
  - 6 patients with mPAP < 30 mmHg (incl. one < 20 mmHg)

- Survival (n=19)

	1-year	2-year	3-year
Actual	100%	100%	100%
Transplant-free	94%	94%	94%
Expected* [95% CI]	75% [68%-82%]	60% [50%-70%]	49% [38%-60%]

* according to the French equation (Humbert M, et al. Eur Respir J 2010)

Sitbon O, et al. Eur Respir J. 2014;43:1691–7

The AMBITION trial

A randomised, multicenter study of first-line AMBrIsentan and Tadalafil combination therapy in subjects with pulmonary arterial hypertensION

To compare 2 treatment strategies in treatment-naïve patients:

Upfront combination therapy (ambrisentan AND tadalafil) vs Monotherapy (ambrisentan OR tadalafil)

Event-driven trial

Primary objective : time to clinical failure

Secondary objectives: change from baseline to week 24 in NT-pro-BNP; Percentage of subjects with satisfactory clinical response; 6MWD; FC; Borg score; safety and tolerability

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

Time To Clinical Failure is a composite endpoint and is defined as the first occurrence of any of the following events:

1. **Death (all-cause)**

2. **Hospitalization for worsening PAH (adjudicated), which comprised any of the following:**
   - Any hospitalization for worsening PAH
   - Lung or heart/lung transplant
   - Atrial septostomy
   - Initiation of parenteral prostanoid therapy

3. **Disease progression (adjudicated), defined as follows:**
   - > 15% decrease from baseline in the 6MWD combined with WHO class III or IV symptoms (at 2 consecutive post baseline clinic visits separated by ≥ 14 days)

4. **Unsatisfactory long-term clinical response (adjudicated), which comprised all 3 of the following criteria:**
   - Receiving ≥ 1 dose of randomized treatment and in the study for ≥ 6 months
   - A decrease from baseline in 6MWD at 2 consecutive post baseline clinic visits separated by ≥ 14 days
   - WHO class III symptoms assessed at 2 clinic visits separated by ≥ 6 months

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

Main Inclusion Criteria

- Subjects must have a diagnosis of Pulmonary Arterial Hypertension (PAH) due to the following:
  a) idiopathic or heritable PAH
  b) PAH associated with:
     I. connective tissue disease
     II. drugs or toxins
     III. Human Immunodeficiency Virus (HIV) infection
     IV. congenital heart defects repaired greater than 1 year prior to screening

- Subjects must have a current diagnosis of being in World Health Organisation (WHO) Functional Class II or III.

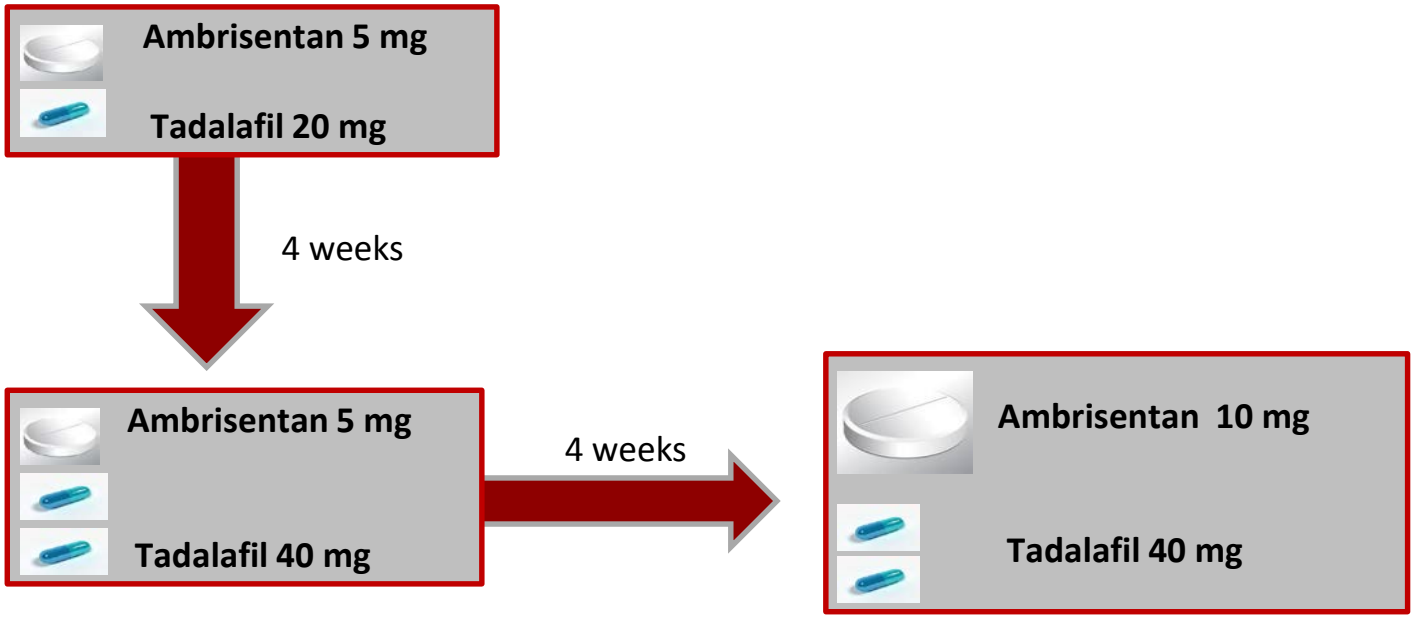
- Subjects must walk a distance of ≥125m and ≤500m at the screening visit

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

Study Design

Patients were randomized 2:1:1 to a

- Combination of Volibris (10mg OD) plus Adcirca (40mg OD) therapy,
- Volibris monotherapy (Volibris 10mg OD + placebo), or
- Adcirca monotherapy (Adcirca 40mg OD + placebo), respectively



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

Results (Primary analysis set)

- 500 patients were randomized to:
  - Combo Therapy (n=253)
  - Monotherapy (n=247)
    - Ambrisentan (n=126)
    - Tadalafil (n=121)

- Mean randomised treatment duration was:
  - Combo Therapy: 78.6 weeks
  - Monotherapy
    - Ambrisentan : 66.6 weeks
    - Tadalafil monotherapy: 71.6 weeks

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

Table. AMBITION: Combination vs Monotherapy

Outcome	Combination (n = 253)	Monotherapy (n = 247)
All-cause deaths (%)	3.6	3.2
Hospitalization (%)	4	12
Improvement in 6-minute walking (m)	49.0	23.8

The treatment effect observed with the primary endpoint was mainly driven by a reduction in hospitalizations. Time to first hospitalization was delayed by 63 percent (hazard ratio = 0.372; 95 percent CI: 0.217, 0.639; p=0.0002).

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

AMBITION:Results

- First-line treatment of PAH with the combination of ambrisentan 10 mg and tadalafil 40 mg **reduced the risk of clinical failure by 50%** compared to pooled ambrisentan and tadalafil monotherapy arm
  (hazard ratio = 0.502; p=0.0002).

- Consistent efficacy findings across key subgroups (NYHA FC II and III)

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

- The combination was also statistically significant
  vs the individual ambrisentan and tadalafil monotherapy groups for the primary endpoint.

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

Secondary Endpoints

Secondary Endpoints [change from baseline to week 24]	Combo	Pooled Mono	Difference and Confidence Interval	P value
NTproBNP (% reduction)	-67.4	-49.7	% difference-35.3; 95% CI:-46.2, -22.2	p<0.0001
% subjects achieving a satisfactory clinical response at week 24	39	29	odds ratio 1.56; 95% CI: 1.05, 2.32	p=0.026
6 Minute Walk Distance (meters, median change)	49.0	23.8	22.75m; 95% CI: 12.00, 33.50	p<0.0001
WHO Functional Class (median change)	0	0	0; 95% CI 0, 0	P=NS
Borg Dyspnoea Scale (median change)	-1.0	-0.5	-0.38; 95% CI: -0.75, 0	N/A

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

Adverse events

- Peripheral oedema, headache, nasal congestion and anaemia were more common in the combination therapy arm than the monotherapy arms.
- There were similar rates of Serious Adverse Events (SAEs) and AEs leading to study drug discontinuation between the three arms.
- No new safety signals were seen for either drug as monotherapy or in the combination therapy arm.

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

Combination Therapy: Summary

- There is growing evidence that combination of drugs targeting different pathophysiologic pathways is effective and safe in PAH either as sequential or up-front
- Up-front combination therapy appears to be superior to initial treatment with monotherapy
- The superiority of up-front combination therapy versus optimized sequential combination therapy remains to be demonstrated

Progress in PAH

- Evolving Paradigm in the evaluation of novel therapies in PAH
- New approach for the use of combination therapy
- **Development of oral drugs targeting the Prostacyclin pathway**

Dugs approved for PAH in Europe

Prostacyclin pathway
Epoprostenol IV Epo thermostable IV
Iloprost inhaled
Treprostinil SC (IV*)
Oral Selexipag

Selexipag phase II trial

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^f, Bruno Degano*, Diana Bonderman, Marcin Kurzyna#, Michela Efficace##, Ruben Giorgino## and Irene M. Lang****

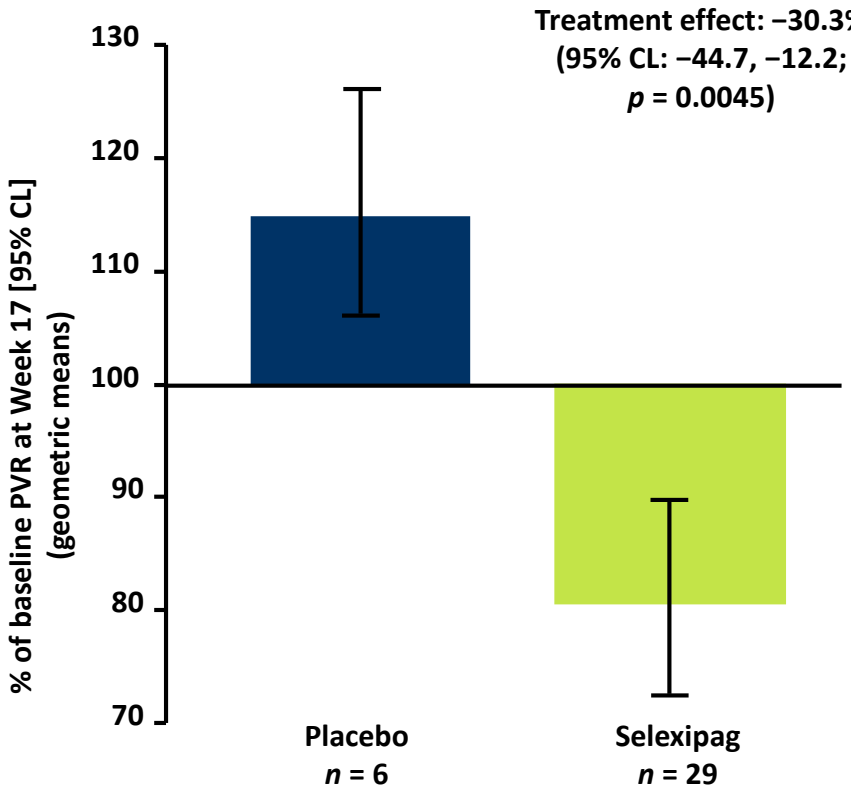
Objective of phase II proof-of-concept study:

To assess the efficacy, safety and tolerability of selexipag in PAH patients

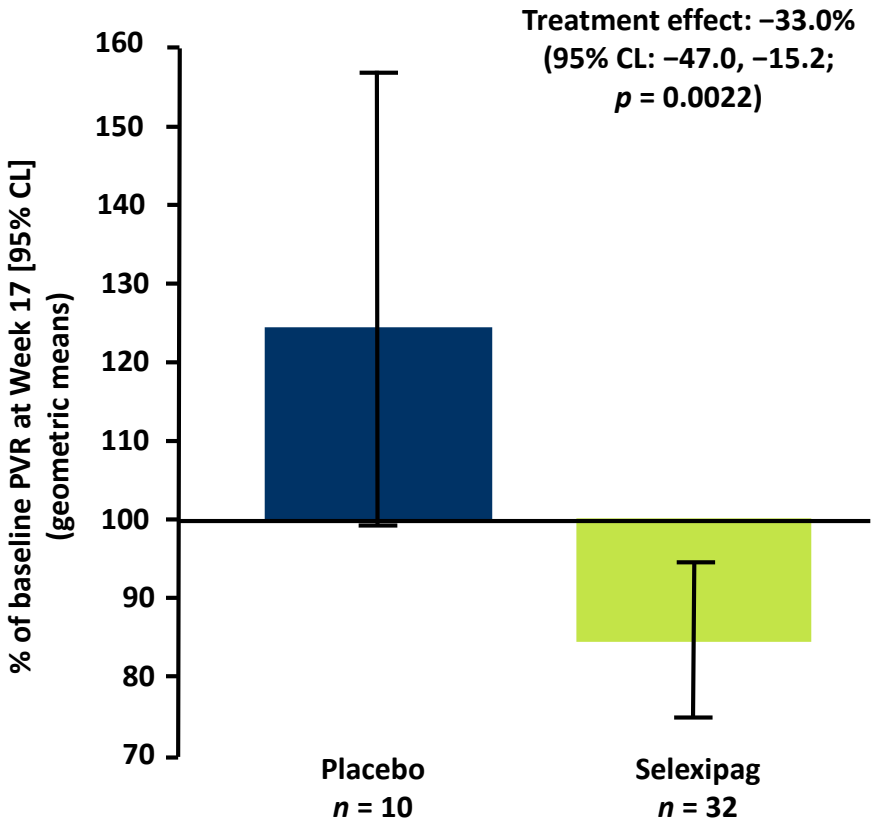
Maximum allowed doe of **800 µg bid**

Selexipag phase II: Significant reduction in PVR

Per protocol analysis



ITT analysis



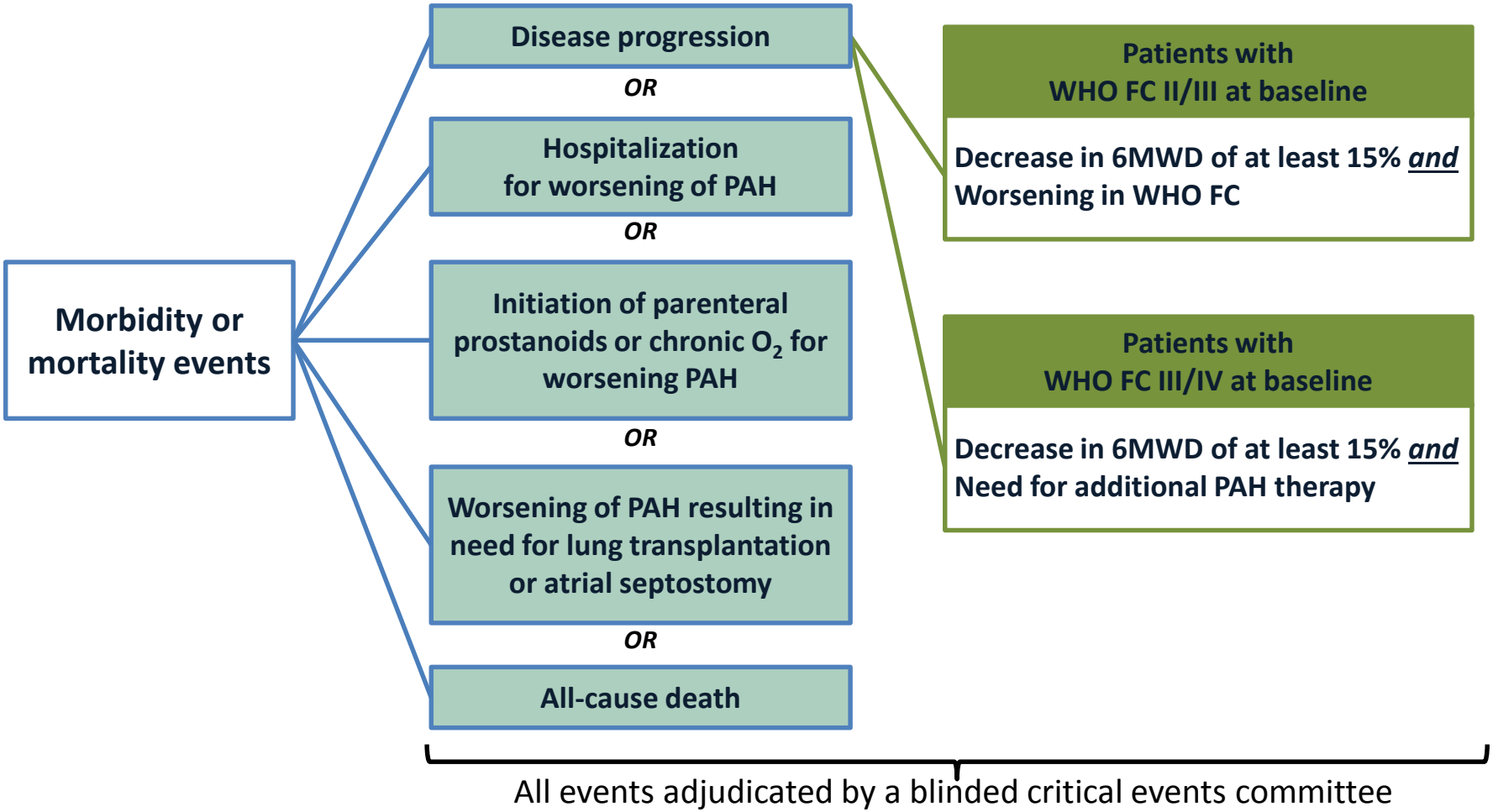
Simonneau G, et al. Eur Respir J 2012; 40: 874–80.

Selexipag in Pulmonary Arterial Hypertension – GRIPHON trial

- GRIPHON: ProstaGlandin I2 Receptor agonist In Pulmonary arterial HypertensiON
- Large, international, multicenter, long-term phase 3 study
- Double-blind, placebo-controlled study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with PAH
- Event-driven study
- Primary outcome measure: Time to first adjudicated morbidity or mortality event (up to 7 days after last study-drug intake)

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

GRIPHON Primary endpoint: Time to first occurrence of death or morbidity due to PH up to EOT



EOT: End of double-blind treatment

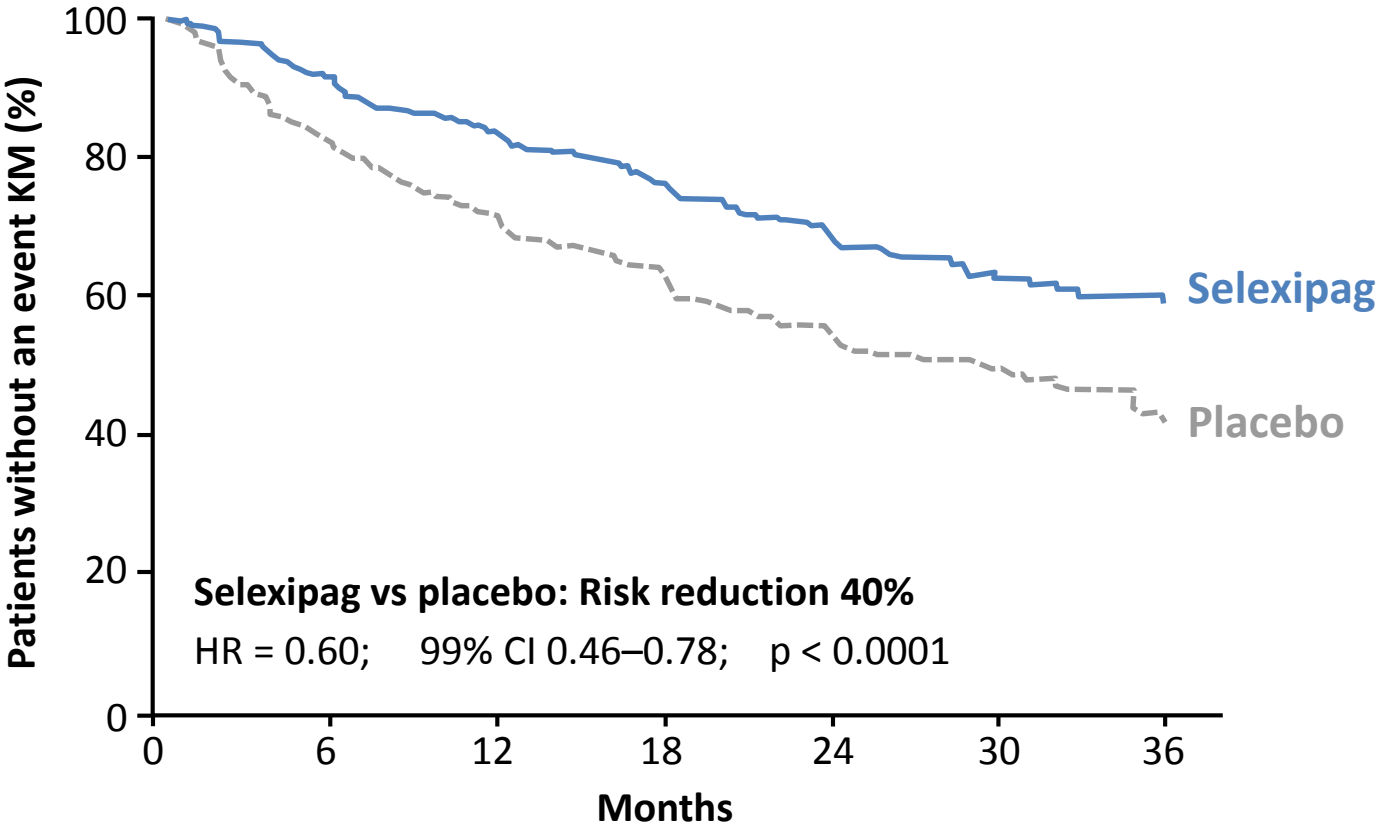
Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

GRIPHON trial – results

- 1156 PAH adult patients included and treated for up to 4.3 years.
- 80% on background treatment with ERA and/or PDE-5i
- Uptitration of selexipag allows each patient's maintenance dose to be individualized based on tolerability (to a maximum of 1600 mcg bid)

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Selexipag reduced the risk of the primary outcome composite of death or morbidity due to PH



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

McLaughlin V, *et al.* Presented at *ACC Annual Congress* 2015.

EOT: End of double-blind treatment

GRIPHON trial – Main results

- Main result: selexipag reduced the risk of a morbidity or mortality event vs placebo by 39% ($p<0.0001$)
- Consistent efficacy findings across subgroups (different doses / etiologies / treatment naïve or on background therapy…)
- The most common AEs that occurred with higher frequency on selexipag than placebo were in-line with those known in PGI_2 therapies

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Lessons from oral prostanoids

- Targeting prostacyclin signalling pathway is of major importance in PAH.
- While prostacyclin analogues have good efficacy in PAH, their delivery systems have many limitations.
- First experiences with oral prostacyclin analogue (beraprost, treprostinil) are quite disapointing due to minor efficacy and importance of adverse effects.
- The first in class oral non-prostanoid IP receptor agonist selexipag has been shown to reduce morbidity and mortality events in an event-driven long-term study.

Quali novità nelle strategie terapeutiche dell'Ipertensione arteriosa polmonare nel 2016?

- Miglior utilizzo dei farmaci attualmente disponibili
- Abbiamo solidi argomenti per un terapia d'attacco combinata
- Superiorità della doppia terapia orale rispetto alla mono nei pazienti in classe NYHA 2 e 3
- Non disponiamo di studi comparativi fra le diverse terapie di associazione e tra associazione d'emble e sequenziale combinata.