A new class of treatment in pulmonary hypertension

What could “Riociguat“ mean to your PAH and CTEPH patients?

성균관대학교 삼성서울병원
순화기 내과
장성아

Overview

RIOCIGUAT MODE OF ACTION

Evidences - Clinical Trial for CTEPH : CHEST 1, 2

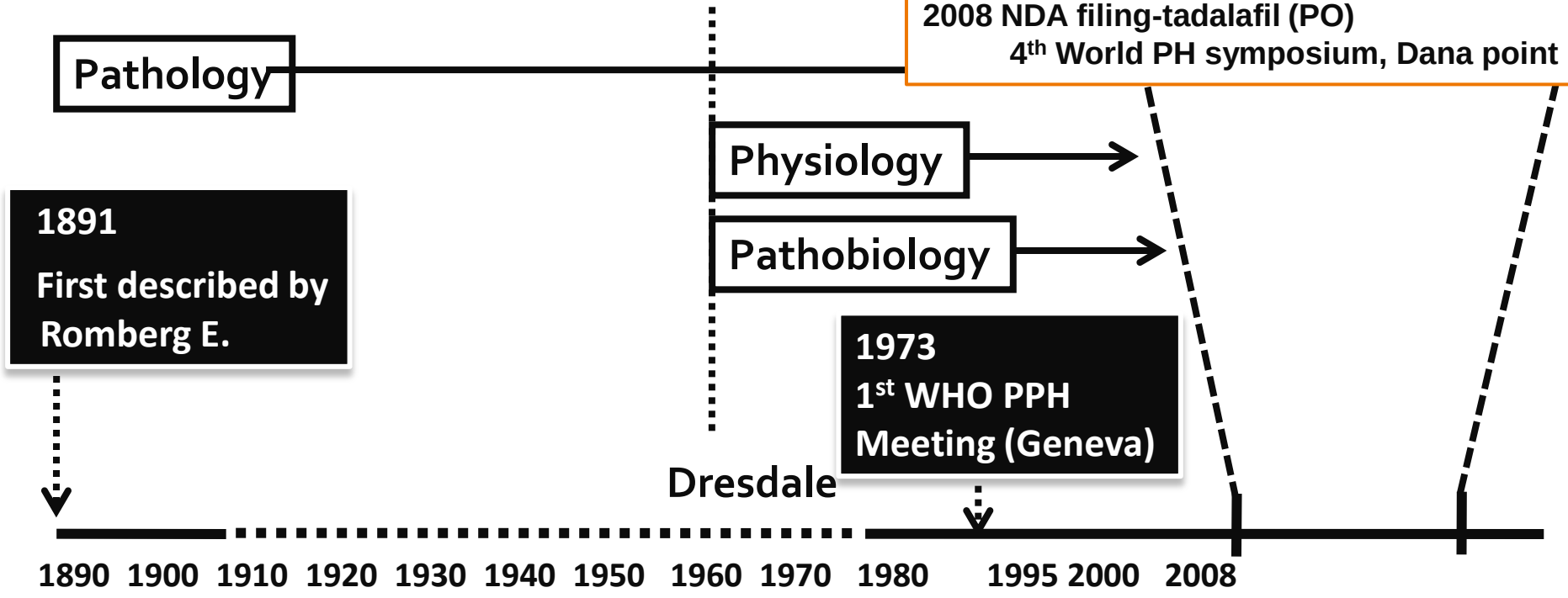
Evidences - Clinical Trial for PAH : PATENT 1, 2

Summary

PAH is Orphan Disease

No More

1995 1st FDA approved drug-epoprostenol
1997 Fenfluramine/dexfluramine withdrawn
1998 2nd WHO PH meeting, Evian
2001 1st oral FDA-approved drug-bosentan
2002 FDA approved trepostinil (SC)
2003 3rd WHO PH meeting, Venice
2004 FDA approved trepostinil (iv)
FDA approved iloprost (inh)
2005 FDA approved sildenafil (PO)
2007 EMEA approved sitaxsentan (PO)
FDA approved ambrisentan (PO)
2008 NDA filing-tadalafil (PO)
4th World PH symposium, Dana point



Approval of PAH Specific Drugs

- 2000 – Epoprostenol (iv), Treprostinil (SQ), Bosentan (PO)
- 2004 – Treprostinil (iv), Iloprost (inhale)
- 2005 – Sildenafil (PO)
- 2009-Tadalafil (PO)
- 2012 – Treprostinil (inhale)
- 2013- Treprostinil (oral), Riociguat (oral) Macitetan (oral)
- 2015- Selexipague (oral)

Pulmonary hypertension
Diagnostic classification

1. Pulmonary arterial hypertension

- Idiopathic PAH
- Familial PAH
- Drug or toxin induced
- Associated with (APAH)
  - Connective tissue diseases
  - HIV
  - Portal hypertension
  - Congenital heart diseases
  - Schistosomiasis
  - Chronic hemolytic anemia
- PPHN

1'. PAH with venous/cap inv (PVOD)

2. PH with left heart disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular heart disease

3. PH with lung disease/hypoxemia

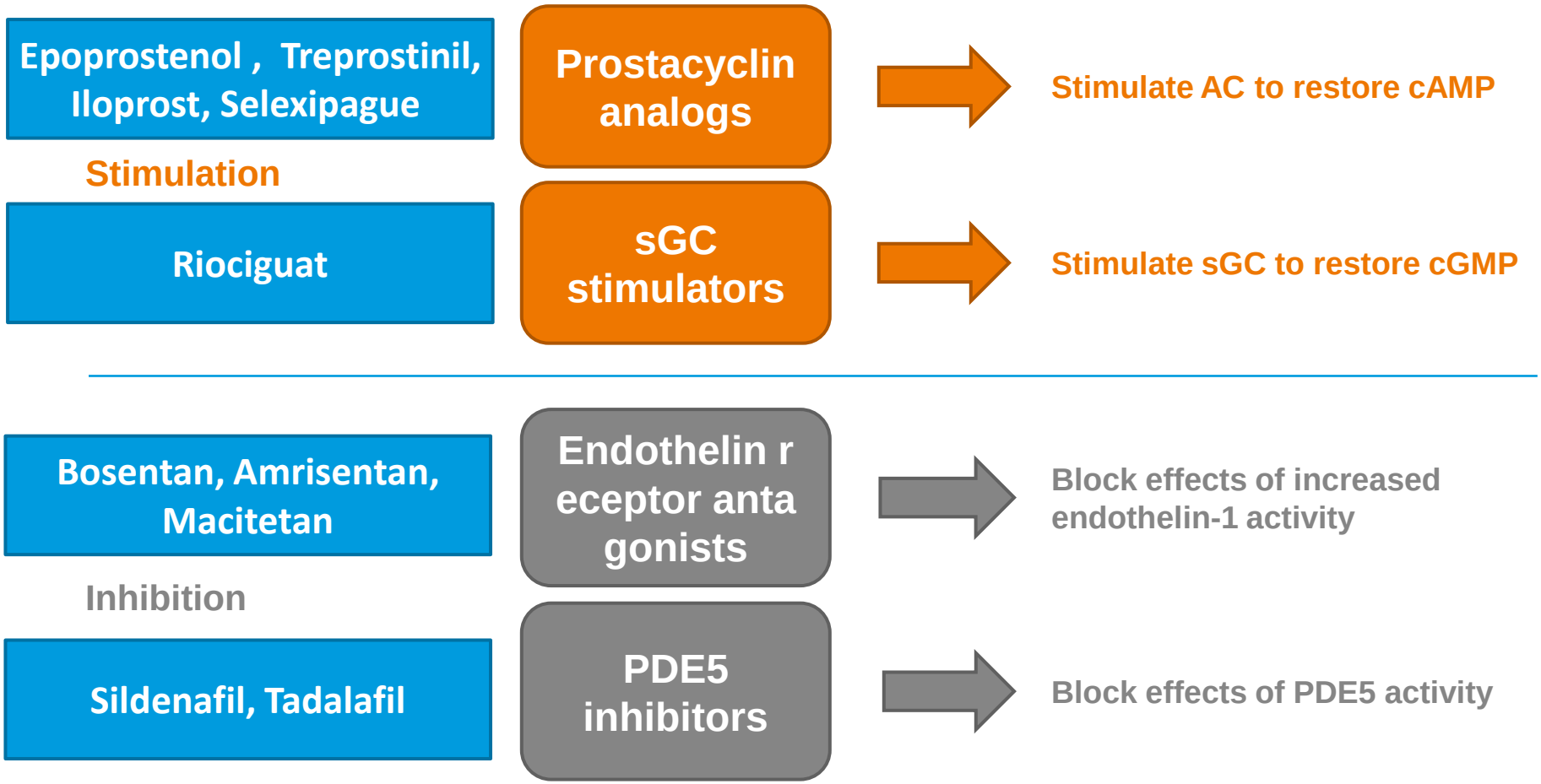
- COPD
- Interstitial lung diseases
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposire to high altitude
- Developmental abnormalities

4. PH due to chronic thrombotic and/or embolic disease

5. PH with unclear and/or multifactorial mechanisms

- Hematological disorder
- Systemic disorder
- Metabolic disorder
- Others

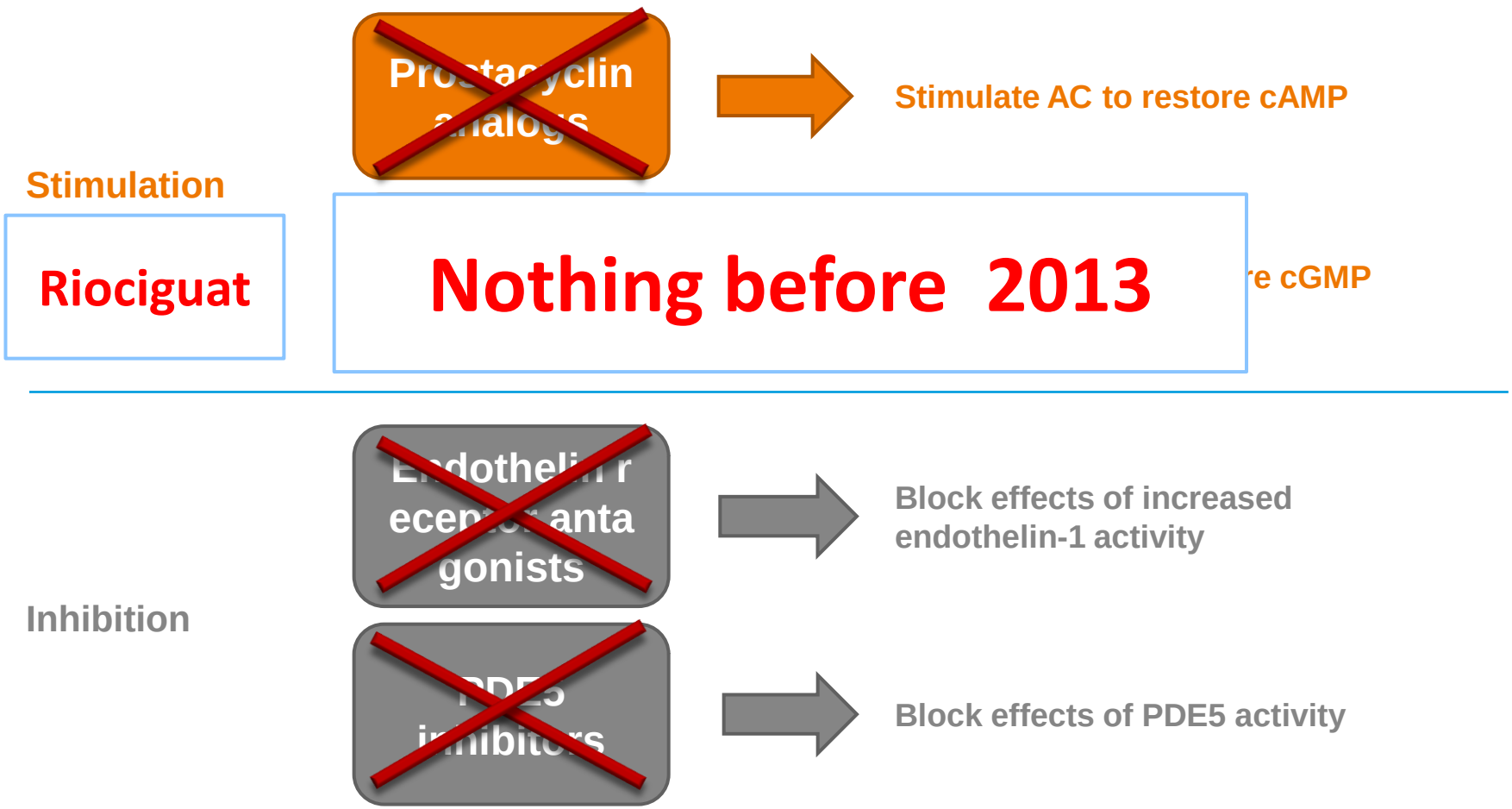
Targeted Therapy for PAH proven in Phase 3 trials



AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; PDE5, phosphodiesterase type 5; sGC, soluble guanylate cyclase.

Taichman DB *et al*. *CHEST* 2014;146:449–75.
Galiè *et al. J Am Coll Cardiol* 2013;62:D60–72.

Targeted Therapy for CTEPH proven in Phase 3 trials



AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; PDE5, phosphodiesterase type 5; sGC, soluble guanylate cyclase.

Taichman DB *et al*. *CHEST* 2014;146:449–75.
Galiè *et al. J Am Coll Cardiol* 2013;62:D60–72.

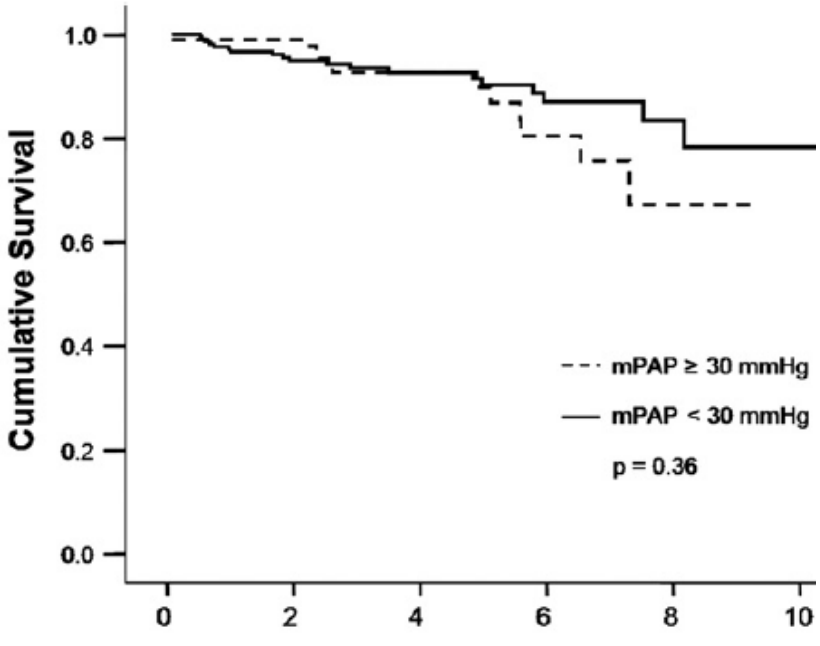
Survival after pulmonary thromboendarterectomy
Effect of residual pulmonary hypertension

3 mo after operation	Group 1 (n = 210)	Group 2 (n = 96)	*P* value
mPAP (mm Hg)	20 ± 5	38 ± 8	<.001
PVR (dynes · s^{-1} · cm^{-5})	181 ± 88	541 ± 250	<.001
CI (L · min^{-1} · m^{-2})	2.5 ± 0.6	2.5 ± 0.62	NS
SMWD (m)	386 ± 106	337 ± 97	<.001
NYHA class I or II (n)	88.1% (170/193)	68.9% (62/90)	<.001

mPAP, Mean pulmonary artery pressure; *PVR*, pulmonary vascular resistance; *CI*, cardiac index; *NS*, not significant; *SMWD*, 6-minute walk distance; *NYHA*, New York Heart Association.

DH Freed et al. J Thorac Cardiovasc Surg 2011;141:383-7

Survival after pulmonary thromboendarterectomy
Effect of residual pulmonary hypertension



Number at risk:						
mPAP < 30 mmHg	210	157	97	52	16	3
mPAP ≥ 30 mmHg	96	85	41	21	6	

FIGURE 3. Effect of residual pulmonary hypertension on survival after hospital discharge. *mPAP*, Mean pulmonary artery pressure.

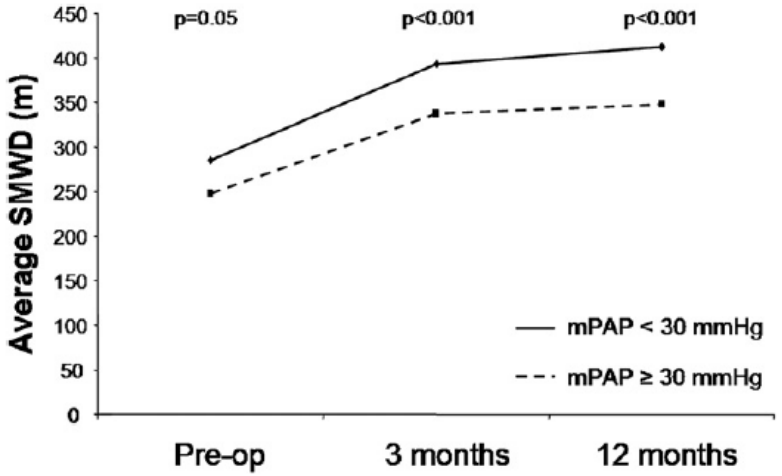
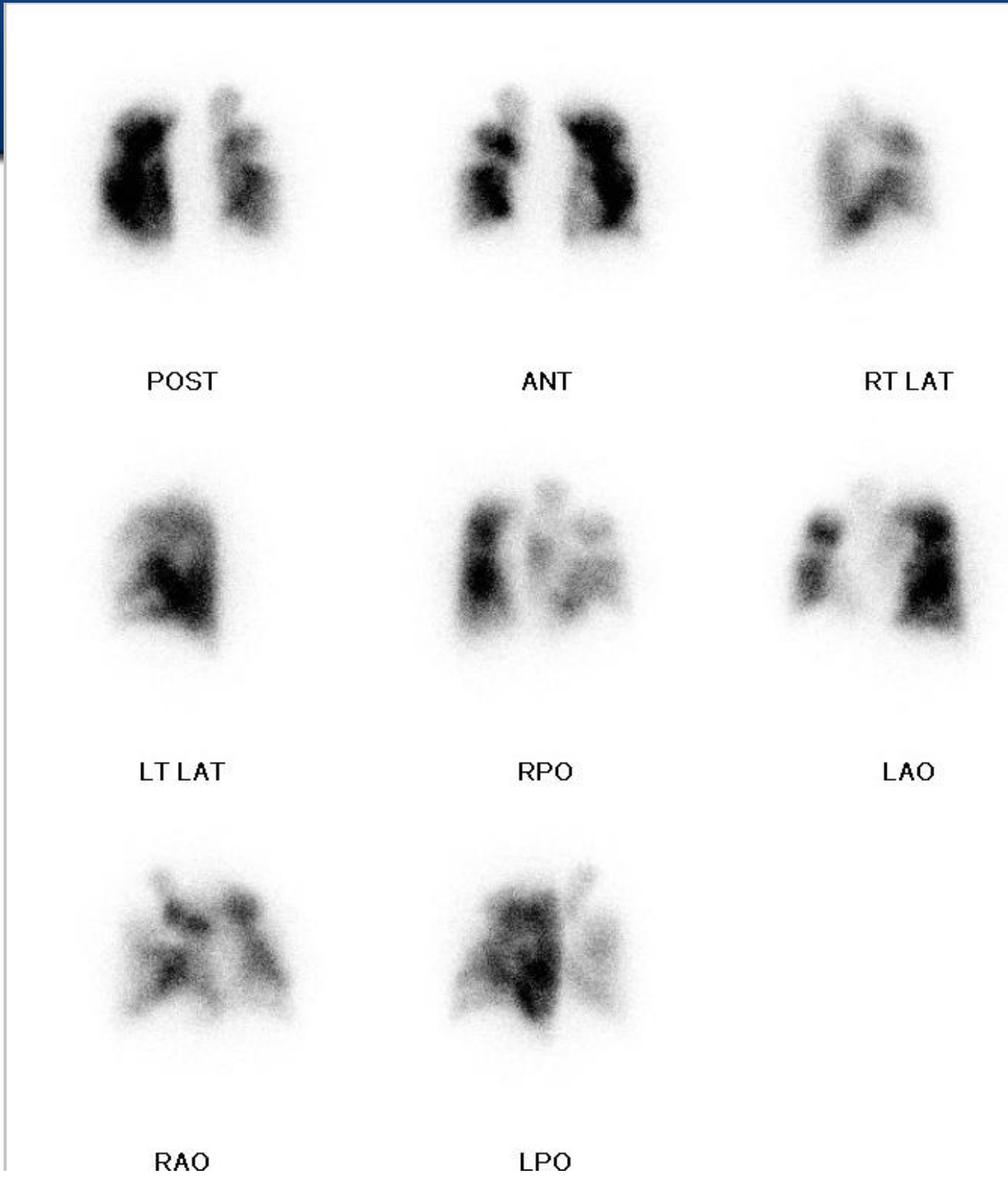
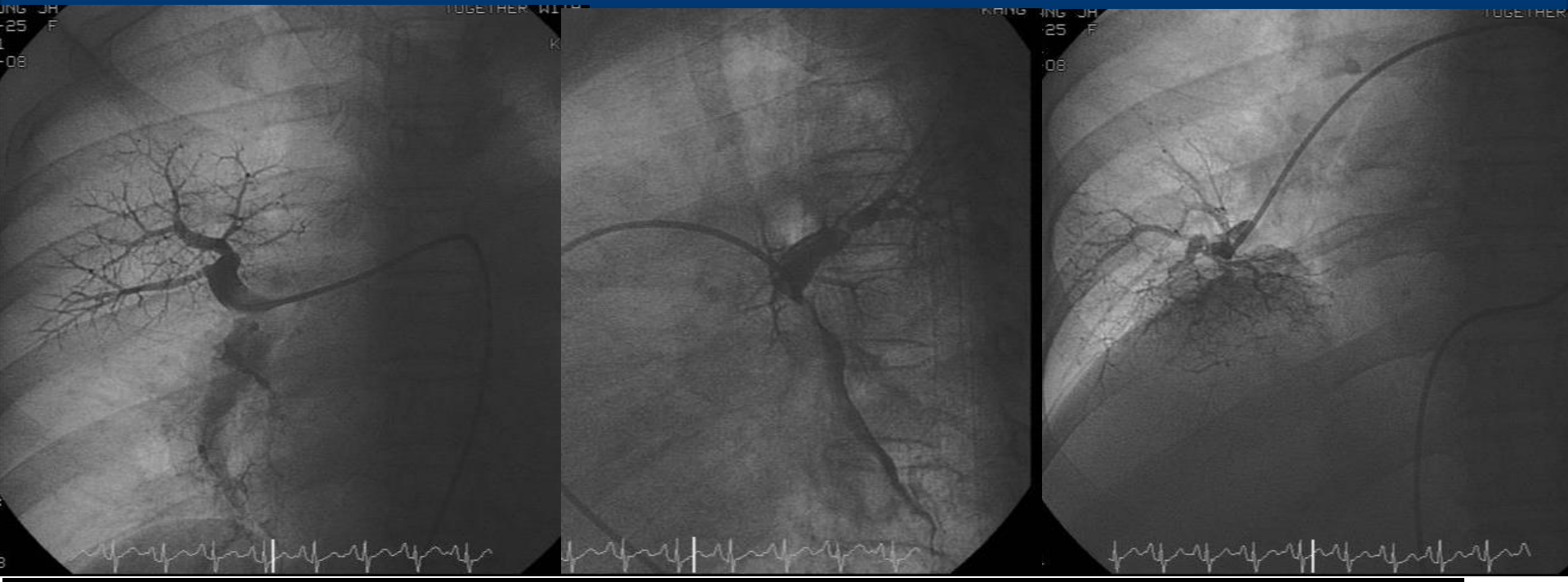


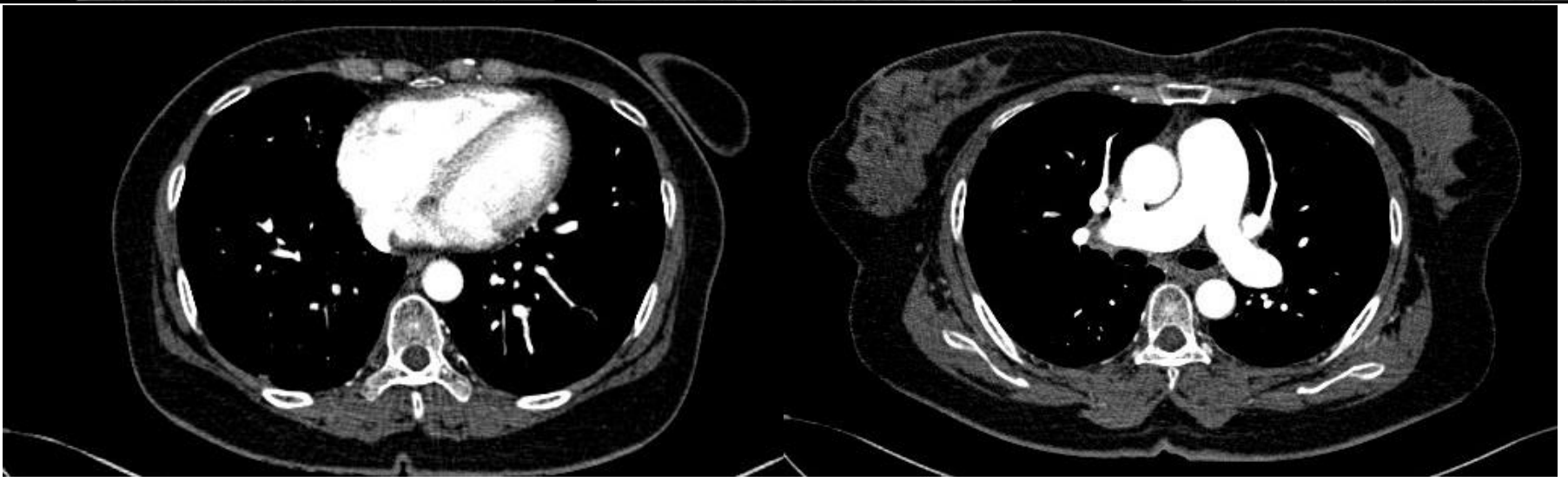
FIGURE 2. Six-minute walk test distance in meters. *mPAP*, Mean pulmonary artery pressure.

DH Freed et al. J Thorac Cardiovasc Surg 2011;141:383-7

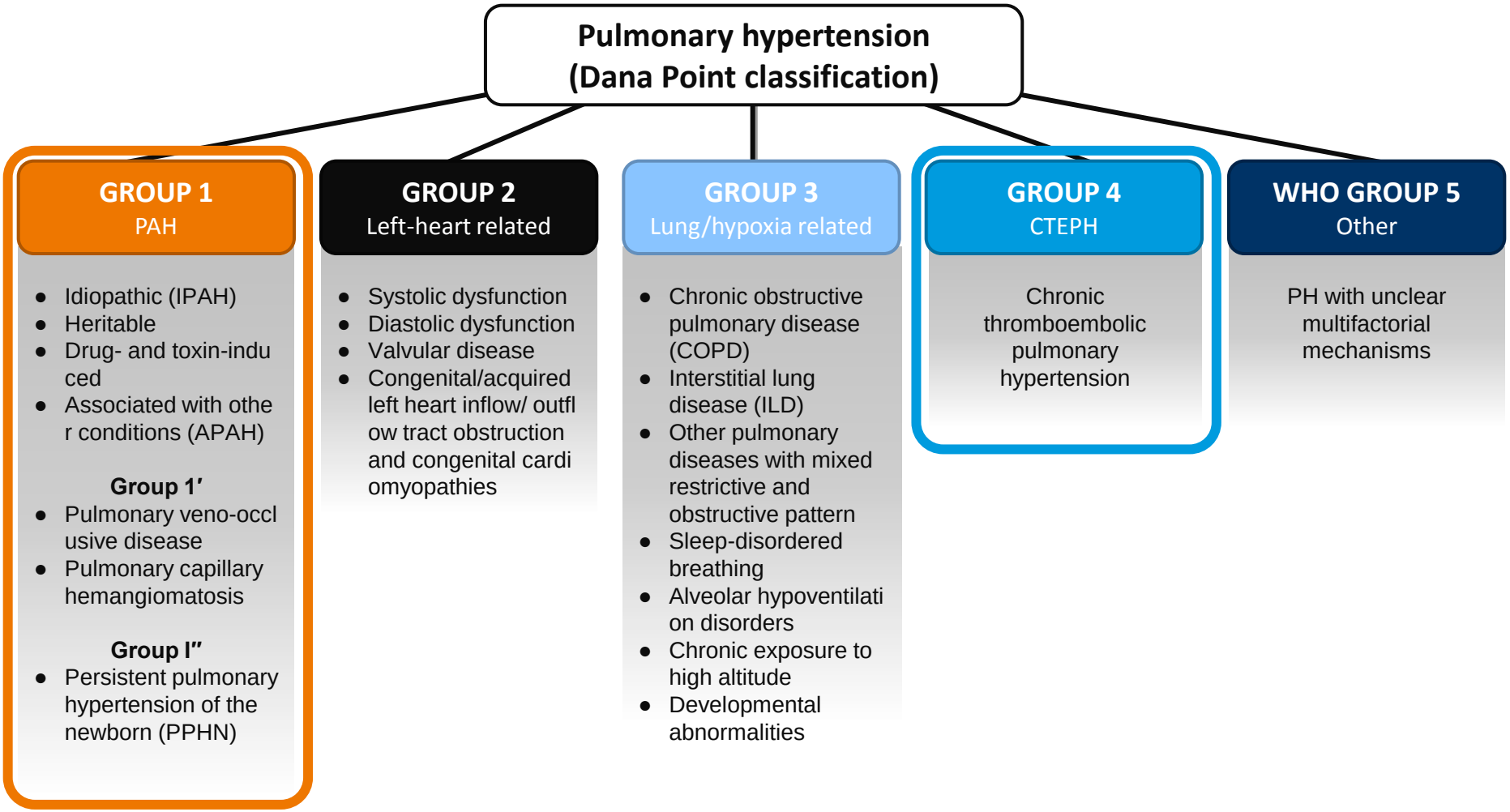
55 YO Woman
Dyspnea on exertion





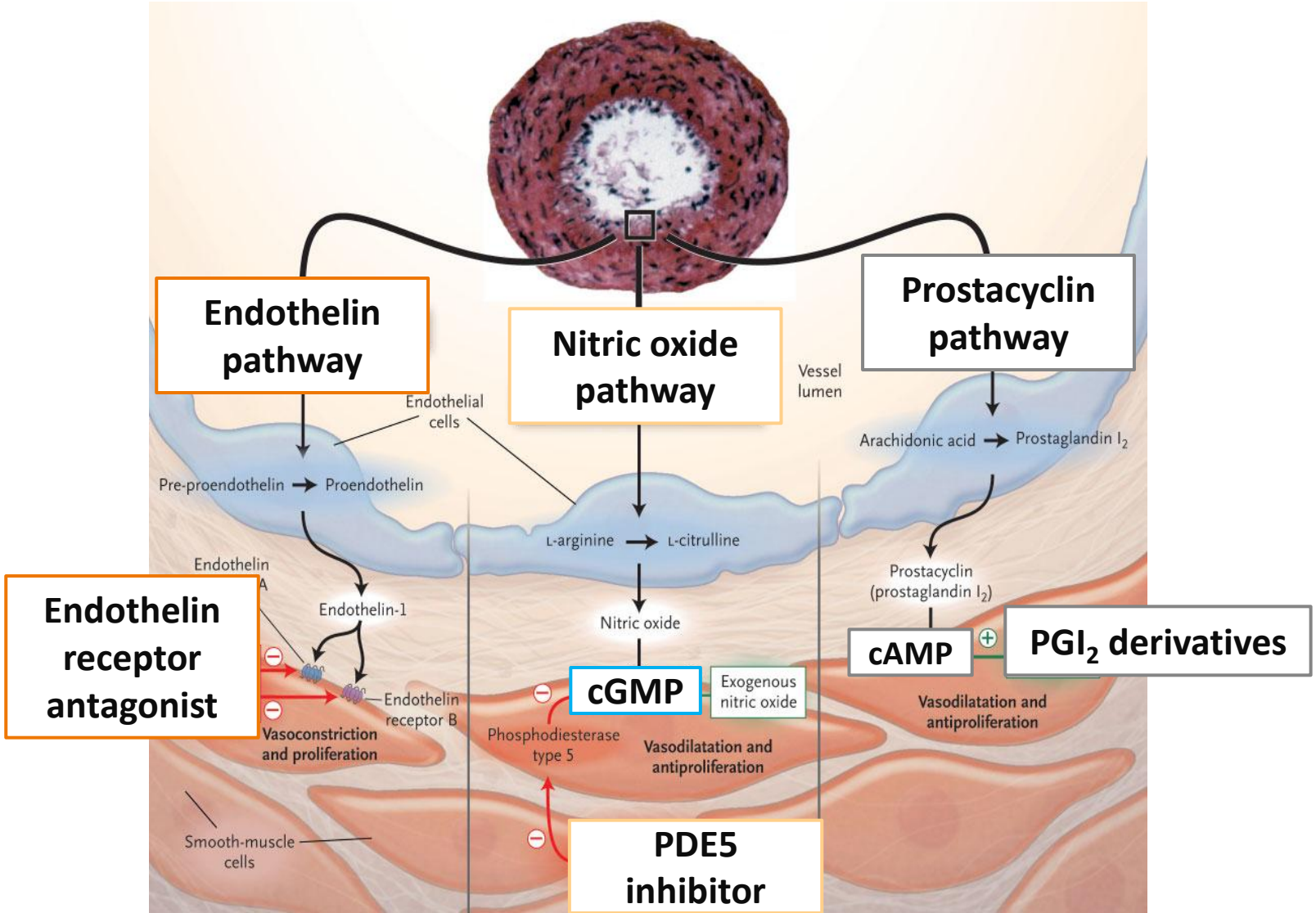


Riociguat is the first specific therapy approved for both PAH and CTEPH*

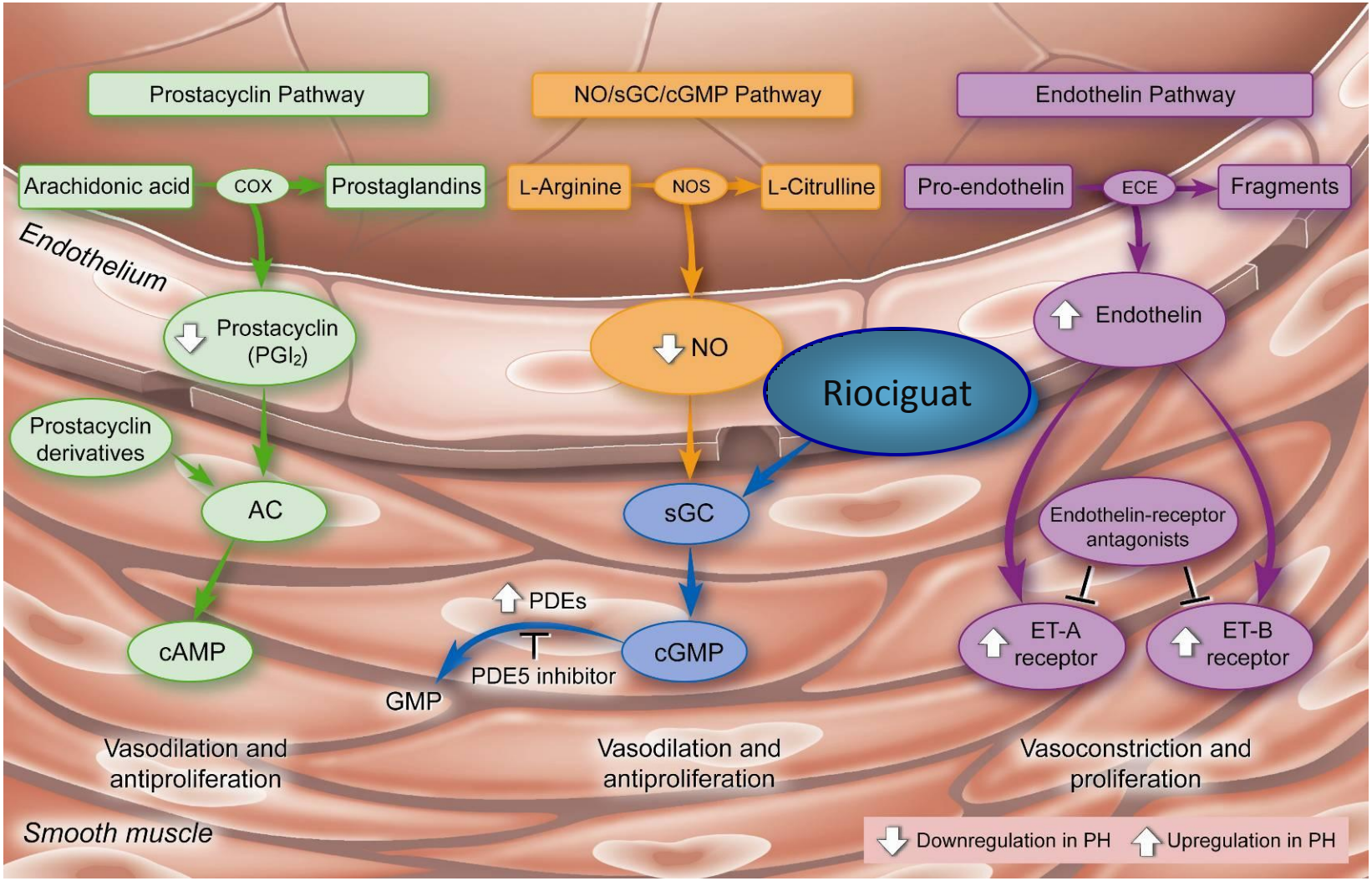


Presented at 5th World Symposium on Pulmonary Hypertension. Nice, France, 27 Feb–1 Mar, 2013.
Simonneau G *et al. J Am Coll Cardiol* 2013;62:D34–41.
* In the US, EU, Canada and Japan

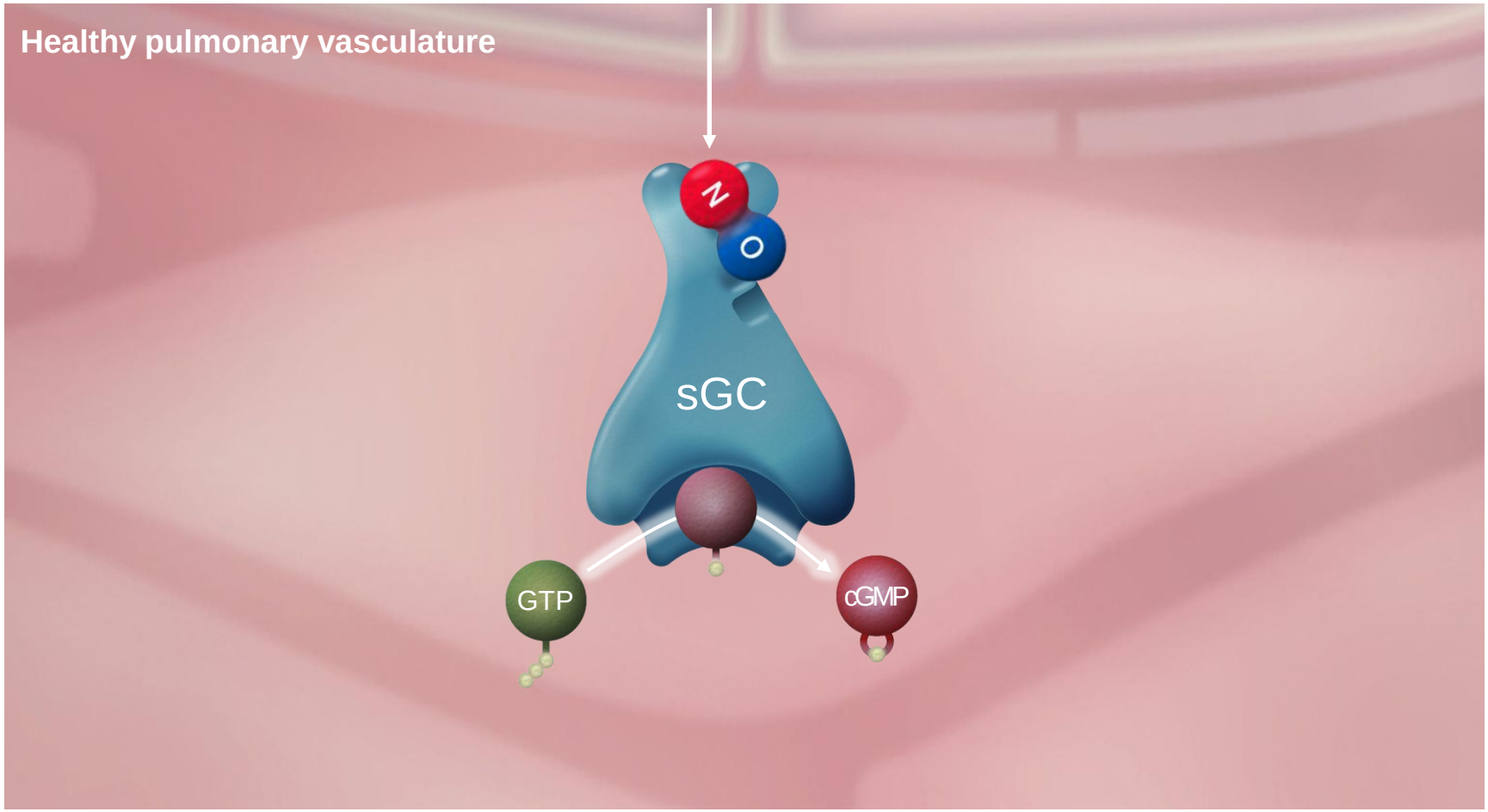
Specific Targets for PAH Treatment



Targets for therapies in PAH



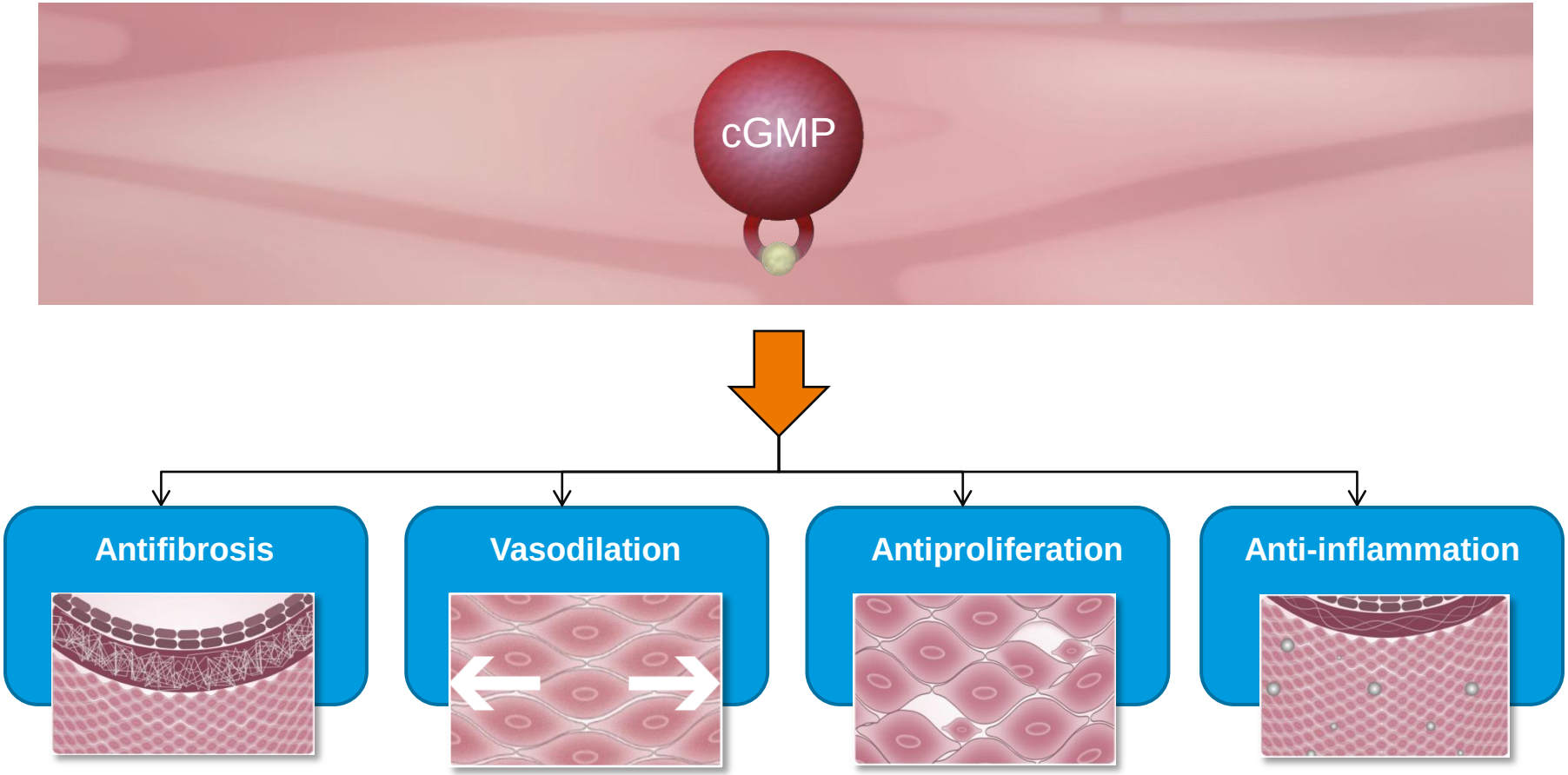
NO binds to sGC, the enzyme that enhances synthesis of the signaling molecule cGMP



cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; sGC, soluble guanylate cyclase.

Stasch J-P & Hobbs AJ. *Handb Exp Pharmacol* 2009;191:277–308. Stasch J-P & Evgenov OV. *Handb Exp Pharmacol* 2013;218:279–313. Follman M *et al. Angew Chem Int Ed Engl* 2013;52:9442–62. Stasch J-P *et al. Circulation* 2011;123:2263–73. Evgenov OV *et al. Nature Rev Drug Disc* 2006;5:755–68.

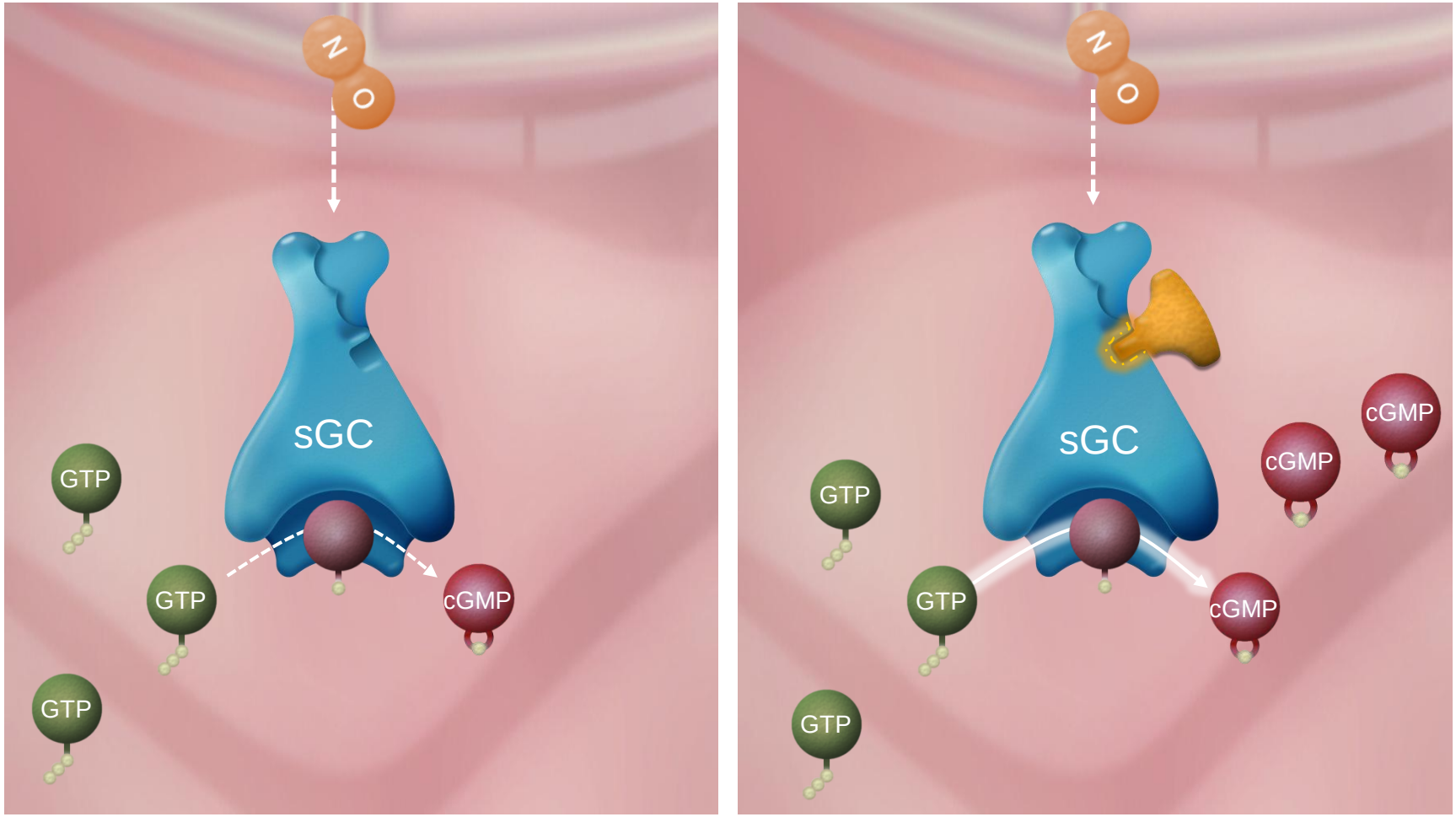
Intracellular cGMP plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis, and inflammation



cGMP, cyclic guanosine monophosphate.

Schlossmann J & Schinner E. *Naunyn Schmiedebergs Arch Pharmacol* 2012;doi:10.1007/s00210-012-0730-6.
Stasch J-P *et al. Circulation* 2011;123:2263–73. Evgenov OV *et al. Nature Rev Drug Disc* 2006;5:755–68.

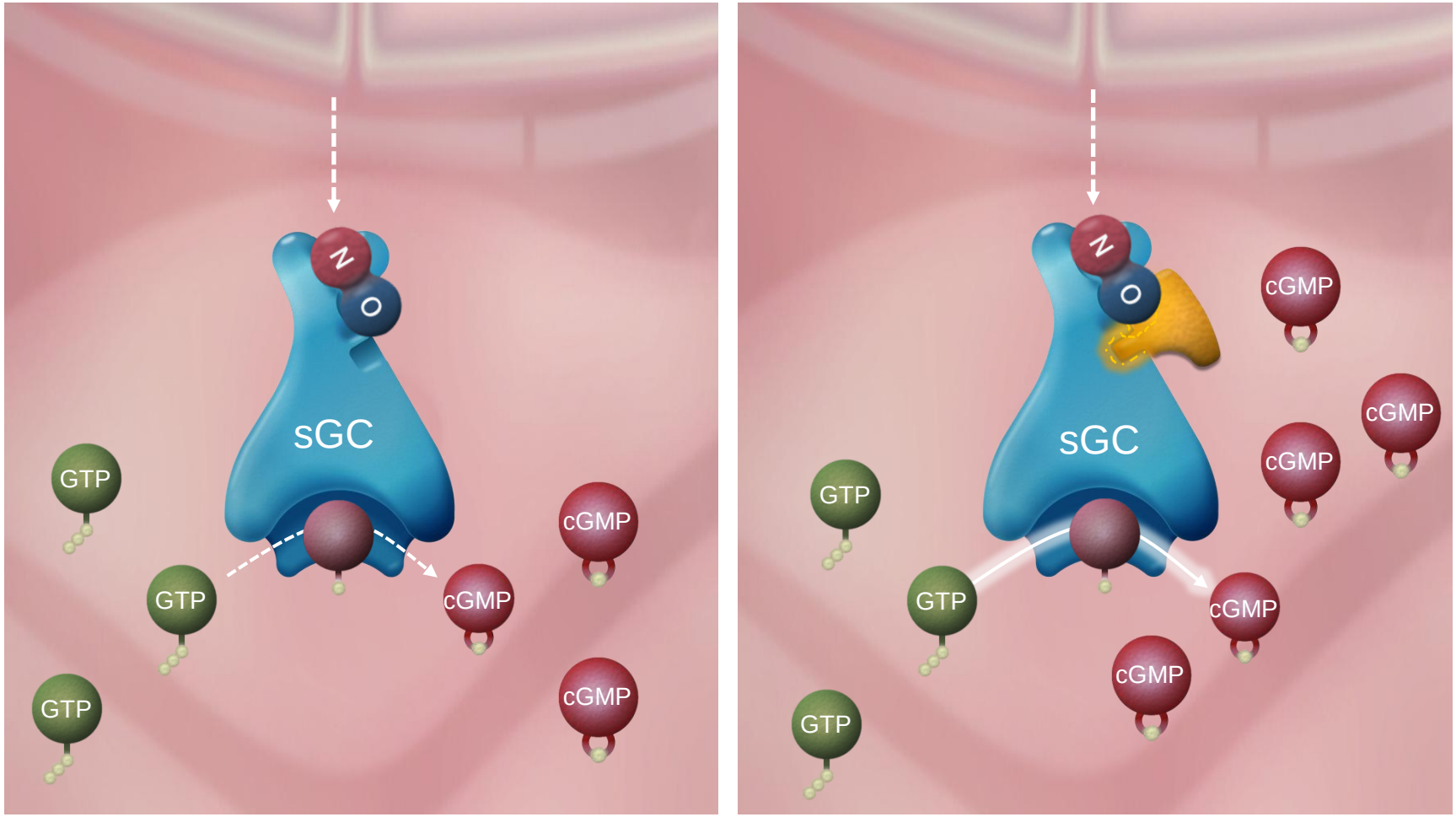
Riociguat directly stimulates sGC via a different binding site, independently of NO



cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; sGC, soluble guanylate cyclase.

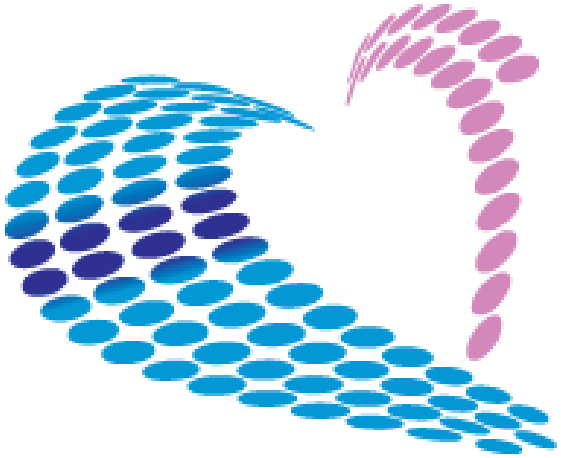
Stasch J-P & Hobbs AJ. *Handb Exp Pharmacol* 2009;191:277–308. Stasch J-P & Evgenov OV. *Handb Exp Pharmacol* 2013;218:279–313. Stasch J-P *et al. Circulation* 2011;123:2263–73. Follman M *et al. Angew Chem Int Ed Engl* 2013;52:9442–62. Ghofrani HA *et al. Future Cardiol* 2010;6:155–66. Schermuly R *et al. Expert Opin Invest Drugs* 2011;20:567–76.

Riociguat also sensitizes sGC to endogenous NO by stabilizing the NO–sGC binding



cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; sGC, soluble guanylate cyclase.

Stasch J-P & Hobbs AJ. *Handb Exp Pharmacol* 2009;191:277–308. Stasch J-P & Evgenov OV. *Handb Exp Pharmacol* 2013;218:279–313. Follman M *et al. Angew Chem Int Ed Engl* 2013;52:9442–62. Stasch J-P *et al. Circulation* 2011;123:2263–73. Ghofrani HA *et al. Future Cardiol* 2010;6:155–66. Schermuly R *et al. Expert Opin Invest Drugs* 2011;20:567–76.



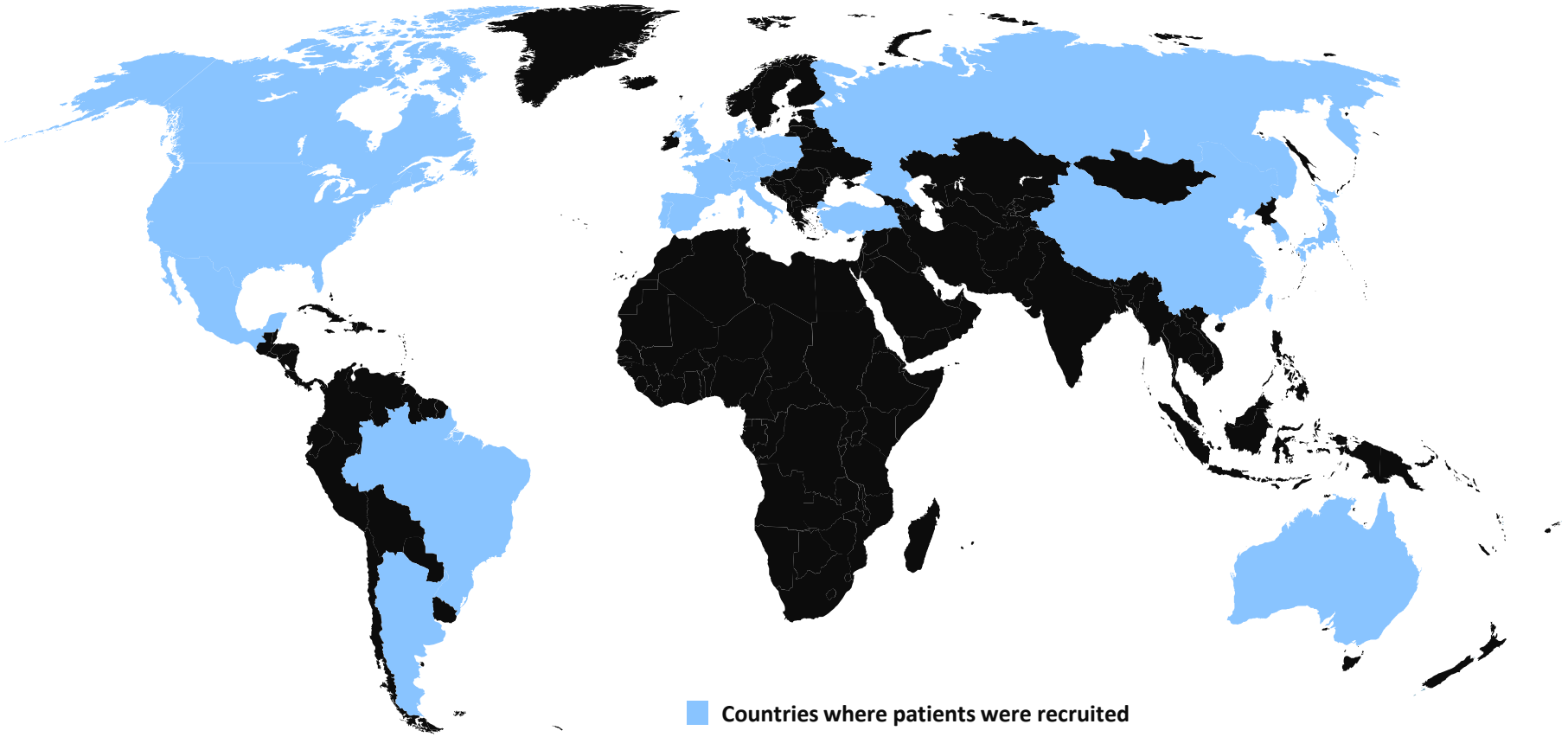
CHEST

Chronic Thrombo**e**mbolic Pulmonary Hypertension sGC-**S**timulator **T**rial

Riociguat

Countries participating in CHEST

CHEST
Chronic Thromboembolic Pulmonary Hypertension sGC-Stimulator Trial
Riociguat



Ghofrani HA, *et al.* N Engl J Med 2013;369:319-29

Objectives and design

Objectives

- To evaluate the efficacy of riociguat in the treatment of patients with inoperable CTEPH or persistent/recurrent PH after surgical treatment

Design

- Multicenter, double-blind, randomized, placebo-controlled study (CHEST-1)
- 89 centers across 26 countries in Europe, South America, North America, Asia, and Australia
- Patients completing CHEST-1 were given the option to enroll in a long-term extension study (CHEST-2)

Outcomes

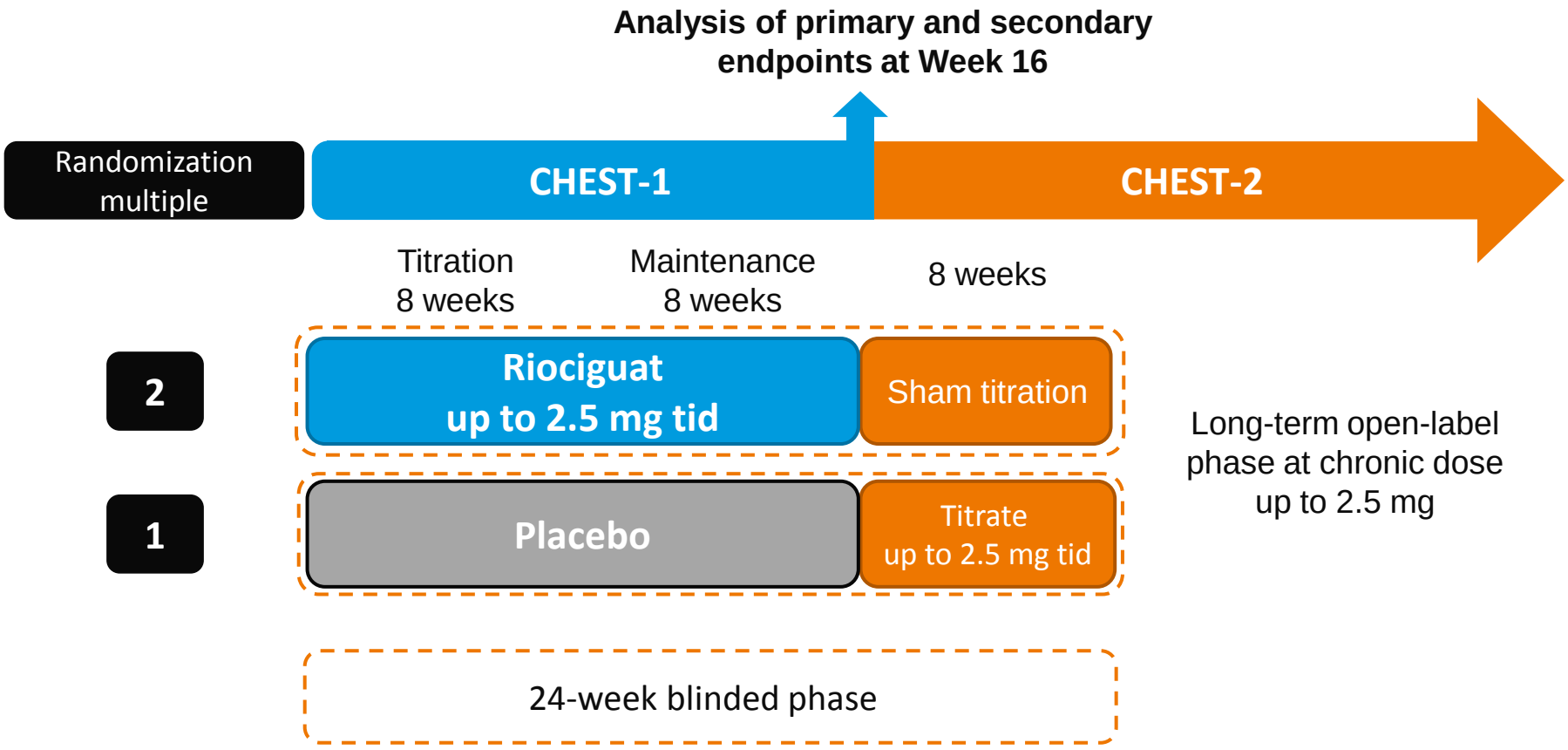
- Primary outcome
  - Change in 6MWD from baseline at Week 16
- Secondary outcomes
  - Pulmonary vascular resistance
  - NT-proBNP
  - WHO functional class
  - Time to clinical worsening
  - Borg dyspnea score
  - Quality of life assessments
  - Safety variables

6MWD, 6-minute walking distance; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; WHO, World Health Organization.

Ghofrani HA, *et al.* N Engl J Med 2013;369:319-29

Study design

CHEST
Chronic Thromboembolic Pulmonary Hypertension sGC-Stimulator Trial
Riociguat

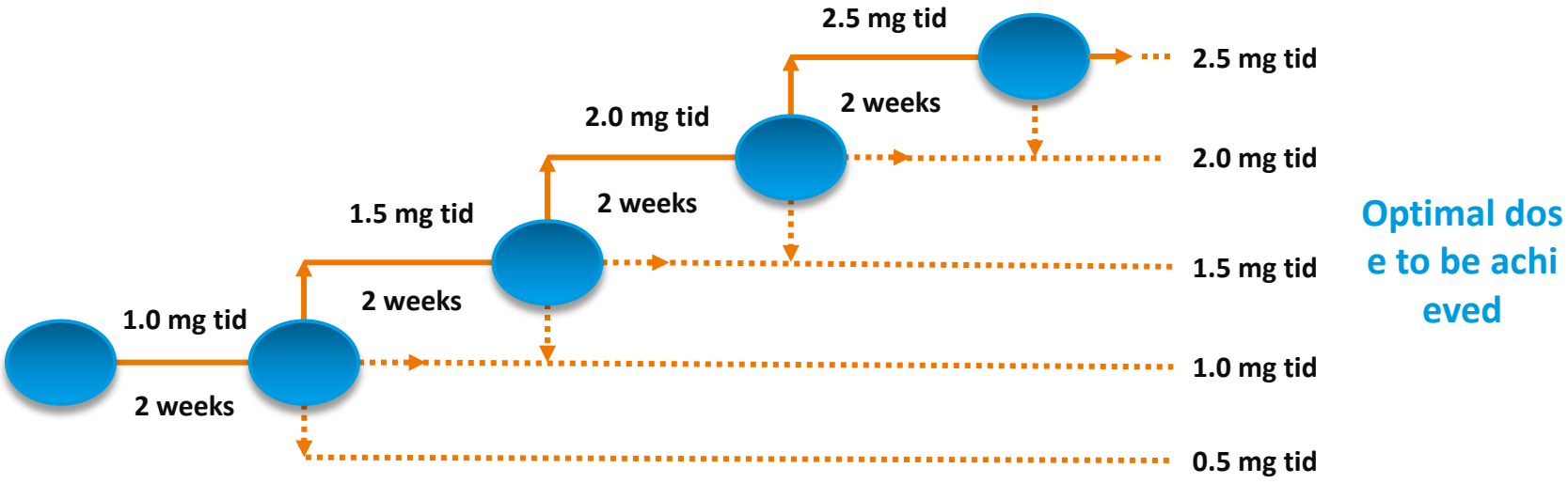


tid, three times daily.

Ghofrani HA, *et al.* N Engl J Med 2013;369:319-29

CHEST titration strategy

- Dose was titrated every 2 weeks according to the peripheral systolic blood pressure measured at trough before intake of the morning dose
  - ≥95 mmHg: increased dose
  - 90–94 mmHg: maintained dose
  - <90 mmHg without symptoms of hypotension: reduced dose
  - <90 mmHg with symptoms of hypotension: treatment discontinued for 24 hours and restarted at a 0.5 mg lower dose



Adjudication of inoperability (further information)

CHEST
Chronic Thromboembolic Pulmonary Hypertension sGC-Stimulator Trial
Riociguat

- CTEPH diagnosis made using ≥2 imaging methods:
  - V/Q scan, pulmonary angiogram (preferred), 64-slice spiral-CT, or MRI angiogram
  - Operability systematically assessed during pretreatment phase in accordance with specified criteria by either an experienced surgeon or central adjudication committee composed of experienced surgeons
    - Assessment made by 3 (of <6) committee members or a preapproved regional expert endarterectomy center
  - Inoperability defined as technical inoperability based on surgical accessibility of the organized thrombi and concordance between surgically accessible vascular obstruction and PVR
  - Patients were eligible if ≥1 of the 3 adjudicators assessed the case as inoperable

PVR, pulmonary vascular resistance; V/Q, ventilation/perfusion.

Ghofrani HA, *et al.* N Engl J Med 2013;369:319-29

CHEST baseline characteristics balanced across randomized groups

CHEST
Chronic Thromboembolic Pulmonary Hypertension sGC-Stimulator Trial
Riociguat

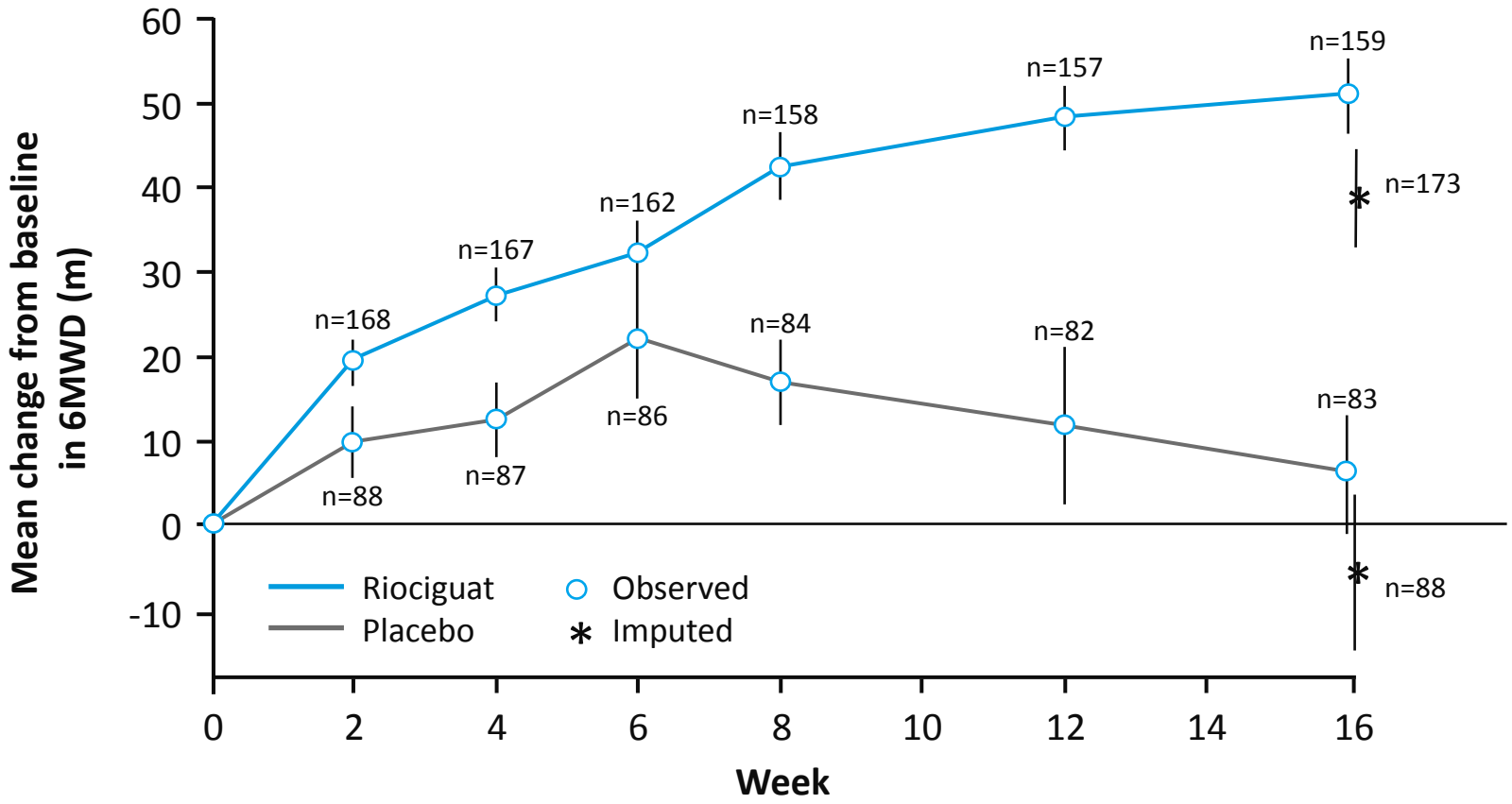
Characteristic	Riociguat (n=173)	Placebo (n=88)
Mean age, years	59	59
Female, %	68	61
Mean PVR[a], dyn·s·cm^{-5}	796	815
mPAP[a], mmHg	45.0	44.0
Mean 6MWD, m	342	356
WHO FC I/II/III/IV, %	2/32/62/5	0/28/68/2[b]
Inoperable/persistent, %	70/30	77/23

[a]All PVRs and mPAPs measured. [b]One patient with missing data at baseline.
6MWD, 6-minute walking distance; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; WHO FC, World Health Organization functional class.

Ghofrani HA, *et al.* N Engl J Med 2013;369:319-29

Primary endpoint (6MWD) achieved

Placebo-corrected treatment effect = **46 m** (95% CI: 25–67 m; *p*<0.0001)



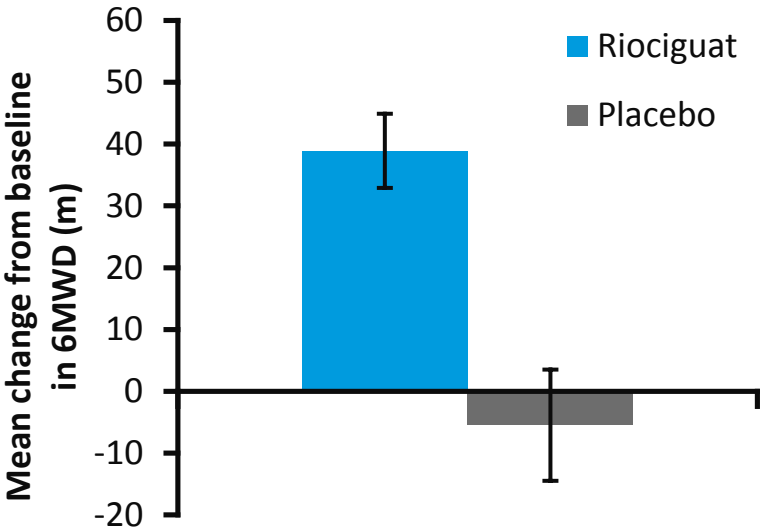
6MWD, 6-minute walking distance.
Last visit = last observed value (not including follow-up) for patients who completed the study or withdrew, except imputed worst value (zero) in case of death or clinical worsening without a termination visit or a measurement at that termination visit.

Ghofrani HA, *et al.* N Engl J Med 2013;369:319-29

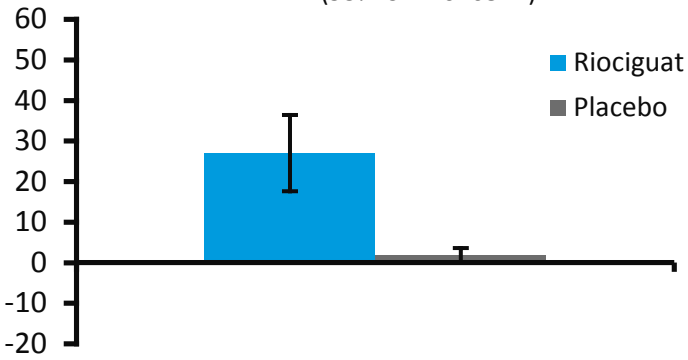
6MWD: Consistent improvement seen in inoperable and persistent/recurrent patients

Primary endpoint: entire population (n=173/88)

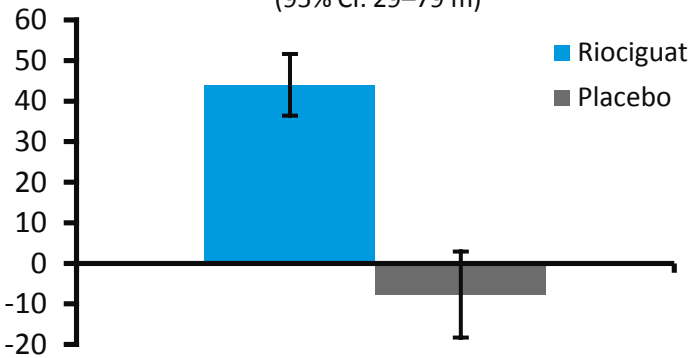
+46 m
***p*<0.0001**
(95% CI: 25–67 m)



Population with persistent/ recurrent PH after PEA (n=52/20)
+27 m (95% CI: -10–63 m)



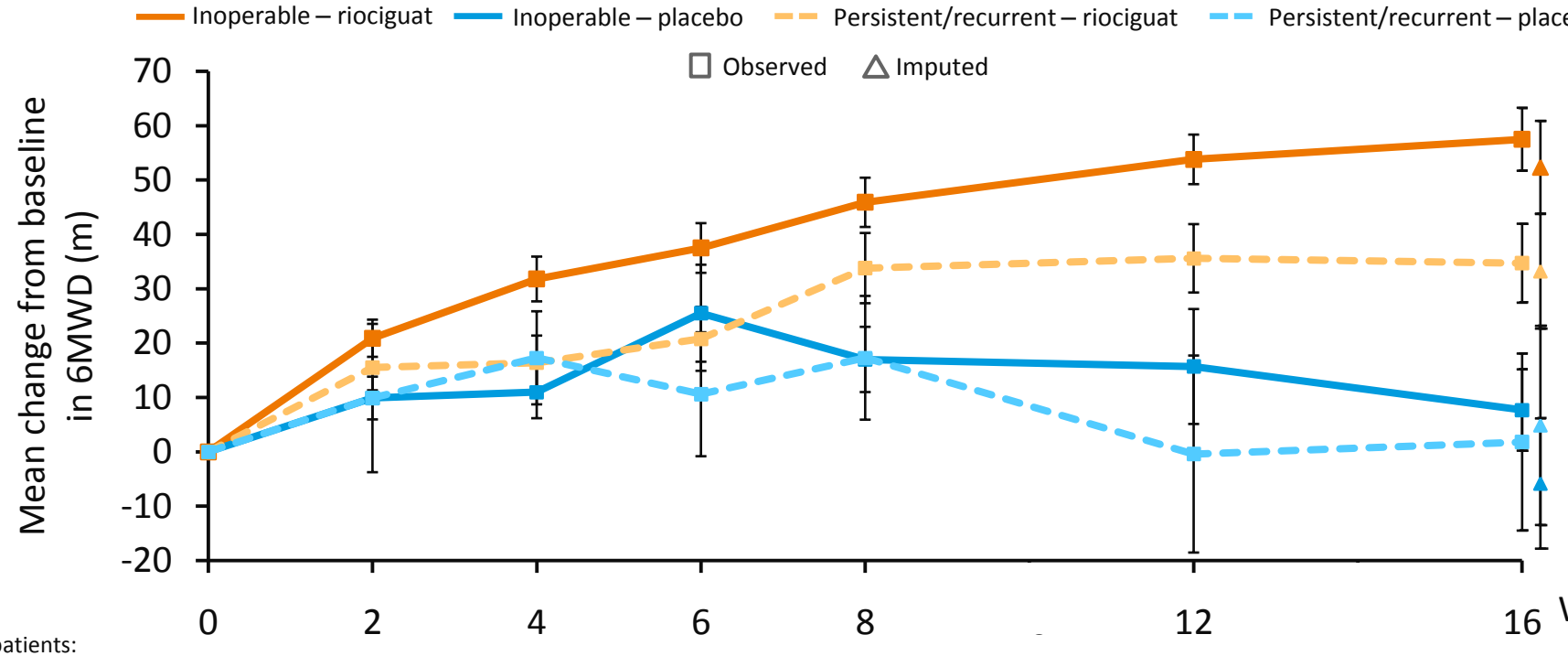
Inoperable population (n=121/68)
+54 m
(95% CI: 29–79 m)



6MWD, 6-minute walking distance; PEA, pulmonary endarterectomy.

Ghofrani HA, *et al.* N Engl J Med 2013;369:319-29

Riociguat improved 6MWD in both inoperable and persistent/recurrent CTEPH patients



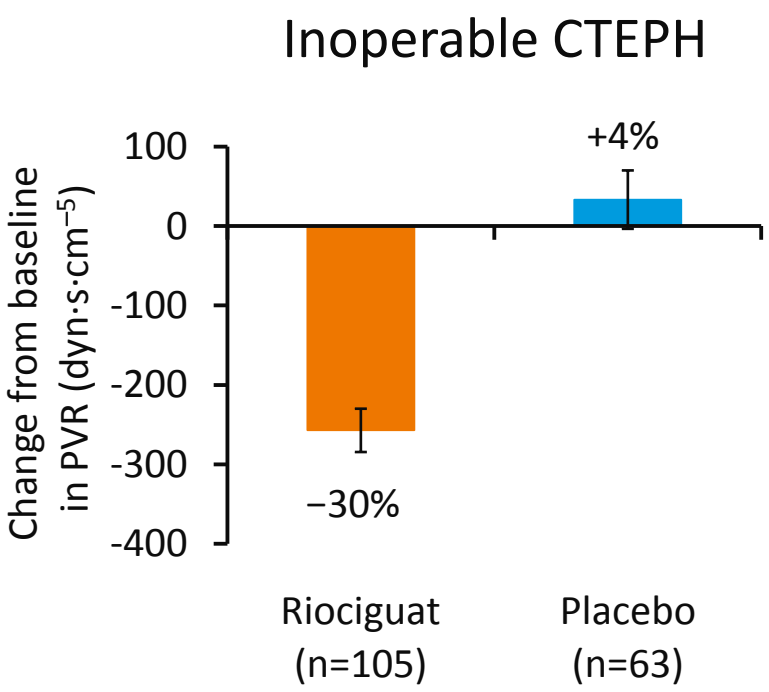
No. of patients:							
Inoperable – riociguat	121	118	117	113	112	110	111
Inoperable – placebo	68	68	67	66	64	63	63
Persistent – riociguat	52	50	50	49	46	47	48
Persistent – placebo	20	20	20	20	20	19	20

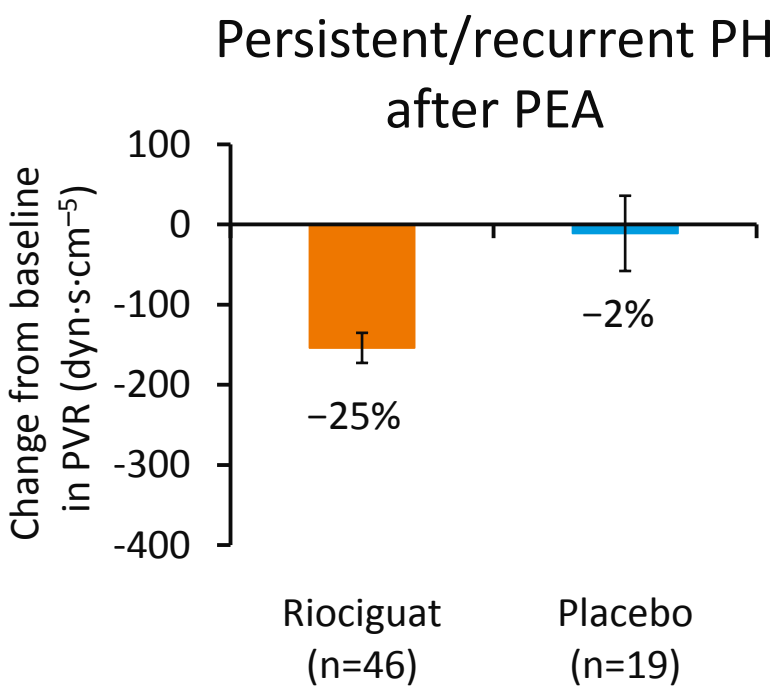
- LS mean difference in overall population: +46 m (95% CI 25 to 67 m; p<0.0001)
  - Inoperable: +54 m (95% CI 29 to 78 m); persistent/recurrent: +26 m (95% CI –16 to 68 m); p-value for interaction = 0.26

Error bars represent ±SEM; LS mean treatment effect taken from ANCOVA; missing values, where the patient withdrew or died, were imputed at Week 16
ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; SEM, standard error of the mean

Mayer E *et al. Eur Respir J* 2013; 42: Suppl 57 (Abstract 1781). Presented at European Respiratory Society Annual Congress, 7-11 September, 2013, Barcelona, Spain.

Riociguat reduces **PVR** across both the inoperable and persistent/recurrent subgroups



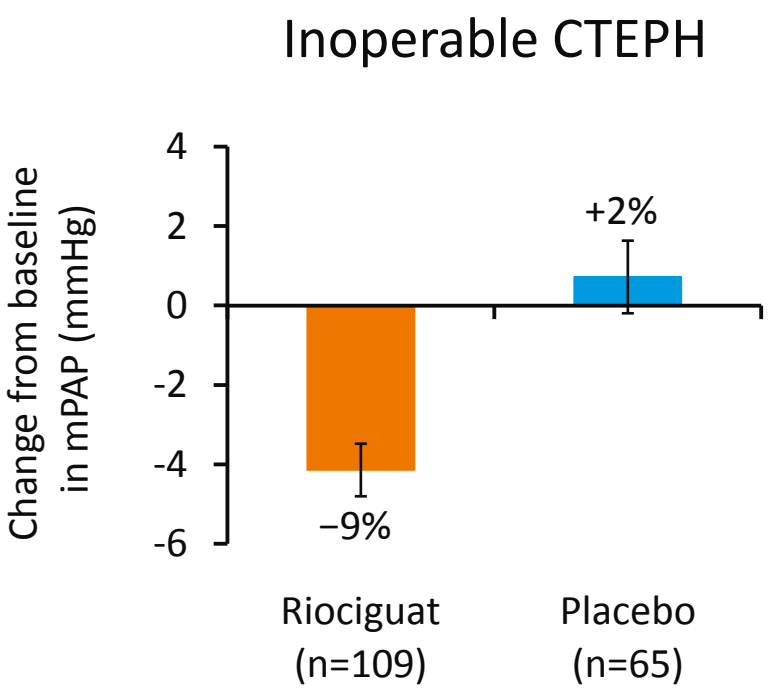


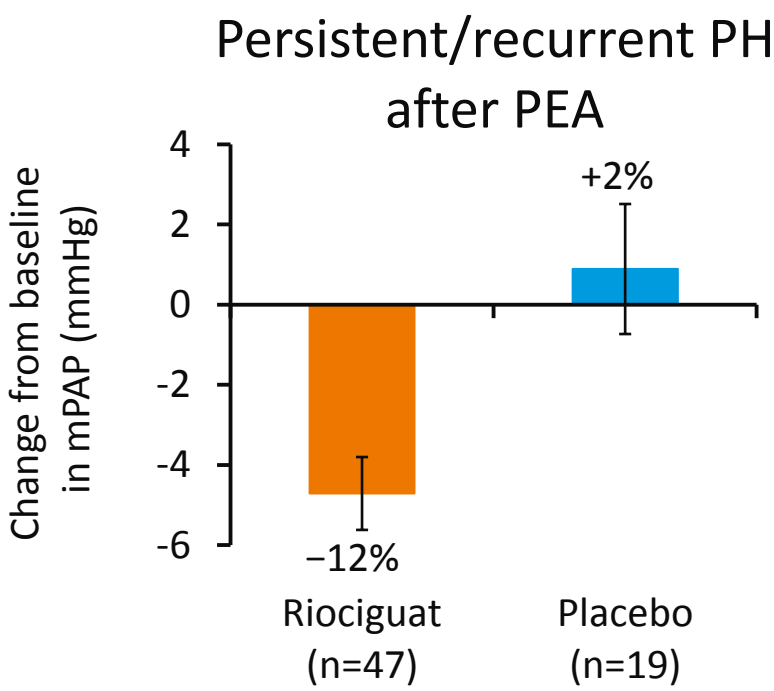
LS mean difference in overall population: −246 dyn·s·cm^{-5} (95% CI: −303 to −190; p<0.0001)

Bars represent mean change from baseline (±SEM)
LS mean treatment effect taken from ANCOVA
SEM, standard error of the mean

Jansa P *et al. Eur Heart J* 2013;34 (suppl 1): P1066. Presented at the European Society of Cardiology Annual Congress, 31 Aug-4 Sept, 2013, Amsterdam, Netherlands.

Riociguat reduces **mPAP** across both the inoperable and persistent/recurrent subgroups



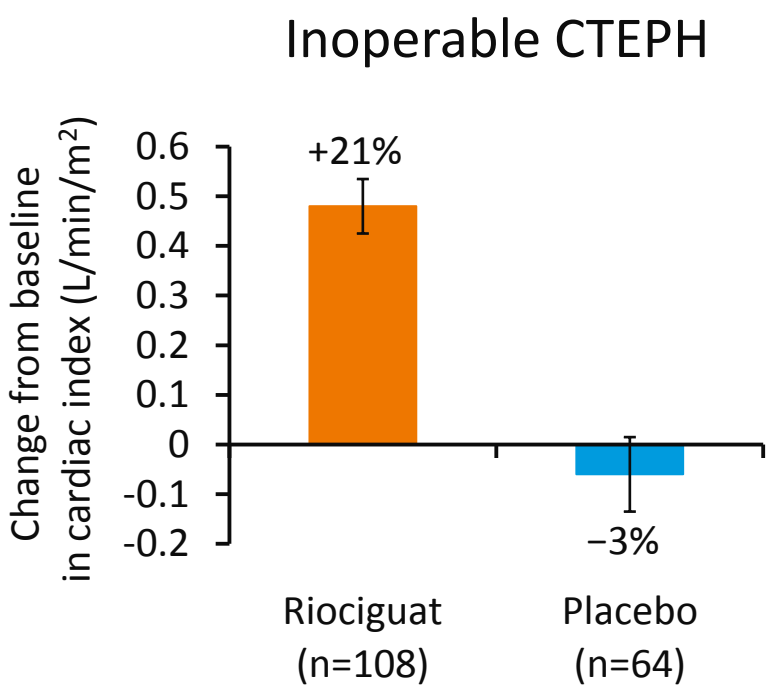


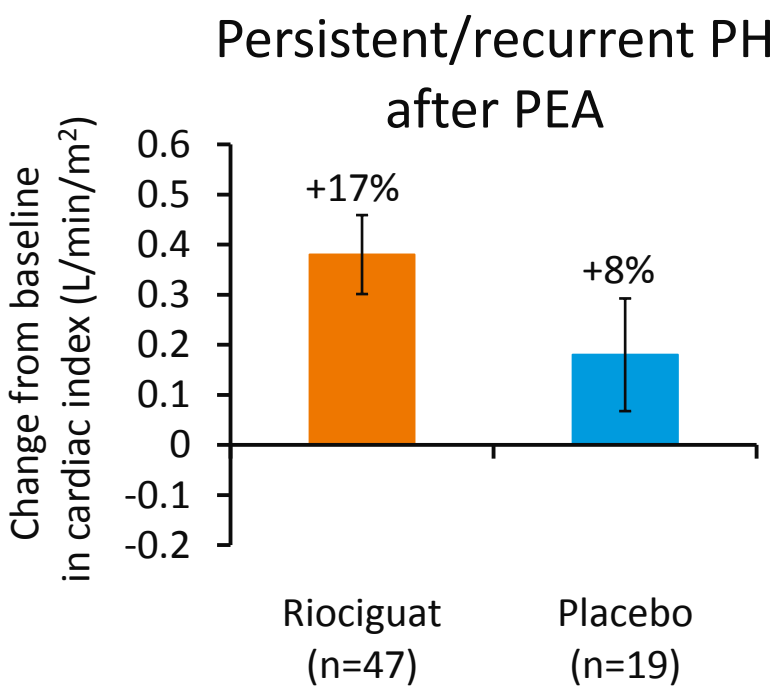
LS mean difference in overall population: −5 mmHg (95% CI: −7 to −3; p<0.0001)

Bars represent mean change from baseline (±SEM)
LS mean treatment effect taken from ANCOVA

Jansa P *et al. Eur Heart J* 2013;34 (suppl 1): P1066. Presented at the European Society of Cardiology Annual Congress, 31 Aug-4 Sept, 2013, Amsterdam, Netherlands.

Riociguat increases **cardiac index** across both the inoperable and persistent/recurrent subgroups





LS mean difference in overall population: +0.5 L/min/m^2 (95% CI: 0.3 to 0.6; p<0.0001)

Bars represent mean change from baseline (±SEM)
LS mean treatment effect taken from ANCOVA

Jansa P *et al. Eur Heart J* 2013;34 (suppl 1): P1066. Presented at the European Society of Cardiology Annual Congress, 31 Aug-4 Sept, 2013, Amsterdam, Netherlands.

Meaningful improvement of cardio-pulmonary hemodynamics and biomarkers

Parameter	Riociguat		Placebo		Placebo-corrected LS-mean difference	Riociguat vs placebo; p value
	Baseline	Mean change from baseline	Baseline	Mean change from baseline		
PVR, dyn·s·cm^{-5}	791	−226 (−29%)	779	+23 (+3%)	−246	<0.0001
mPAP, mmHg	45.2	−4.3 (−10%)	44.4	+0.8 (+2%)	−5.0	<0.0001
CI, L/min/m^2	2.26	+0.45 (+20%)	2.19	−0.01 (0%)	0.47	<0.0001
NT-proBNP, ng/L	1508	−291 (−19%)	1706	+76 (+4%)	−444	<0.0001

CI, cardiac index; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PVR, pulmonary vascular resistance.

Ghofrani HA, *et al.* N Engl J Med 2013;369:319-29

Improvement of WHO Functional Class and reduced rate of clinical worsening

Significant WHO Functional Class improvement (*p*=0.0026)

	Riociguat	Placebo
Improved, %	33	15
Stable, %	62	78
Deteriorated, %	5	7

Clinical worsening

	Riociguat	Placebo
Number of patients with clinical worsening, n (%)	4 (2.3)	5 (5.7)
Hospitalization due to PH	0	1 (1.1)
Start of new PH treatment	2 (1.2)	1 (1.1)
Decrease in 6MWD due to PH	1 (0.6)	2 (2.3)
Persistent worsening of FC due to PH	0	1 (1.1)
Death	2 (1.2)	3 (3.4)

6MWD, 6-minute walking distance; FC, functional class.

Ghofrani HA, *et al.* N Engl J Med 2013;369:319-29

Good tolerability and safety profile

Adverse event	Riociguat (n=173)	Placebo (n=88)
Ten most frequently reported AEs, n (%)		
Headache	43 (25)	12 (14)
Dizziness	39 (23)	11 (13)
Dyspepsia	31 (18)	7 (8)
Peripheral edema	27 (16)	18 (20)
Nasopharyngitis	26 (15)	8 (9)
Nausea	19 (11)	7 (8)
Vomiting	17 (10)	3 (3)
Diarrhea	17 (10)	4 (5)
Hypotension	16 (9)	3 (3)
Upper respiratory tract Infection	10 (6)	4 (5)

AE, adverse event.

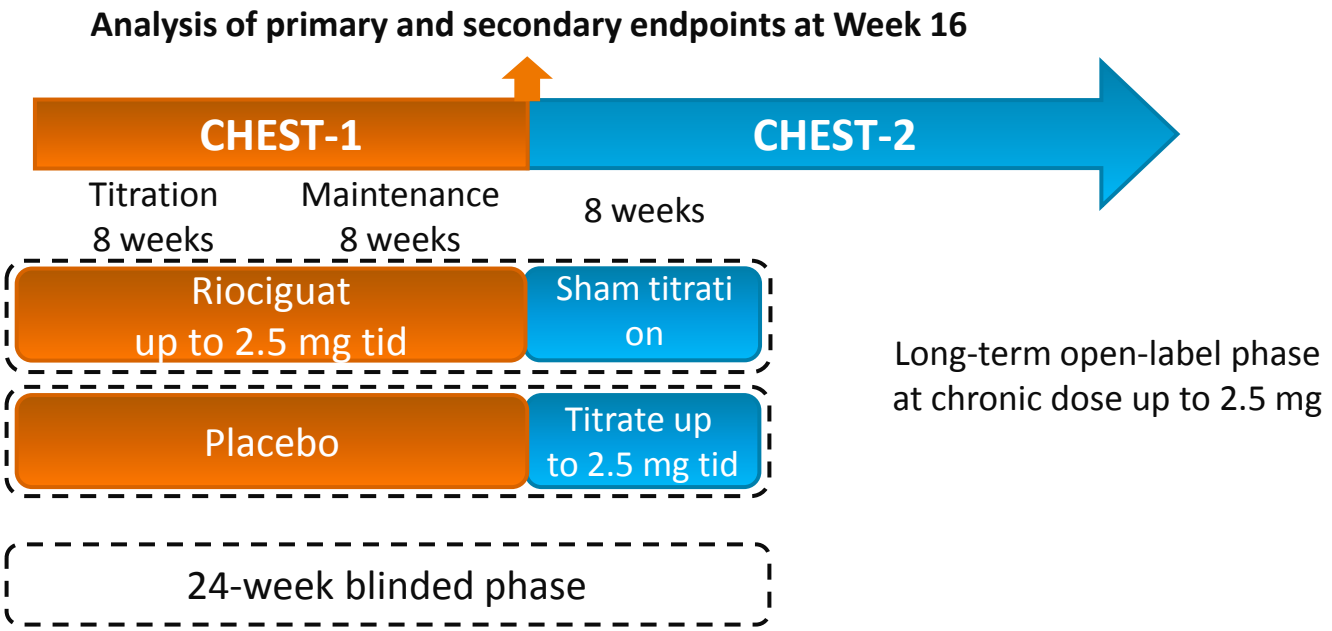
Ghofrani HA, *et al.* N Engl J Med 2013;369:319-29

CHEST-1 : Conclusions

- Riociguat is the first therapy to significantly improve **both 6MWD and hemodynamics in patients with inoperable CTEPH and persistent/recurrent PH after PEA**
- Riociguat improved a range of **hemodynamic parameters, including PVR, mPAP, and cardiac index**
- Improvements in hemodynamics were seen in both the inoperable and persistent/recurrent subgroups, although the improvements were somewhat greater in the inoperable subgroup

Jansa P *et al. Eur Heart J* 2013;34 (suppl 1): P1066. Presented at the European Society of Cardiology Annual Congress, 31 Aug-4 Sept, 2013, Amsterdam, Netherlands.

CHEST-2 study design

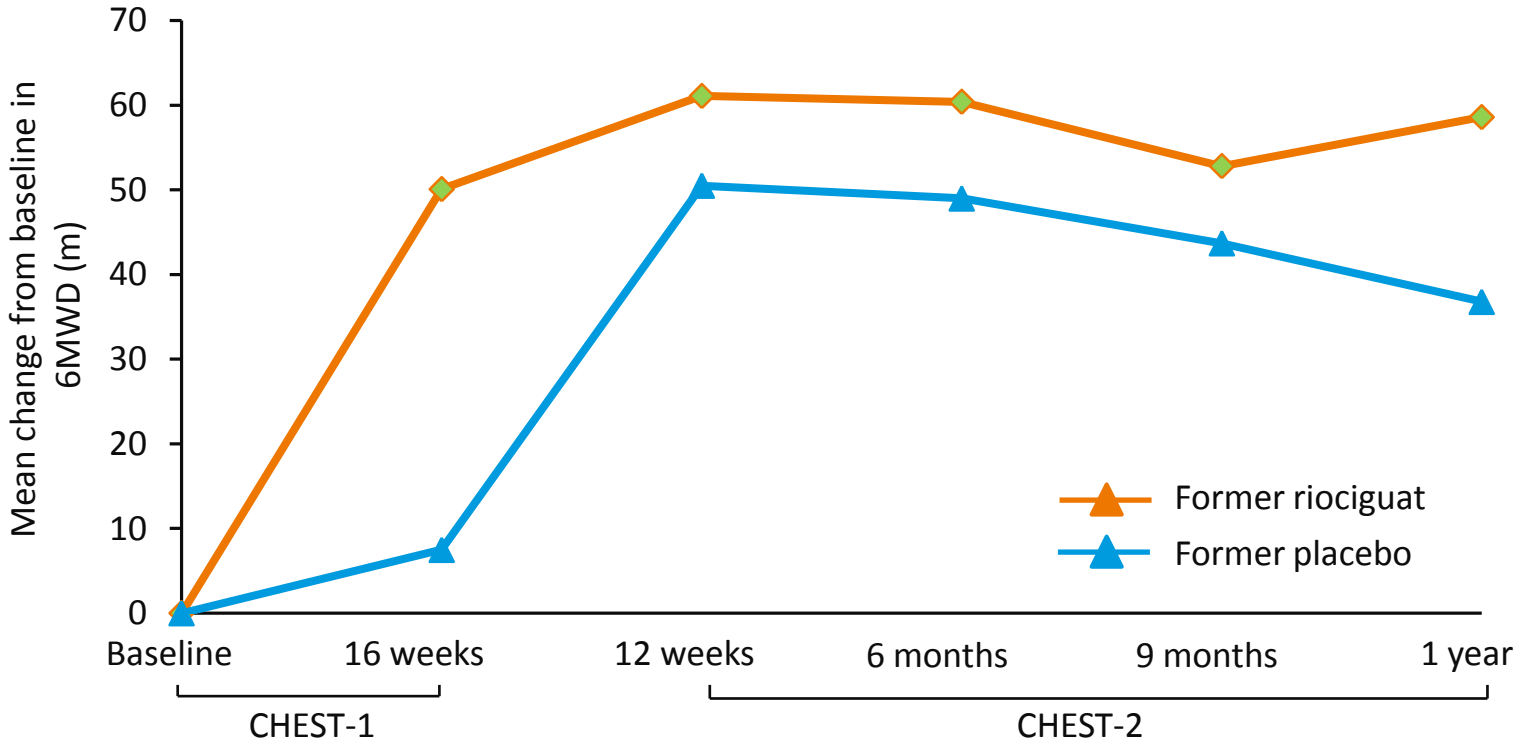


- Of the 261 patients in CHEST-1, 243 completed CHEST-1 and 237 entered CHEST-2
- At the cut-off, mean treatment duration was 582 days, median treatment duration was 526 days, and total riociguat exposure was 378 patient-years

tid, three times daily

Simonneau G *et al. Chest* 2013;144:1023A. Presented at the CHEST Annual Congress, 26-31 October, 2013, Chicago, USA.

Effects of riociguat on 6MWD in CHEST-2 (observed data)

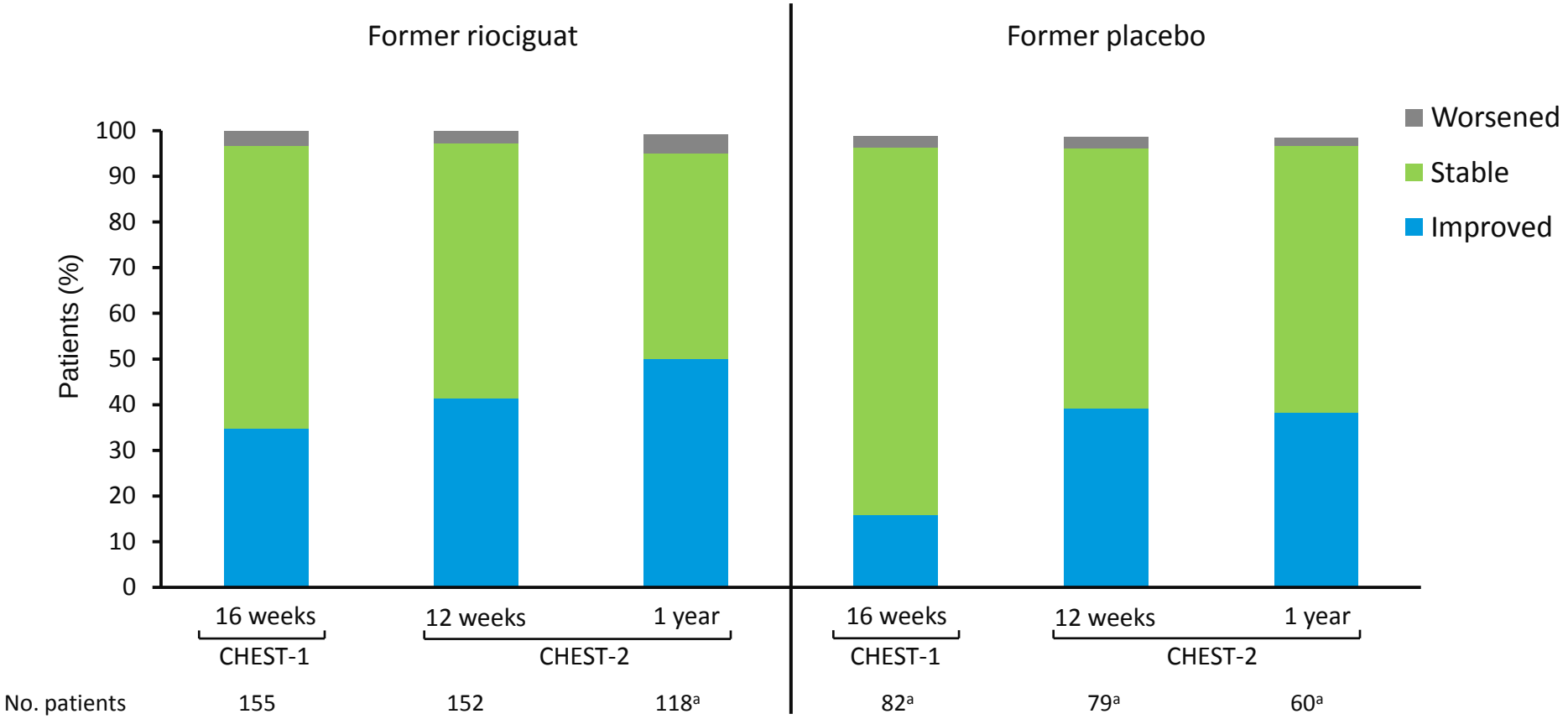


Absolute values						
Former riociguat	345	396	406	406	400	411
Former placebo	360	368	414	411	408	405
No. patients						
Former riociguat	155	154	145	143	143	114
Former placebo	82	81	75	75	72	58

Data shown are observed values

Simonneau G, et al. Am J Respir Crit Care Med 2013;187:A5365

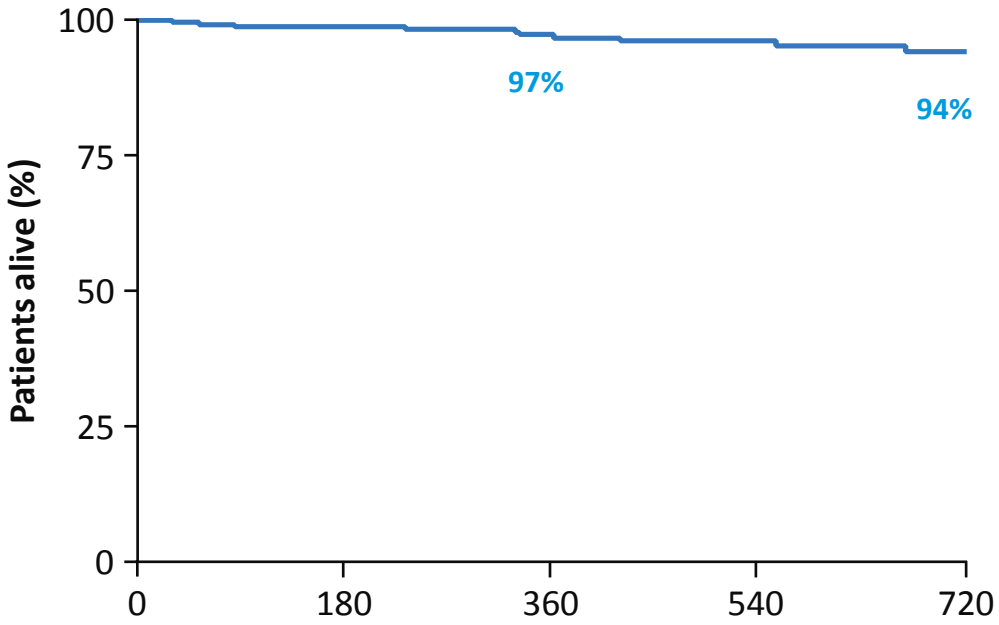
Effects of riociguat on WHO FC in CHEST-2



[a]Data missing for one patient
Data shown are observed values
WHO FC : World Health Organization Functional Cass

Simonneau G, et al. Am J Respir Crit Care Med 2013;187:A5365

CHEST-2 overall survival



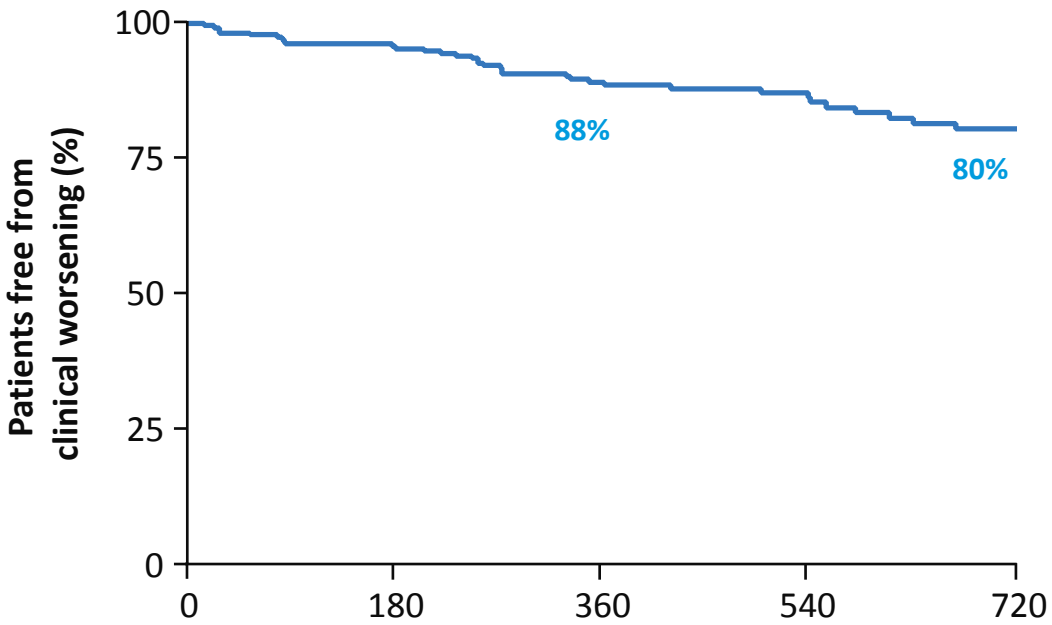
- The survival rate at 1 year was 97% (mean treatment duration was 582 days)
- This is based on 70% of patients being alive at 1 year, 3% having died, 24% having not yet reached 1 year and 4% having dropped out of the study[a]

	Time from start of extension study treatment (days)				
No. patients alive at time point	237	223	166	105	74
No. deaths	0	3	6	8	10

[a]Numbers do not add up to 100% due to rounding

Simonneau G, et al. Am J Respir Crit Care Med 2013;187:A5365

CHEST-2 clinical worsening



The rate for clinical worsening-free survival at 1 year was 90% (mean treatment duration 582 days)

	Time from start of extension study treatment (days)				
No. patients that reached time point without clinical worsening	237	218	155	96	65
No. patients with clinical worsening	0	10	24	28	34

Simonneau G, et al. Am J Respir Crit Care Med 2013;187:A5365

Clinical worsening events during CHEST-2

Clinical worsening event, n (%)	Former riociguat (n=155)	Former placebo (n=82)	Total (n=237)
Total	26 (17)	12 (15)	38 (16)
Pulmonary endarterectomy	1 (<1%)	1 (1)	2 (1)
Hospitalization due to PH	5 (3)	1 (1)	6 (3)
Start of new PH treatment	12 (8)	7 (9)	19 (8)
Decrease in 6MWD due to PH	2 (1)	1 (1)	3 (1)
Persistent worsening of WHO FC due to PH	5 (3)	1 (1)	6 (3)
Death	9 (6)	4 (5)	13 (5)

CHEST-2 data cut-off March 2013

Simonneau G, et al. Am J Respir Crit Care Med 2013;187:A5365

Riociguat was well tolerated with a good long-term safety profile

AE, n (%)	Total (n=237)
Number of patients with at least one study drug-related AE	109 (46)
Study drug-related AE in ≥5% of patients	
Dizziness	24 (10)
Dyspepsia	19 (8)
Syncope	17 (7)
Hypotension[a]	11 (5)

[a]Defined by systolic blood pressure <90 mmHg
CHEST-2 data cut-off March 2013; mean treatment duration was 582 days

Simonneau G, et al. Am J Respir Crit Care Med 2013;187:A5365

CHEST-1 and -2 conclusions:

- **Riociguat is the first drug to consistently demonstrate clinical efficacy in a placebo-controlled study in CTEPH**
- **In patients with inoperable CTEPH or persistent/recurrent PH after PEA, significant improvements :**
  - **primary endpoint (6MWD after 16 weeks in patients with CTEPH)**
  - **Across clinically meaningful secondary endpoints, including PVR, NT-proBNP, and WHO FC**
- **Riociguat was well tolerated and the long-term data confirm riociguat's safety profile**
- **The 1-year data of CHEST-2 demonstrate sustained benefits in 6MWD and WHO functional class**

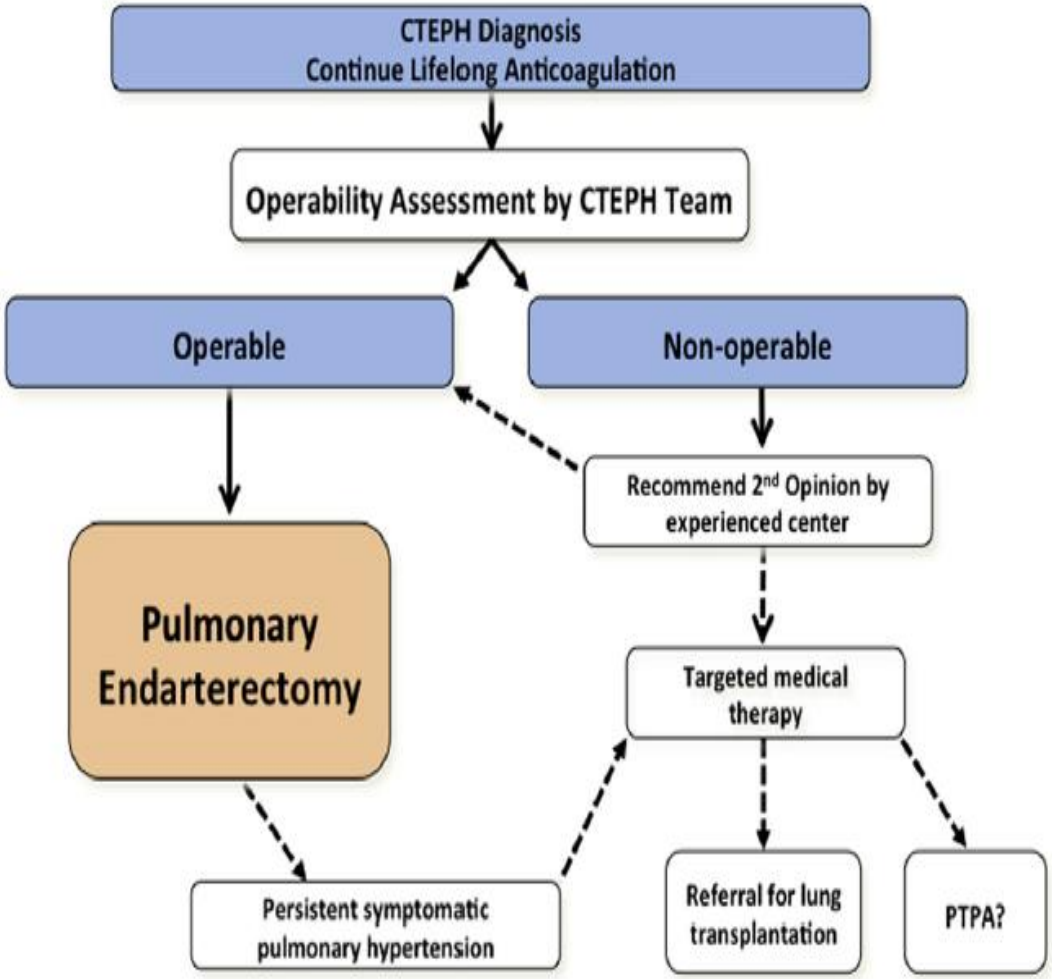
6MWD, 6-minute walking distance; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PEA, pulmonary endaterectomy; PVR, pulmonary vascular resistance; WHO FC, World Health Organization functional class.

Ghofrani HA *et al. N Engl J Med* 2013. *In Press.*
Simonneau G, *et al*. Poster presented at the 5th World Symposium on PH, Nice, France, 28 Feb–1 Mar, 2013.

Inclusion Criteria of CHEST study

- **To evaluate the efficacy of riociguat in the treatment of patients with inoperable CTEPH or persistent/recurrent PH after surgical treatment**

CTEPH: Treatment Algorithm



(J Am Coll Cardiol 2013;62:D92–9)

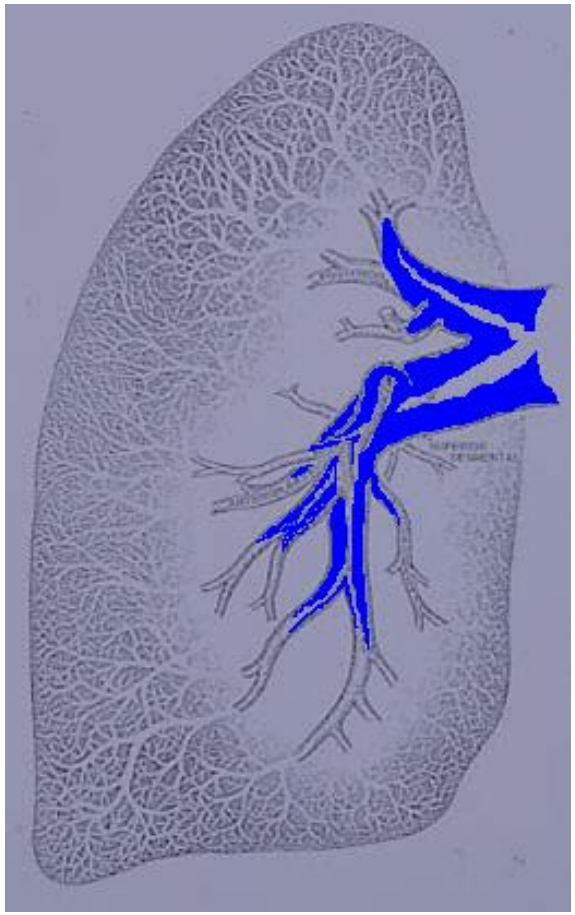
CTEPH: Treatment Algorithm

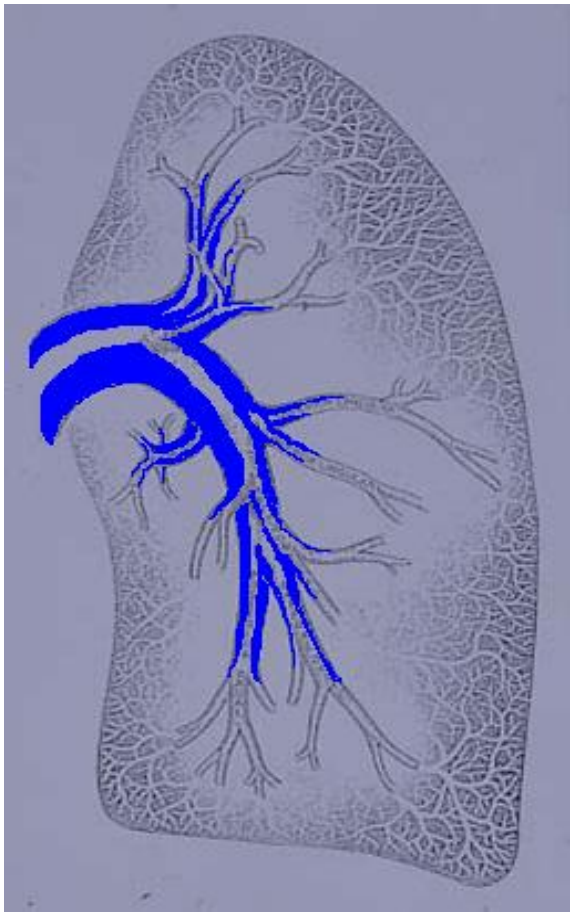
- All persons in whom PH is suspected should receive a ventilation/perfusion scan to screen for CTEPH.
- All persons diagnosed with CTEPH should be assessed for potentially curative PTE surgery by an expert center.

(J Am Coll Cardiol 2013;62:D92–9)

ANATOMY

PROXIMAL LESIONS

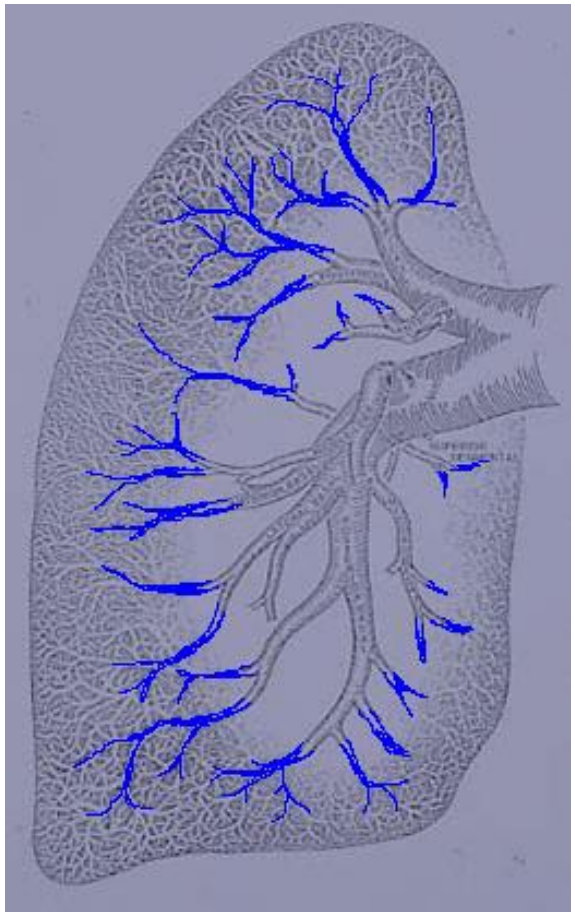


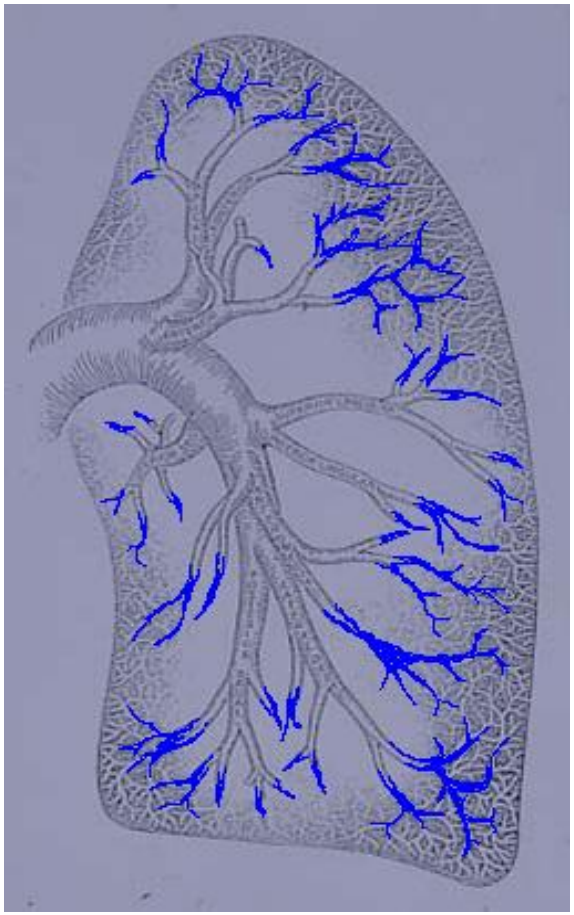


From Dr. AM D'Armini's slideshare\
(University of Pavia School of Medicine)

ANATOMY

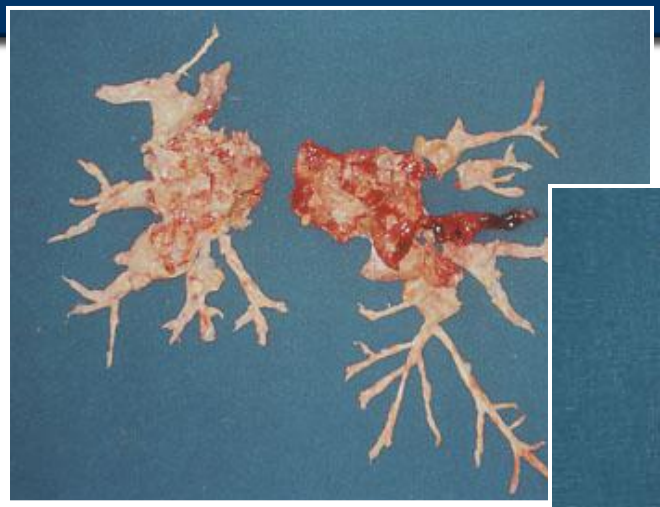
DISTAL LESIONS





From Dr. AM D'Armini's slideshare\
(University of Pavia School of Medicine)

JAMIESON TYPE I vs. TYPE II vs. TYPE III

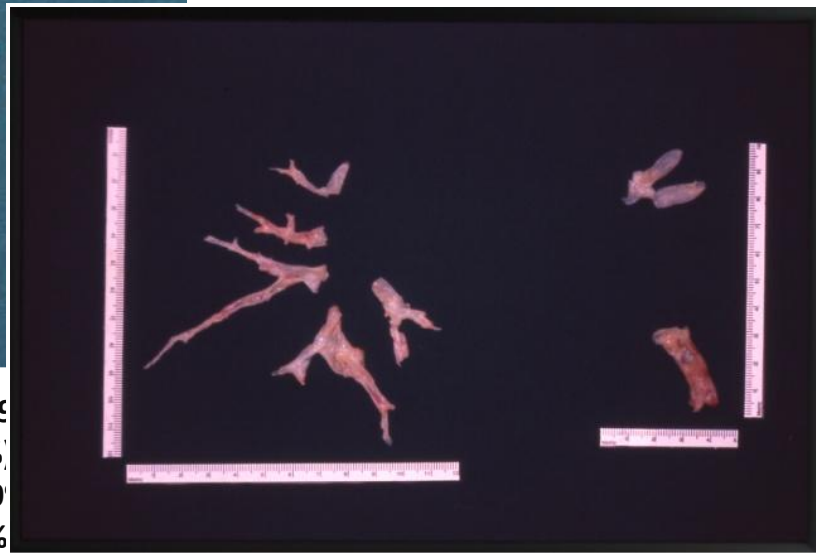


L.M.E.L. - 65 yrs M - Oct 2004 - PEA #1

mPAP	39	→	19	(-51%)
CO	4.4	→	5.4	(+23%)
PVR	665	→	222	(-66%)

G.A.C. - 52 yrs F - Jul 2003 - PEA #9

mPAP	48	→	27	(-44%)
CO	2.1	→	4.2	(+100
PVR	1638	→	381	(-77%



B.A. - 43 yrs F - May 2009 - PEA #233

mPAP	49	→	19	(-61%)
CO	3.3	→	5.0	(+52%)
PVR	1067	→	224	(-79%)

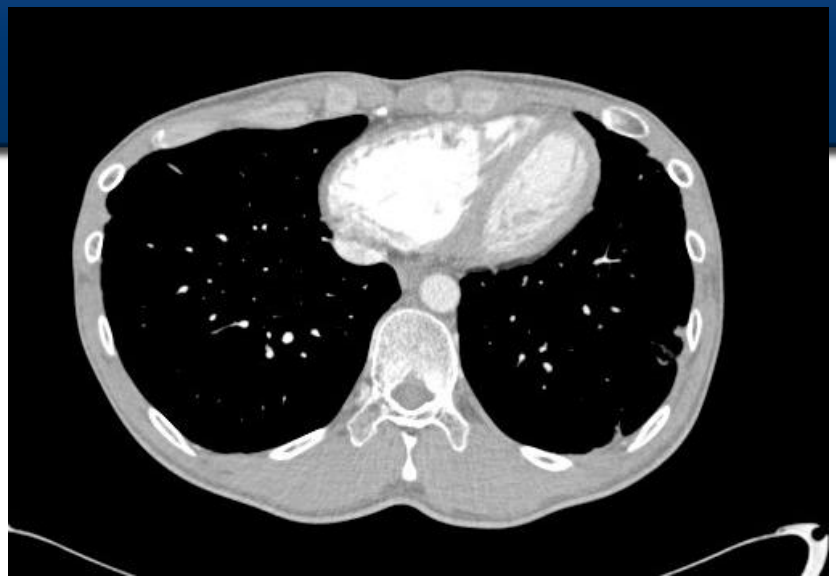
From Dr. AM D'Armini's slideshare\
(University of Pavia School of Medicine)

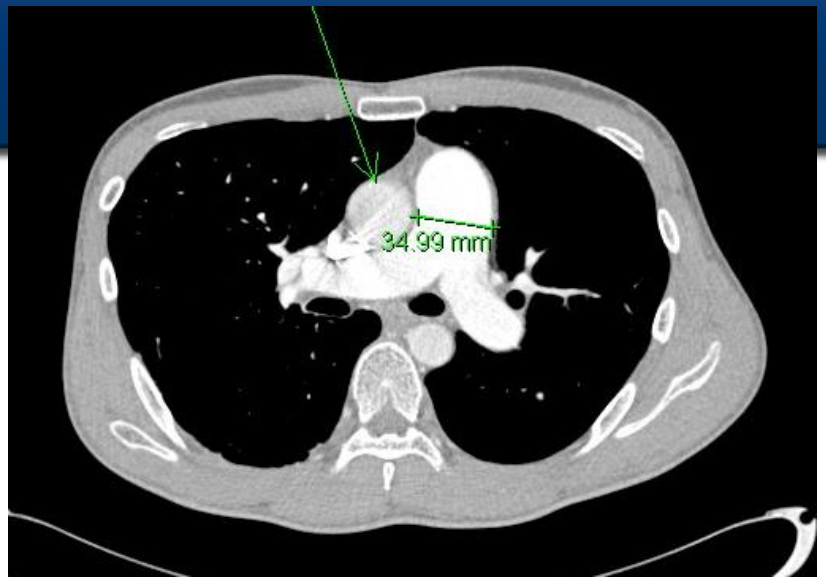
35YO Male with dyspnea on exertion

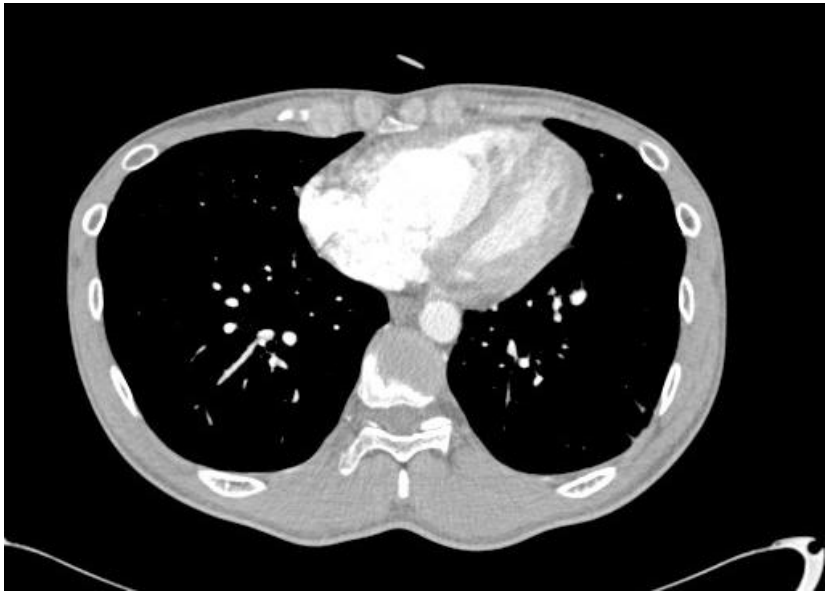
- Dyspnea for 1 year
- Diagnosed as pulmonary embolism
- Current medication : Ambrisentan, warfarin, nifedipine

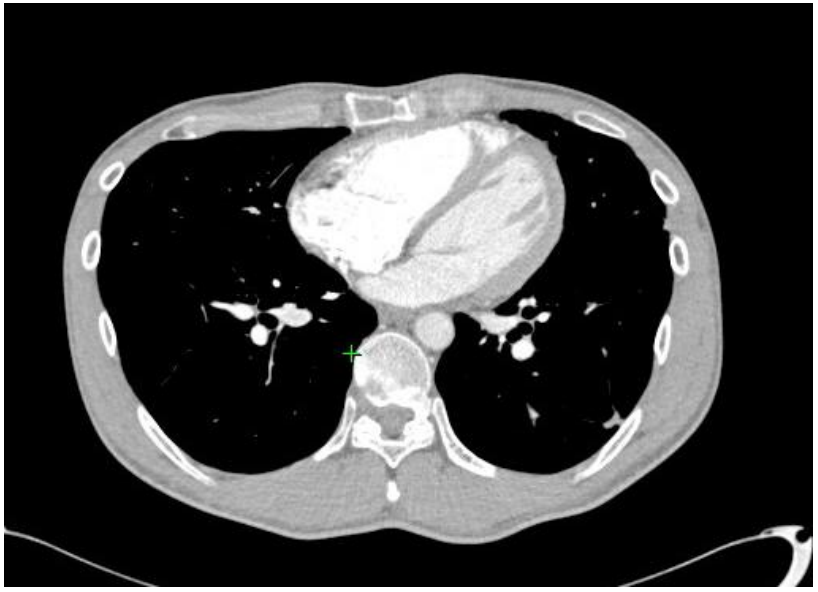
→ no improvement after medication

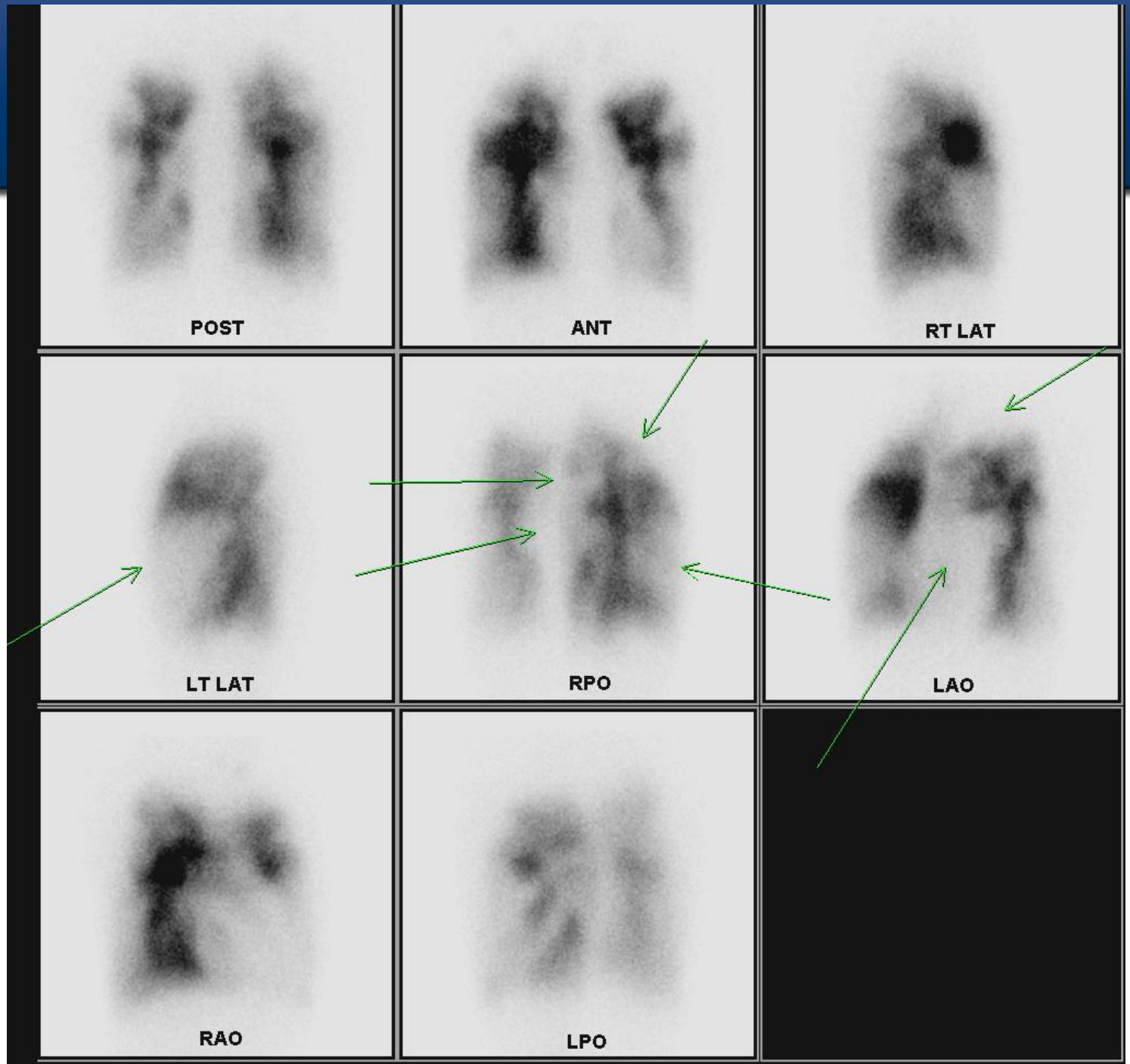
- Dyspnea on exertion WHO Fc III
- Patient said “inoperable disease” (same opinion from the two different tertiary hospital (University Hospital))

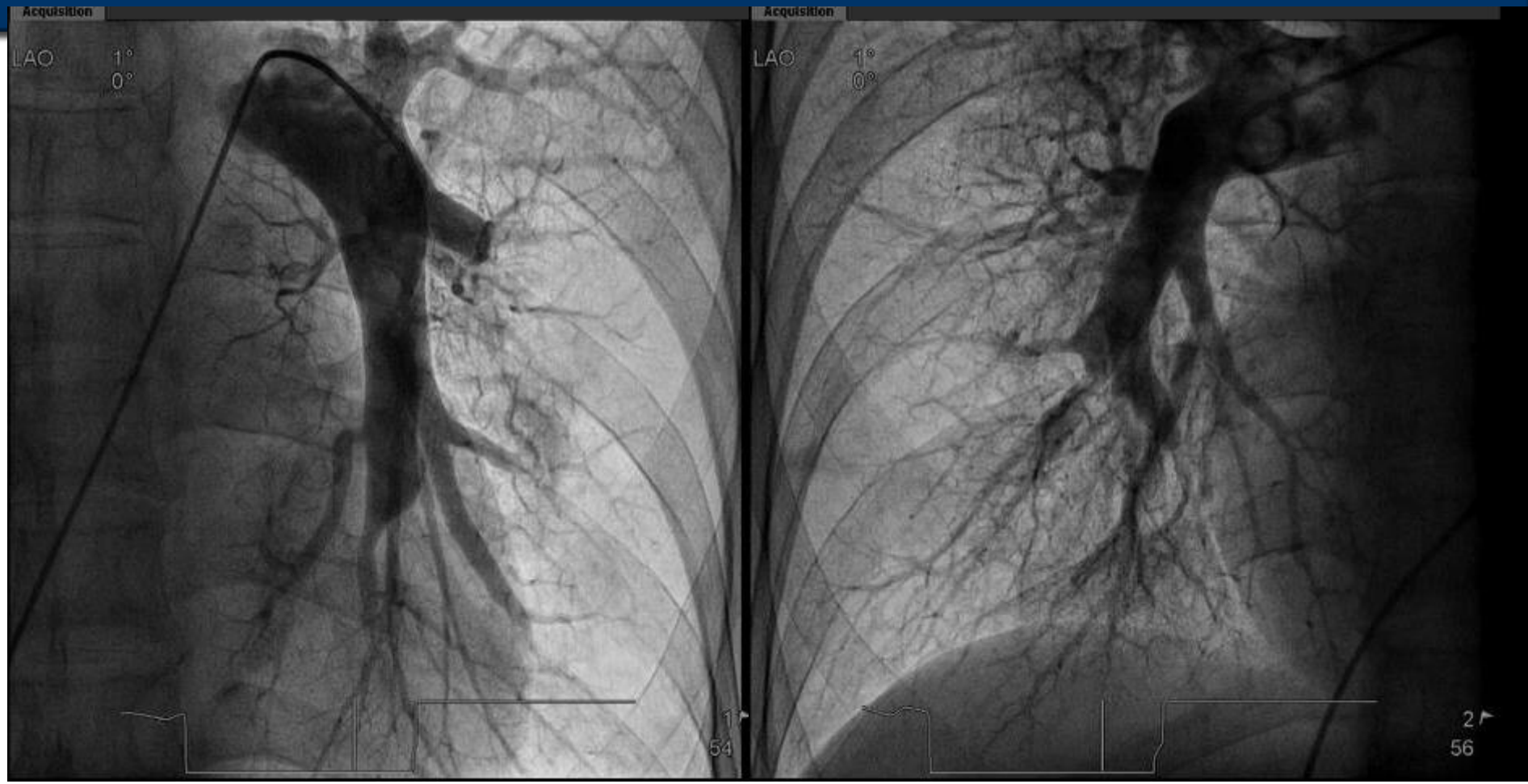



34.99 mm

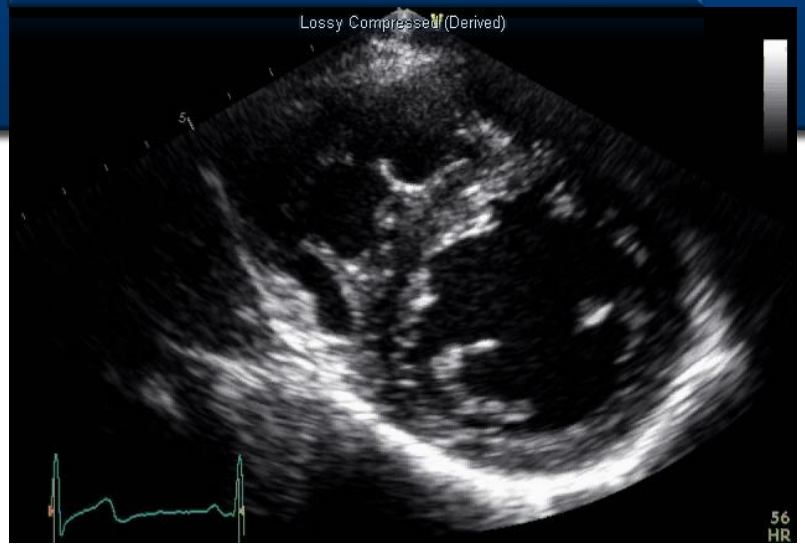


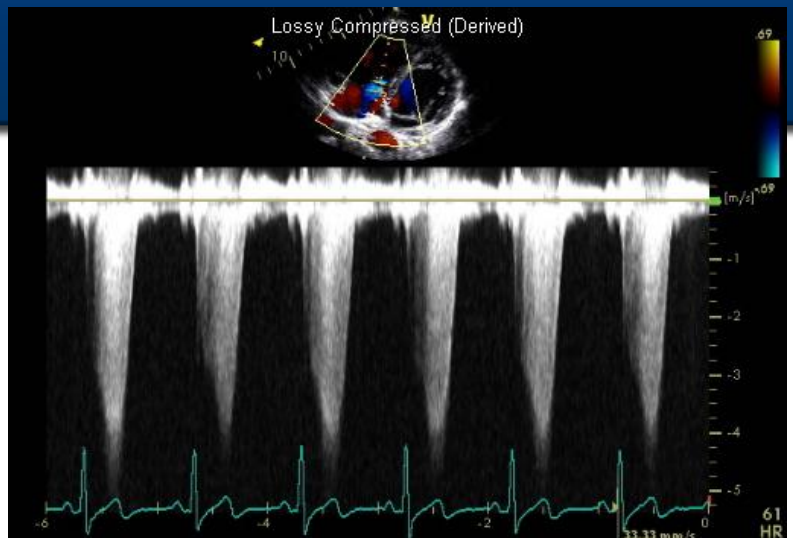



POST
ANT
RT LAT
LT LAT
RPO
LAO
RAO
LPO


Acquisition
LAO 1°
0°
1
54
Acquisition
LAO 1°
0°
2
56

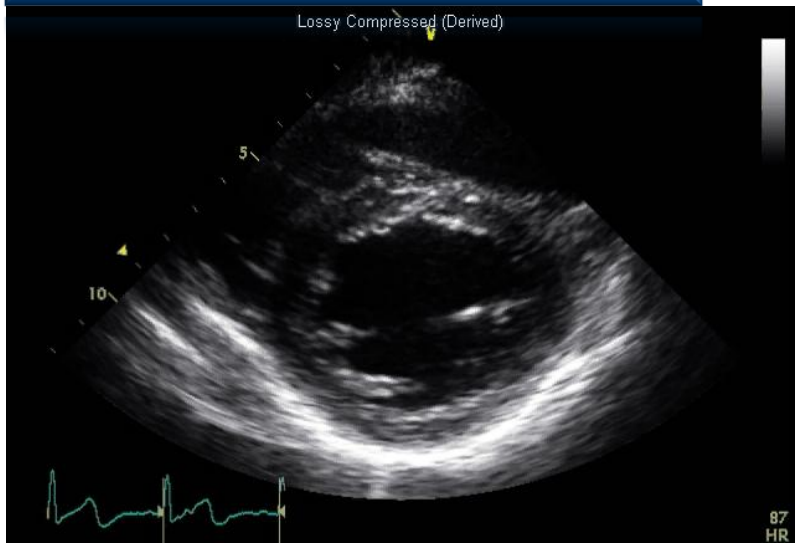
Pre Op

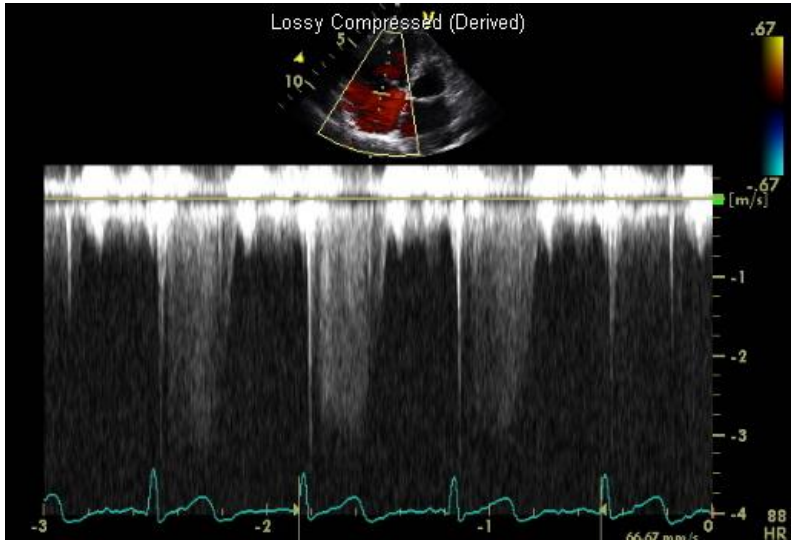




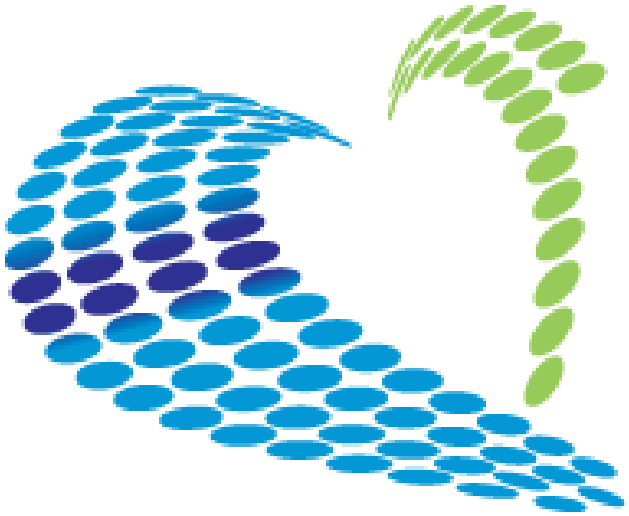
RVSP by TR Vmax = 80mmHg

Post Op





RVSP by TR Vmax = 43mmHg



PATENT

Pulmonary **A**rterial Hyper**ten**sion
sGC-Stimulator **T**rial

Riociguat

Objectives and design

Objectives

- To evaluate the efficacy and tolerability of riociguat in the treatment of patients with PAH who were treatment naïve or on stable treatment with an ERA or non-in travenous PCA

Design

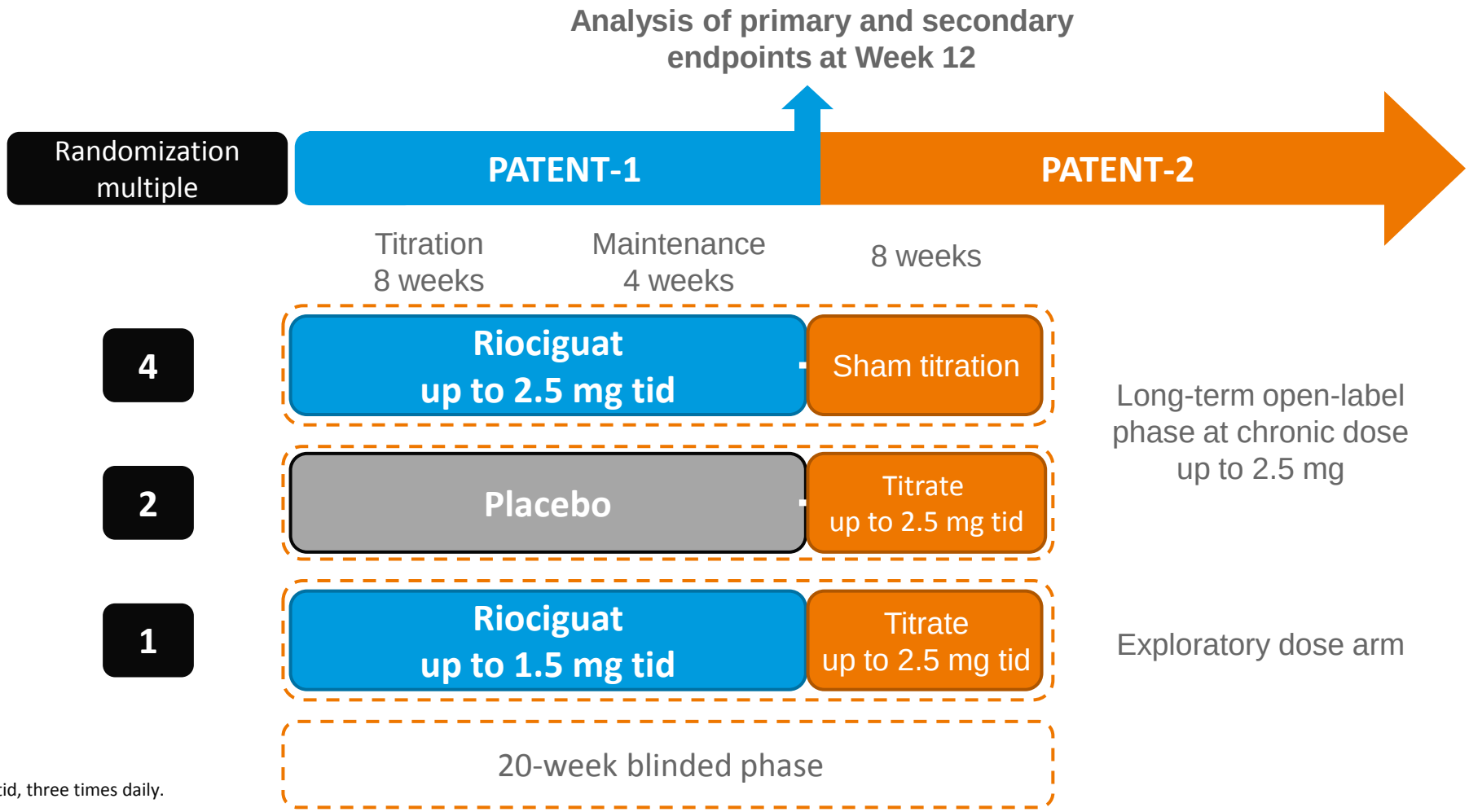
- Multicenter, double-blind, randomized, place bo-controlled study (PATENT-1)
- 124 centers across 30 countries in Europe, So uth America, North America, Asia, and Austr alia
- Patients completing PATENT-1 were given the option to enroll in a long-term exte nsion study (PATENT-2)

- **Outcomes**
  - Primary outcome: Change in 6MWD from baseline at week 12
  - Secondary outcomes:
    - Pulmonary vascular resistance
    - NT-proBNP
    - WHO functional class
    - Time to clinical worsening
    - Borg dyspnea score
    - Quality of life assessments
  - Safety variables

6MWD, 6-minute walking distance; ERA, endothelin receptor antagonist; PCA, prostacyclin analog; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; WHO, World Health Organization.

Ghofrani HA *et al. N Engl J Med 2013;369:330-40.*

Study design



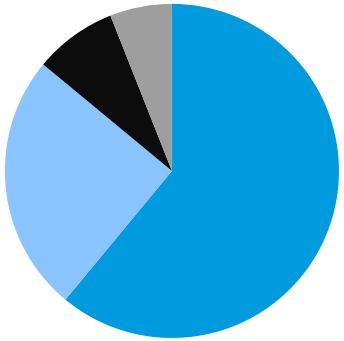
tid, three times daily.

Ghofrani HA *et al. N Engl J Med 2013;369:330-40.*

Baseline characteristics balanced across randomized groups

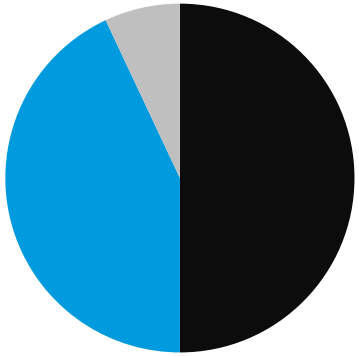
PATENT
Pulmonary Arterial Hypertension sGC-Stimulator Trial
Riociguat

	Riociguat (n=254)	Placebo (n=126)
Mean age, years	51	51
Female, %	80	78
Mean PVR[a], dyn·s·cm^{-5}	791	834
mPAP[a], mmHg[‡]	46.9	48.9
Mean 6MWD, m	361	368
WHO FC I/II/III/IV, %	2/43/55/<1	3/48/46/2[b]



Etiology

IPAH	61%
CTD-APAH	25%
CHD-APAH	8%
Other	6%



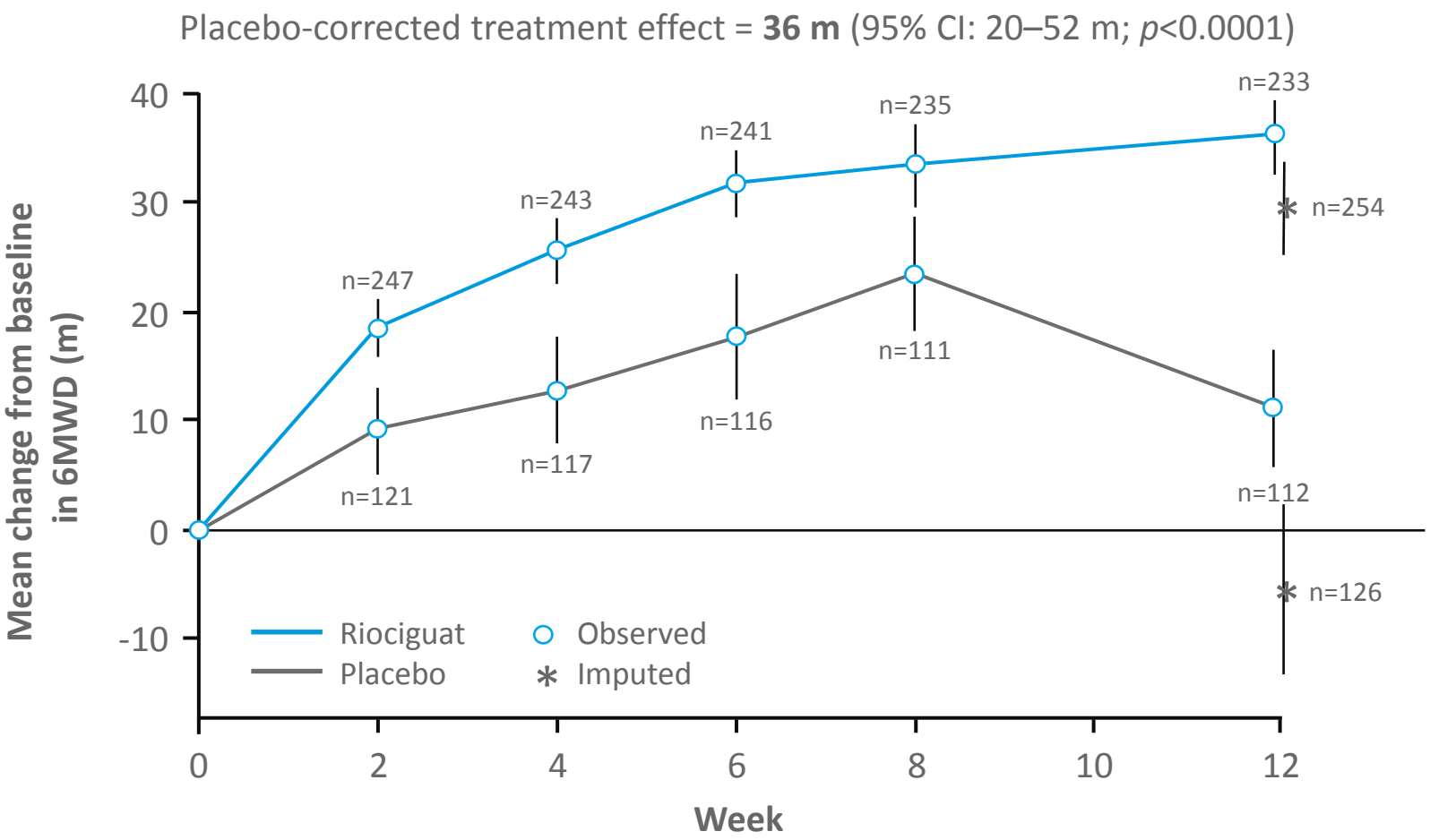
Prior treatment

Naïve	50%
Pre-treated ERAs	44%
Pre-treated PCAs	6%

[a]All PVRs and mPAPs measured. [b]1 patient with missing data at baseline.
6MWD, 6-minute walking distance; APAH, associated pulmonary arterial hypertension; CHD, congenital heart disease; CTD, connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; ERA, endothelin receptor antagonist; mPAP, mean pulmonary arterial pressure; PCA, prostacyclin analog; PVR, pulmonary vascular resistance; WHO FC, World Health Organization functional class.

Ghofrani HA *et al. N Engl J Med 2013;369:330-40.*

Primary endpoint (6MWD) achieved



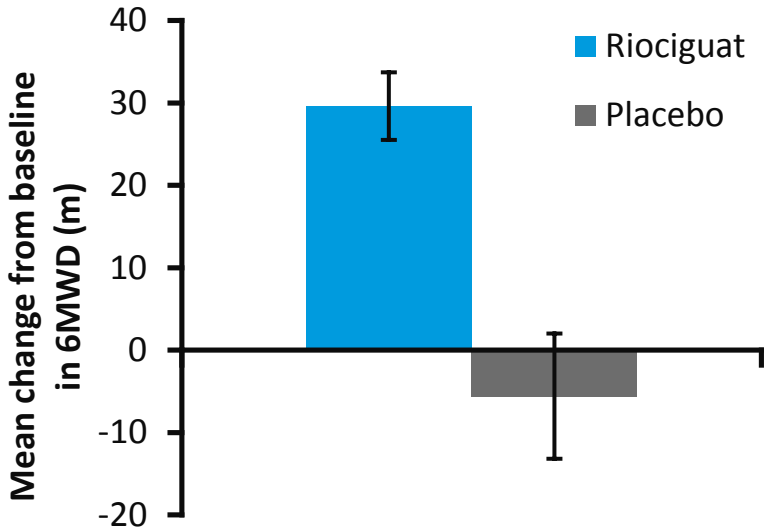
Last visit = last observed value (not including follow-up) for patients who completed the study or withdrew, except imputed worst value (zero) in case of death or clinical worsening without a termination visit or a measurement at that termination visit. 6MWD, 6-minute walking distance.

Ghofrani HA *et al. N Engl J Med 2013;369:330-40.*

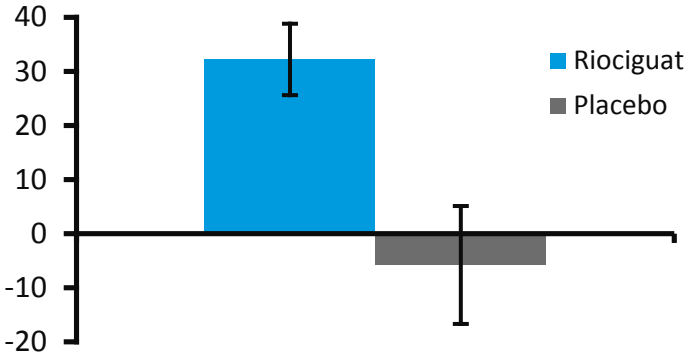
6MWD: consistent improvement seen in treatment-naïve and retreated patients

Primary endpoint: entire population (n=254/126)

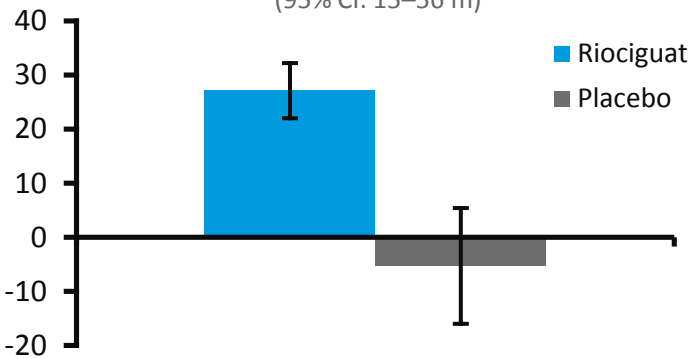
+36 m
***p*<0.0001**
(95% CI: 20–52 m)



Naïve population (n=123/66)
+38 m
(95% CI: 15–62 m)



Pretreated population (n=131/60)
+34 m
(95% CI: 15–56 m)



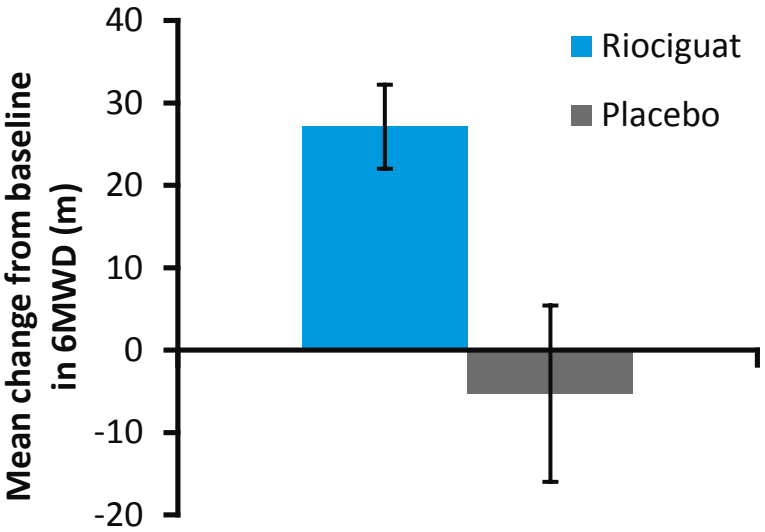
6MWD, 6-minute walking distance.

Ghofrani HA *et al. N Engl J Med 2013;369:330-40.*

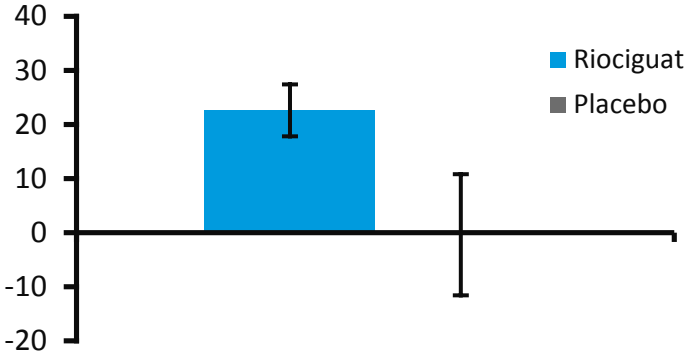
6MWD: consistent improvement shown with background therapy ERAs or PCAs

Pretreated population (n=131/60)

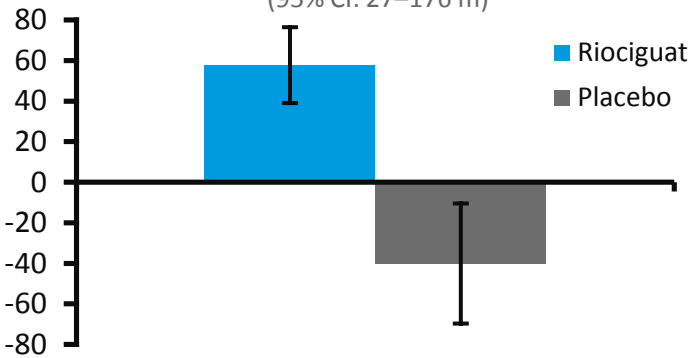
+34 m
(95% CI: 15–56 m)



ERA population (n=113/54)* +24 m
(95% CI: 5–47 m)



PCA population (n=20/7)[a] +106 m
(95% CI: 27–176 m)



[a]3 patients on ERA/PCA combination double counted.
6MWD, 6-minute walking distance; ERA, endothelin receptor antagonist; PCA, prostacyclin analog.

Ghofrani HA *et al. N Engl J Med 2013;369:330-40.*

Meaningful improvement of cardio-pulmonary hemodynamics and biomarkers

Parameter	Riociguat		Placebo		Placebo-corrected LS-mean difference	Riociguat vs placebo; *p* value
	Baseline	Mean change from baseline	Baseline	Mean change from baseline		
PVR, dyn·s·cm^{-5}	791	−223 (−28%)	834	−9 (−1%)	−226	<0.0001
mPAP, mmHg	47.1	−3.9 (−8%)	48.9	−0.5 (−1%)	−3.8	0.0002
CI, L/min/m^2	2.52	+0.54 (+21%)	2.49	−0.02 (−1%)	+0.56	<0.0001
NT-proBNP, ng/L	1027	−198 (−19%)	1228	+232 (+19%)	−432	<0.0001

CI, cardiac index; LS, least squares; mPAP, mean pulmonary arterial pressure;
NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PVR, pulmonary vascular resistance.

Ghofrani HA *et al. N Engl J Med 2013;369:330-40.*

Improvement of functional class and quality of life

PATENT
Pulmonary Arterial Hypertension sGC-Stimulator Trial
Riociguat

Functional class improvement (p=0.0033)

	Riociguat	Placebo
Improved, %	21	14
Stable, %	76	71
Deteriorated, %	3	14

Quality of life assessments

Parameter	Riociguat		Placebo		Placebo-corrected LS-mean difference	Riociguat vs placebo; p value
	Baseline	Mean change from baseline	Baseline	Mean change from baseline		
General QOL Instrument (EQ-5D)	0.68	0.03	0.68	−0.02	0.06	0.066
PAH specific QOL Instrument (LPH)	42.4	−6.0	41.6	0.4	−6.2	0.0019

EQ-5D, EuroQol Group 5-Dimension Self-Report Questionnaire; LPH, living with pulmonary hypertension; LS, least squares; QOL, quality of life.

Ghofrani HA *et al. N Engl J Med 2013;369:330-40.*

Significant reduction in clinical worsening events

PATENT
Pulmonary Arterial Hypertension sGC-Stimulator Trial
Riociguat

	Riociguat (n=254)	Placebo (n=126)
Number of patients (%) with clinical worsening*	3 (1.2)	8 (6.3)
Hospitalization due to PH	1 (0.4)	4 (3.2)
Start of new PH treatment	1 (0.4)	5 (4.0)
Decrease in 6MWD due to PH	1 (0.4)	2 (1.6)
Persistent worsening of FC due to PH	0	1 (0.8)
Death	2 (0.8)	3 (2.4)

*p=0.0046 (time to clinical worsening).
6MWD, 6-minute walk distance; FC, functional class.

Ghofrani HA *et al. N Engl J Med 2013;369:330-40.*

PATENT-2 study

Objectives

- To evaluate long-term safety, tolerability and efficacy of riociguat in patients with PAH

Endpoints

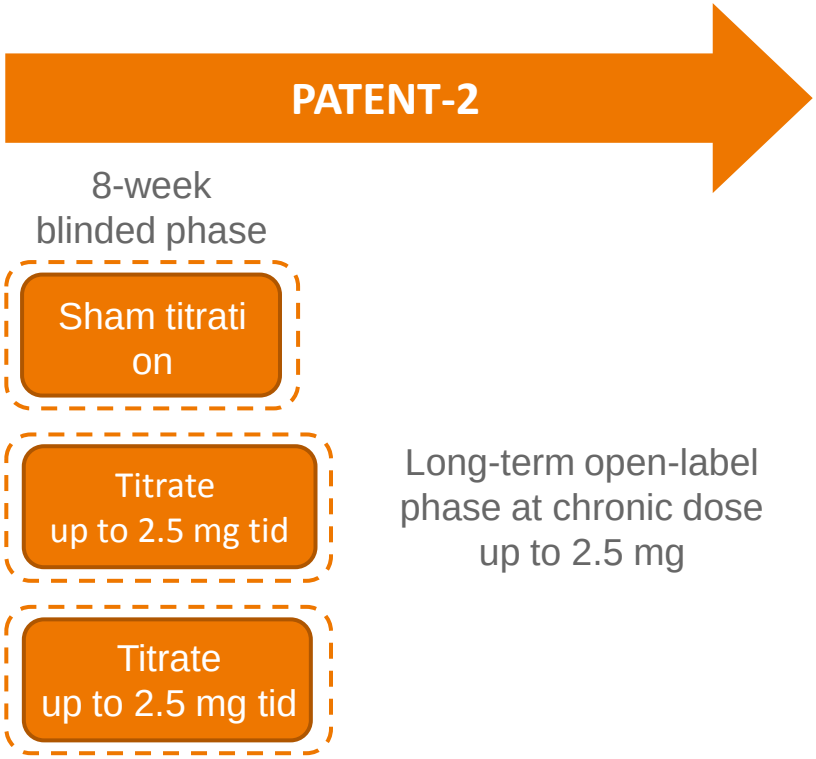
- **Primary endpoints**:
  - Safety and tolerability
- **Secondary endpoints**:
  - 6MWD*, NT-proBNP, WHO FC, Borg dyspnea score, QoL assessments, time to clinical worsening

*up to 4 years and 10 months

mPAP, mean pulmonary arterial pressure; QoL, quality of life

Ghofrani HA *et al. N Engl J Med* 2013..
Rubin L *et al*. Am J Respir Crit Care Med 187; 2013: A3531

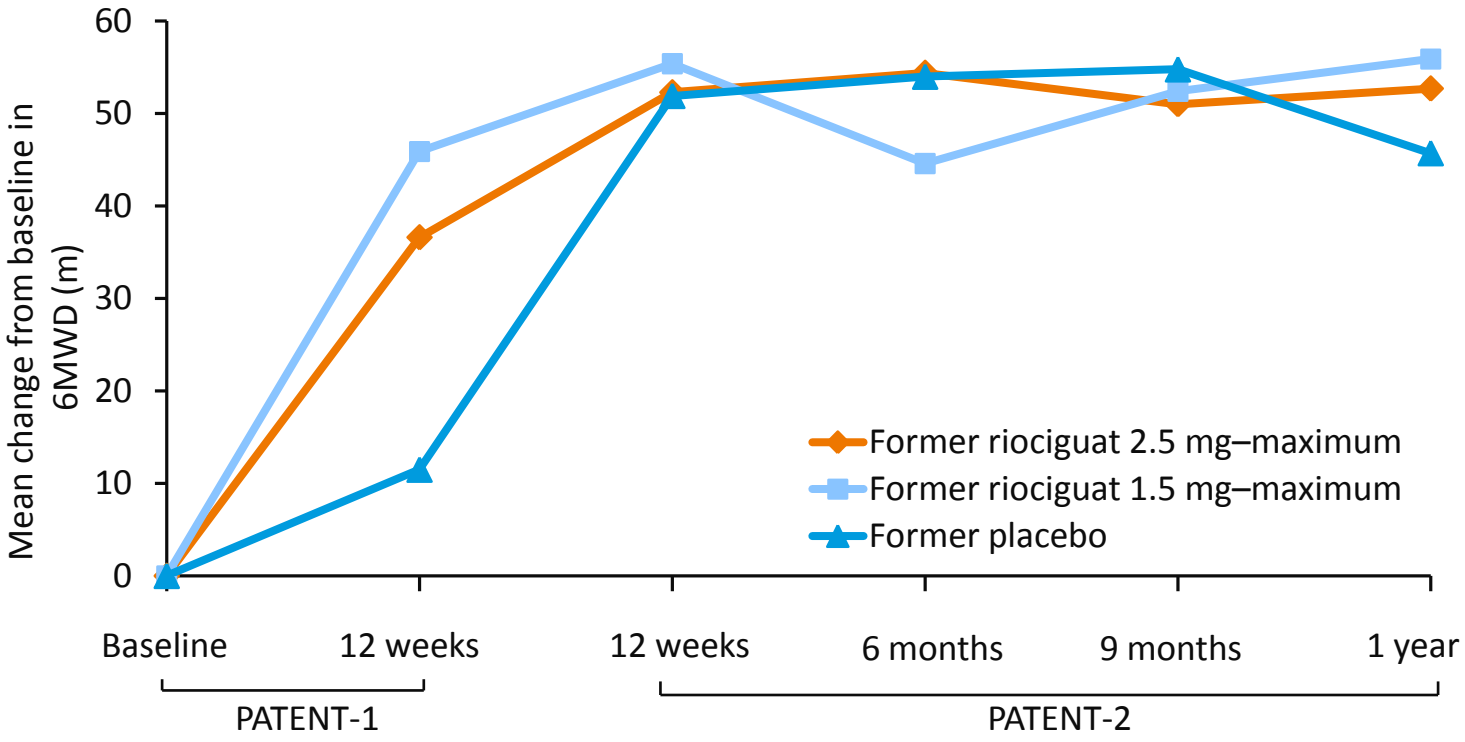
PATENT-2 Study design



- 98% of patients from PATENT-1 study entered PATENT-2 study (n=396)
- Stable ERAs or non-iv prostanoids permitted

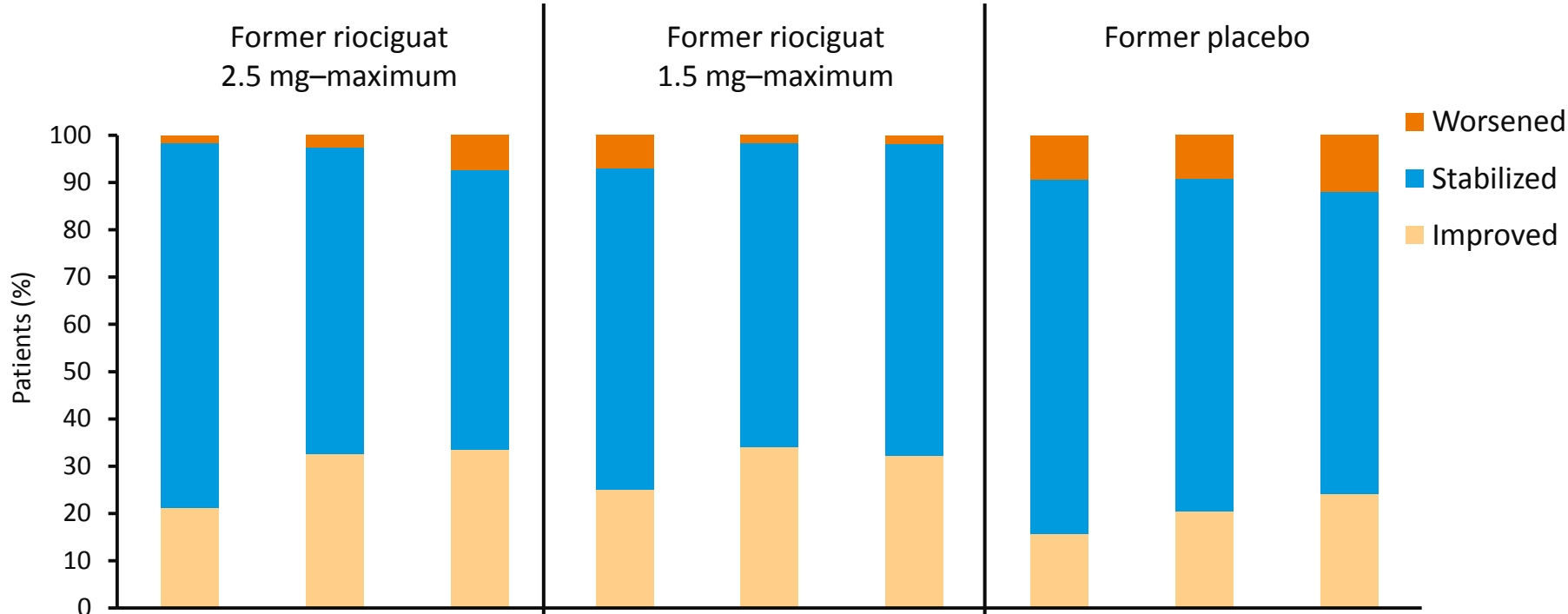
Ghofrani HA *et al. N Engl J Med* 2013..
Rubin L *et al*. Am J Respir Crit Care Med 187; 2013: A3531

Effects of riociguat on 6MWD in PATENT-2 (observed data)



Rubin L *et al*. Am J Respir Crit Care Med 187; 2013: A3531

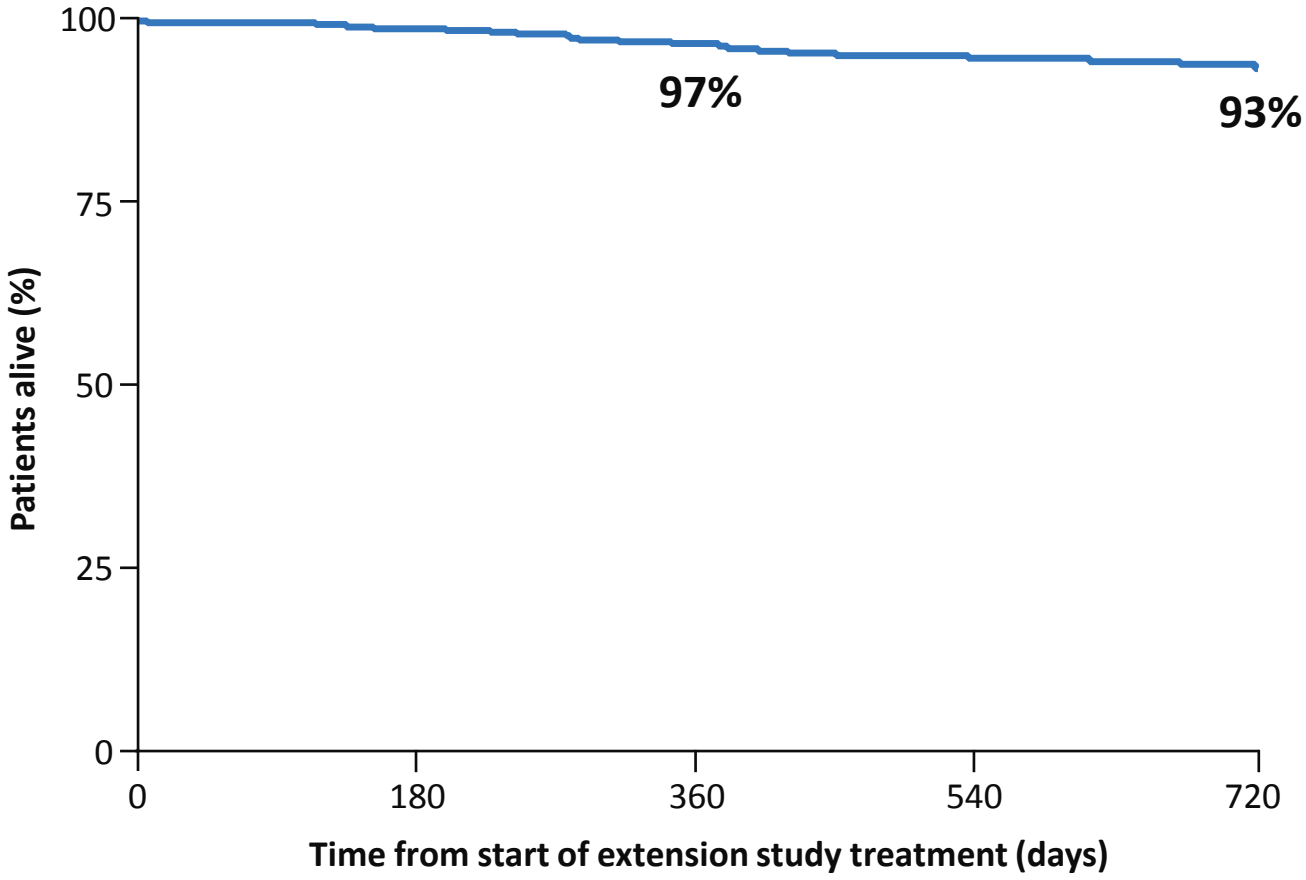
Effects of riociguat on WHO FC in PATENT-2



No. of observed	228	223	199	55	56	51	108	107	89
No. of imputations	3	8	32	1	0	5	0	1	19

Rubin L *et al*. Am J Respir Crit Care Med 187; 2013: A3531

PATENT-2 overall survival



No. of patients alive at timepoint	396	377	310	234	168
No. of deaths	0	4	12	18	21

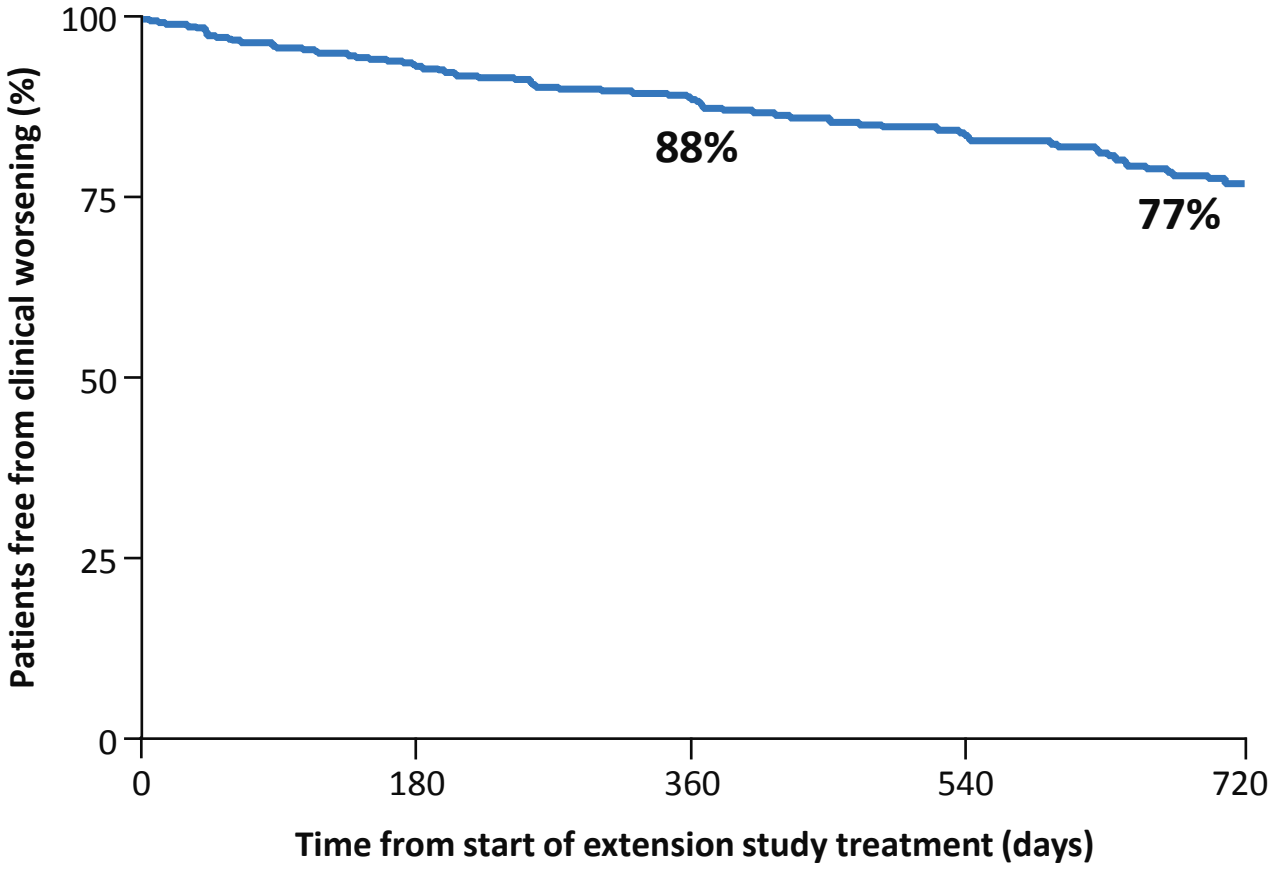
Rubin L *et al*. Am J Respir Crit Care Med 187; 2013: A3531

Clinical worsening events during PATENT-2

	Total population (n=396)
No. of patients (%) with clinical worsening	84 (21)
Heart/lung transplant	2 (1)
Hospitalization due to PH	41 (10)
Start of new PH treatment	60 (15)
Decrease in 6MWD due to PH	10 (3)
Persistent worsening of WHO FC due to PH	5 (1)
Death	27 (7)

Rubin L *et al*. Am J Respir Crit Care Med 187; 2013: A3531

PATENT-2 Time to Clinical Worsening



No. of patients who reached timepoint without clinical worsening	396	360	288	209	145
No. of patients with clinical worsening	0	26	43	60	73

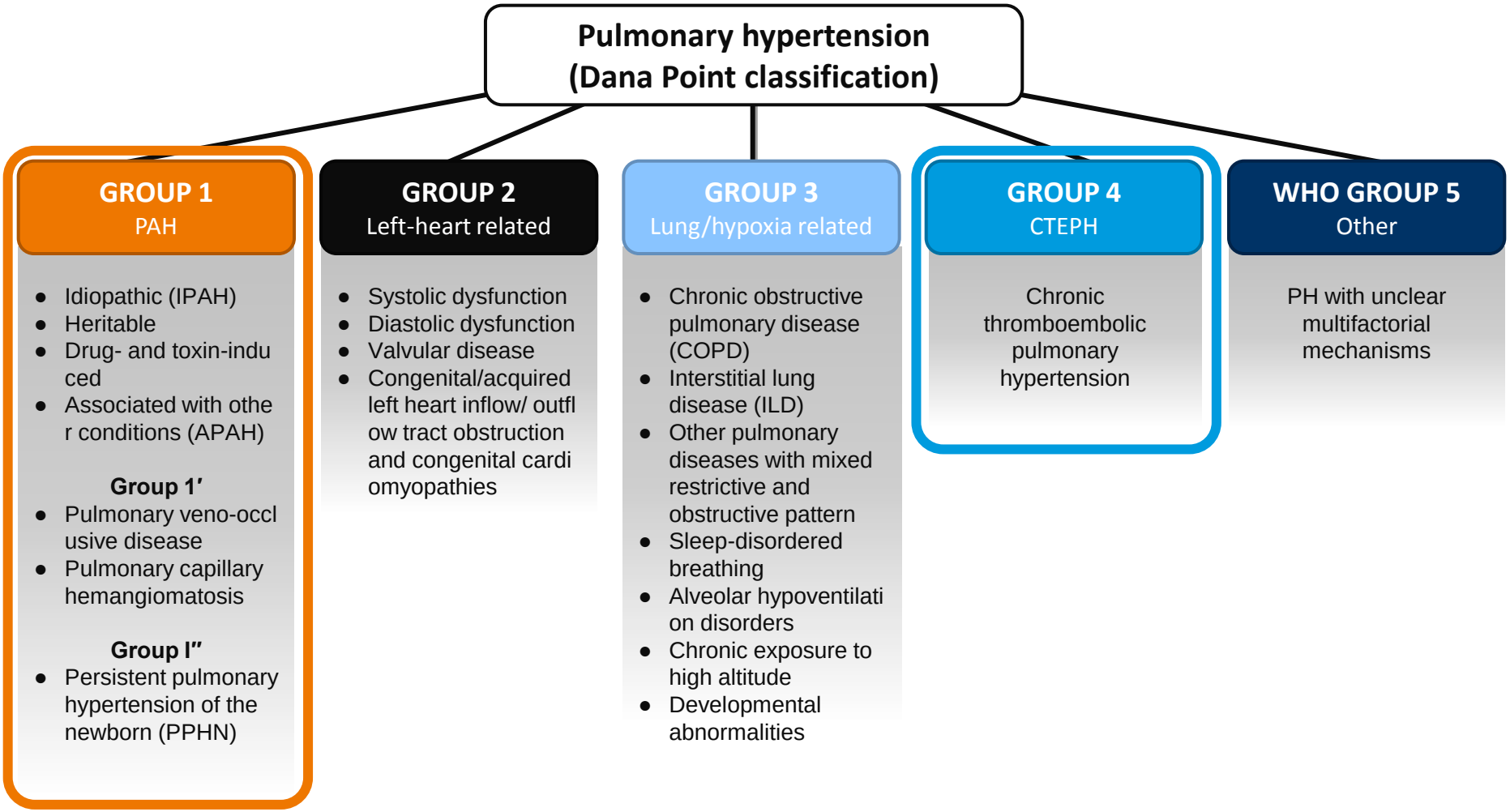
Rubin L *et al*. Am J Respir Crit Care Med 187; 2013: A3531

Conclusions

- Riociguat was well tolerated in patients with PAH with a good long-term safety profile
- The outcome of pulmonary bleeding-related SAEs was resolved in most cases, there was no association between dose and event
- Improvements in 6MWD and WHO FC observed during the 12-week PATENT-1 study were sustained during the PATENT-2 long-term extension study

Rubin L *et al*. Am J Respir Crit Care Med 187; 2013: A3531

Riociguat is the first specific therapy approved for both PAH and CTEPH*



Presented at 5th World Symposium on Pulmonary Hypertension. Nice, France, 27 Feb–1 Mar, 2013.
Simonneau G *et al. J Am Coll Cardiol* 2013;62:D34–41.
* In the US, EU, Canada and Japan