New drugs for pulmonary hypertension

서울대병원 소아청소년과
김기범

2015.4.18.

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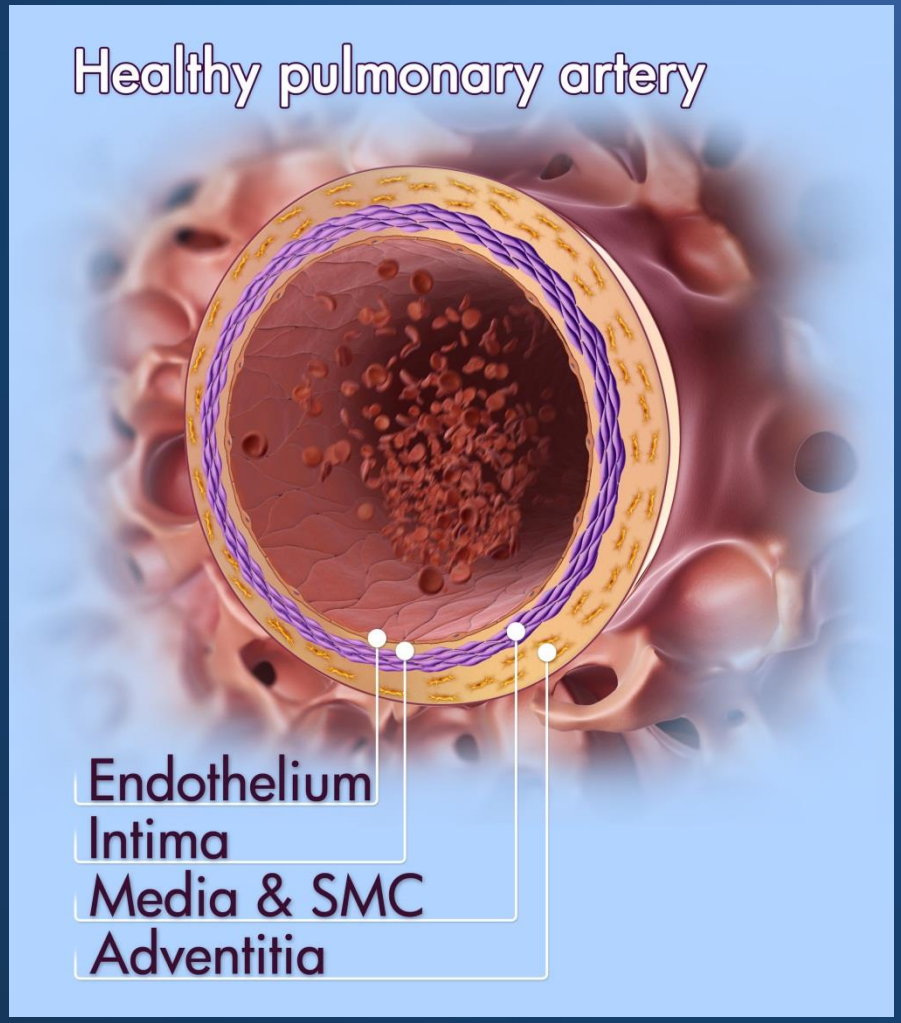
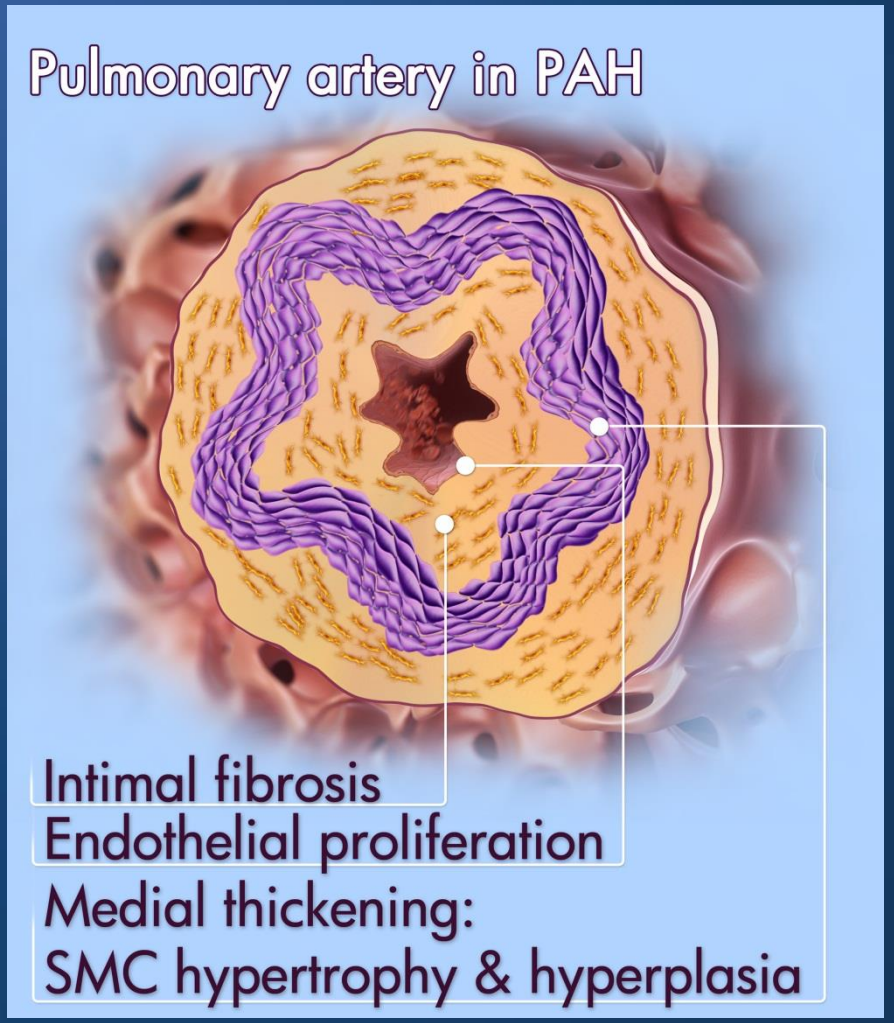
Pulmonary remodelling
From healthy state to PAH state

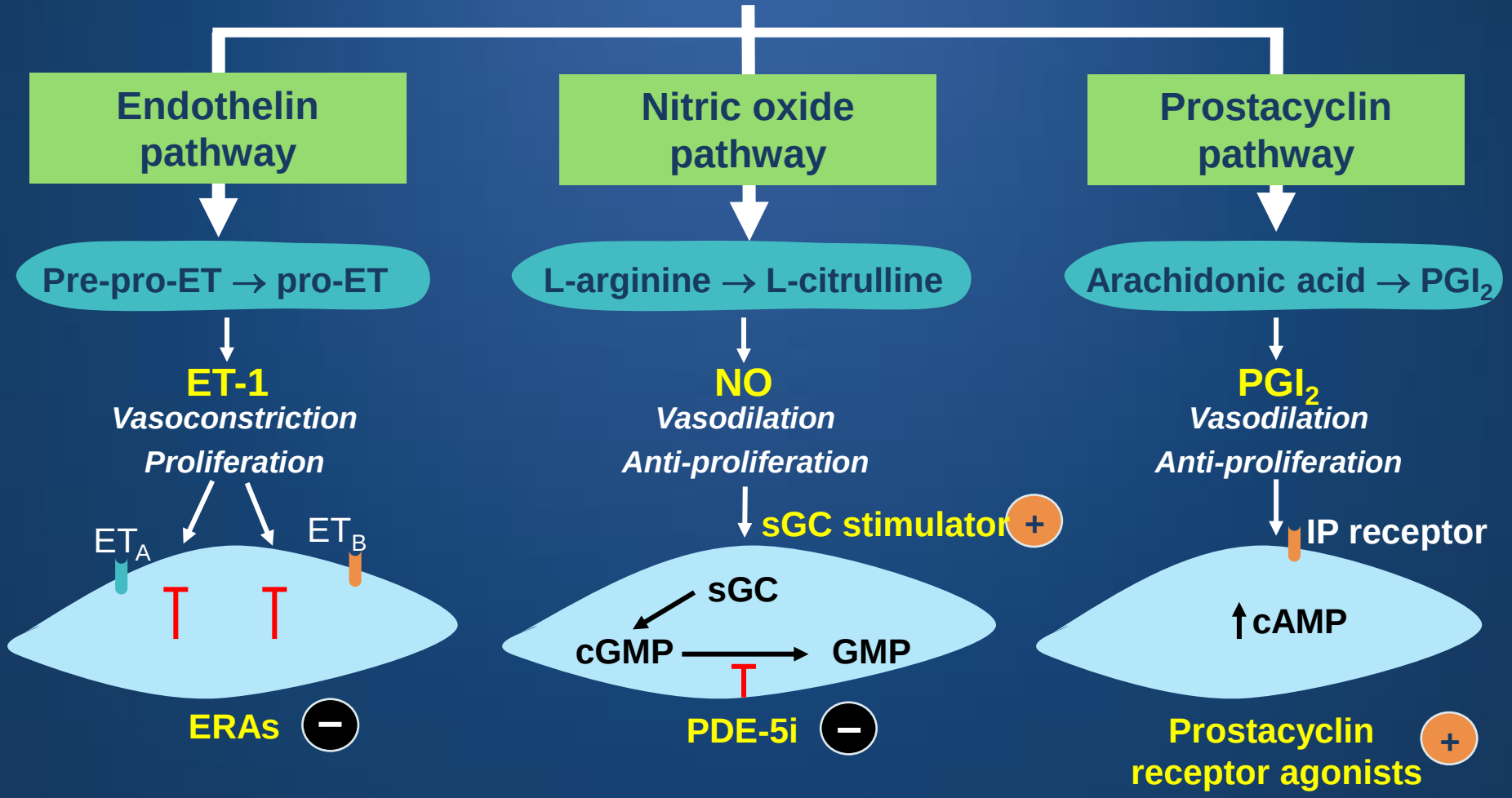




SMC: smooth muscle cells

(Adapted from Galiè N, *et al. Eur Heart J* 2010; 31:2080-6)

Key pathways in the pathophysiology of PAH



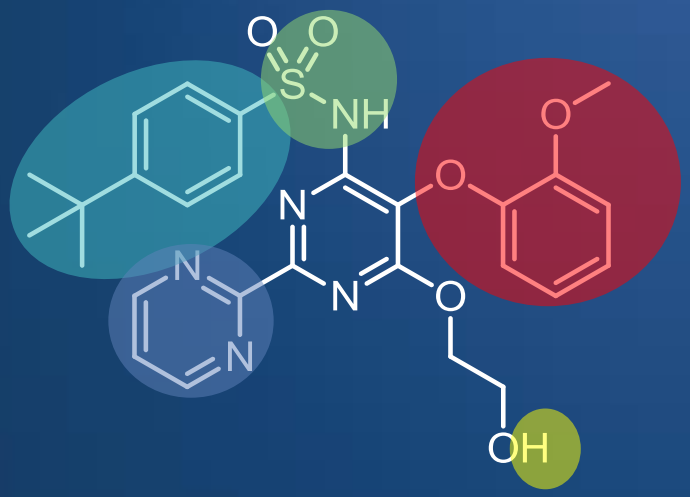
cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; NO: nitric oxide; PDE-5i: phosphodiesterase-5 inhibitor; PGI_2: prostacyclin; sGC: soluble guanylate cyclase

(Humbert M, et al. N Engl J Med 2004; 351:1425-36)

Macitentan

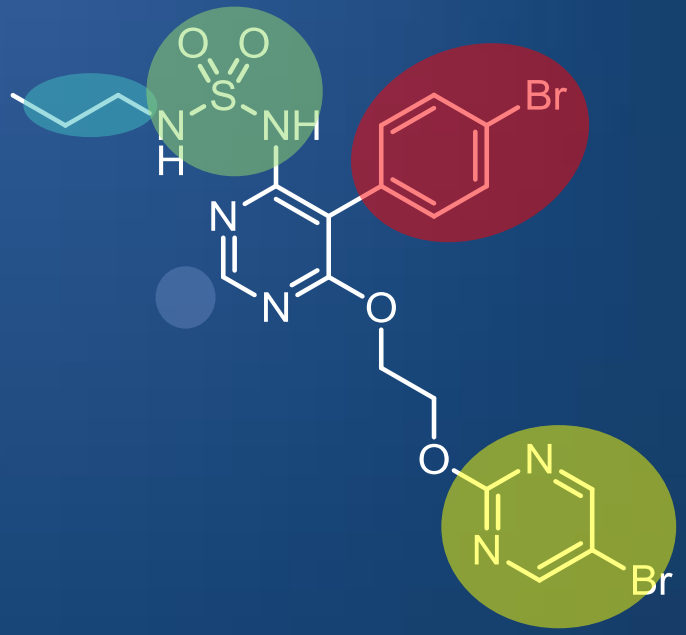
Dual endothelin receptor antagonist

Macitentan – A novel sulfamide



Bosentan

slightly higher affinity for ET-A than ET-B



Macitentan

Improved affinity for ET-B

(Bolli M, et al. J Med Chem 2012; 55:7849-61)

Key pre-clinical features of macitentan

1. • Tissue penetration ↑
2. • Receptor binding and affinity ↑
3. • Improved efficacy ↑
4. • Favourable safety and tolerability profile ↑

The SERAPHIN study

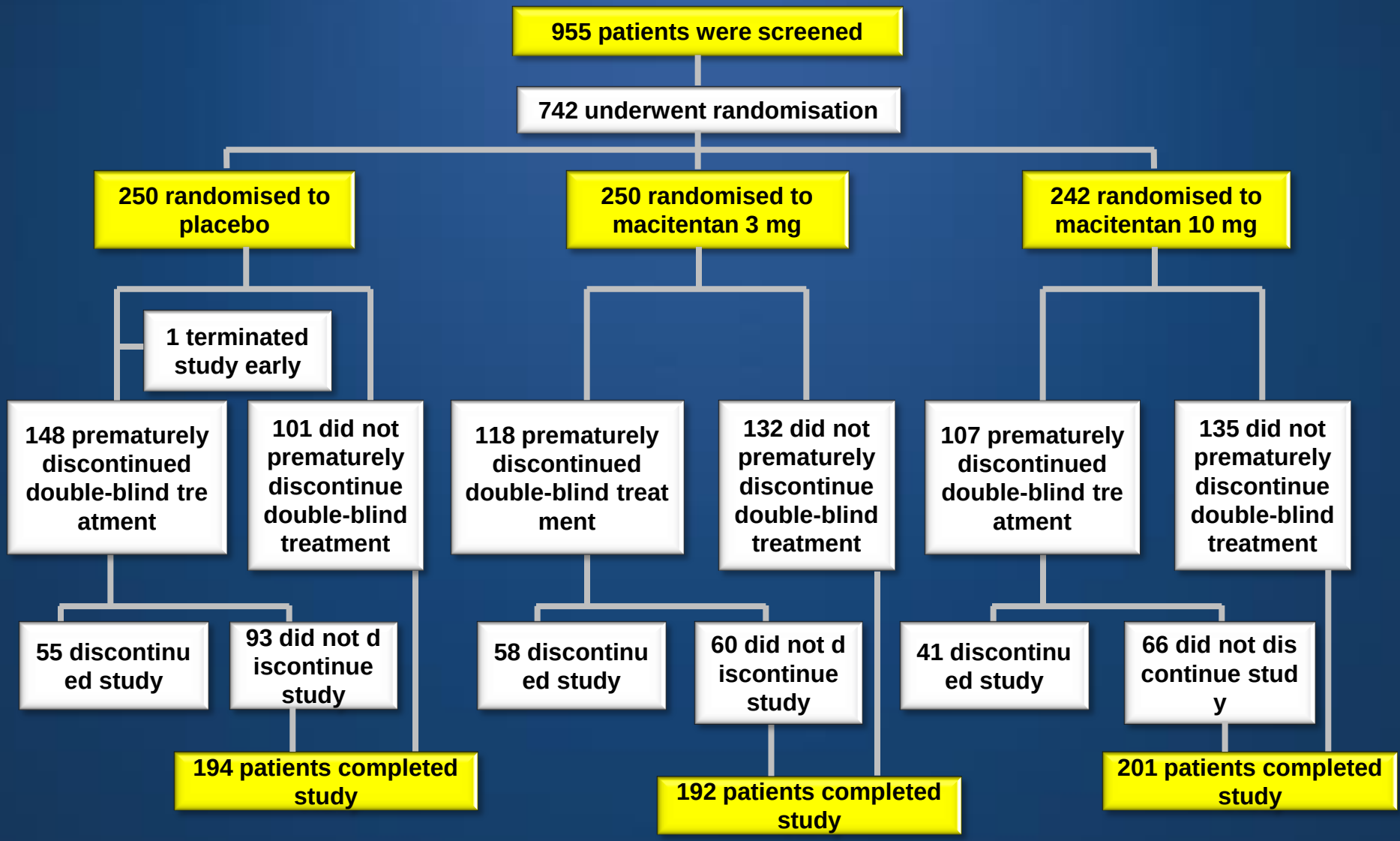
- Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome
  - A multi-centre, double-blind, randomized phase III clinical trial
  - Global, event-driven study investigating long-term benefits of **macitentan** in patients with PAH
  - Has a novel and robust endpoint, measuring time to the first morbidity or mortality event

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

SERAPHIN study centres

151 centres from almost **40 countries**

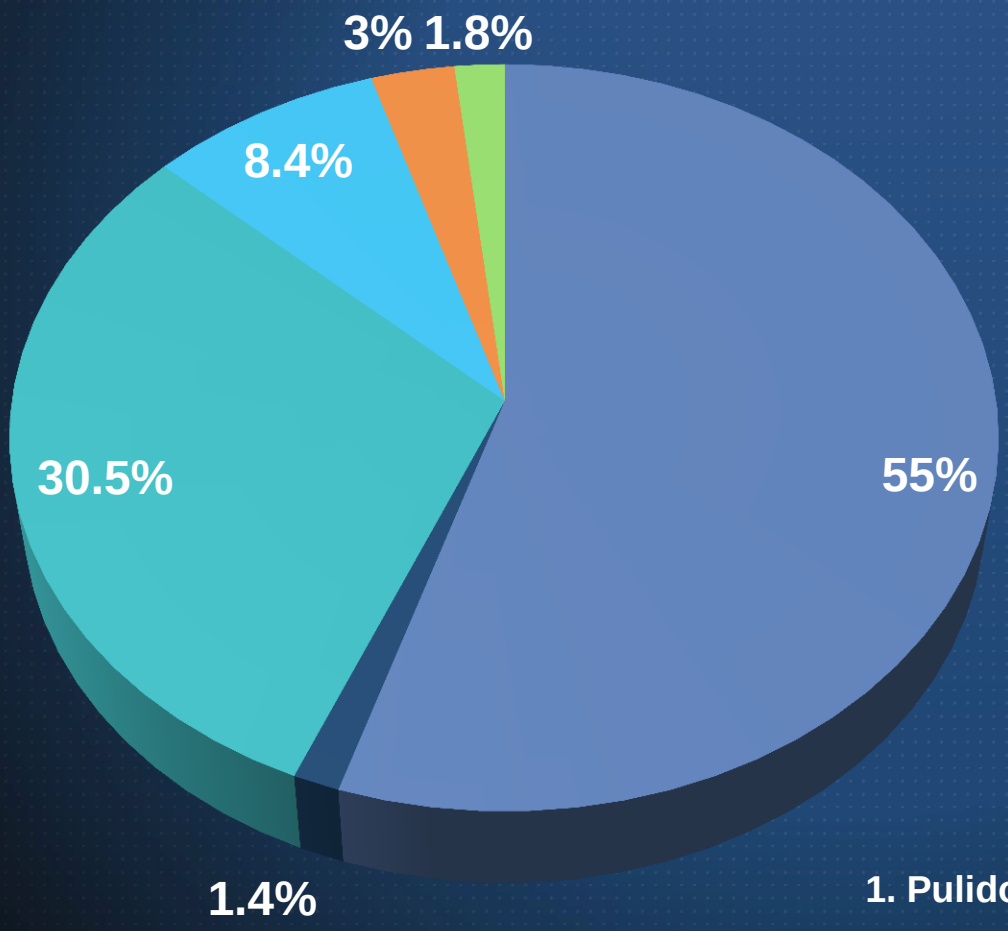
The SERAPHIN study



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

Patient demographics: PAH aetiology

Total number of patients[1]: 742

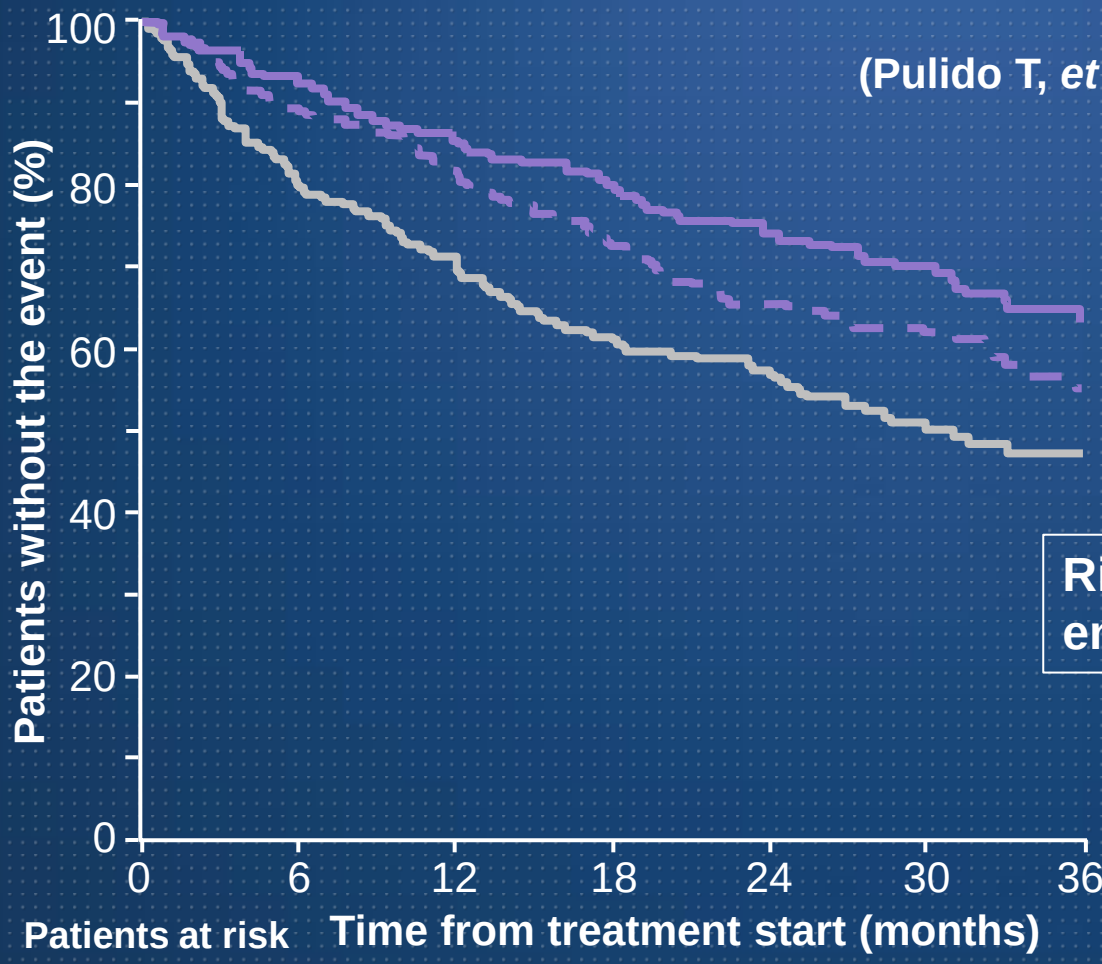


1. Pulido T, *et al. N Engl J Med* 2013; 369: 809-18.
2. Actelion data on file.

*Simple shunt at least 1 year post-surgical repair[2]

Primary endpoint: Morbidity and mortality up to end of treatment

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



Macitentan 10 mg: 45%

Macitentan 3 mg: 30%

Placebo

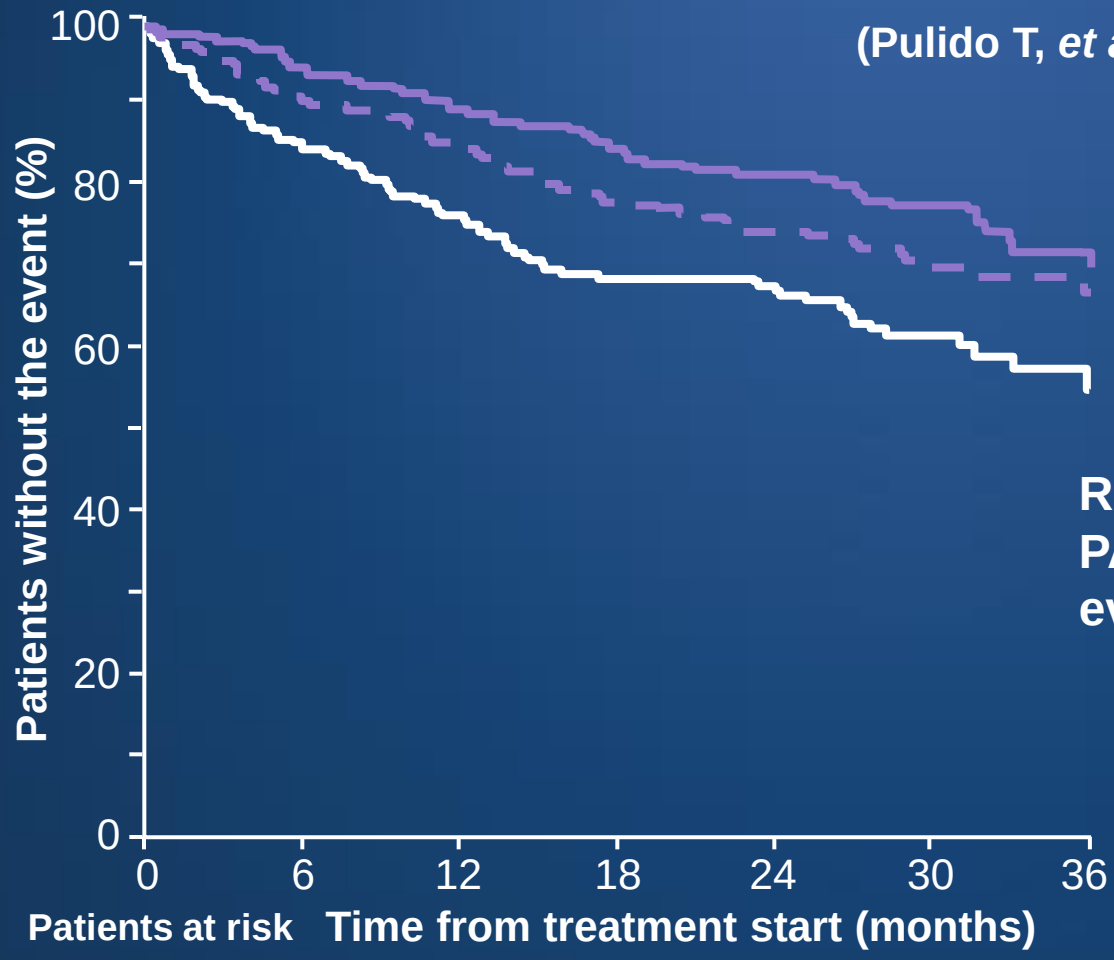
Risk reduction of primary endpoint event vs placebo

Patients at risk

242	208	187	171	155	91	41	Macitentan 10 mg
250	213	188	166	147	80	32	Macitentan 3 mg
250	188	160	135	122	64	23	Placebo

Secondary endpoint: Death due to PAH or hospitalisation for PAH

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



Macitentan 10 mg: 50%

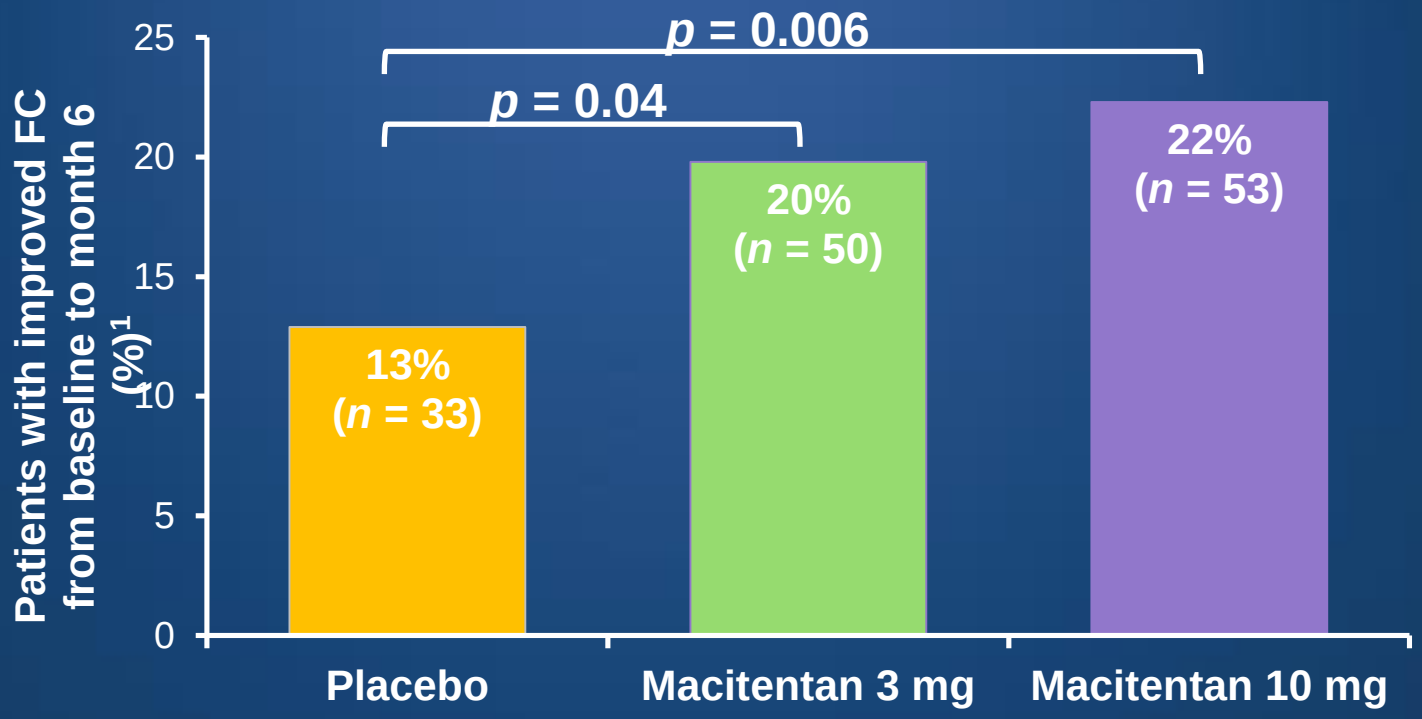
Macitentan 3 mg: 33%

Placebo

Risk reduction of death due to PAH or hospitalisation for PAH event vs placebo

Patients at risk							
242	203	183	166	152	86	39	Macitentan 10 mg
250	208	181	159	144	77	31	Macitentan 3 mg
250	188	155	132	119	62	22	Placebo

Secondary endpoint: Change from baseline to month 6 in WHO FC

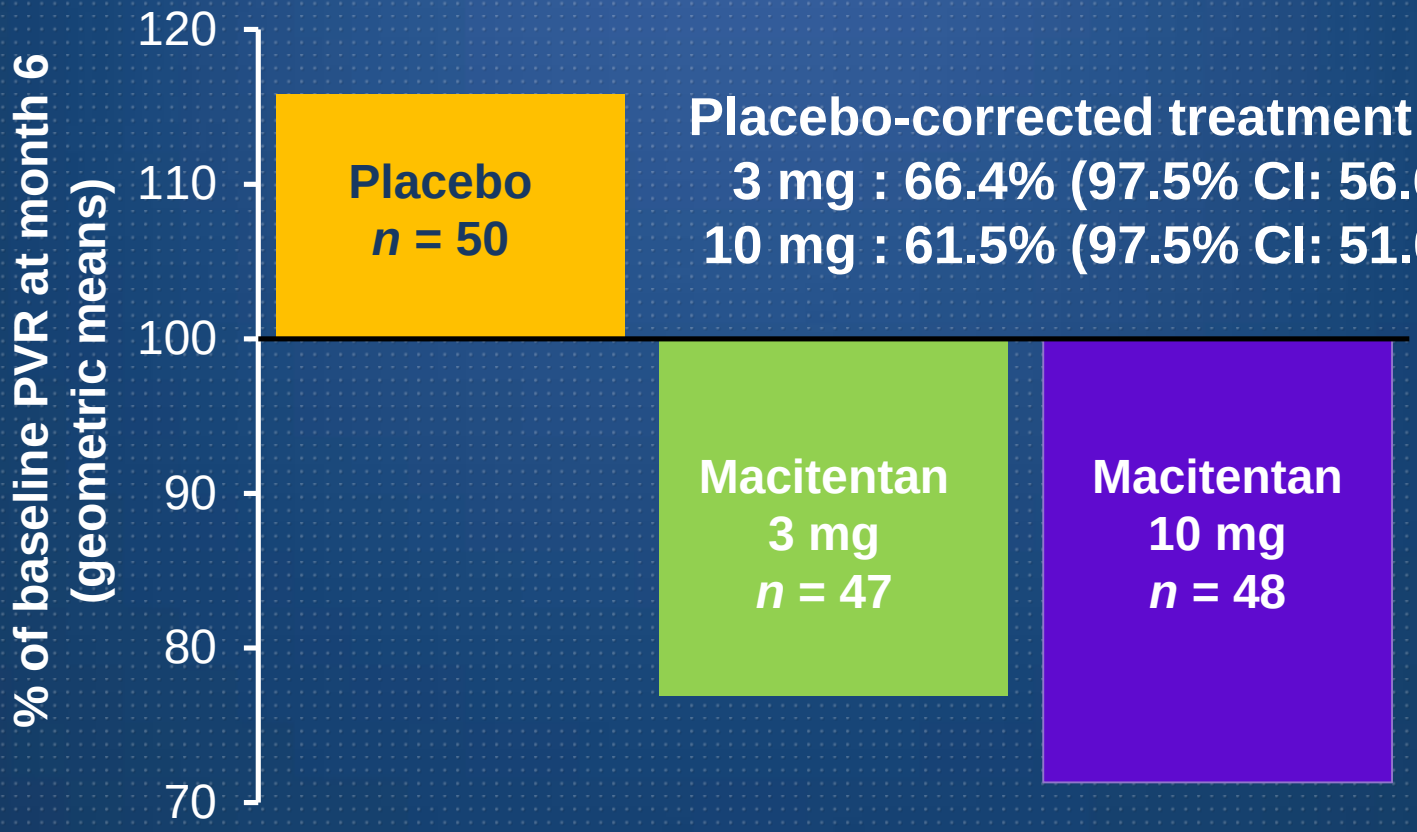


- Patients on macitentan 3 mg had a **54%** greater chance to improve FC status[2]
- Patients on macitentan 10 mg had a **74%** greater chance to improve FC status[3]

1. Pulido T, *et al. N Engl J Med* 2013; 369: 809-18.
2. Actelion data on file.
3. OPSUMIT (macitentan) SmPC 2014.

Change from baseline to month 6 in pulmonary vascular resistance

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



Placebo-corrected treatment effect*:
3 mg : 66.4% (97.5% CI: 56.6, 77.8)
10 mg : 61.5% (97.5% CI: 51.0, 74.3)

- **This translates into a 34% reduction in PVR in the macitentan 3 mg group and a 38% reduction in the macitentan 10 mg group**

*Ratio of geometric means vs placebo (%)

Adverse events

Adverse event, n (%)	Placebo *n* = 249	Macitentan 3 mg *n* = 250	Macitentan 10 mg *n* = 242
Patients with ≥ 1 AE	240 (96.4)	240 (96.0)	229 (94.6)
PAH worsening	87 (34.9)	75 (30.0)	53 (21.9)
Peripheral edema	45 (18.1)	40 (16.0)	44 (18.2)
Upper respiratory tract infection	33 (13.3)	50 (20.0)	37 (15.3)
Right ventricular failure	56 (22.5)	37 (14.8)	32 (13.2)
Headache	22 (8.8)	33 (13.2)	33 (13.6)
Nasopharyngitis	26 (10.4)	37 (14.8)	34 (14.0)
Dizziness	27 (10.8)	24 (9.6)	26 (10.7)
Cough	30 (12.0)	20 (8.0)	21 (8.7)
Bronchitis	14 (5.6)	20 (8.0)	28 (11.6)
Anaemia	8 (3.2)	22 (8.8)	32 (13.2)
Dyspnea	22 (8.8)	26 (10.4)	18 (7.4)

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

Adverse events and laboratory abnormalities previously associated with ERAs

	Placebo *n* = 249	Macitentan 3 mg *n* = 250	Macitentan 10 mg *n* = 242
Mean treatment duration, weeks	85.3	99.5	103.9
ALT or AST > 3 x ULN, % (*n*/N)	4.5 (11/244)	3.6 (9/247)	3.4 (8/236)
ALT or AST > 3 x ULN and bilirubin > 2 x ULN, % (*n*/N)	1.7 (4/237)	2.1 (5/241)	1.7 (4/230)
Haemoglobin ≤ 8 g/dl, % (*n*/N)	0.4 (1/237)	1.7 (4/241)	4.3 (10/230)
Peripheral oedema, % (*n*/N)	18.1 (45/249)	16.0 (40/250)	18.2 (44/242)

- Up to 28 days after study drug discontinuation
- ULN: upper limit of normal

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

Market release of Macitentan

- FDA approval: October 18th, 2013
  - Brand name: **Opsumit**
- Korea
  - MFDS approval: November 13th, 2014
  - 2015년 말이나 2016년 초 launching 예정

[효능효과]

- WHO 기능분류 II~III 단계에 해당하는 PAH (WHO Group I) 성인 환자의 장기 치료.
- 특발성 폐동맥고혈압, 유전성 폐동맥고혈압, 결합조직질환과 연관된 폐동맥고혈압, 선천성 심장질환과 연관된 폐동맥고혈압 환자에서 유효성이 입증되었다.

Macitentan usage, adult

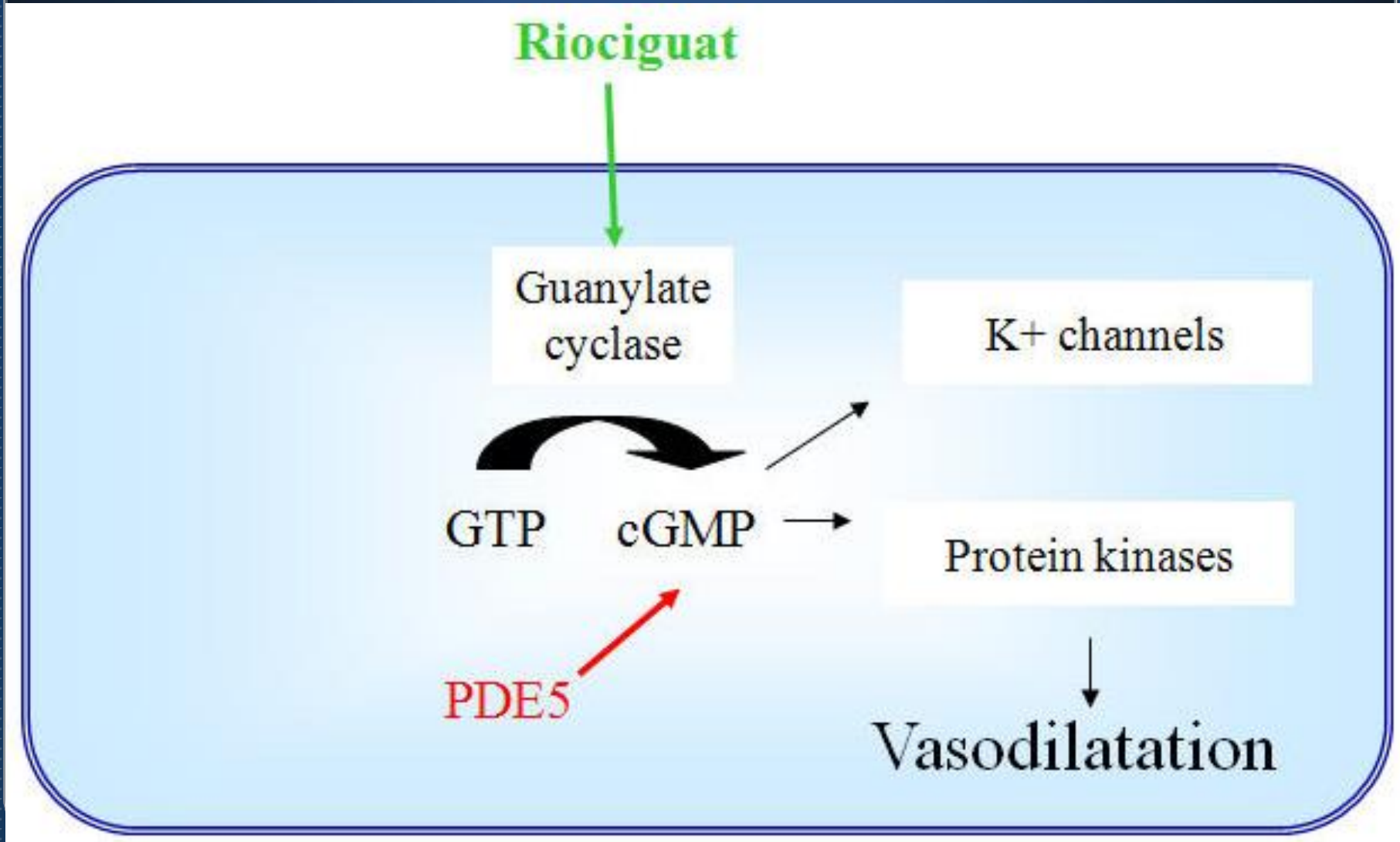
- 10 mg once daily, diet 와 무관
- Full blood count : every 3-4 months.
- No liver toxicity was seen in SERAPHIN study

  - liver function tests is still needed monthly

Riociguat

A soluble guanylate cyclase stimulator

Mechanism of Riociguat effect



Riociguat Phase 3 studies

FIRST Phase 3 RCT of an sGC stimulator in PAH

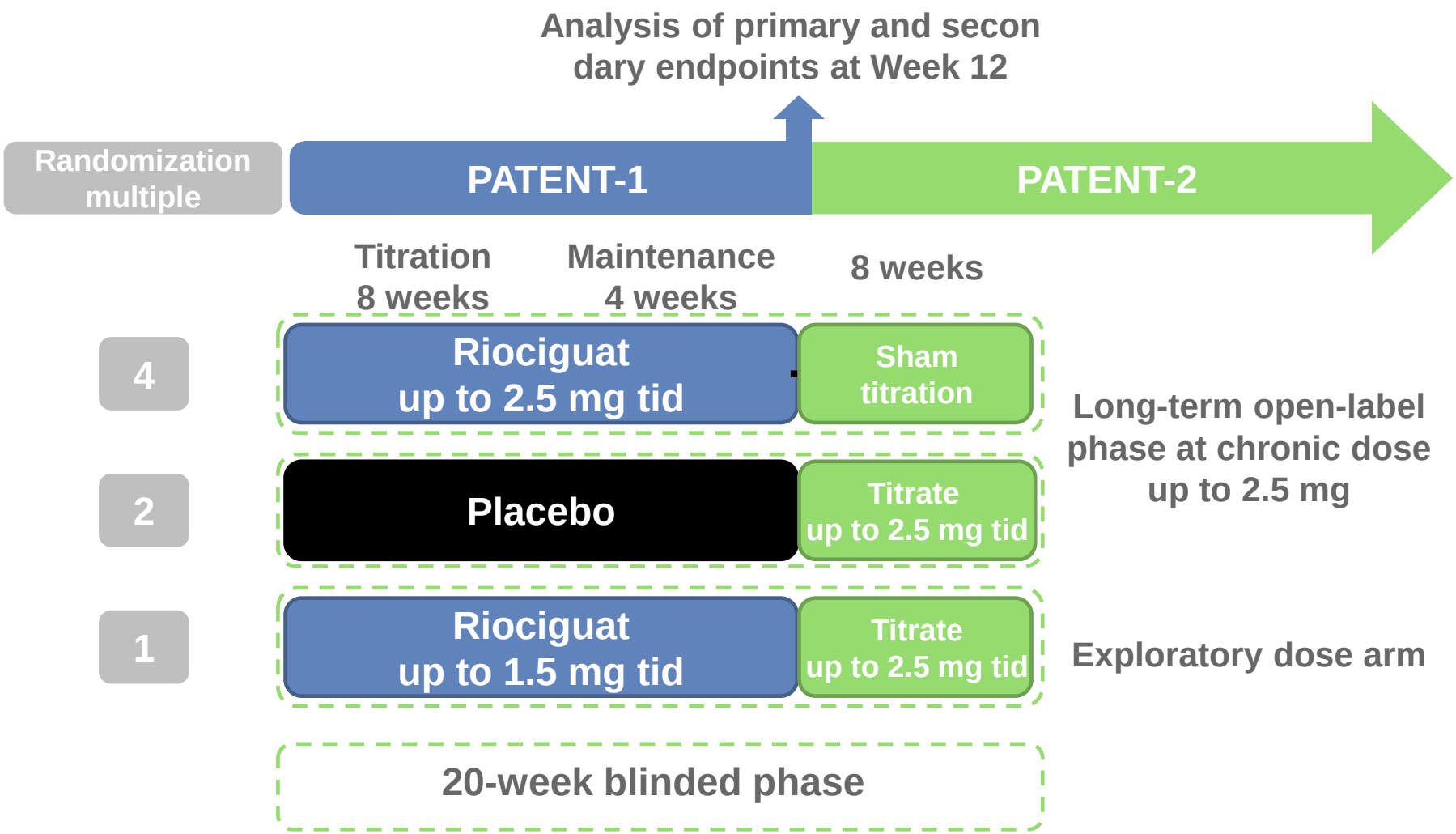
FIRST Phase 3 RCT of an sGC stimulator in inoperable CTEPH

•RCT, randomized controlled trial; sGC, soluble guanylate cyclase.

• Ghofrani HA *et al. N Engl J Med* 2013; 369: 330 - 340.
• Ghofrani HA *et al. N Engl J Med* 2013; 369: 319 -329

Study design

PATENT
Pulmonary Arterial Hypertension sGC-Stimulator Trial
Riociguat



(Ghofrani HA *et al. N Engl J Med* 2013; 369:330 -340)

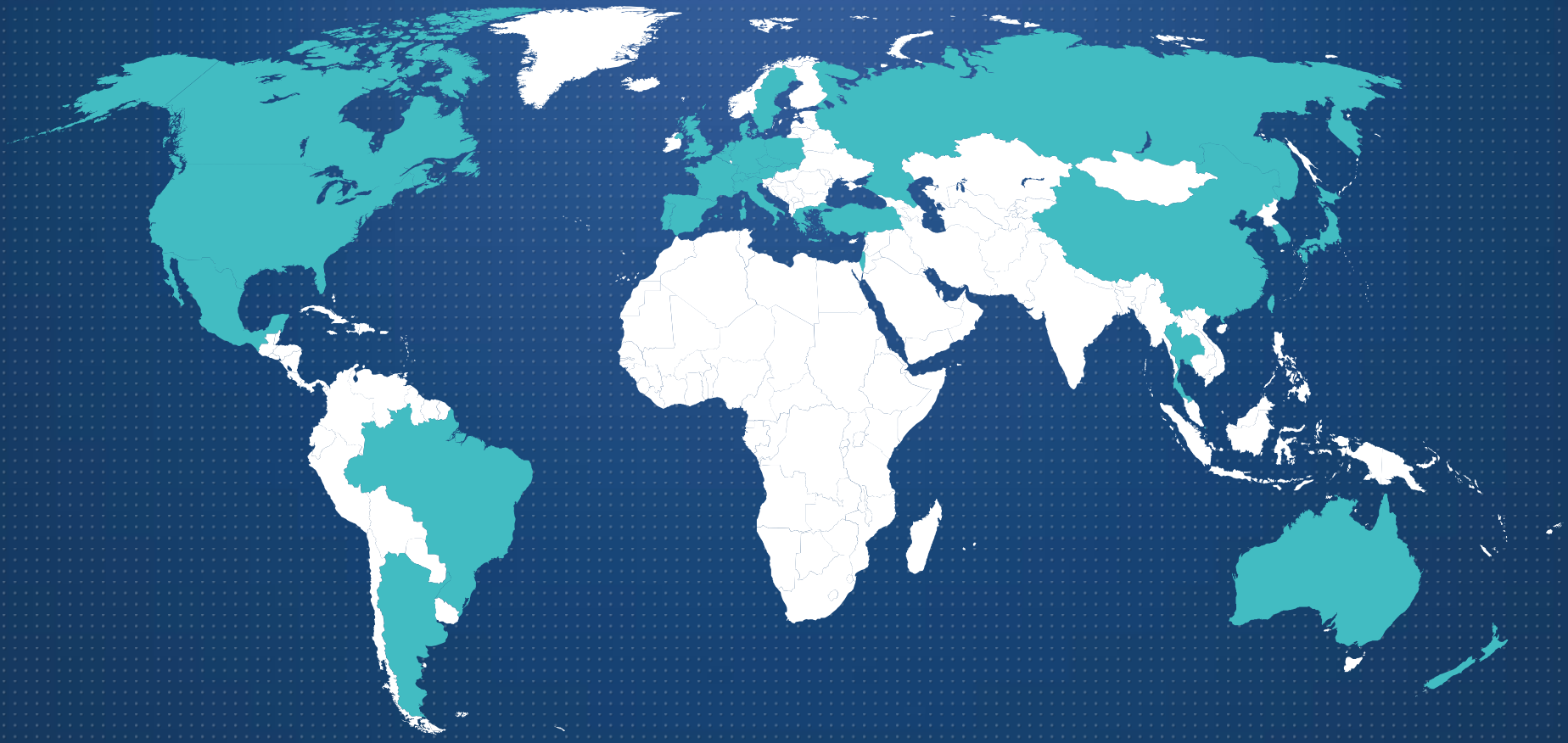
Inclusion criteria

- Age **18–80** years
- Symptomatic PAH (WHO group 1)
  - Idiopathic PAH
  - Familial PAH
  - Associated PAH due to congenital heart disease (if surgically corrected)
  - Associated PAH due to connective tissue disease
  - Associated PAH due to portal hypertension with liver cirrhosis
  - Associated PAH due to anorexigen or amphetamine use
- 6MWD at baseline 150–450 m
- PVR >300 dyn·sec·cm^{-5} and mPAP ≥25 mmHg
- Treatment naïve or on stable treatment with an ERA or PCA (oral, inhaled, or subcutaneous) for ≥3 months

cf) 6MWD, 6-minute walking distance; ERA, endothelin receptor antagonist; mPAP, mean pulmonary arterial pressure; PCA, prostacyclin analog; PVR, pulmonary vascular resistance.

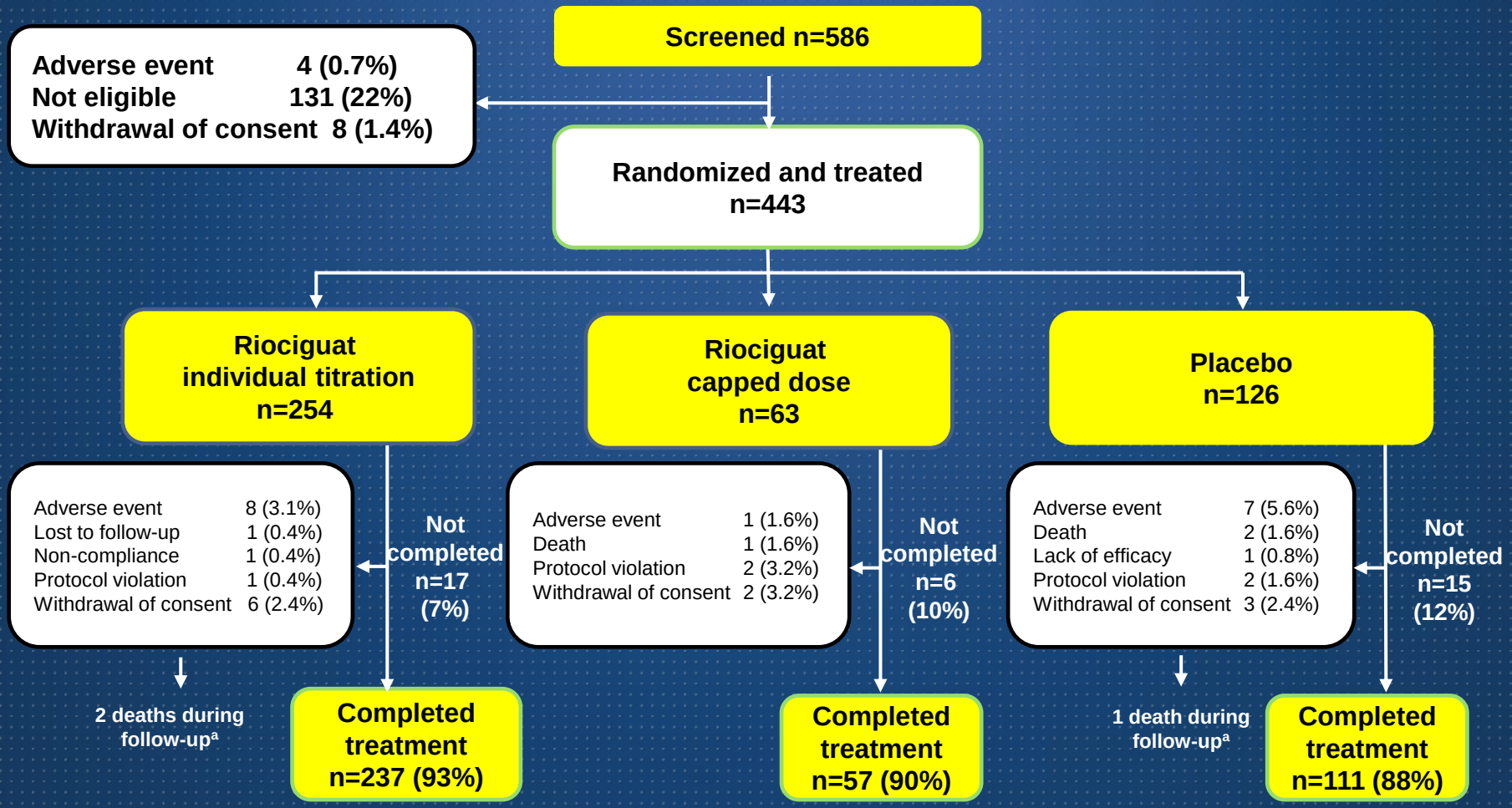
(Ghofrani HA *et al. N Engl J Med* 2013; 369:330 -340)

PATENT study centres



Countries where patients were recruited

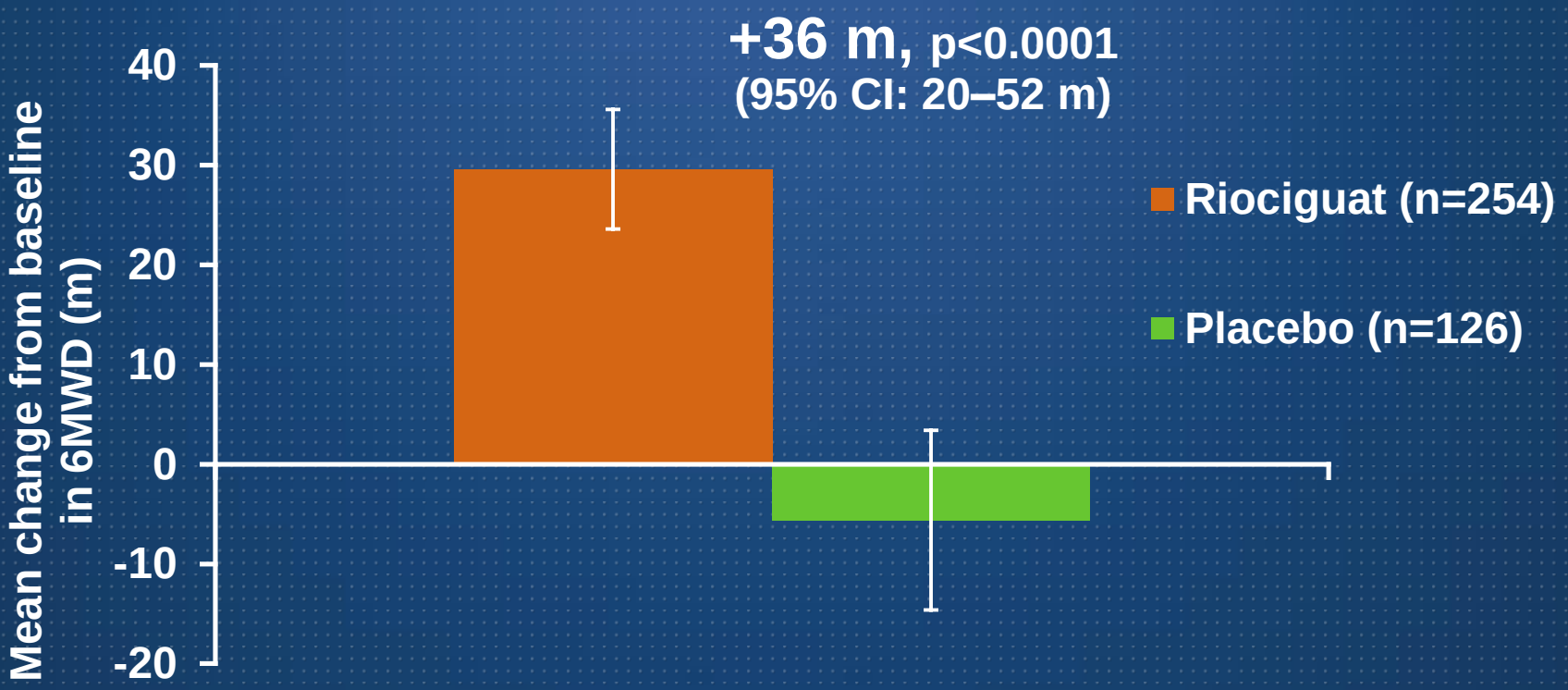
Patient disposition



- [a]Safety follow-up phase: 30 days (only for patients who did not enter PATENT-2 or who stopped study medication prematurely).

(Ghofrani HA *et al. N Engl J Med* 2013; 369:330 -340)

Primary endpoint (6MWD)



(Ghofrani HA *et al. N Engl J Med* 2013; 369:330 -340)

Meaningful improvement of cardiopulmonary 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

(Ghofrani HA *et al. N Engl J Med* 2013; 369:330 -340)

Adverse events

Adverse event (treatment emergent)	Riociguat (n=254)	Placebo (n=126)
Ten most frequently reported AEs, n (%)		
Headache	69 (27)	25 (20)
Dyspepsia	48 (19)	10 (8)
Peripheral edema	44 (17)	14 (11)
Nausea	40 (16)	16 (13)
Dizziness	40 (16)	15 (12)
Diarrhea	35 (14)	13 (10)
Nasopharyngitis	26 (10)	14 (11)
Dyspnea	16 (6)	14 (11)
Cough	12 (5)	13 (10)
Vomiting	26 (10)	11 (9)
AEs of special interest, n (%)		
Hypotension	**25 (10)**	3 (2)
Syncope	3 (1)	5 (4)

(Ghofrani HA *et al. N Engl J Med* 2013; 369:330 -340)

Market release of Riociguat

- FDA approval: Oct. 8th, 2013
  - Brand name: **Adempas**
  - for the treatment of **pulmonary arterial hypertension (PAH)** and the treatment of **chronic thromboembolic pulmonary hypertension (CTEPH)**
- **Korea**
  - 2015.6 월 launching 예정 (for CTEPH)
  - PAH 에 대해서는 적응증 받지 못함.

Riociguat usage, adult

- Initial dose: 1 mg PO tid

  - consider 0.5 mg PO tid if patient may not tolerate hypotensive effect

- If systolic blood pressure >95 mmHg and no symptoms of hypotension

  ➔ up-titrate dose by 0.5 mg PO tid with dose increases no sooner than 2 weeks apart to highest tolerated dose (not to exceed 2.5 mg PO TID)

- If symptoms of hypotension occur

  ➔ decrease dose by 0.5 mg TID

Treprostinil

Epoprostenol analogue

EchoCG (1999.1.16. 7.4 year-old)

- VSD (PM with IE+TE), large, R-> L shunt
- ASD: 2’, moderate
- PDA: not small

- TR: mild, peak vel. – 4.5 m/sec
- Atrial septum : sl. deviated to the LA
- PR: mild, peak vel. – 4 m/sec

Pre-op cath (99.1.18) and Op. (99.1.20)

	Room air	FiO2 1.0	FiO2 1.0 +NO 10 ppm
Sys PA pr. mmHg	110	113	106
Mean PA pr. mmHg	82	87	80
Rp, WU	14.2	11	8.7
Qp/Qs	0.47	1	1.3
Rp/Rs	2.1	1	0.79

- VSD closure, PDA ligation,
- ASD closure with 2.7 mm fenestration

EchoCG (2002.12.30. 3 years after Op.)

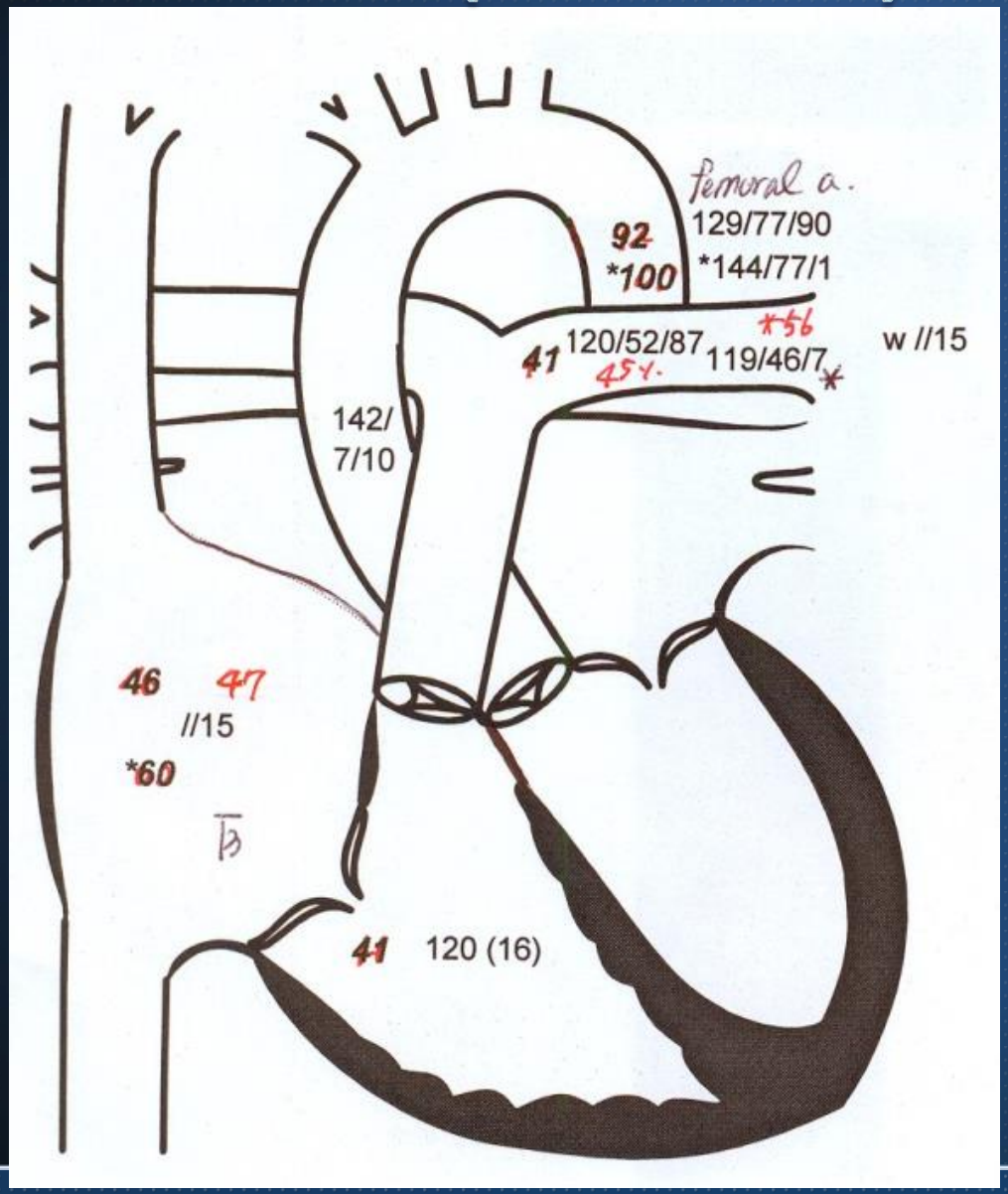
- VSD closed.
- **TR** : mild to moderate, peak vel **4.6m/sec**.
- Slightly enlarged RA and RV.
- PI : mild.

F/U cath. (2002.12.30) and Pul. HTN Tx.

- PA pr. : 100/48/73 mmHg

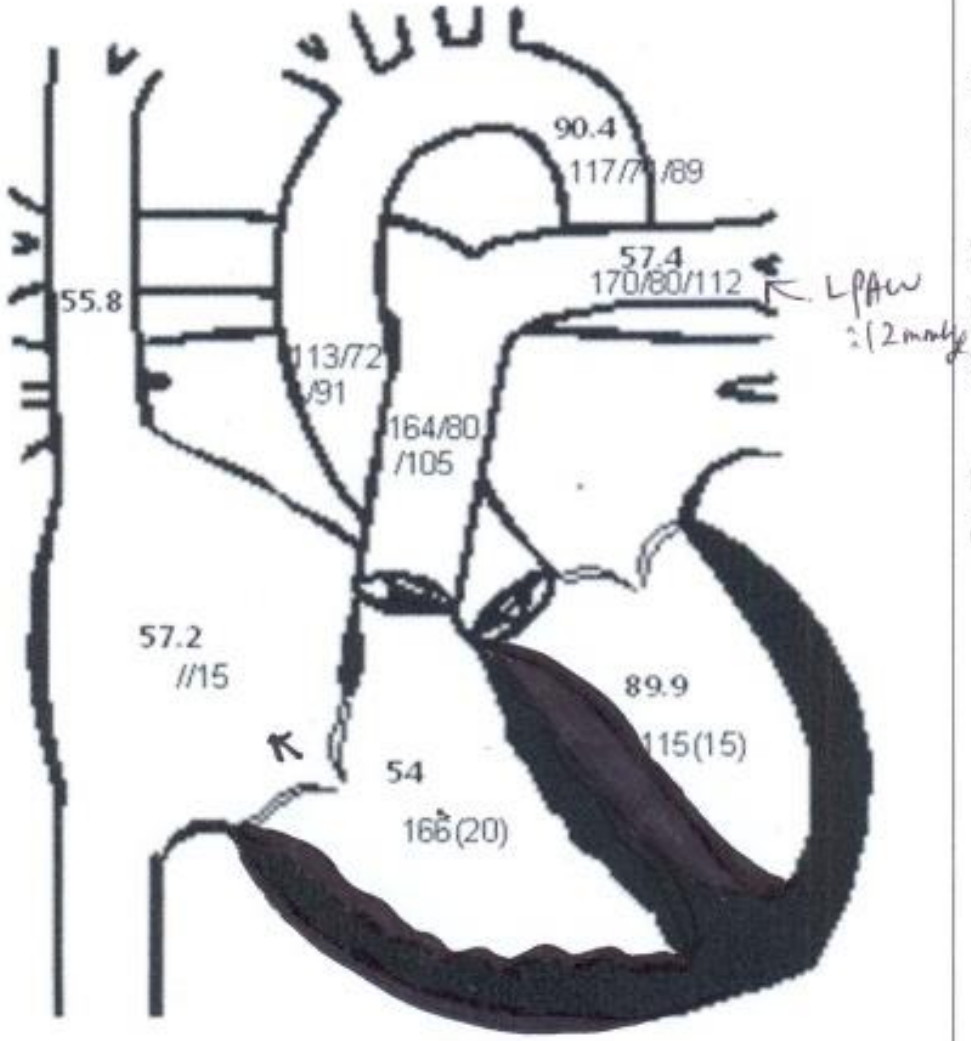
➔ Sildenafil start

F/U cath. (2007. 2.15) and Pul. HTN Tx.



➔ **Bosentan addition**

F/U cath. (2010. 2.25) and Pul. HTN Tx.



Diagnosis/Intervention

Primary pulmonary HTN

s/p VSD, ASD closure (1999.01)

<Cath finding>

1.severe Pulmonary HTN

-mean PA pressure :105mmHg

2. severely enlarged RV, squeezed LV(by echo)

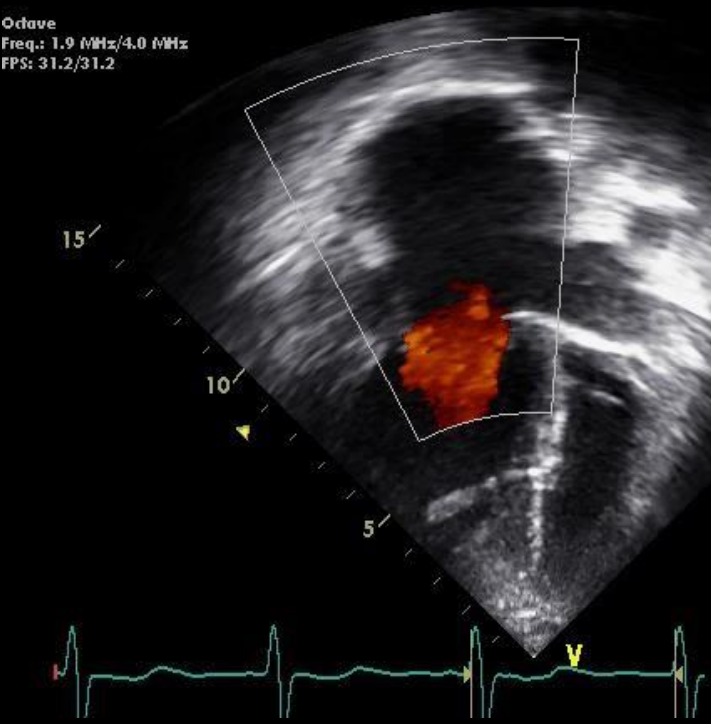
3. TR : mild to moderate(by echo)

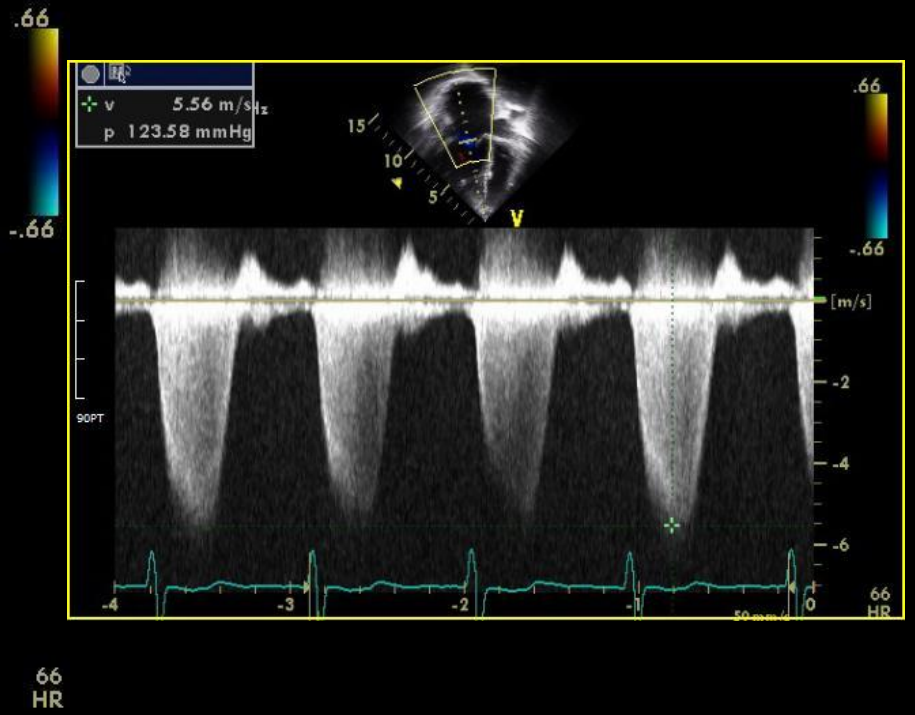
Rp/Rs= 47.1/35= 1.34

Qp/Qs=1.0

Rp : 376 dynes·sec·cm^{-5}

EchoCG (2012.4.30)





66
HR

TR peak vel. : 5.56 m/sec

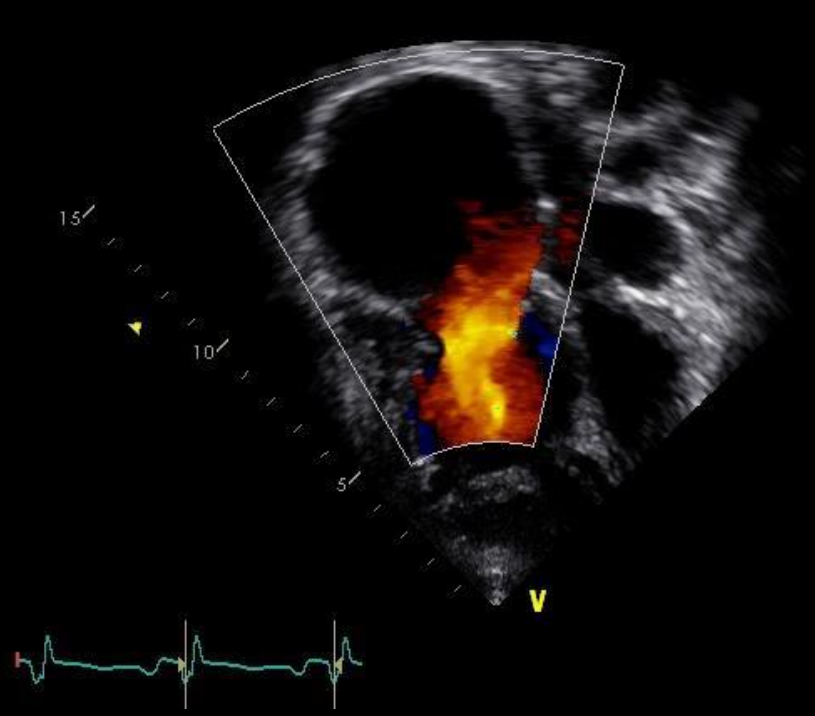
Admission (2014.7.15)

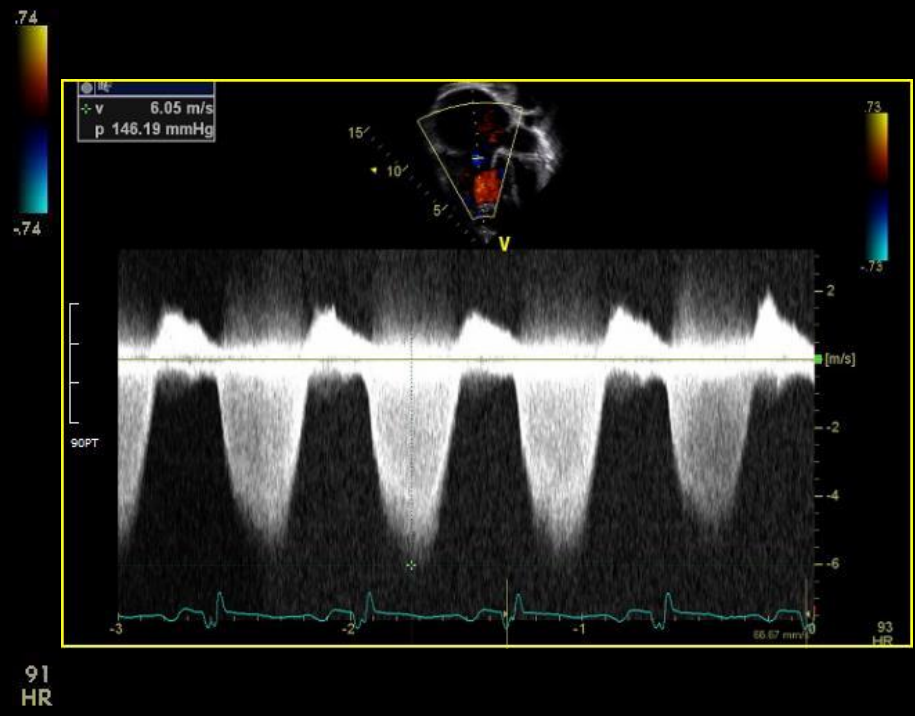
- C.C. : epigastric discomfort, nausea, L/E edema
  - onset : 1 month ago
- SpO2: 75-80% (Room air)
- BNP: 1695 pg/mL
- Total bil: 2.6 mg/dL

- **RV failure with congestive hepatopathy**

➔ IV dobutamine, Ventavis nebulizer, oxygen supply

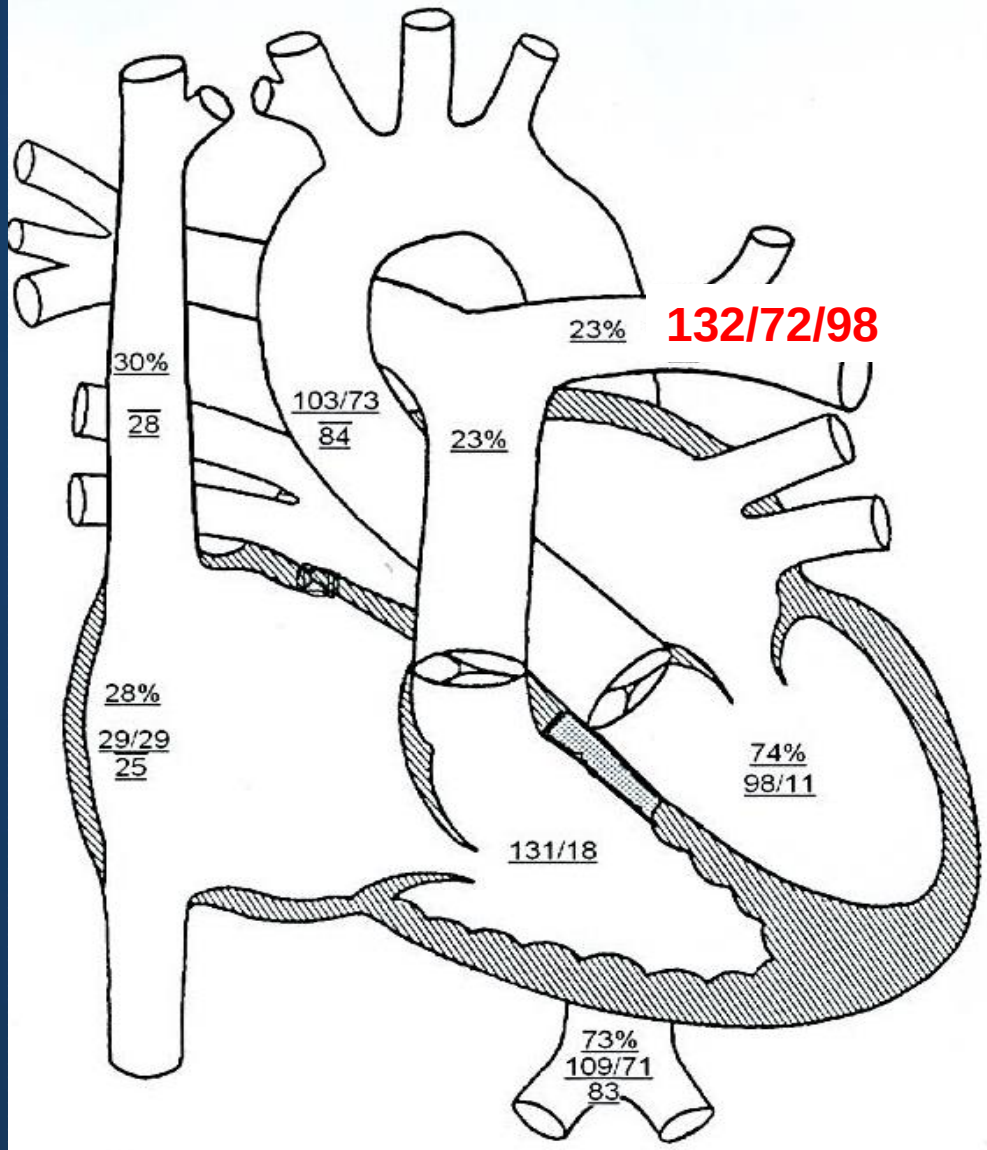
EchoCG (2014.7.29)





TR peak vel. : 6.05 m/sec

F/U cath. (2014.7.28)



Age at cath: 22 years
Gender: Female

Attending: 김기범
Fellow: 이선향
Referring:

Height: 154.3 cm Weight: 34.0 kg
BSA = 1.24 m©÷

Fluoro: 26.00 min Contrast: 0.00 mL
Vein: Right femoral 7fr
Artery: Right femoral 4fr

Set 1

Qp = 1.65 L/min (1.33 L/min/m²)
Qs = 1.96 L/min (1.58 L/min/m²)
Rp = 50.90 units (63.12 units x m²)
Rs = 29.63 units (36.74 units x m²)
Qp/Qs = 0.84 : 1 | Rp/Rs = 1.72

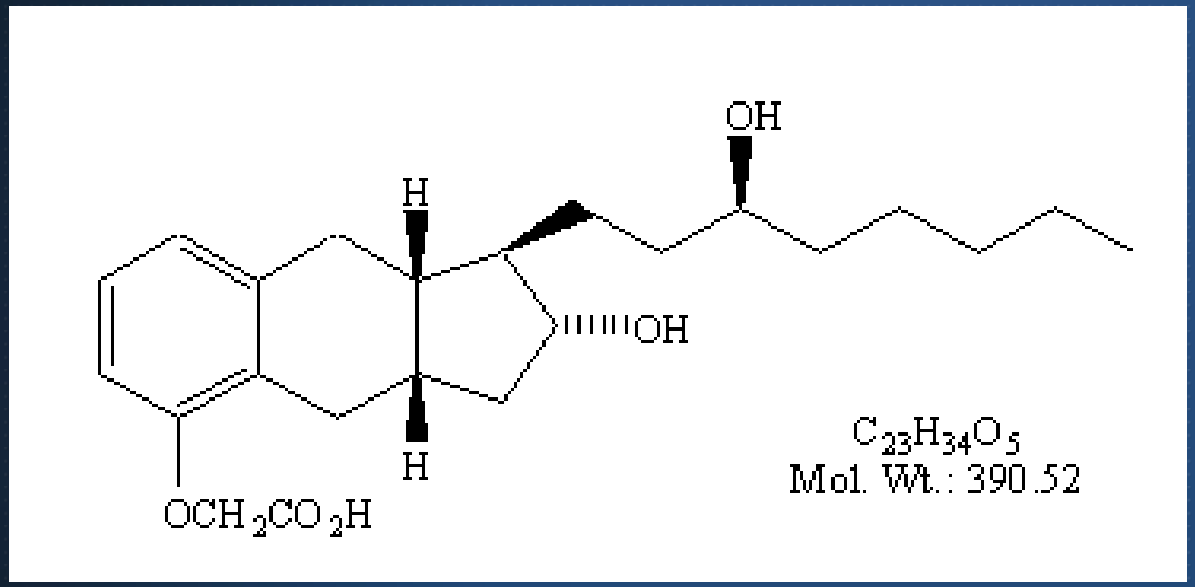
Heart Rate: 92 bpm
VO2: 120 ml/min/m²
Hemoglobin: 13.0 gm/dL

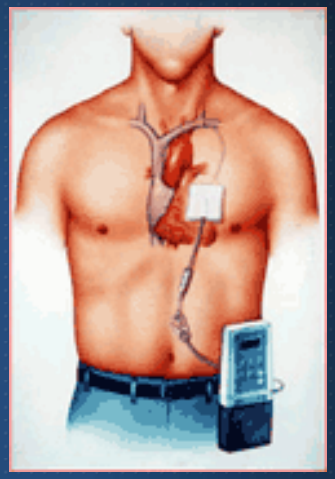
Inspired O2: 28%
pH:
pCO2:
pO2:
HCO3:

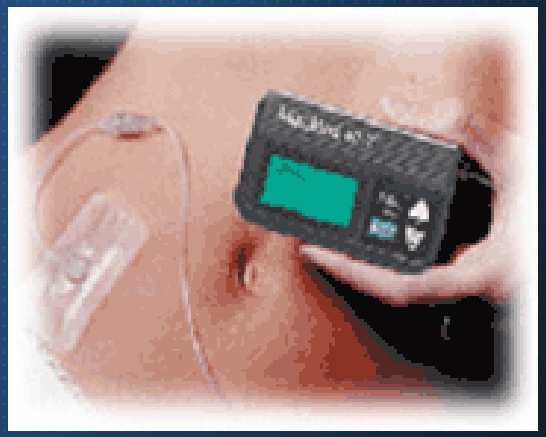
Thermo CO:

%O2	Site	Sys/A	Dias/V	Mean
30	SVC			28
28	RA	29	29	25
	RV	131	18	
23	PA			
	RPA			
23	LPA	137	72	98

Treprostinil (Remodulin®)







prostacyclin vasodilator

direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation

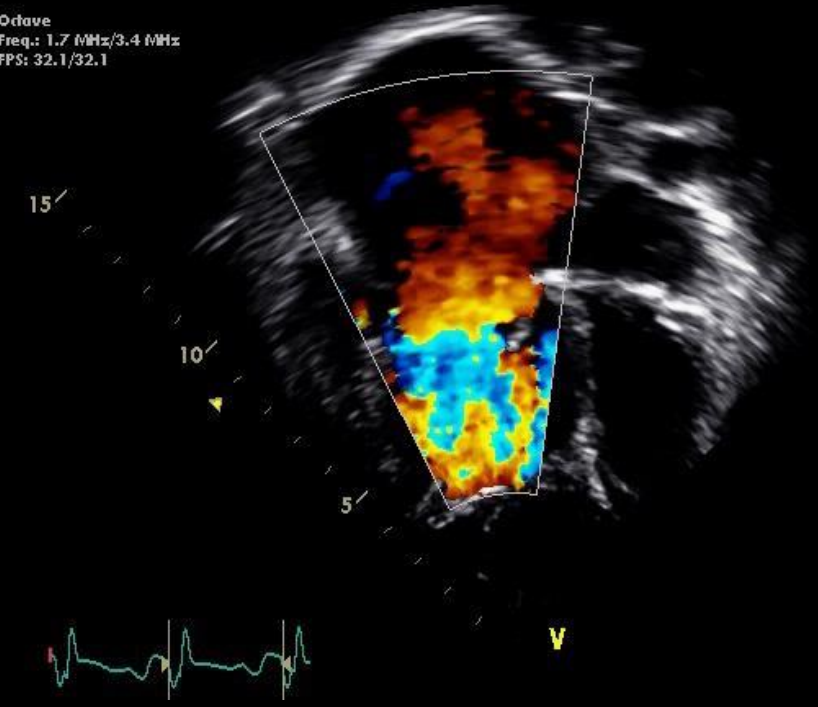
Market release of Treprostinil

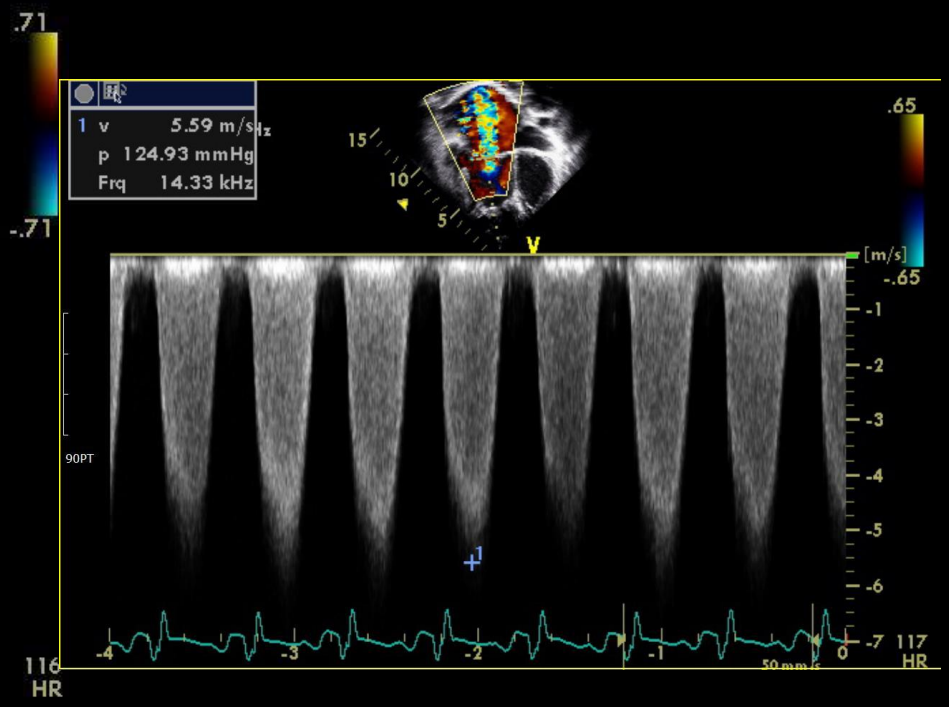
- FDA approval: May 21st, 2002
  - Brand name: **Remodulin**
  - for the treatment of **pulmonary arterial hypertension (PAH)** and the treatment of **chronic thromboembolic pulmonary hypertension (CTEPH)**
- MFDS approval: Feb. 8th, 2010

보험 고시 제2010-98호

구 분	세부인정기준 및 방법
Treprostinil 1mg/mL, 2.5mg/mL, 5mg/mL 주사제 (품명:레모둘린주사) **2.5mg/mL 20ml/병 [급여] - 5,720,000원 -**	아래와 같은 기준으로 투여 시 요양급여를 인정하며, 허가사항 범위이지만 동 인정기준 이외에 투여한 경우에는 약값 전액을 환자가 부담토록 함. - 아 래 - ◦ 대상환자 NYHA 분류 단계 Ⅳ에 해당하는 폐동맥 고혈압(WHO Group Ⅰ) 환자 중 아래 질환으로 진단이 확인된 환자로서 기존의 폐동맥 고혈압 약제(Iloprost 흡입액과 Bosentan hydrate 경구제)에 반응하지 않거나 금기인 경우 - Idiopathic pulmonary arterial hypertension 또는 - Familial pulmonary arterial hypertension 또는 - Pulmonary arterial hypertension associated with collagen vascular disease 또는 - Pulmonary arterial hypertension associated with congenital systemic to pulmonary shunts

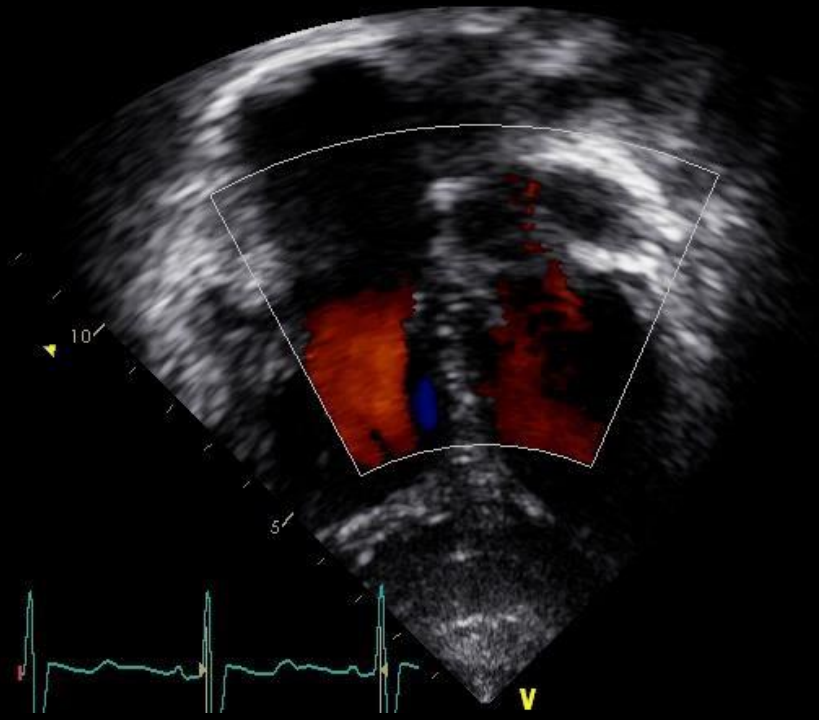
EchoCG (2014.8.8)





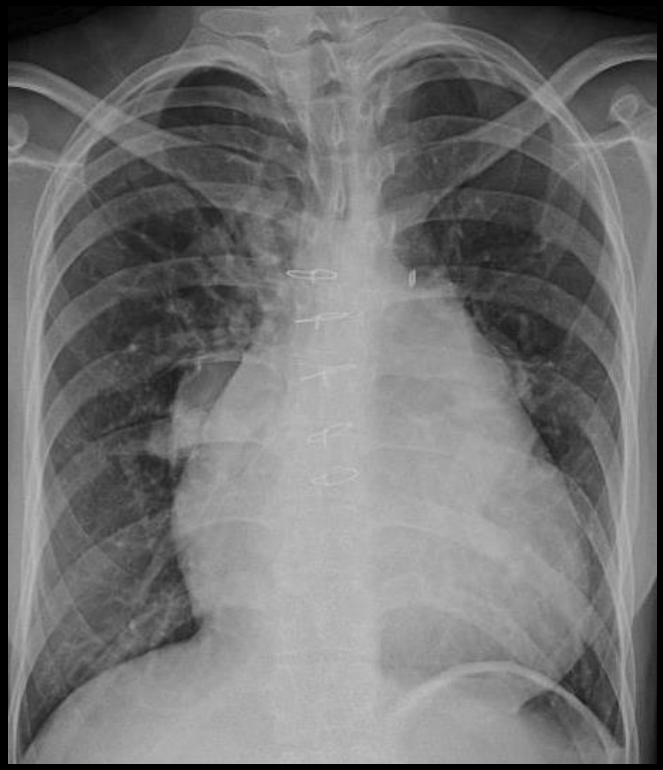
- Severe TR
- Peak vel. : 5.59 m/sec

EchoCG (2015.4.7)

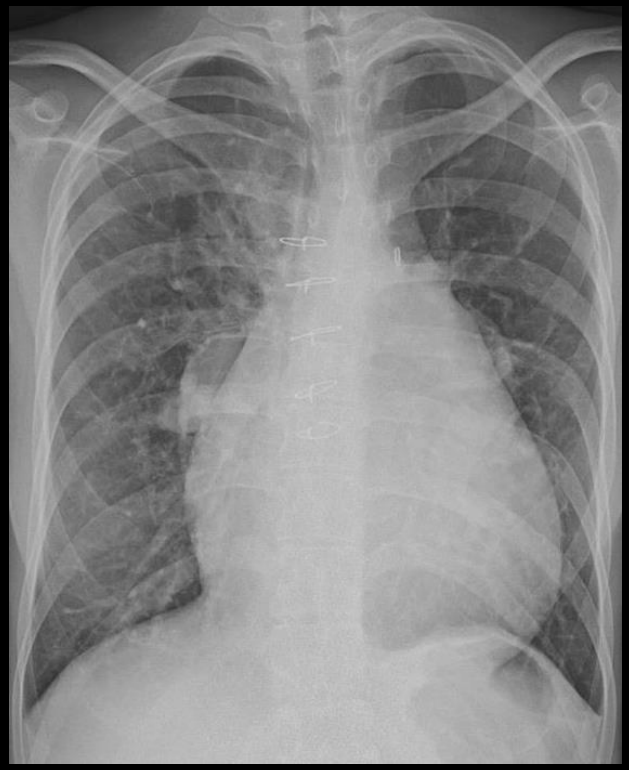


- **Mild TR**
- **Peak vel. : 5 m/sec**

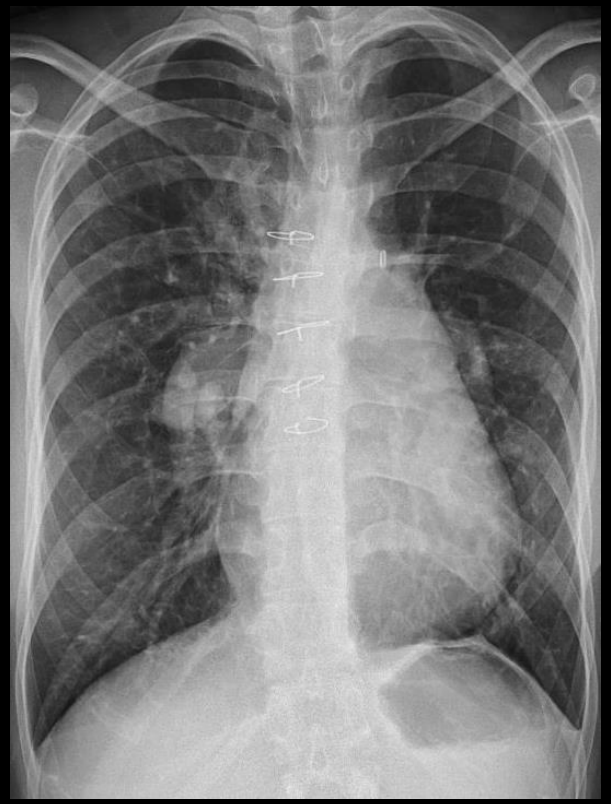
Chest PA



2014.7.15.
SpO2: 75-80%



2014.8.27.
SpO2: 90%



2015.4.7.
SpO2: 95%

Treprostinil usage

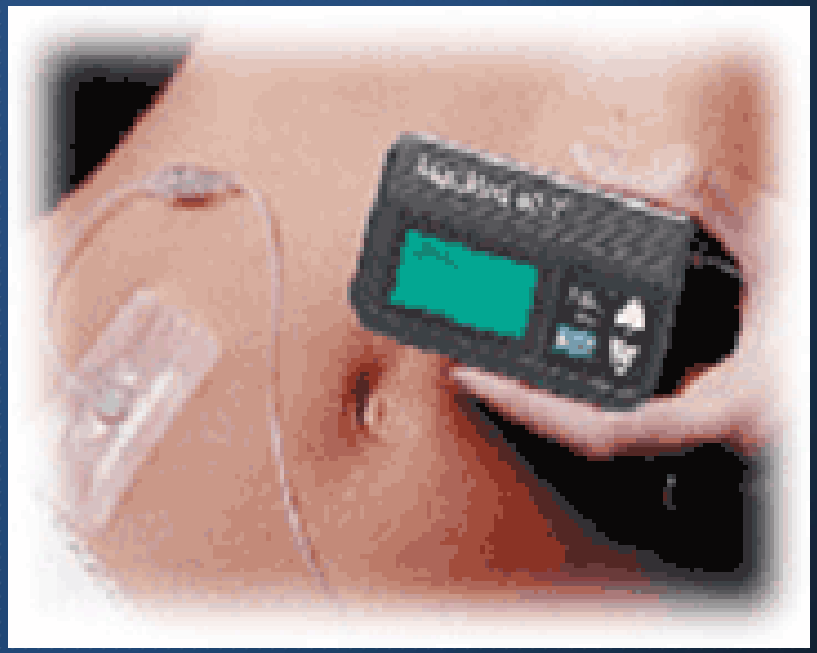
- Initiated at 1.25 ng/kg/min (or 0.625 ng/kg/min if not tolerated)
- Dose increase based on clinical response
  - Increments of 1.25 ng/kg/min per week for the first 4 weeks
  - After week 4, increments of 2.5 ng/kg/min per week
- Dosage adjustments can be undertaken more frequently as tolerated
- There is limited experience with doses >40 ng/kg/min in controlled clinical studies

*** 소아 및 청소년**

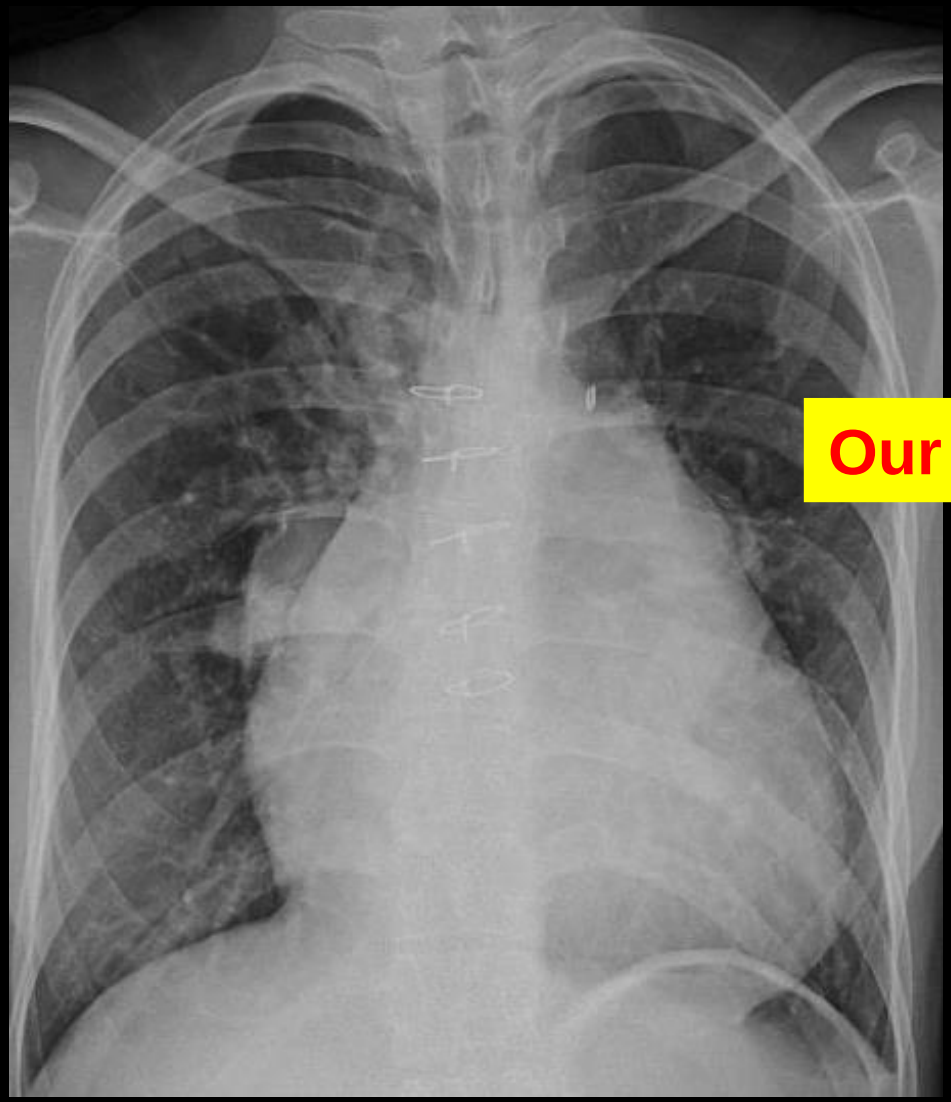
소아 및 청소년 환자에 대한 안전성 및 유효성은 확립되어 있지 않다.

SC Remodulin Side effects

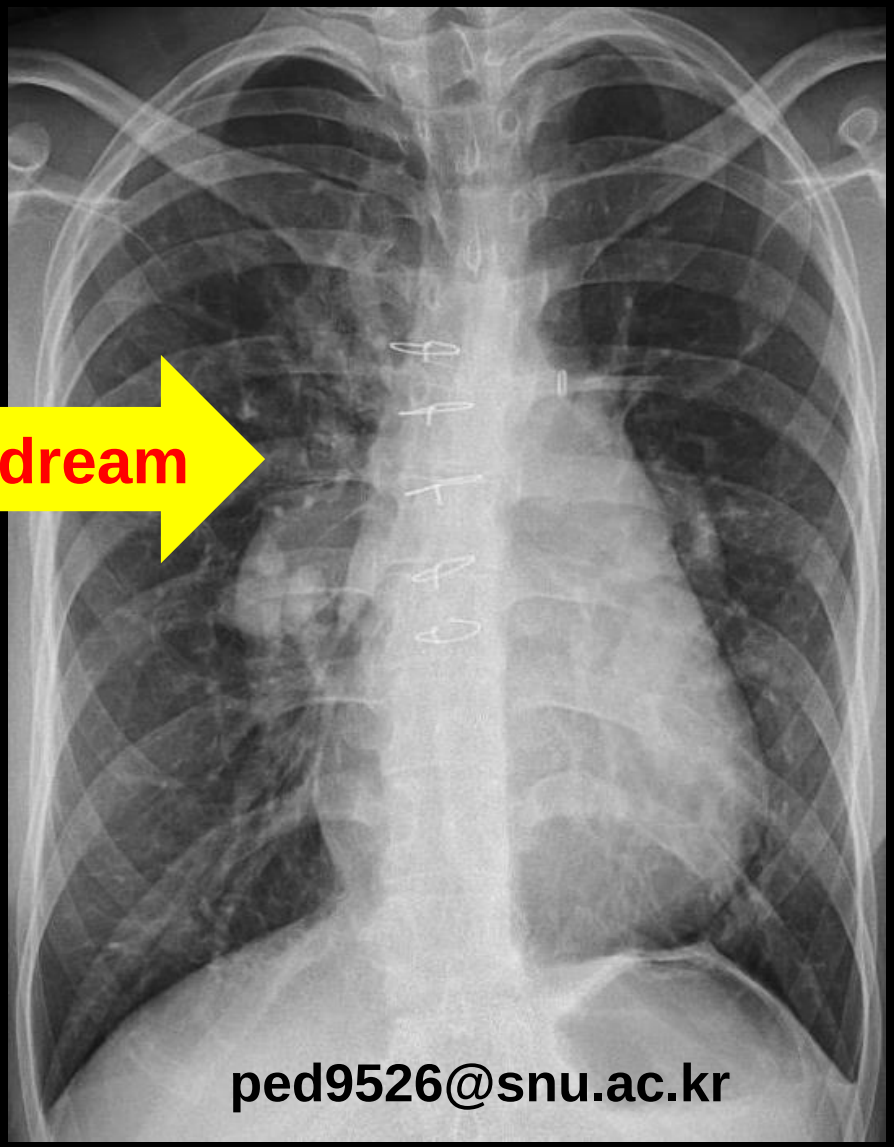
- Common Side Effects
  - Injection site pain
  - Headache
  - Jaw pain
  - Nausea
  - Diarrhea
  - Anxiety
  - Flushing



Thank You for Attention



Our dream



ped9526@snu.ac.kr