# The Development of Inhaled Therapies for Pulmonary Hypertension

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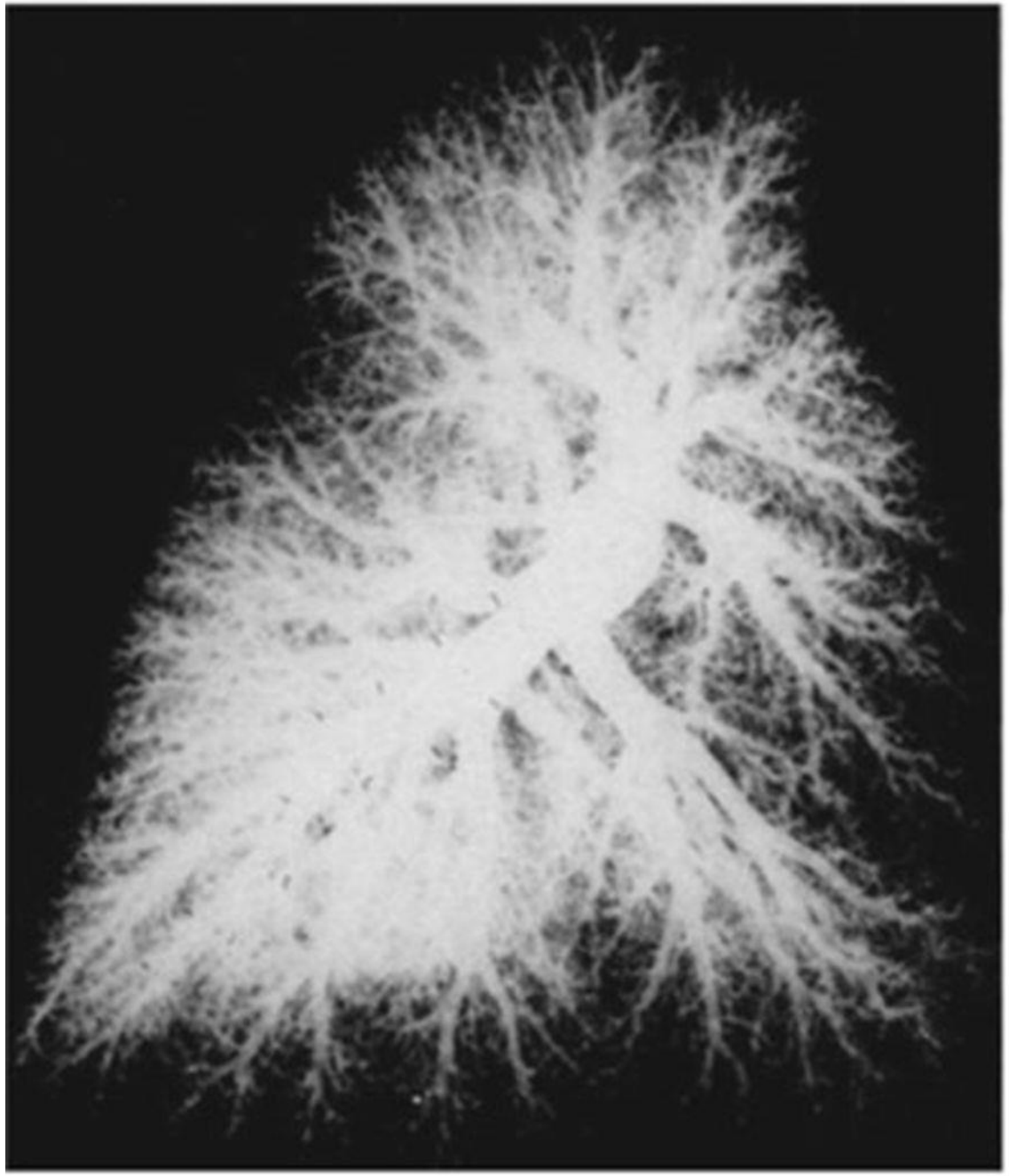
IMPERIAL

Imperial College Healthcare NHS

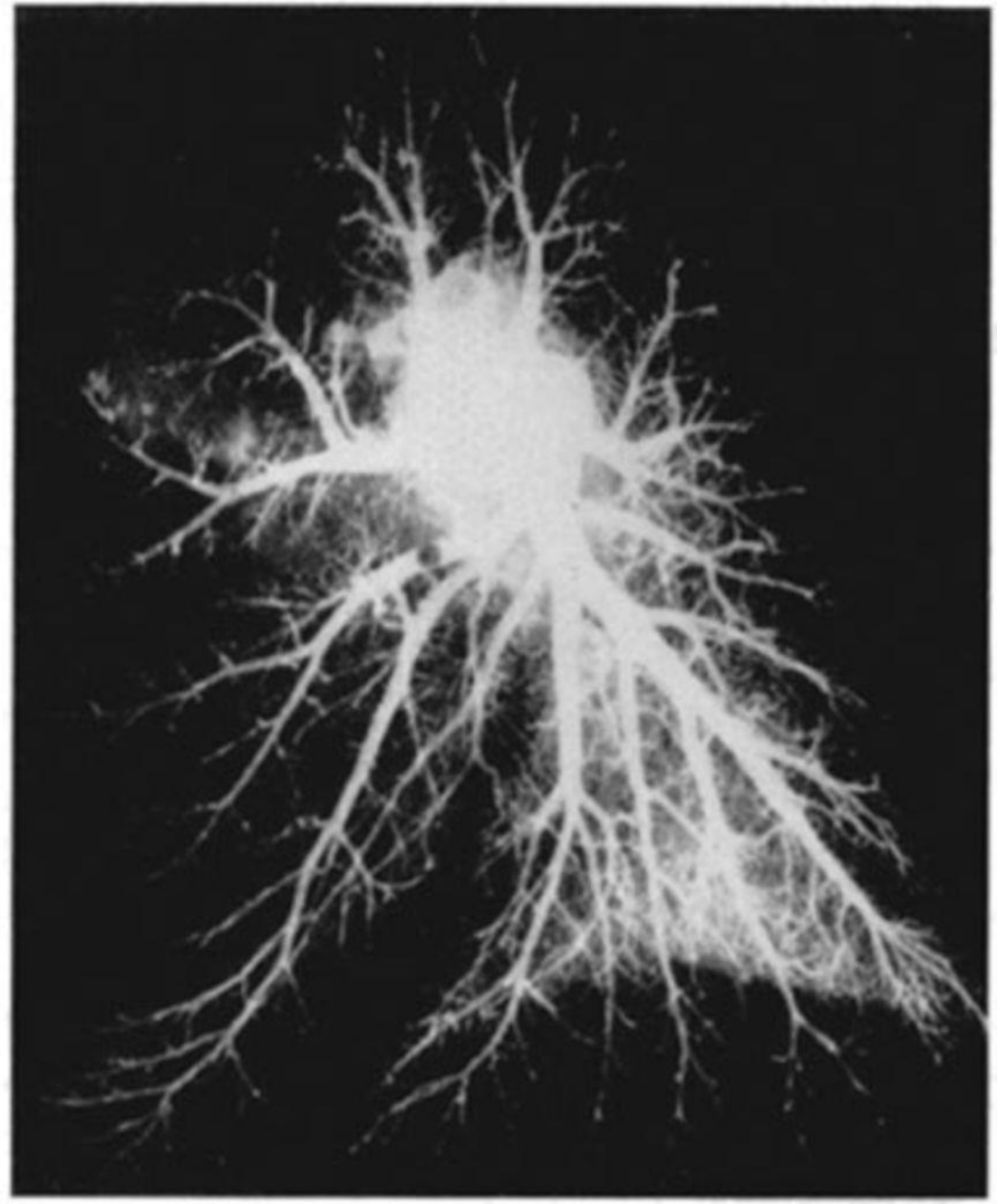
NHS Trust

# Disclosures

- Honoraria for lectures
  - Merck Sharp & Dohme Ltd, Janssen
- Honoraria for scientific advisory boards / steering committees
  - Janssen, Gossamer Bio, Merck Sharp & Dohme Ltd, United Therapeutics, Apollo Therapeutics, Liquidia, Altavant, Aerovate, Morphic
- Congress support
  - Janssen
- Stocks
  - ATXA Therapeutics, Circular, Calibre Biometrics, iOWNA, OneWelbeck Clinic

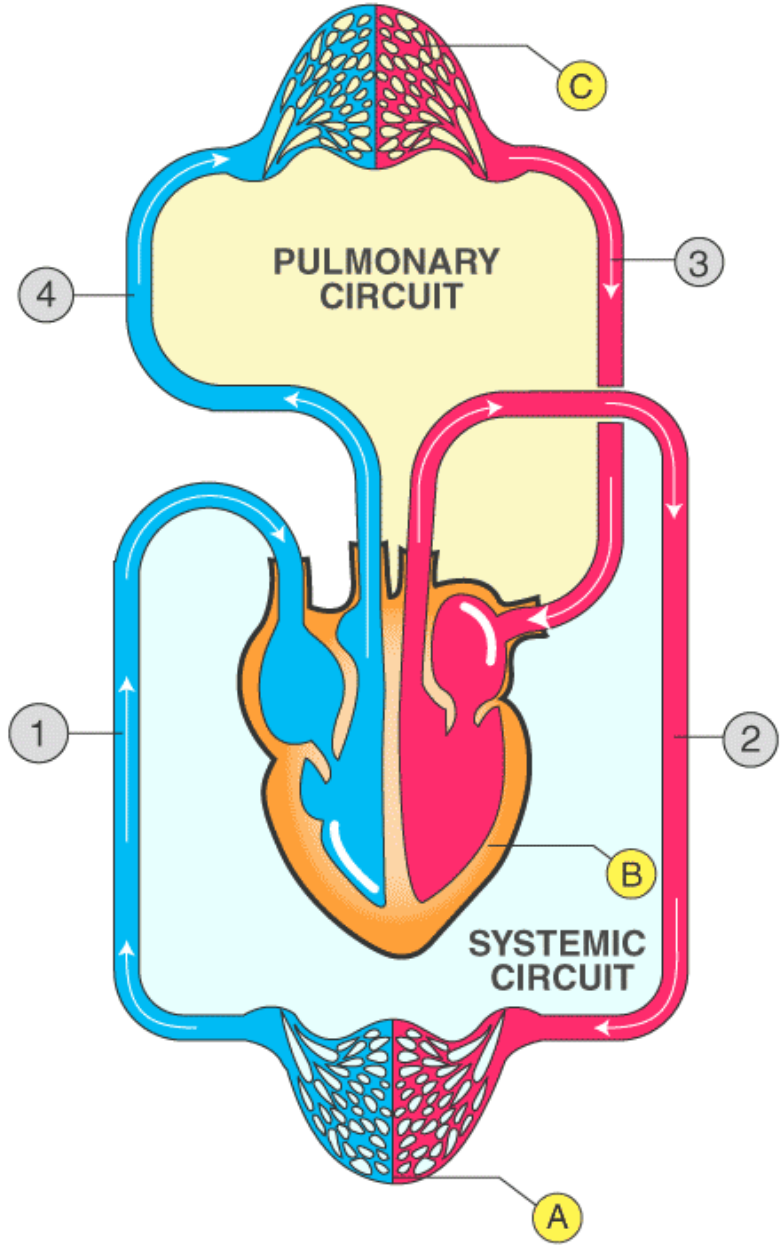


Normal



IPAH for 6 months

# DOUBLE CIRCULATION




1. Vena cava from body
2. Aorta to body
3. Pulmonary vein from lungs
4. Pulmonary artery to lungs

A. Capillaries of body organs apart from the lungs
B. Heart
C. Lung capillaries

# Why?

1. Deposit drug in area of lung most likely to benefit and not cause harm
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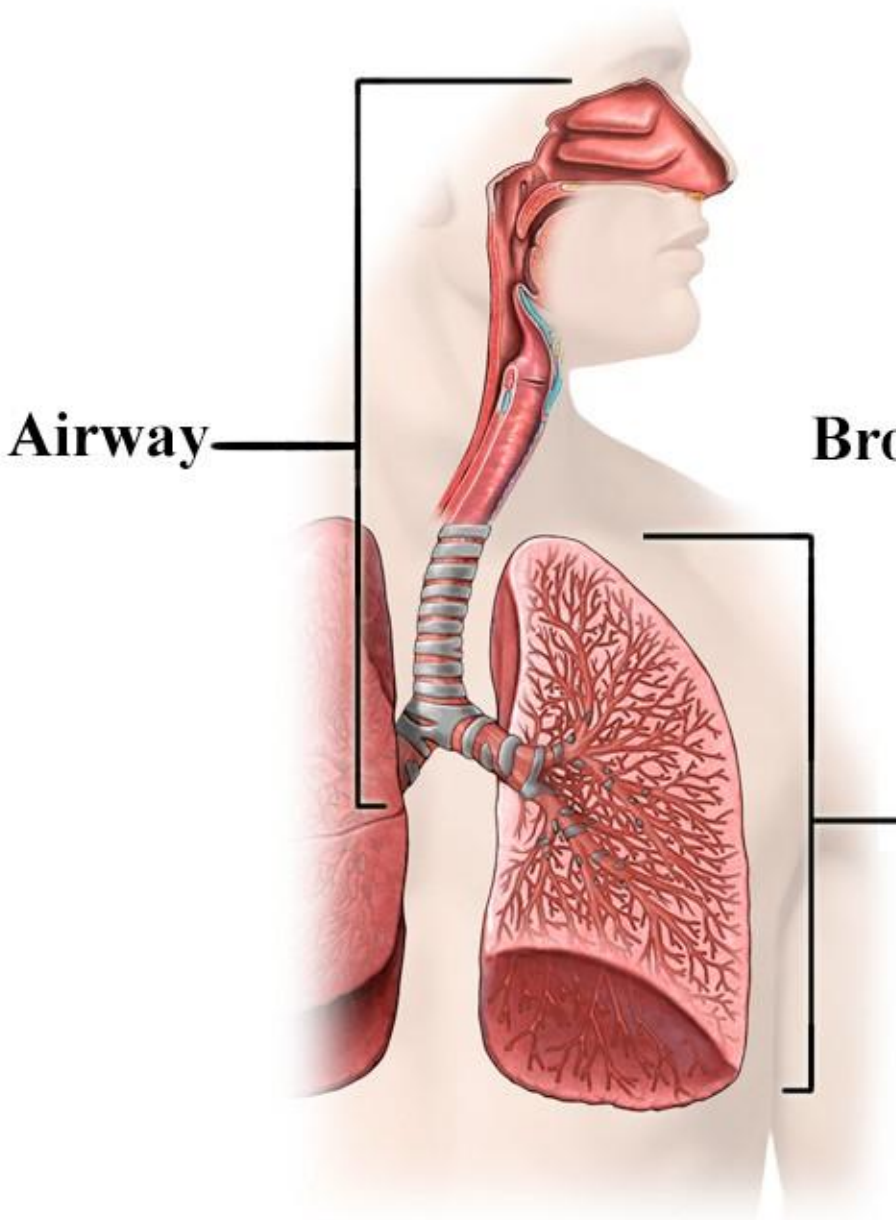
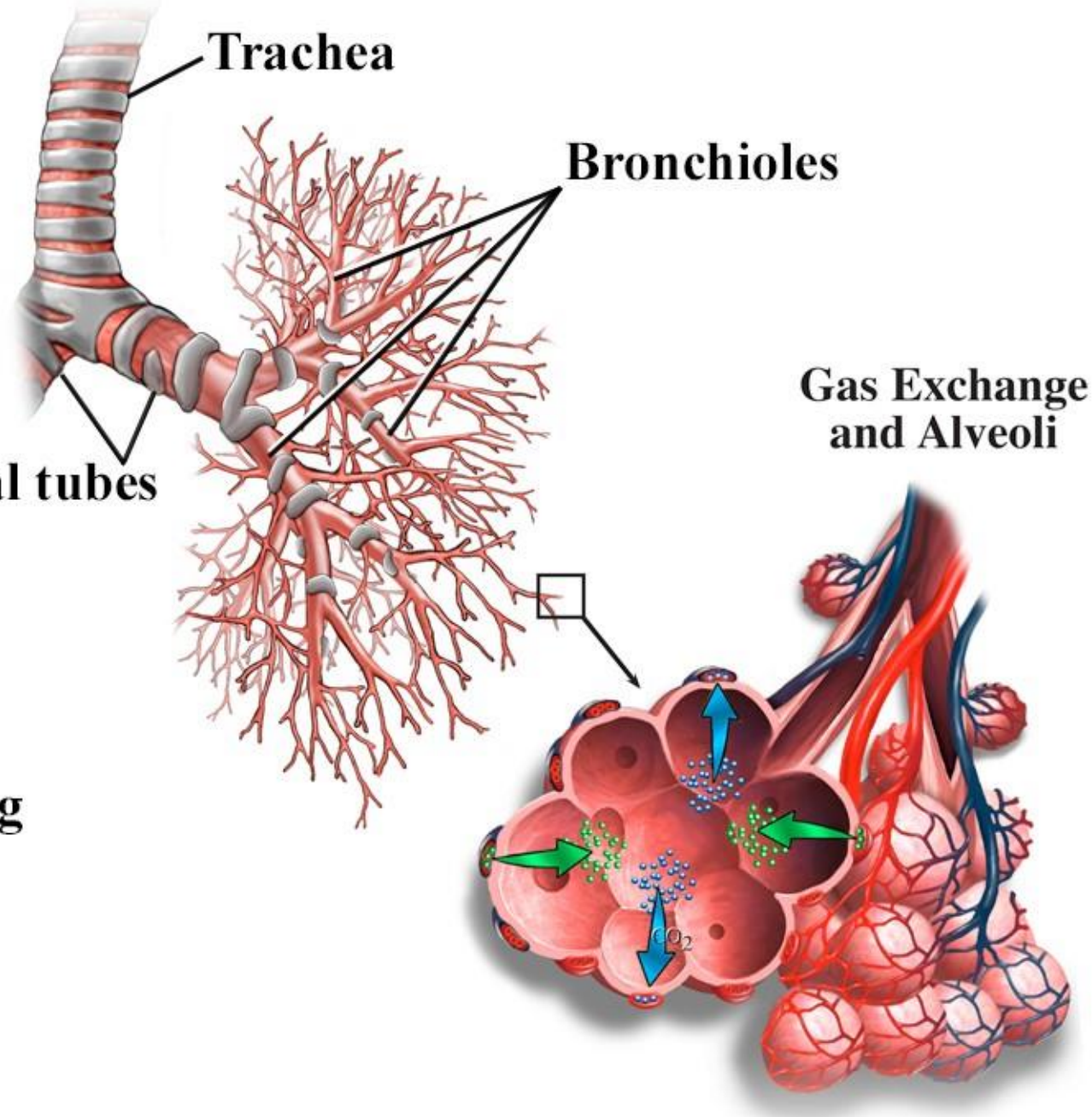
5. Administer a fast-acting therapy to act as an as required medication

# Respiratory Anatomy



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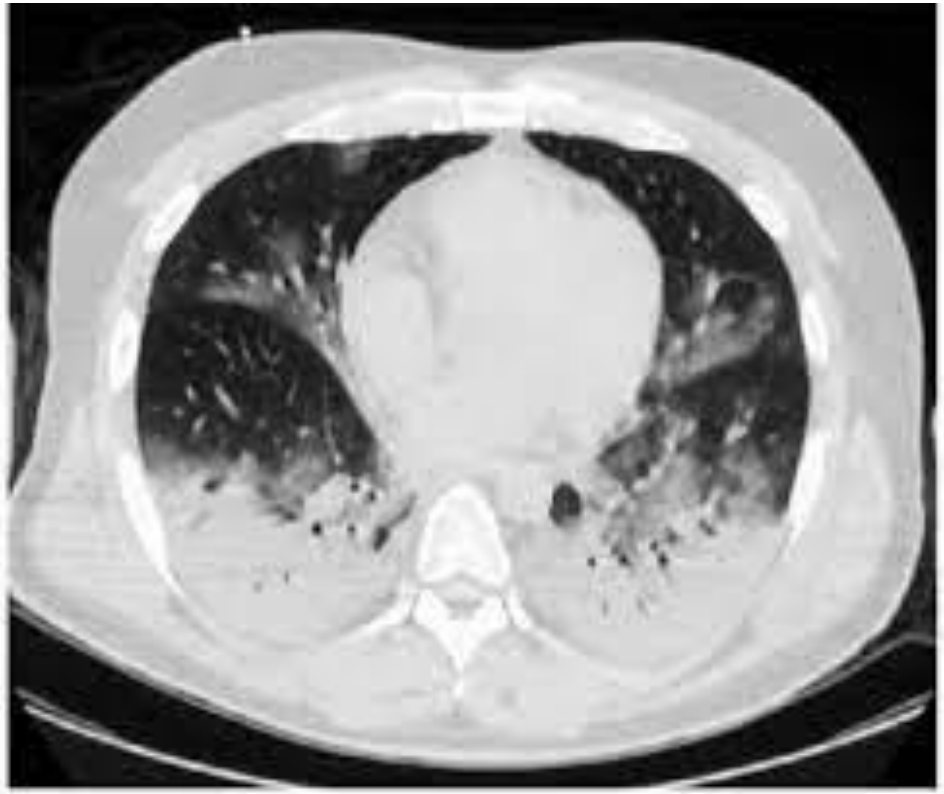
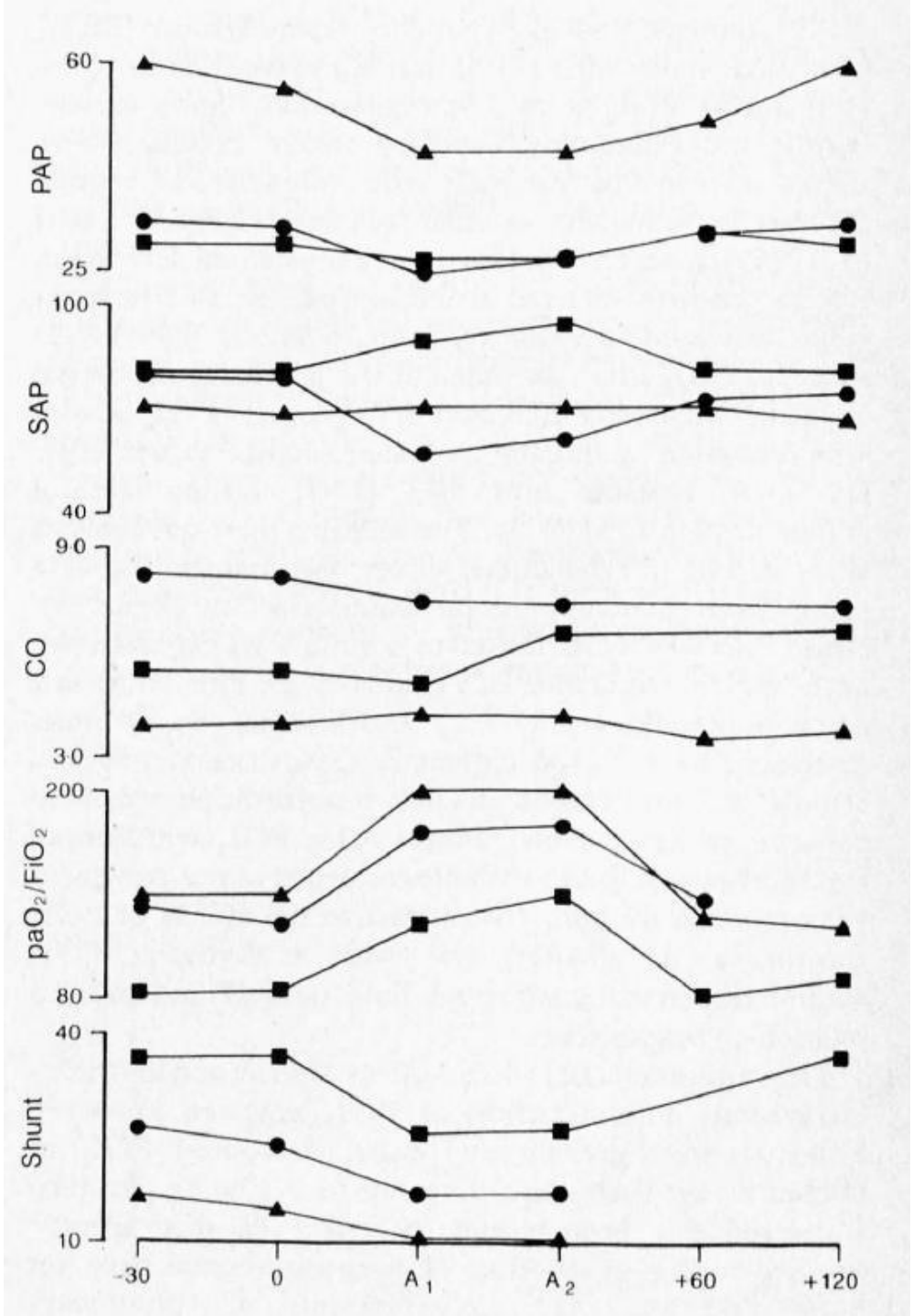
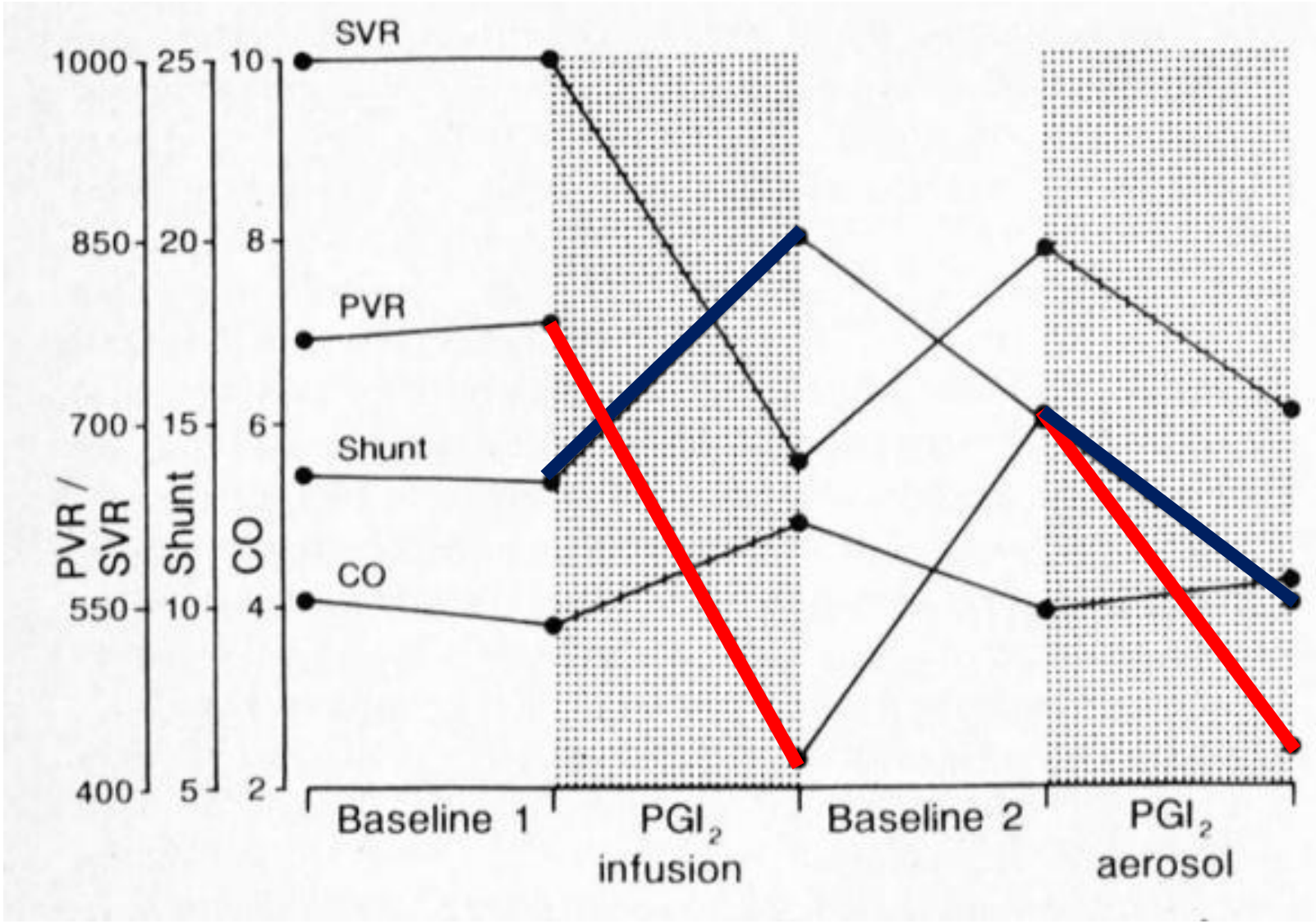
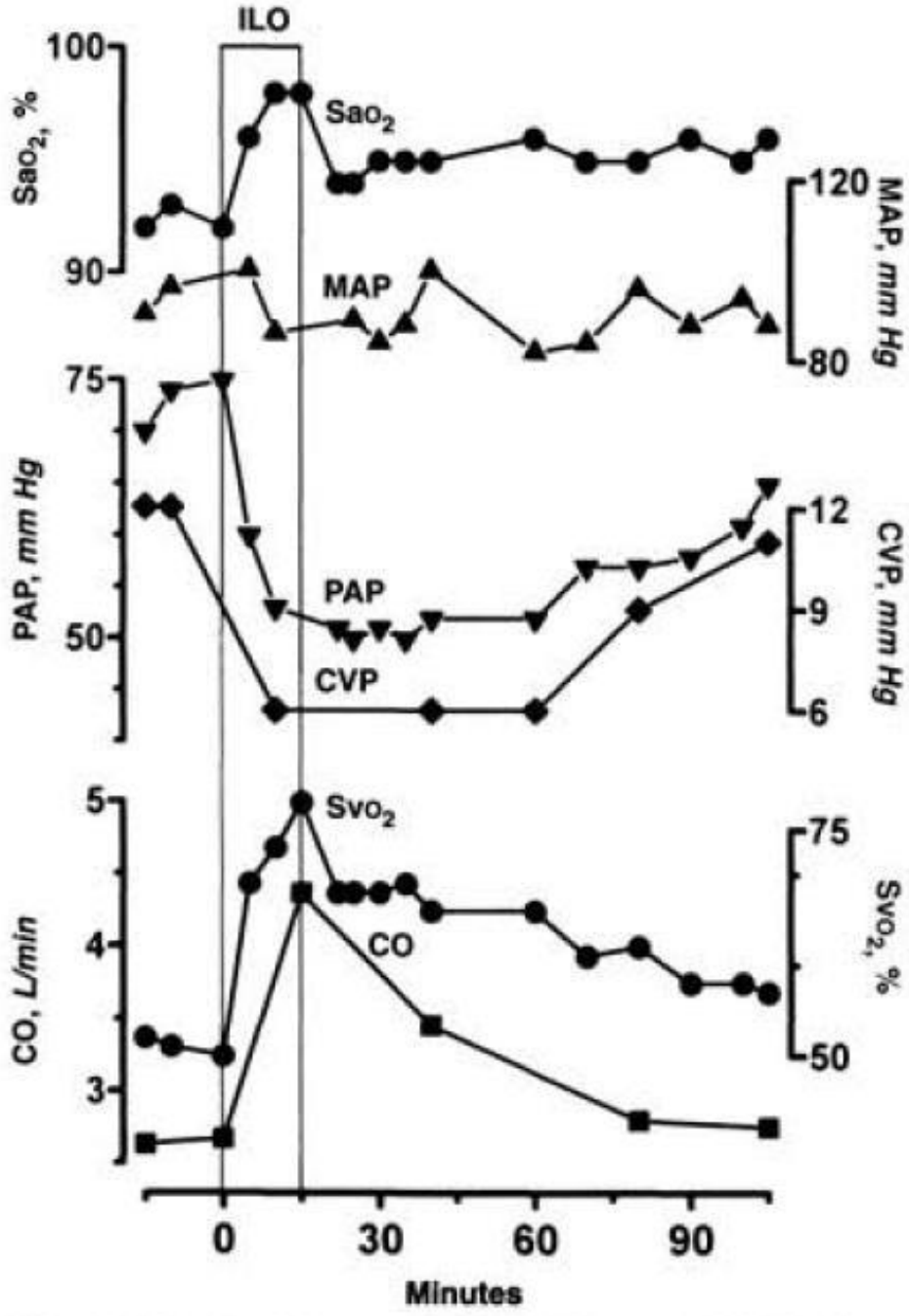


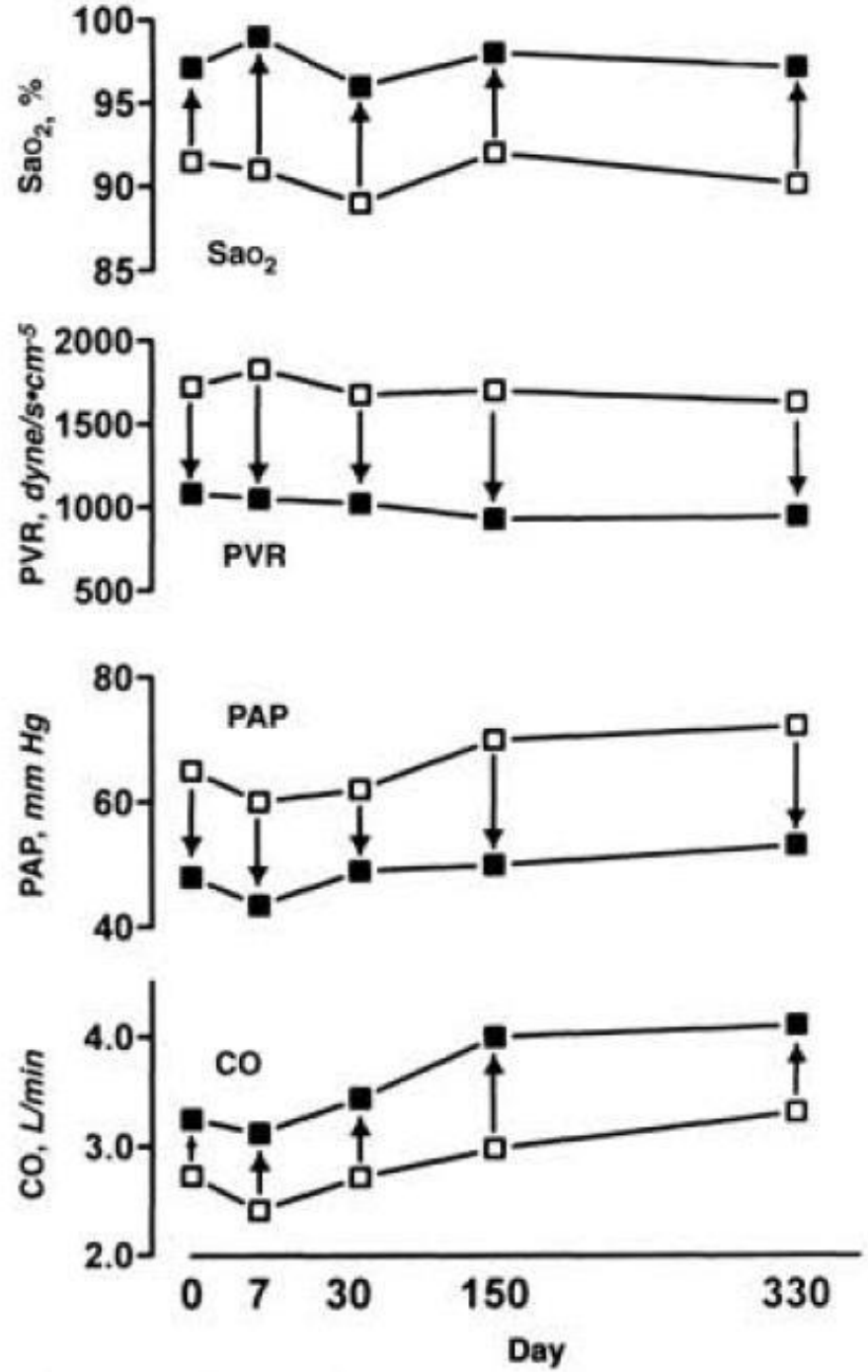
Walmrath D, Schneider T, Pilch J, Grimminger F, Seeger W. Aerosolised prostacyclin in adult respiratory distress syndrome. Lancet 1993, 342:961-962






Half-life of drug
~ 2-3 mins


ILO
100
90
Sao2, %
Sao2
MAP
120
80
MAP, mm Hg
75
50
PAP, mm Hg
PAP
CVP
12
9
6
CVP, mm Hg
5
4
3
CO, L/min
Svo2
CO
75
50
Svo2, %
0
30
60
90
Minutes


100
95
90
85
Sao2, %
Sao2
2000
1500
1000
500
PVR, dyne/s•cm-5
PVR
80
60
40
PAP, mm Hg
PAP
4.0
3.0
2.0
CO, L/min
CO
0
7
30
150
330
Day

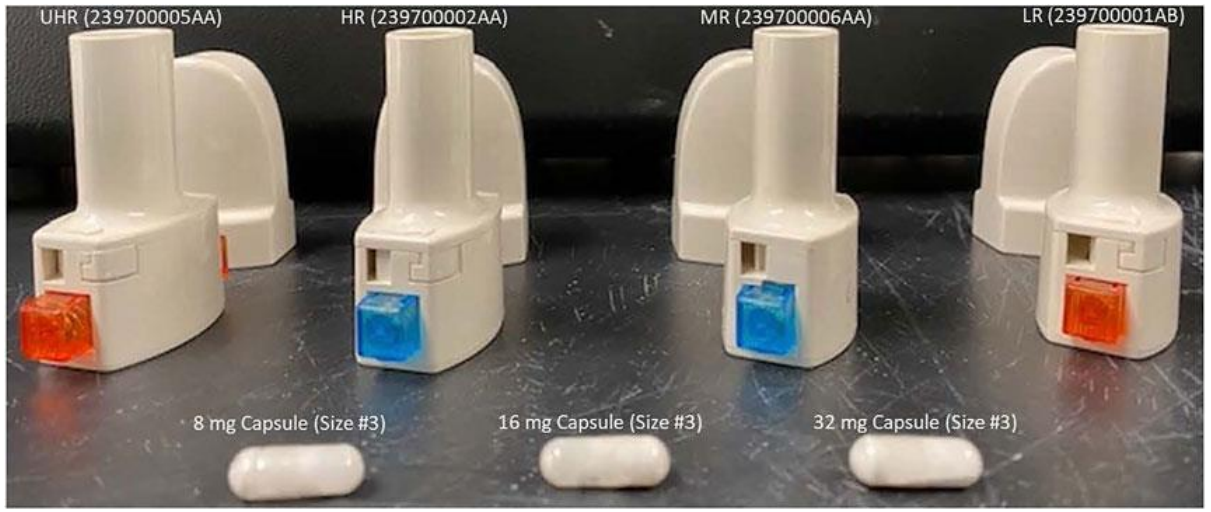
Iloprost

Treprostinil aerosol

Treprostinil DPI

Tyvaso

Yutrepia




Treprostinil Palmitil DPI

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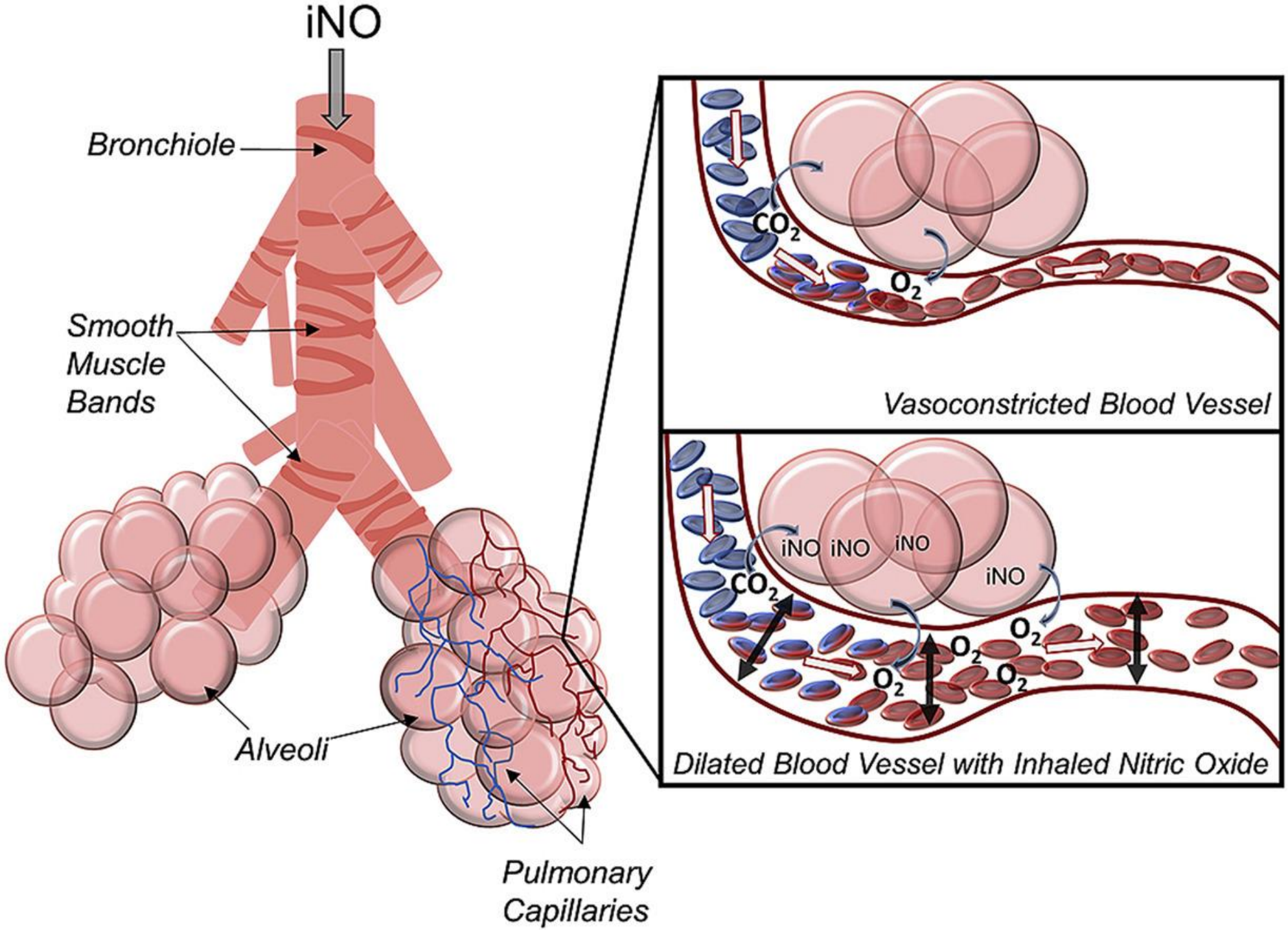
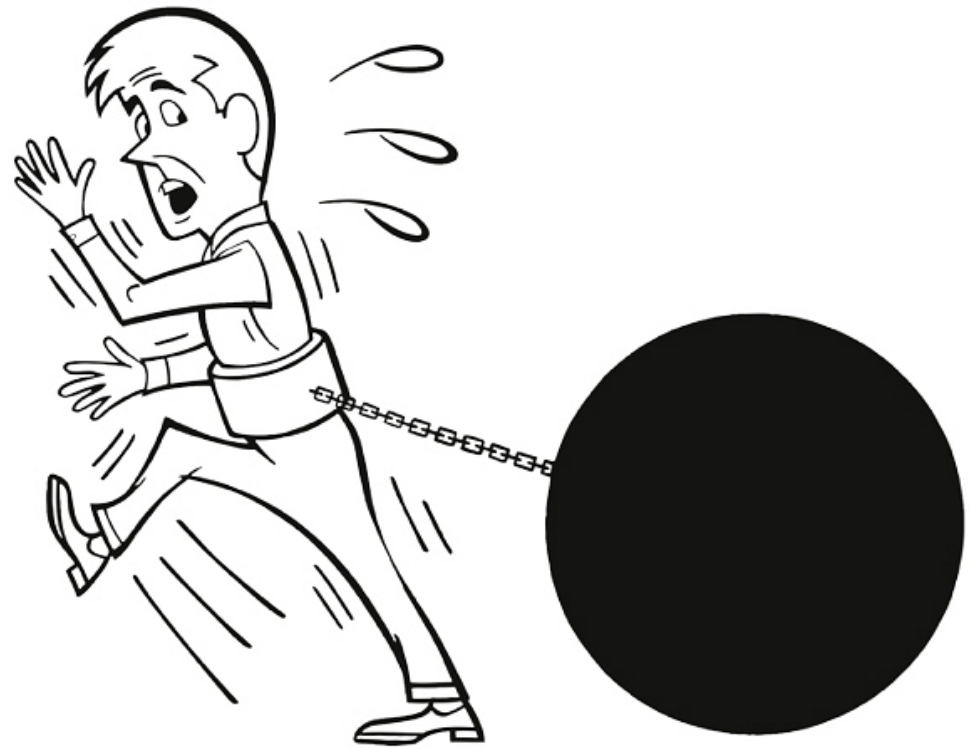
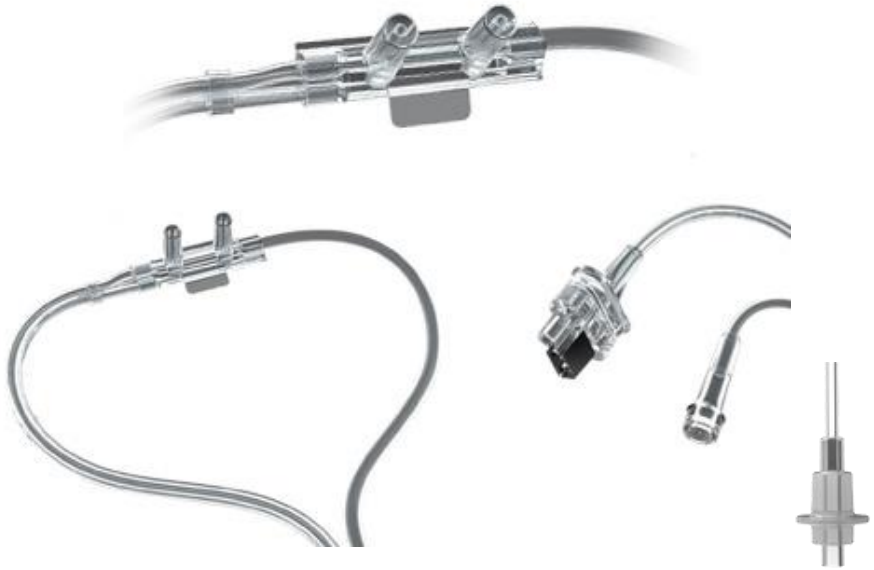

iNO
Bronchiole
Smooth Muscle Bands
Alveoli
Pulmonary Capillaries
CO2
O2
Vasoconstricted Blood Vessel
iNO iNO iNO
iNO
CO2
O2
O2
O2
O2
Dilated Blood Vessel with Inhaled Nitric Oxide




eNOfit

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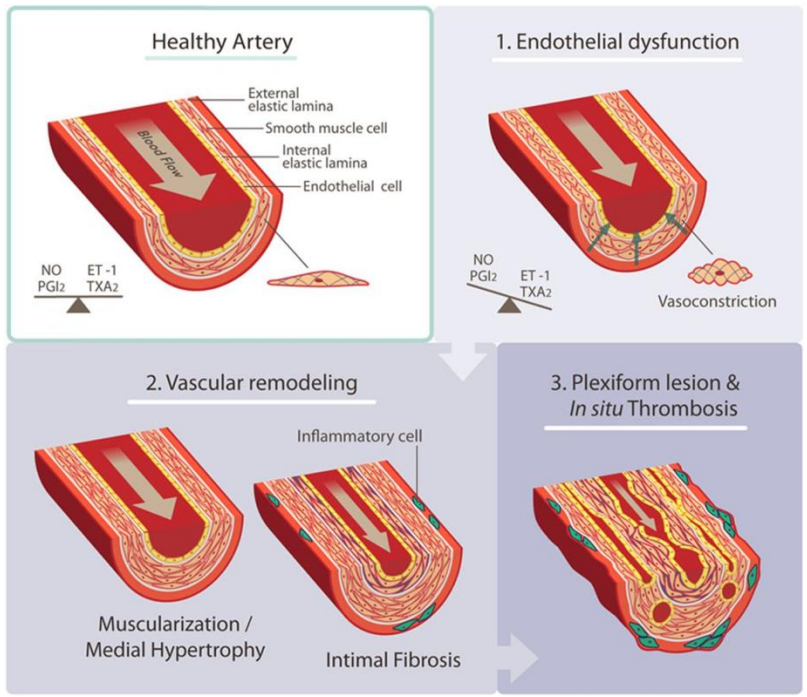
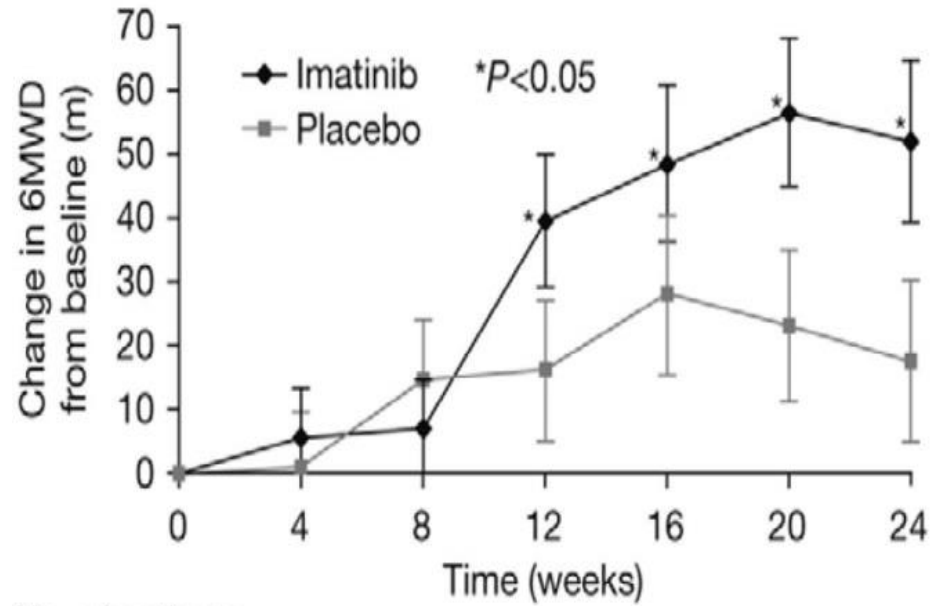


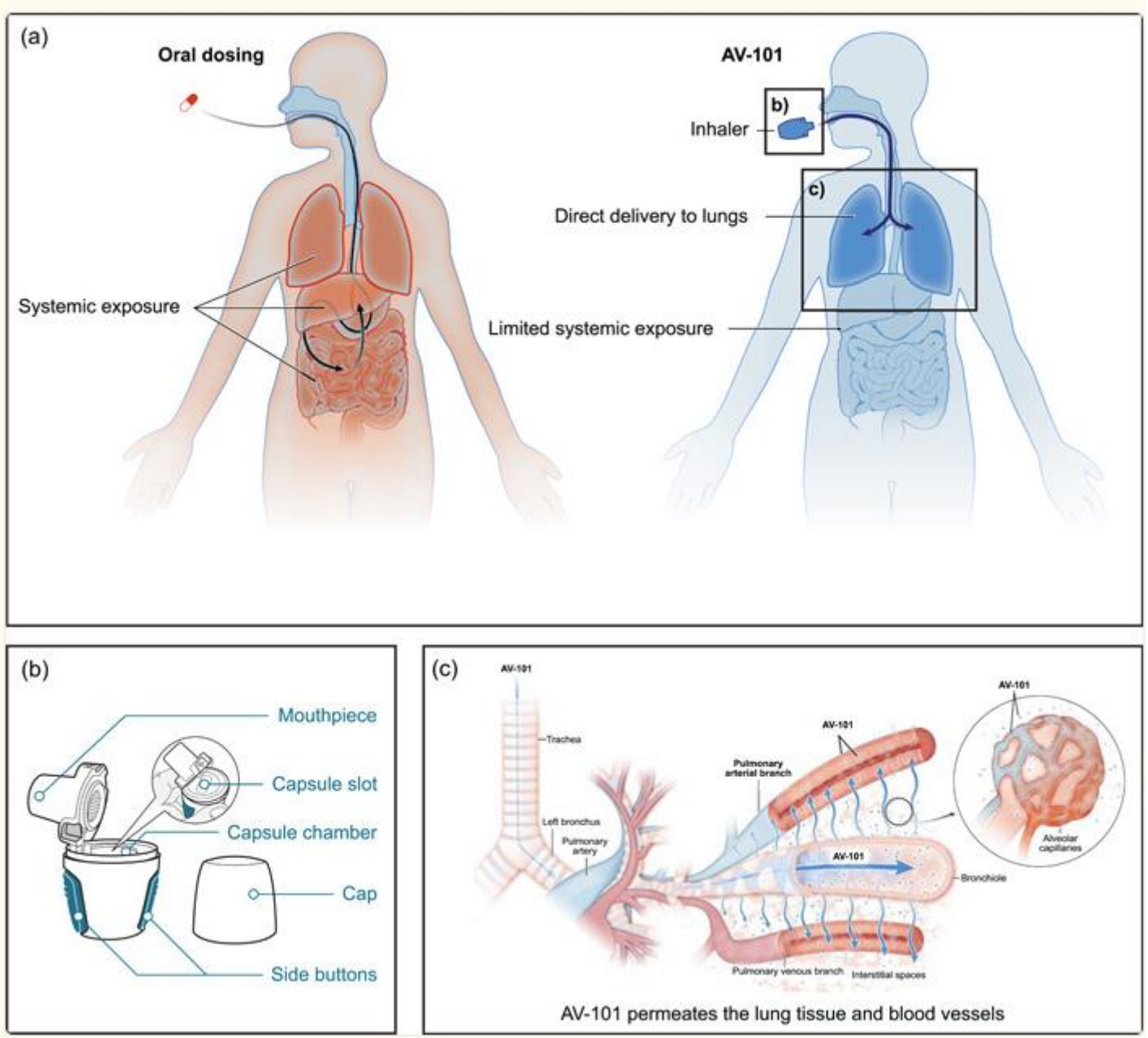




No. of patients

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Imatinib | 103 | 89 | 84 | 76 | 71 | 72 | 66 |
| Placebo | 98 | 93 | 91 | 88 | 82 | 84 | 80 |

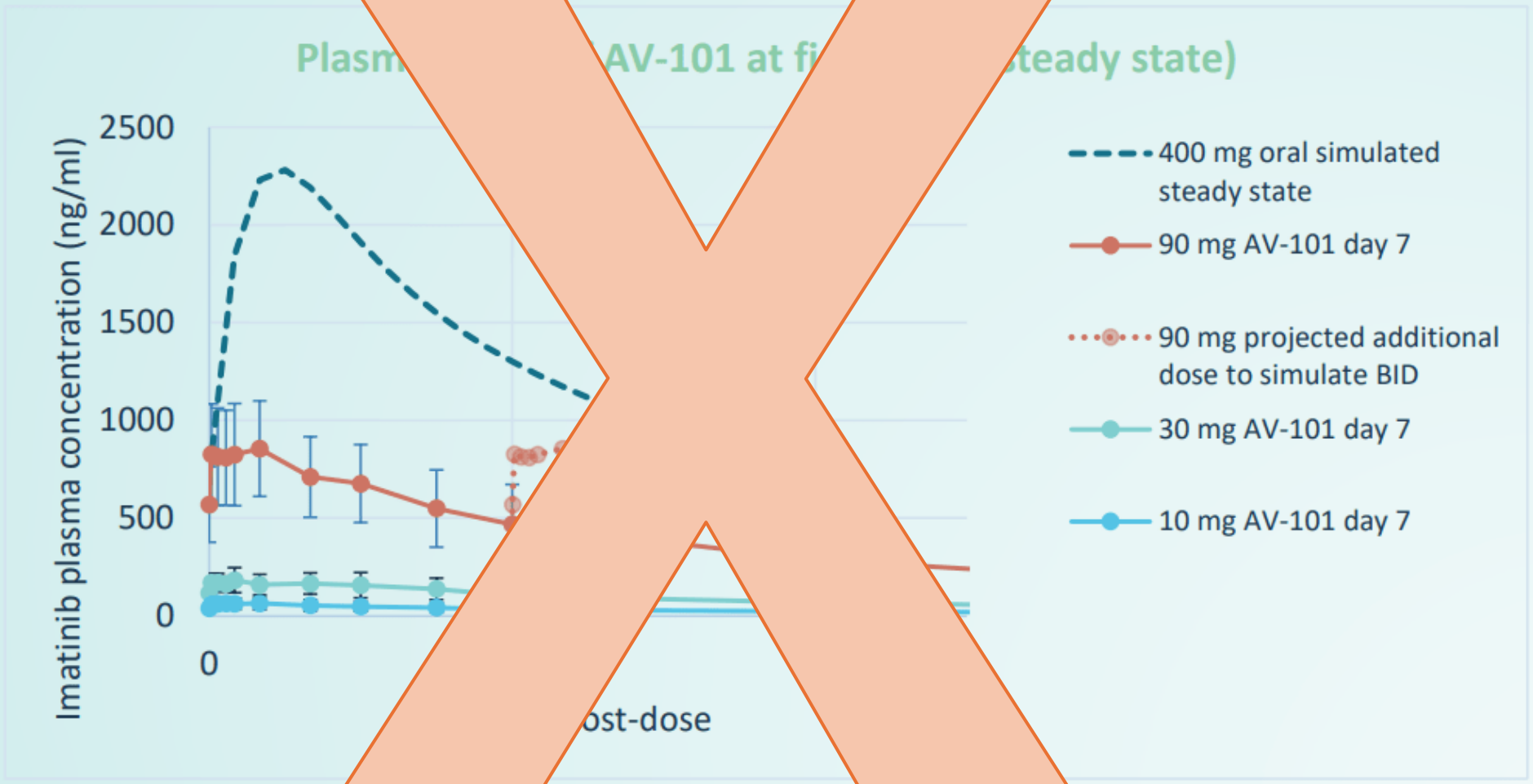
**Hoeper et. al, Circulation, 2013**

*New drug approval for Imatinib in PAH was discontinued due to side effects*




AV-101 permeates the lung tissue and blood vessels

# AV-101 Phase 1 Trial: Lower Systemic Exposures Observed

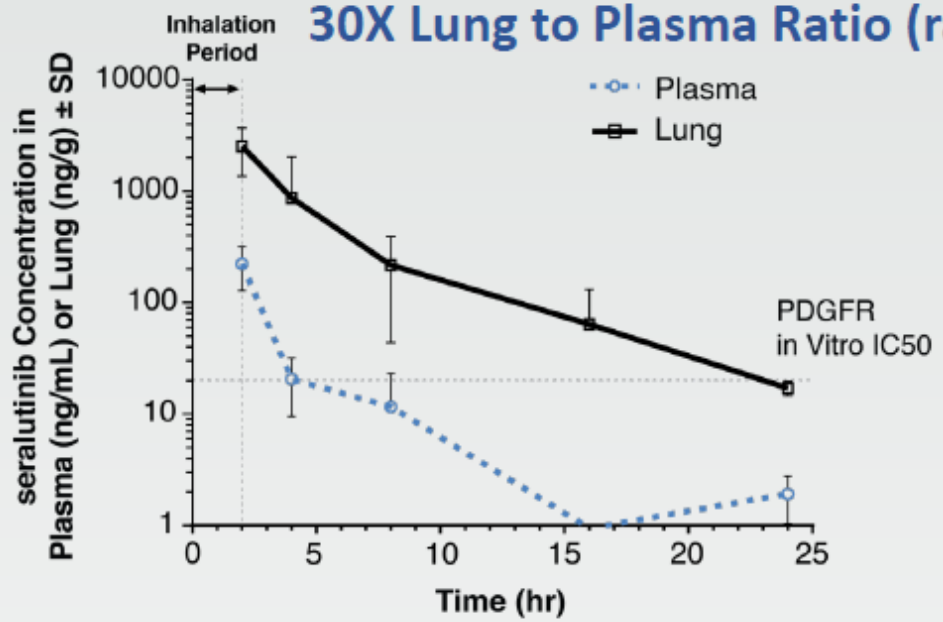



Systemic exposures for all doses of AV-101 observed to be lower than simulated steady-state exposure of 400 mg of oral imatinib

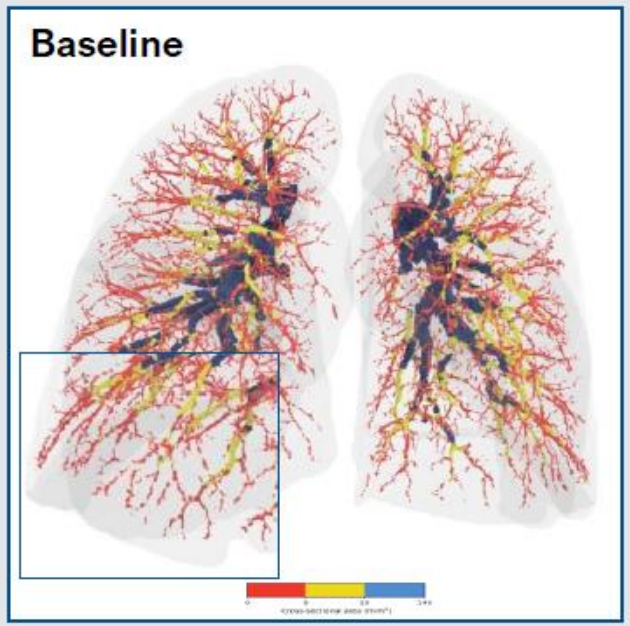
## Potent PDGFR, CSF1R and c-KIT inhibitor

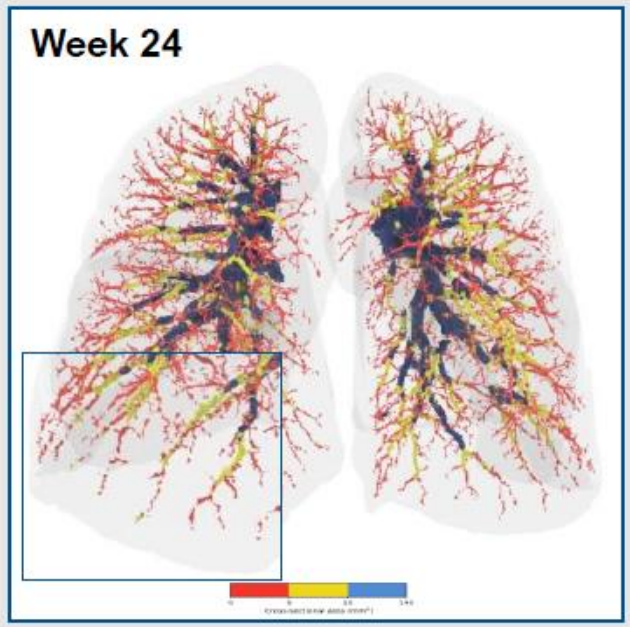
| Compound | Cell Based IC50 (nM) | | | | |
|---|---|---|---|---|---|
| | H1703 PDGFRα | HLF PDGFβ>α | PASMC PDGFRα=β | CSF1R | c-KIT |
| Seralutinib | 32 | 29 | 33 | 8 | 14 |
| Imatinib | 62 | 579 | 419 | 1032 | 230 |

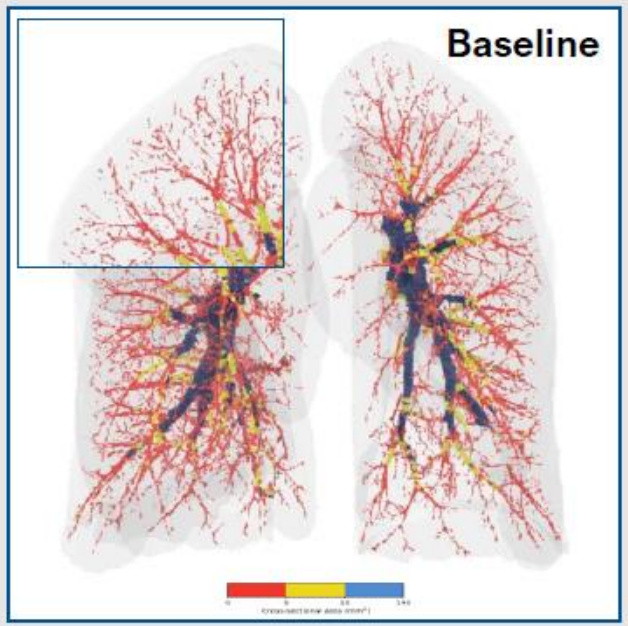
## 30X Lung to Plasma Ratio (rat)

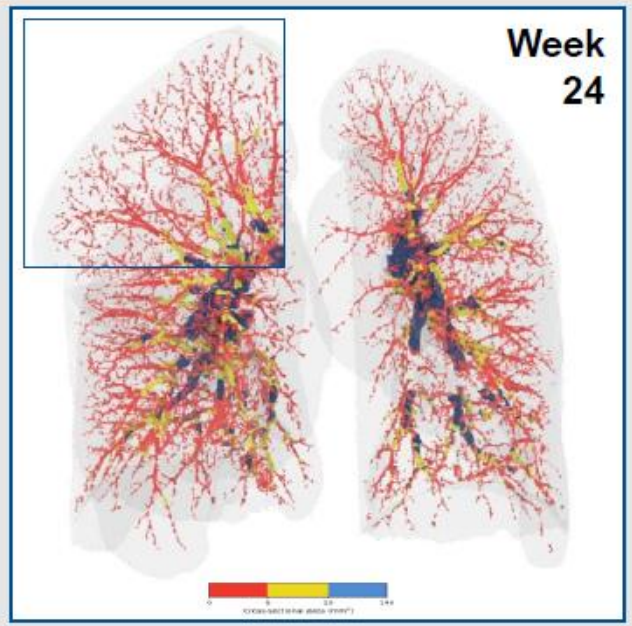



# Examples of CT (FRI) Imaging: Placebo vs. Seralutinib



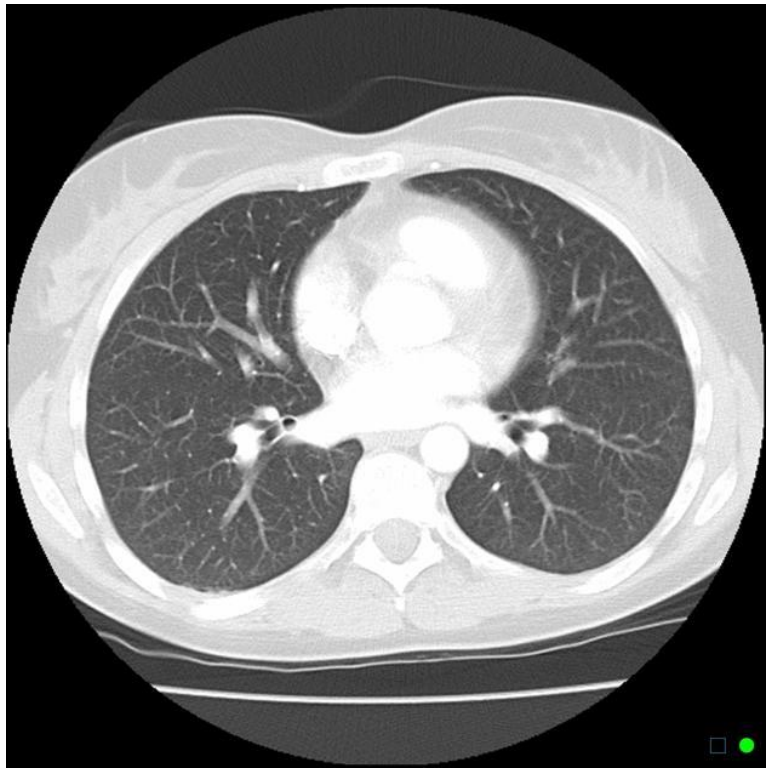



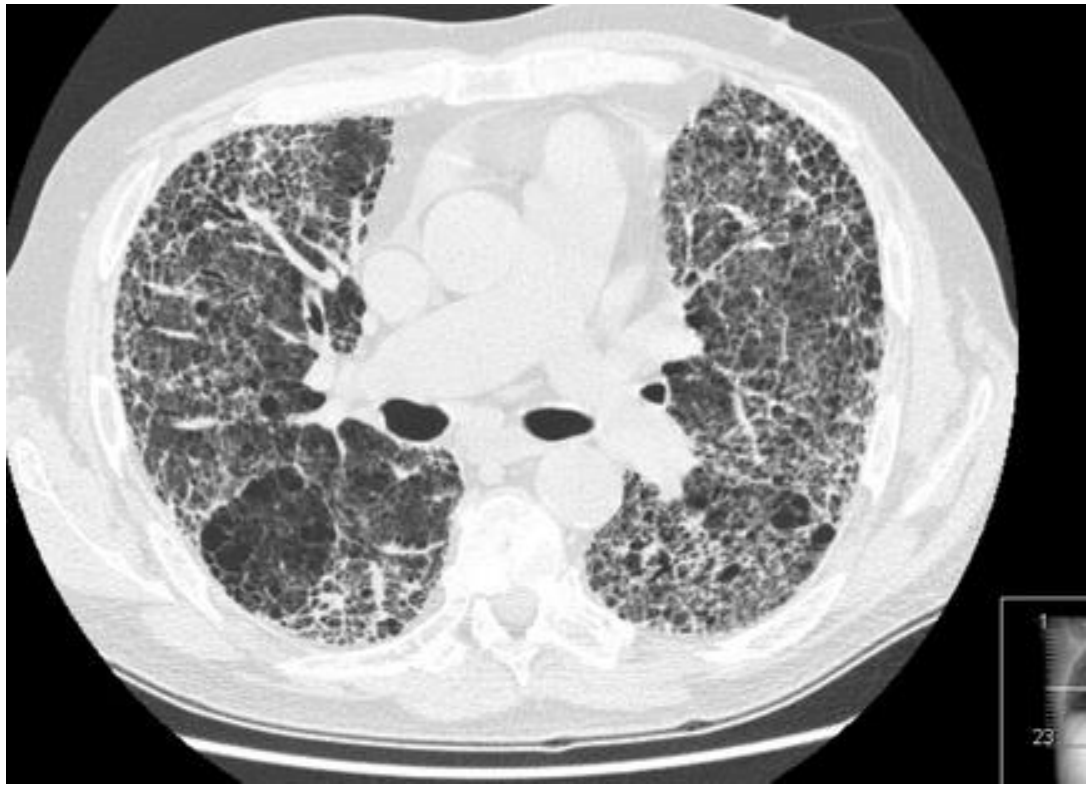




| Placebo subject | Female, 24 y, IPAH (FC II) | Seralutinib subject | Female, 58 y, IPAH (FC II) |
|---|---|---|---|
| **PAH meds** | PDE5-i + prostacyclin | **PAH meds** | ERA + PDE5-i + prostacyclin |

# Increasing trend to move into lung fibrosis Pulmonary Hypertension





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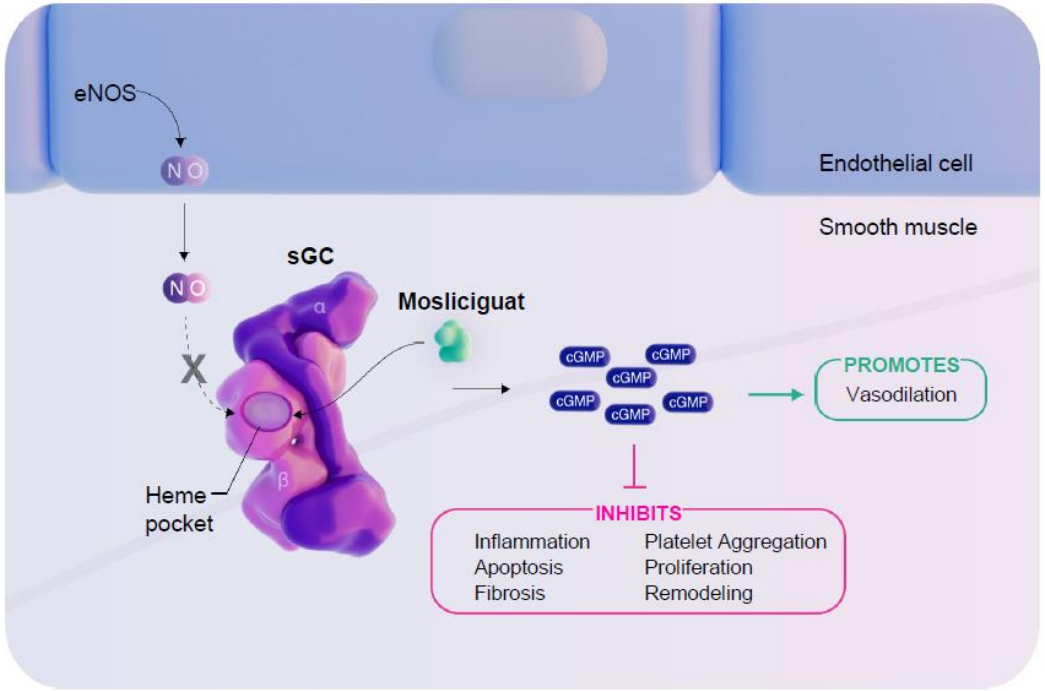


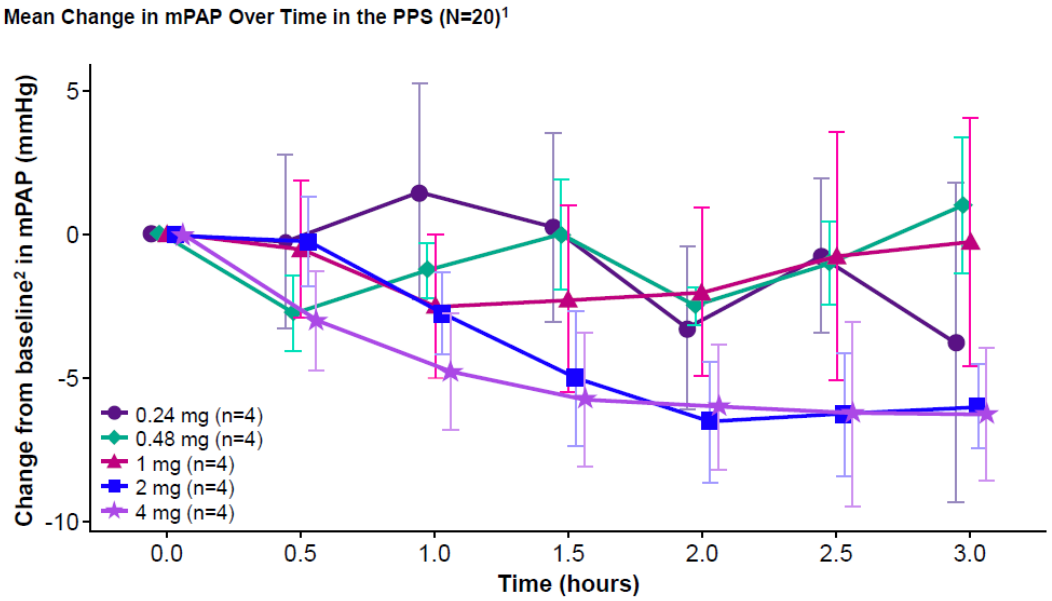


*These data are from PAH and CTEPH

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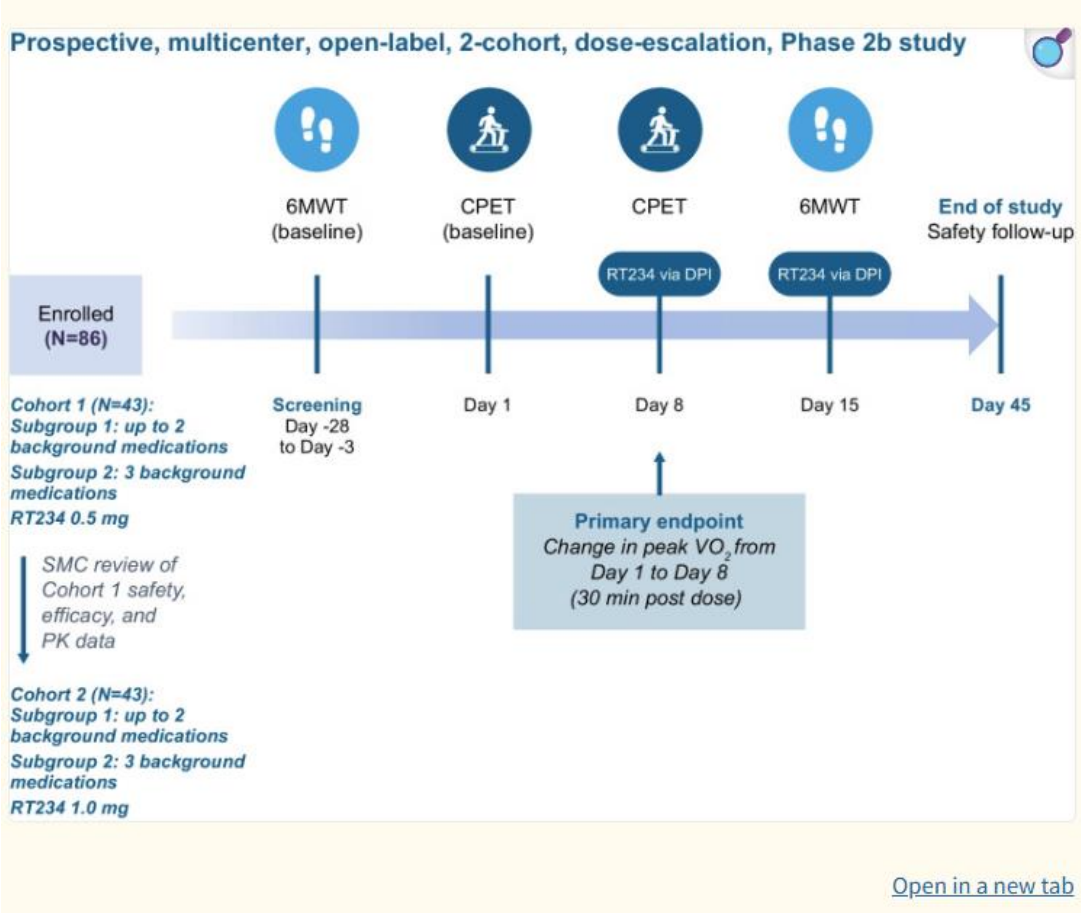
# PRN use???


631479v1
Mfd. by
Plastiape S.p.A.,
Osnago, Italy AOS™ DPI
for use with vardenafil
inhalation powder


Prospective, multicenter, open-label, 2-cohort, dose-escalation, Phase 2b study
6MWT (baseline)
CPET (baseline)
CPET
6MWT
End of study
Safety follow-up
RT234 via DPI
RT234 via DPI
Enrolled (N=86)
Cohort 1 (N=43):
Subgroup 1: up to 2 background medications
Subgroup 2: 3 background medications
RT234 0.5 mg
Screening Day -28 to Day -3
Day 1
Day 8
Day 15
Day 45
SMC review of Cohort 1 safety, efficacy, and PK data
Primary endpoint
Change in peak VO2 from Day 1 to Day 8
(30 min post dose)
Cohort 2 (N=43):
Subgroup 1: up to 2 background medications
Subgroup 2: 3 background medications
RT234 1.0 mg
Open in a new tab