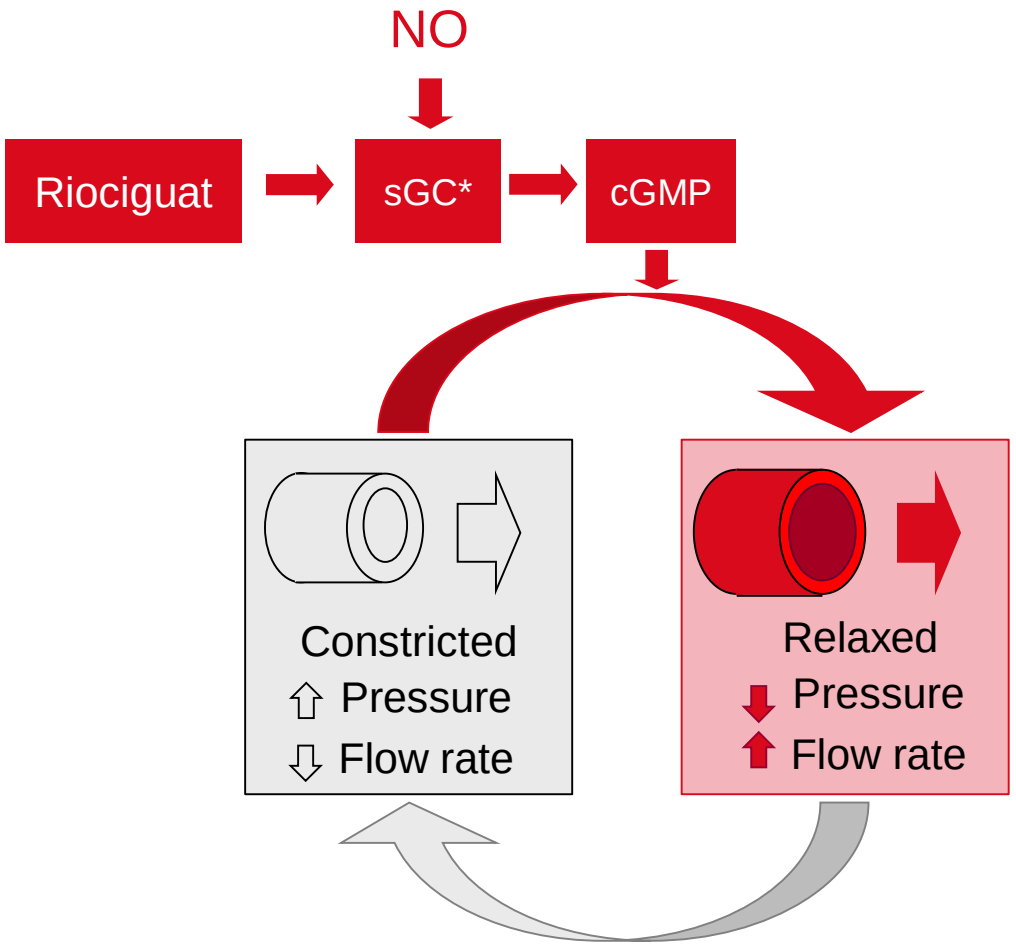
Riociguat: Mode of action

Riociguat increases the sensitivity of native soluble guanylate cyclase (sGC) to NO

Riociguat directly stimulates the native sGC independently of NO

Both actions lead to vasodilatation (and anti-proliferation)

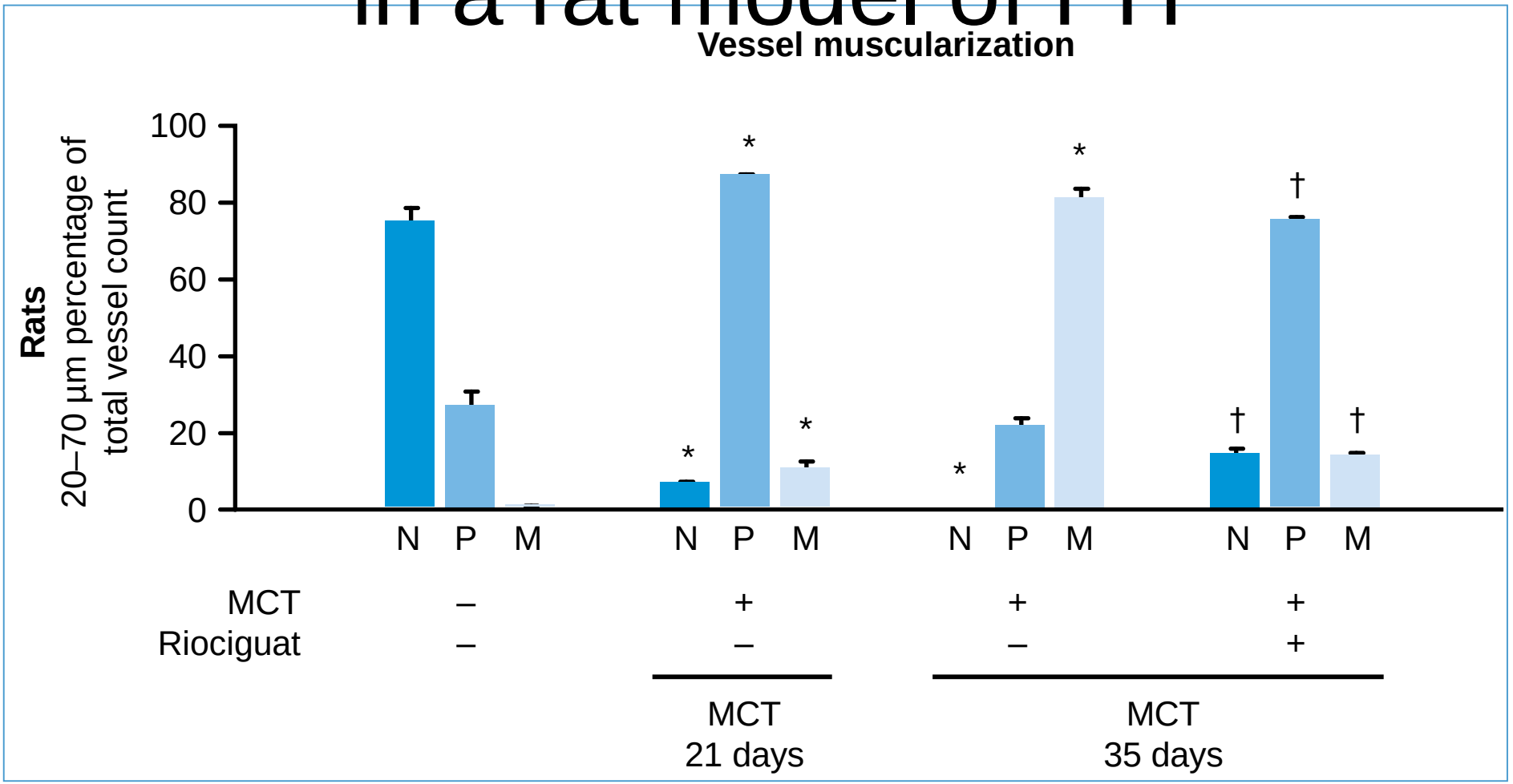
Effect of riociguat is not limited by low NO levels (unlike PDE-5-I)



* native (intact)

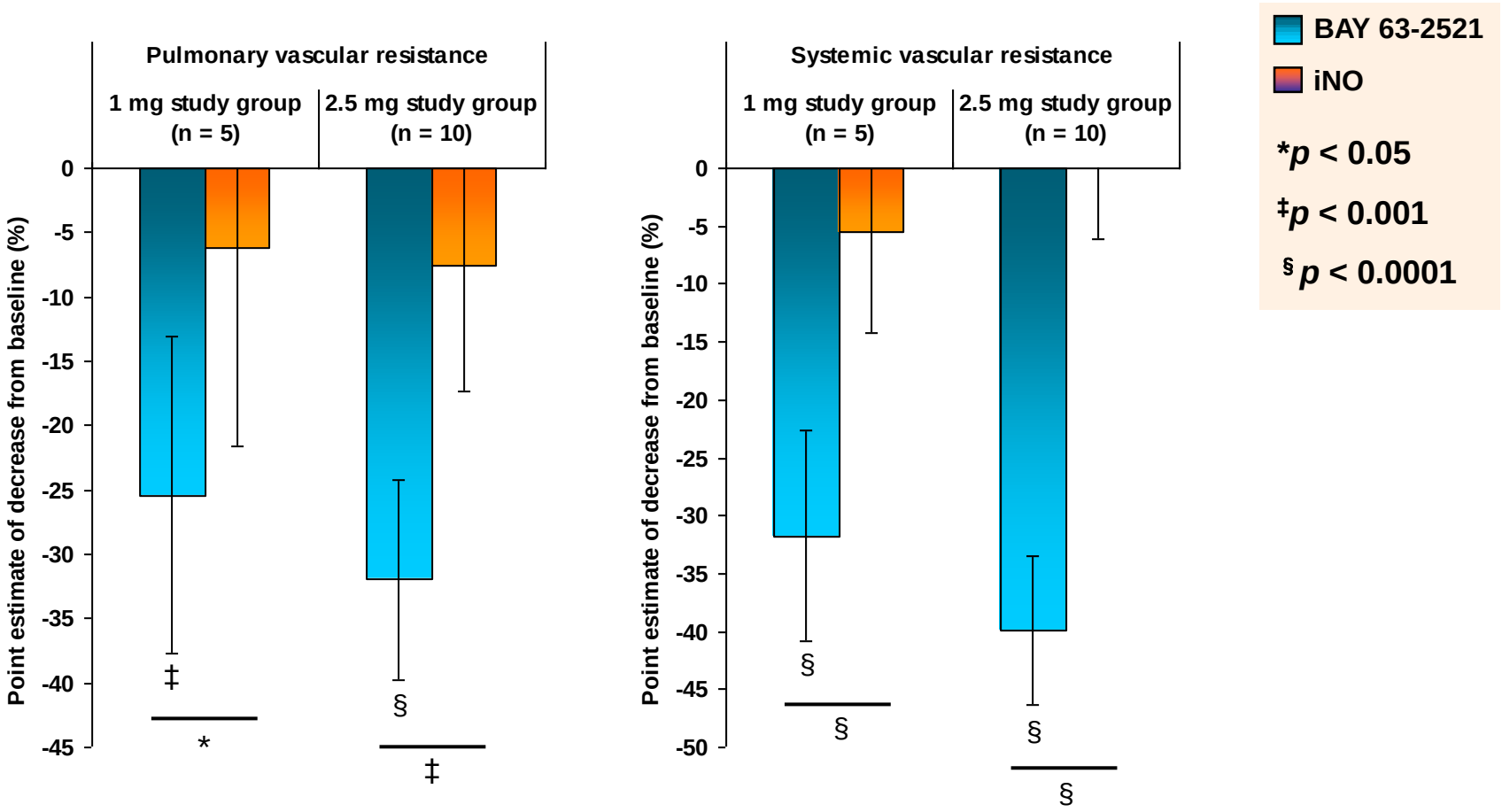
PDE-5-I = phosphodiesterase-5-inhibitor
NO = mitroc oxide

Anti-remodeling effects of riociguat in a rat model of PH



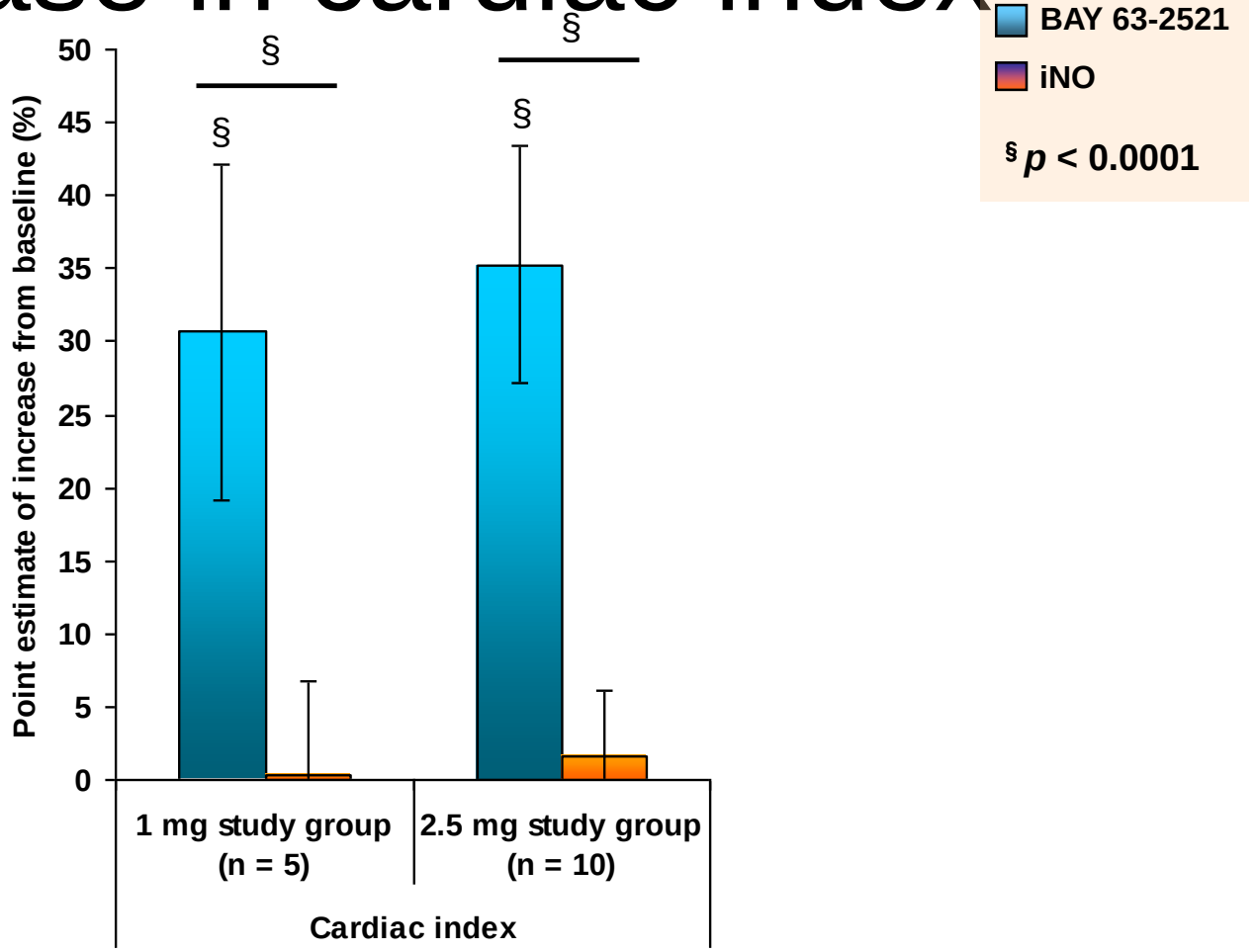
*p < 0.05 versus control animals without PH; †p < 0.05 versus untreated animals with PH at day 35.
N, non-muscularized; P, partially muscularized; M, fully muscularized.
Schermuly et al., ERJ 2008

Haemodynamic effects of BAY 63-2521: decrease in vascular resistance



Grimminger et al., ERJ 2009

Haemodynamic effects of BAY 63-2521: increase in cardiac index



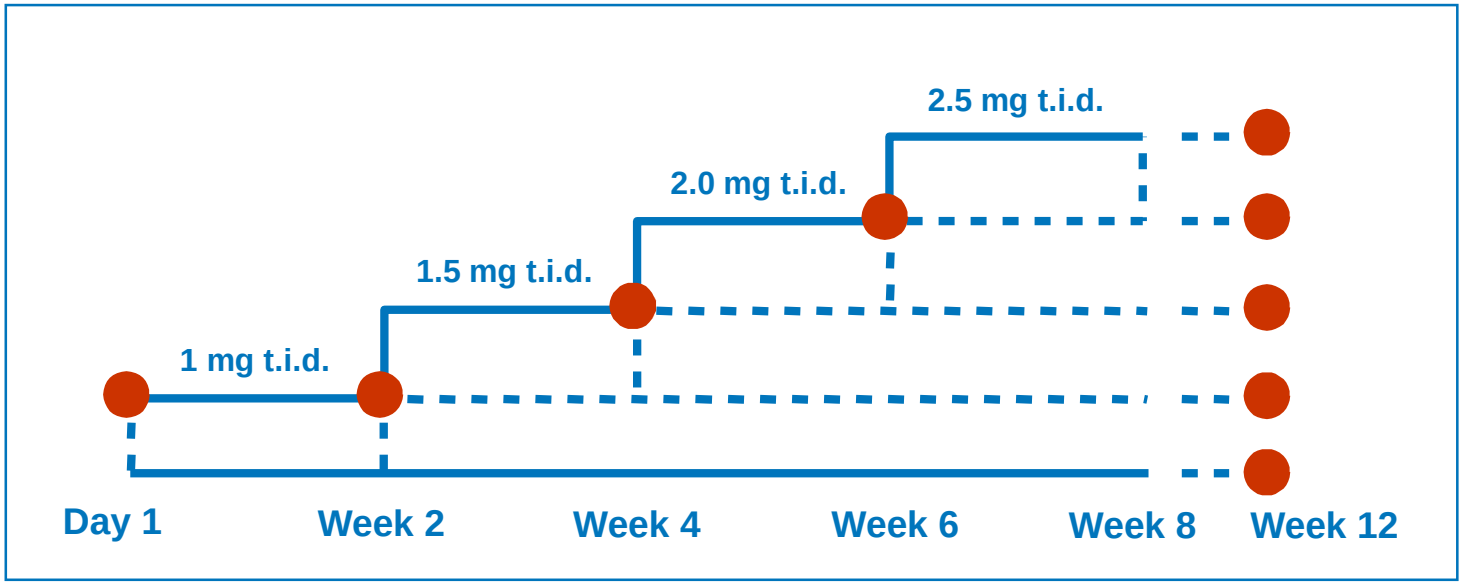
Grimminger et al., ERJ 2009

Riociguat phase 2 study

- Multicenter, open-label, individual dose-titration study
- Primary objective: to investigate the safety, tolerability and feasibility of individual titration of riociguat according to peripheral systolic blood pressure
- Secondary objectives: to assess the pharmacodynamics and pharmacokinetics of riociguat

Dose titration scheme

- If trough SBP > 100 mmHg, increase dose (+0.5 mg t.i.d.)
- If trough SBP 90–100 mmHg, maintain dose
- If trough SBP < 90 mmHg without symptoms of hypotension, reduce dose (–0.5 mg t.i.d.)
- If trough SBP < 90 mmHg with symptoms of hypotension, restart after 24 hours with reduced dose (–0.5 mg t.i.d.)



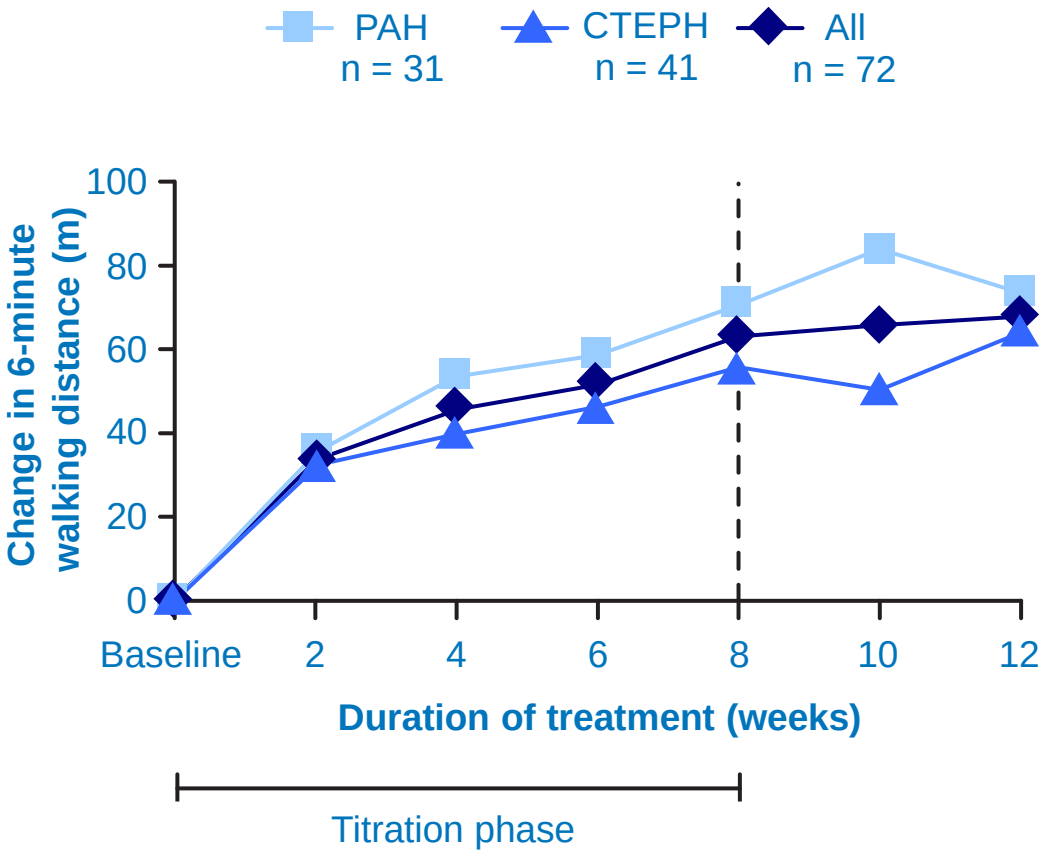
Baseline demographics

Demographic variable	n (%) or mean
Total patients	75 (100%)
PAH	33 (44%)
CTEPH	42 (56%)
Age (years)	60.3 (range: 19–76)
Race	
White	75 (100%)
Sex	
Men	34 (45%)
Women	41 (55%)
Body mass index (kg/m^2)	26.1 (SD: 4.4)

Baseline hemodynamic and functional parameters

Parameter	n (%) or mean ± SD
mPAP (mmHg)	45.3 ± 10.8
CO (L/min)	4.1 ± 1.1
RAP (mmHg)	6.6 ± 4.3
PCWP (mmHg)	8.0 ± 4.2
PVR/SVR	45.7 ± 15.7
NYHA class: I II III IV	 0 (0%) 15 (21%) 56 (78%) 1 (1%)
6-minute walking distance (m)	354.4 ± 111.0

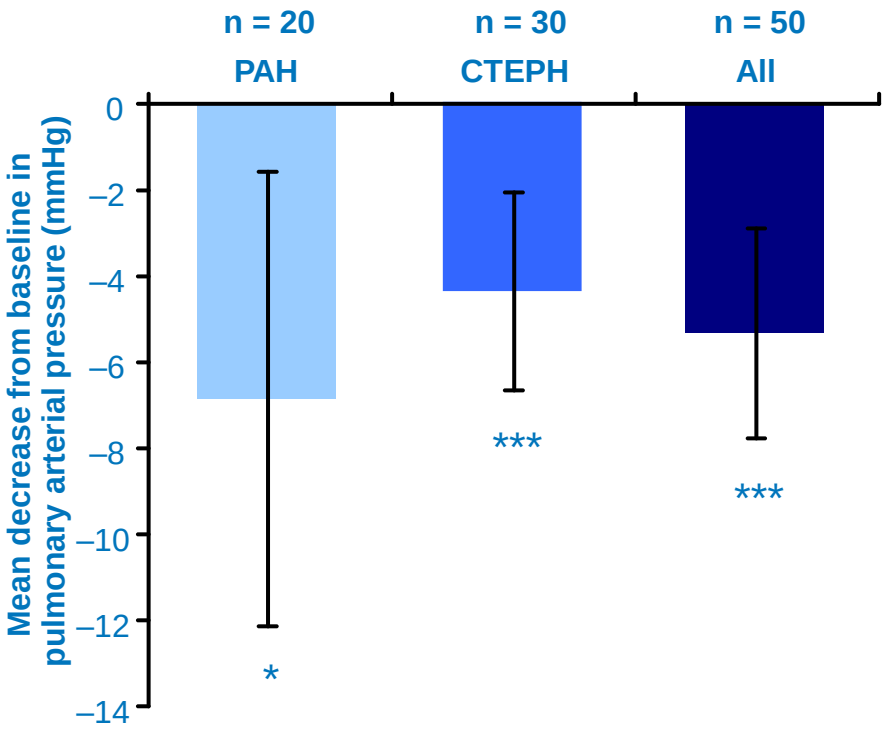
Six-minute walking distance: all patients

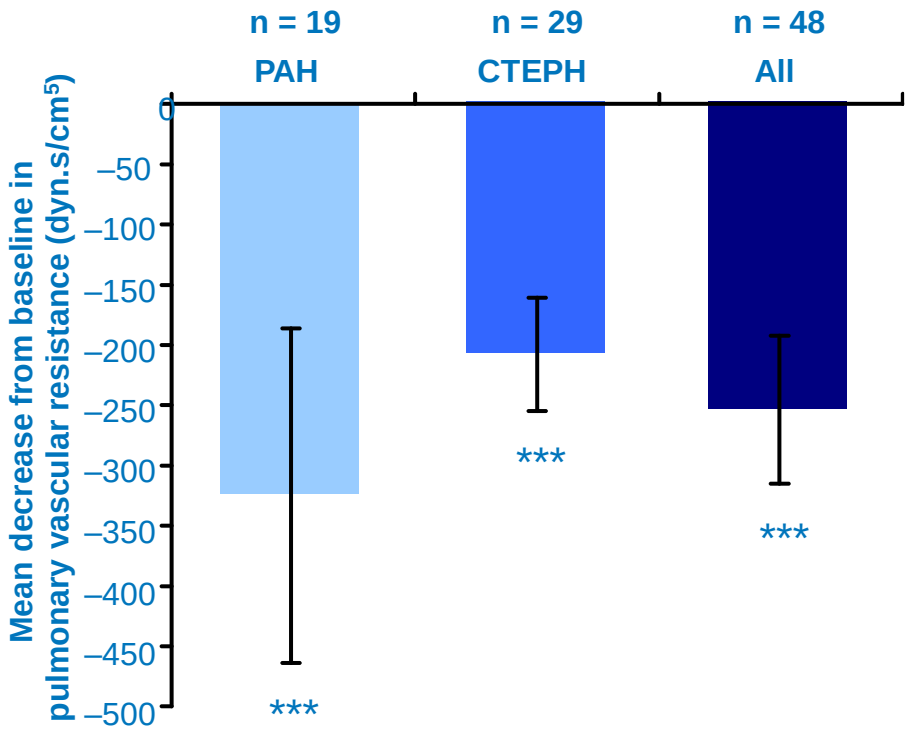


Baseline values

PAH: 316.7 ± 127.4; CTEPH: 382.9 ± 88.1; All: 354.4 ± 111.0

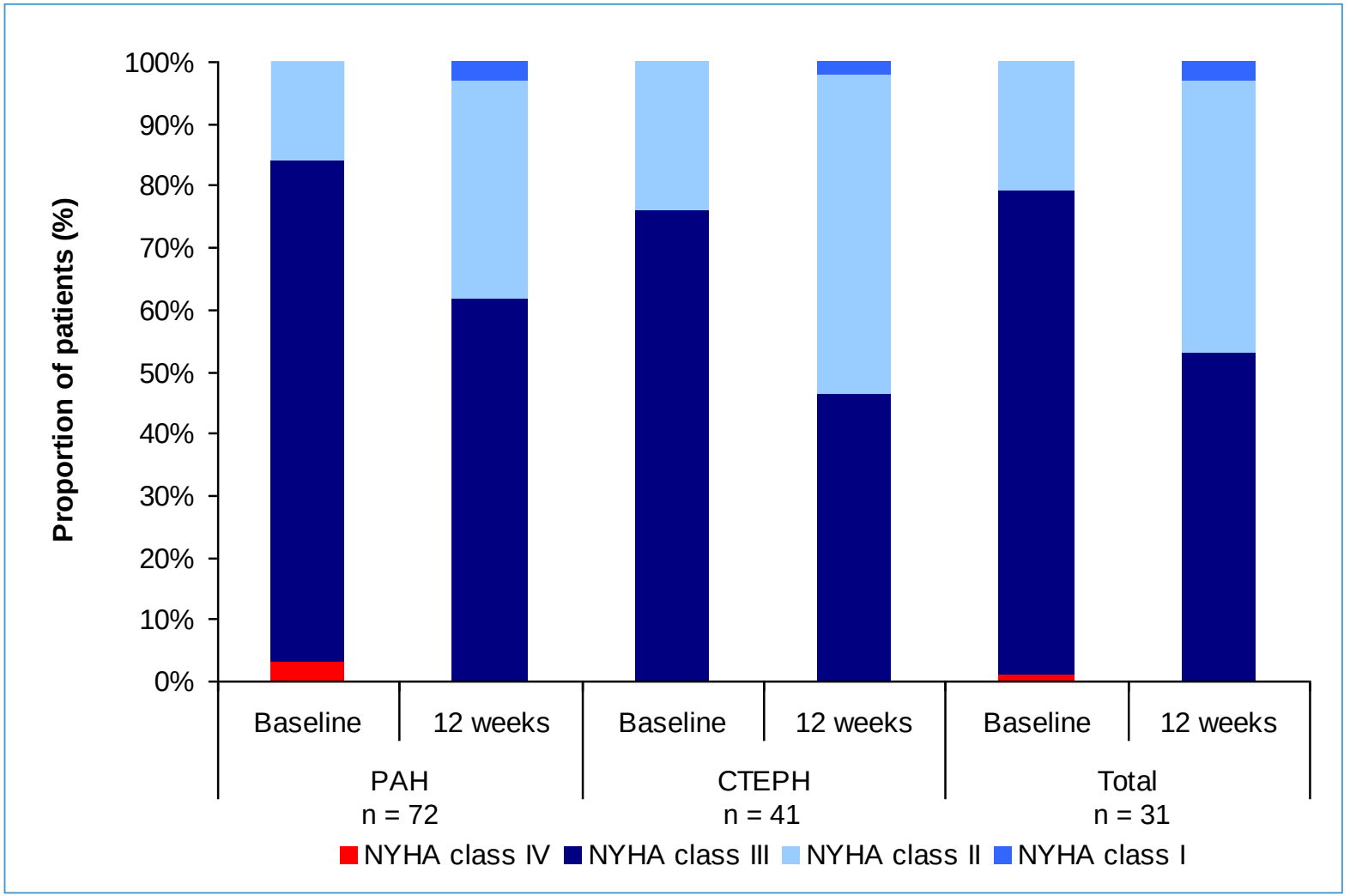
Pulmonary arterial pressure and pulmonary vascular resistance





*$p < 0.05$; ***$p < 0.001$

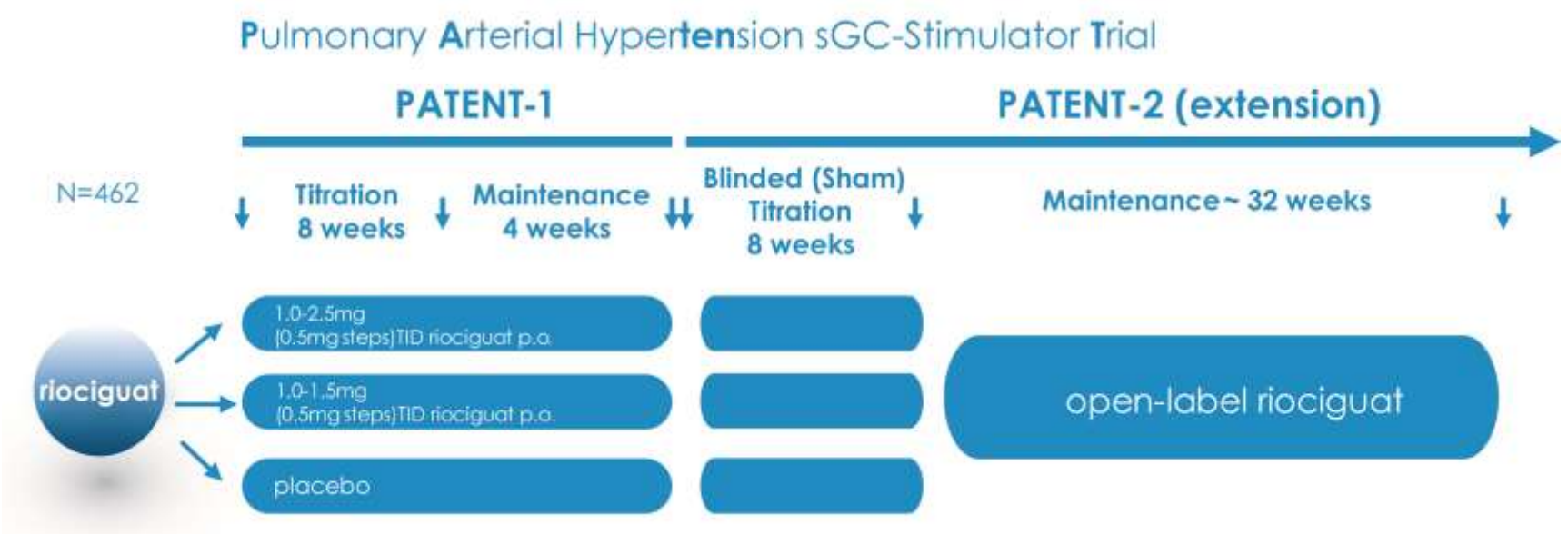
Functional class



CTEPH, chronic thromboembolic pulmonary hypertension; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension

Riociguat phase III clinical program: PATENT -1 and -2

PATENT: Pulmonary Arterial Hypertension sGC-Stimulator Trial



Primary Outcome Measure

- **Change from baseline in 6 Minute Walk Test after 16 weeks***

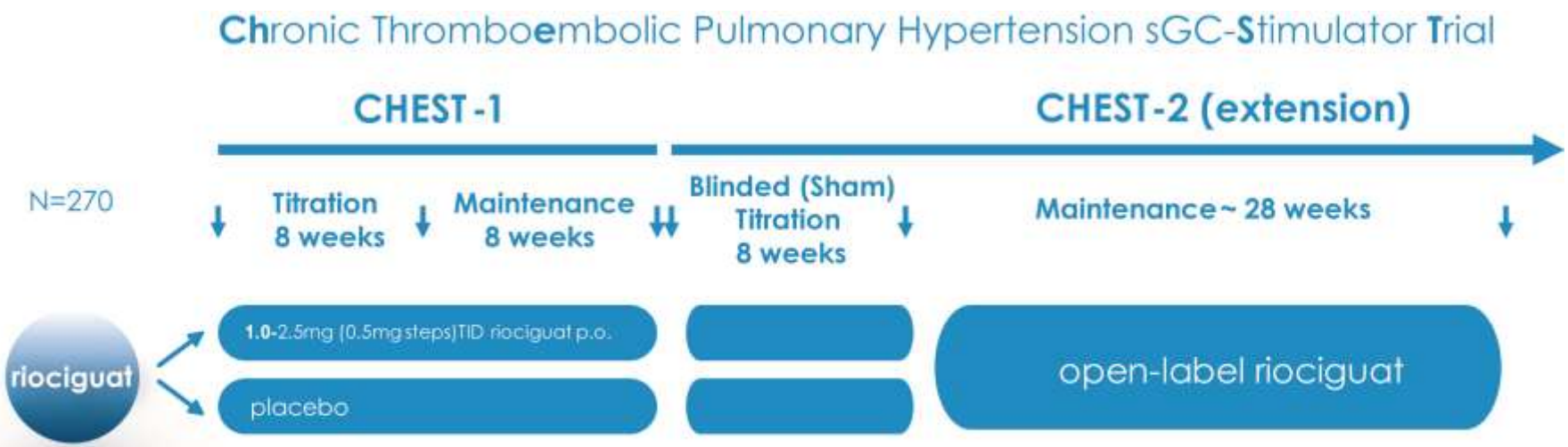
*Secondary outcome in extension, ** primary outcome in extension;
p.o.: per os - oral; TID: three times daily; NT-pro BNP: N-terminal pro brain natriuretic peptide; EQ-5D: quality-of-life measures; MLHF-Q: Minnesota Living with Heart Failure Questionnaire

Secondary Outcome Measures

- **Change from baseline in Pulmonary Vascular Resistance (PVR), change from baseline in WHO functional class, change from baseline in NT-pro BNP, change from baseline in Borg dyspnea, change from baseline in EQ-5D and MLHF-Q, time to clinical worsening**
- **Safety****

Riociguat phase III clinical program: CHEST -1 and -2

CHEST: Chronic Thromboembolic Pulmonary Hypertension sGC-Stimulator Trial



Primary Outcome Measure

- **Change from baseline in 6 Minute Walk Test after 16 weeks***

*Secondary outcome in extension, ** primary outcome in extension;
p.o.: *per os* - oral; TID: three times daily; NT-pro BNP: N-terminal pro brain natriuretic peptide; EQ-5D: quality-of-life measures; MLHF-Q: Minnesota Living with Heart Failure Questionnaire

Secondary Outcome Measures

- **Change from baseline in Pulmonary Vascular Resistance (PVR), change from baseline in WHO functional class, change from baseline in NT-pro BNP, change from baseline in Borg dyspnea, change from baseline in EQ-5D and MLHF-Q, time to clinical worsening**
- **Safety****