# Effects of riociguat in patients with inoperable chronic thromboembolic pulmonary hypertension versus persistent/recurrent pulmonary hypertension after pulmonary endarterectomy: 2-year efficacy results from the CHEST-2 study

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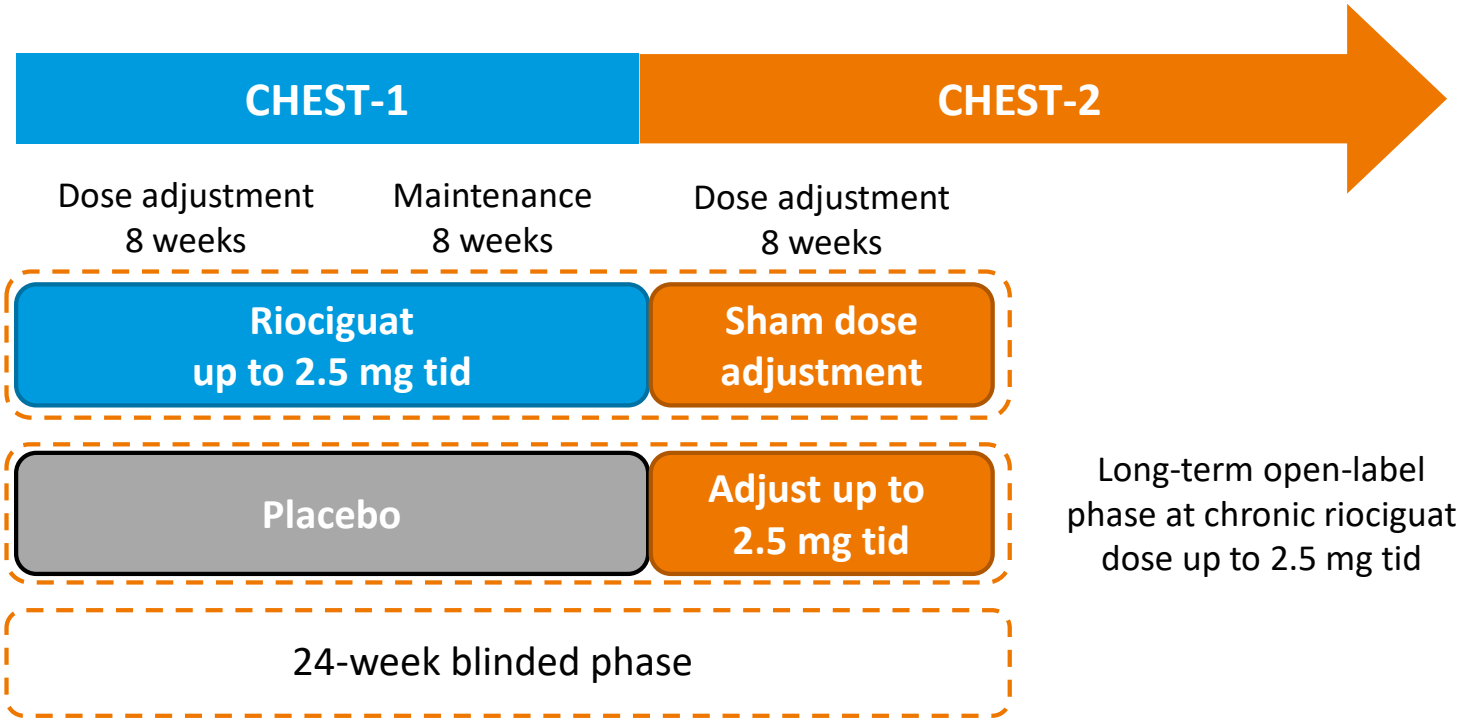
# Introduction

- In the CHEST-1 study, the sGC stimulator riociguat was assessed in patients with inoperable CTEPH or persistent/recurrent PH after PEA[1]
- After 16 weeks of treatment with riociguat, significant improvements were seen in:
  - Exercise capacity (6MWD)
  - Clinically relevant secondary endpoints, including PVR, NT-proBNP, and WHO FC
- These improvements were sustained at 2 years in the CHEST-2 open-label extension[2]
- Here we compare the safety and efficacy of riociguat at 2 years in the subgroups of patients with inoperable CTEPH and persistent/recurrent PH following PEA at 2 years using the final data-cut of CHEST-2 (March 2014), when most patients had received at least 2 years of riociguat treatment[2]

6MWD, 6-minute walking distance; CTEPH, chronic thromboembolic pulmonary hypertension; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; PH, pulmonary hypertension; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; sGC, soluble guanylate cyclase; WHO FC, World Health Organization functional class

1. Ghofrani HA, et al. N Engl J Med 2013;369:319–329;
2. Simonneau G, et al. Lancet Respir Med 2016;4:372–380

# CHEST study design




- Patients with inoperable CTEPH or persistent/recurrent PH after PEA were eligible to participate in CHEST-2 after completing CHEST-1 without ongoing riociguat-related SAEs

SAE, serious adverse event; tid, three times daily

# Safety profile of riociguat in the inoperable and persistent/recurrent subgroups

| AEs, n (%) | Inoperable CTEPH (n=172) | Persistent/recurrent PH after PEA (n=65) |
|---|---|---|
| AEs of special interest in >5% of overall population | | |
| Syncope | 20 (12) | 3 (5) |
| Hypotension | 16 (9) | 2 (3) |
| Other AEs of interest | | |
| Hemoptysis or pulmonary hemorrhage | 8 (5) | 5 (8) |
| Drug-related AEs | 90 (52) | 24 (37) |
| SAEs | 89 (52) | 40 (62) |
| Discontinuation due to AEs | 12 (7) | 2 (3) |
| Deaths | 15 (9) | 9 (14) |

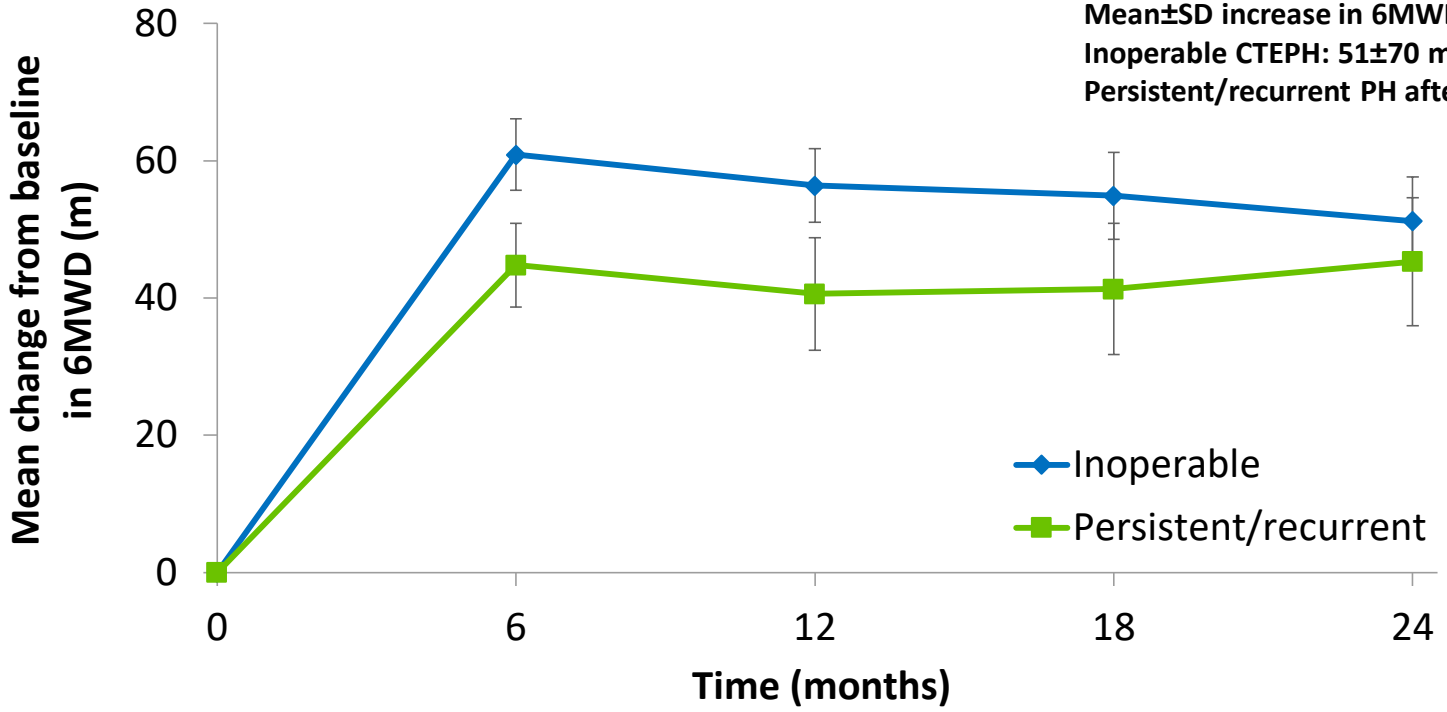
- Syncope and hypotension were more common among patients with inoperable CTEPH compared with persistent/recurrent PH after PEA

Median treatment duration: 116 weeks (range 2–232 weeks)
AE, adverse event

# Most frequent AEs in the inoperable and persistent/recurrent subgroups

| AEs, n (%) | Inoperable CTEPH (n=172) | Persistent/recurrent PH after PEA (n=65) |
|---|---|---|
| Any AE | 170 (99) | 63 (97) |
| AEs in >15% of overall population | | |
| Nasopharyngitis | 50 (29) | 17 (26) |
| Peripheral edema | 38 (22) | 17 (26) |
| Dizziness | 37 (22) | 15 (23) |
| Diarrhea | 30 (17) | 13 (20) |
| Cough | 24 (14) | 13 (20) |

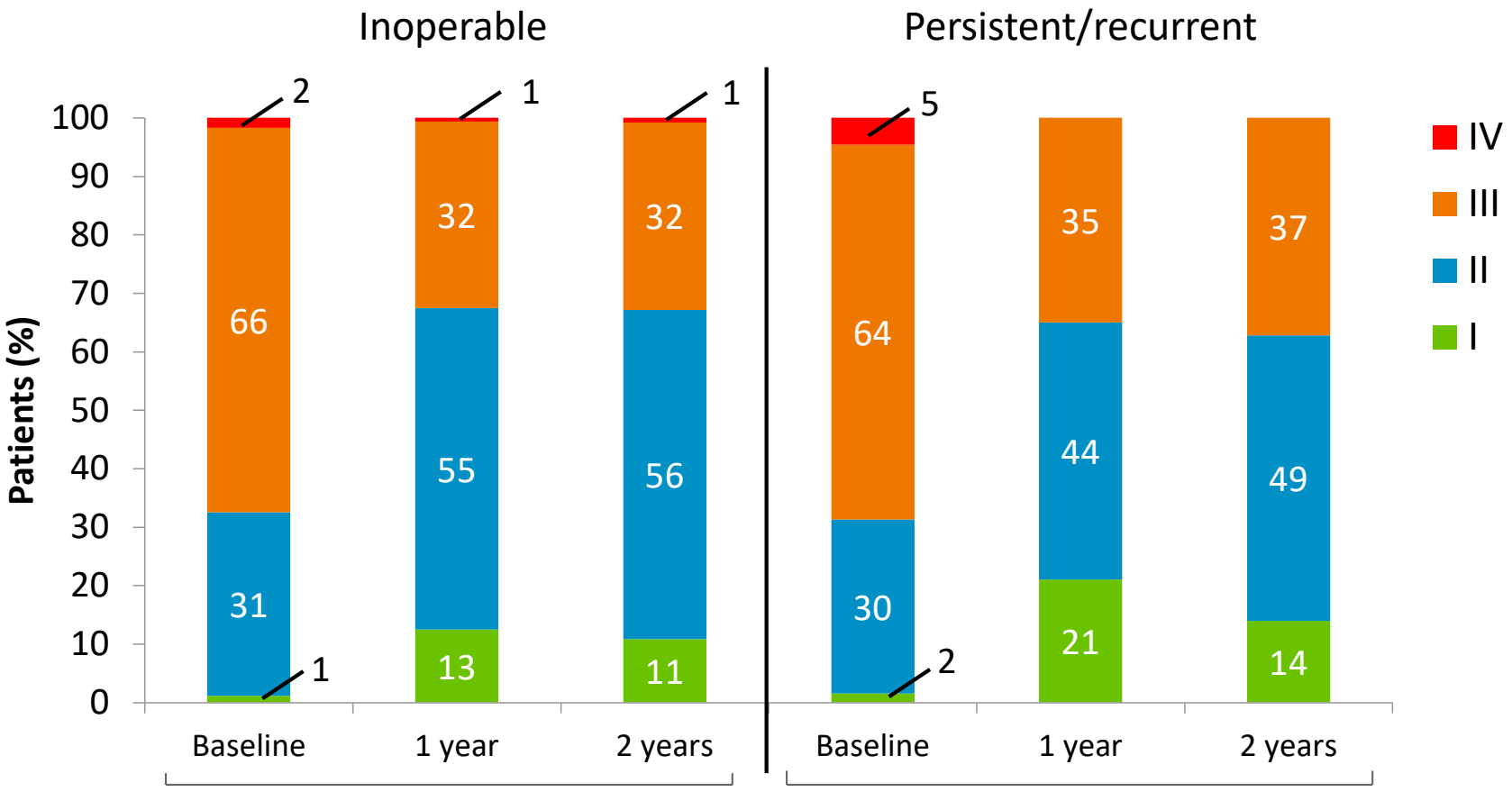
# Improvements in 6MWD were more pronounced in the inoperable subgroup at 1 and 2 years




| | | | | | |
|---|---|---|---|---|---|
| **Mean 6MWD absolute values (m)** | | | | | |
| Inoperable | 346 | 408 | 405 | 407 | 407 |
| Persistent/recurrent | 363 | 407 | 403 | 405 | 405 |
| **Number of patients** | | | | | |
| Inoperable | 172 | 158 | 154 | 146 | 119 |
| Persistent/recurrent | 65 | 60 | 55 | 53 | 43 |

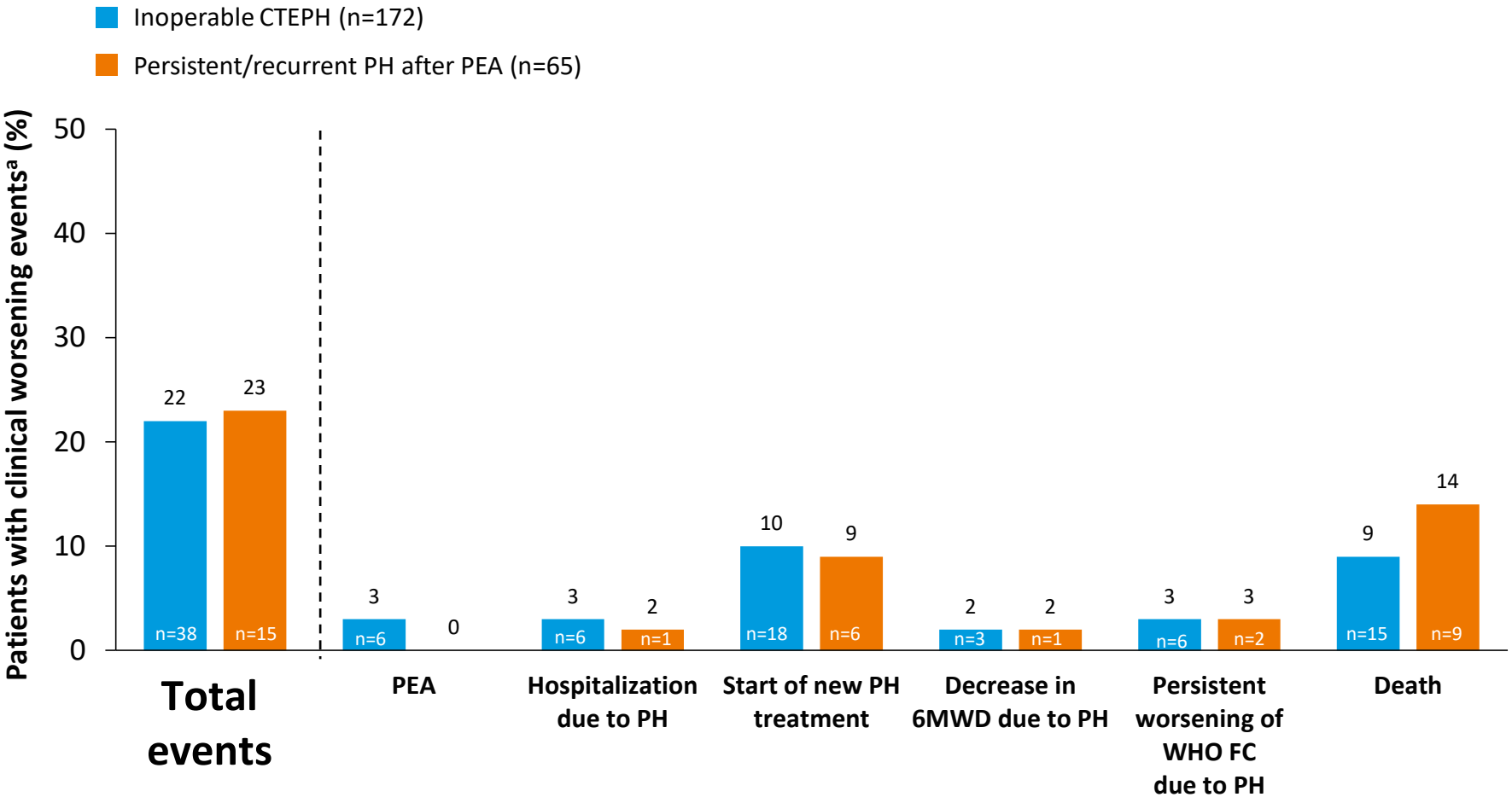
Graph shows mean±standard error of the mean; data are observed values
SD, standard deviation

# Improvements in WHO FC were similar in both subgroups




Data shown are observed values
Percentages may not add up to 100% due to rounding

# Incidence of clinical worsening




[a]Patients could experience more than one clinical worsening event

# Conclusions

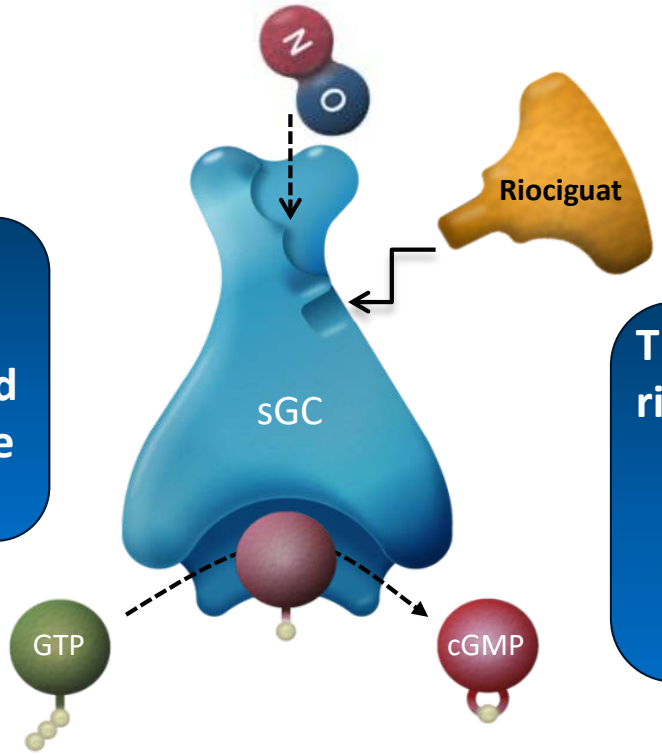
- Riociguat had an acceptable long-term safety profile in patients with inoperable CTEPH or persistent/recurrent PH after PEA
  - No new safety signals were identified
- The overall frequency of clinical worsening events was similar in the inoperable and persistent/recurrent subgroups
- In patients remaining in the CHEST-2 study, improvements in 6MWD and WHO FC were sustained at 2 years in both subgroups

# Thank you

# Back-up slides

# Riociguat's mechanism of action

**PH is associated with endothelial dysfunction, impaired synthesis of NO, and insufficient stimulation of the NO–sGC–cGMP pathway[1,2]**




**The novel sGC stimulator riociguat[1,3]:**

- **Directly stimulates sGC independent of NO**
- **Increases the sensitivity of sGC to NO**

**sGC stimulation results in increased generation of cGMP[1,3]**

cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide

1. Stasch JP, et al. Circulation 2011;123:2263–2273;
2. Giaid A, et al. N Engl J Med 1995;333:214–221;
3. Ghofrani HA, et al. Future Cardiol 2010;6:155–166

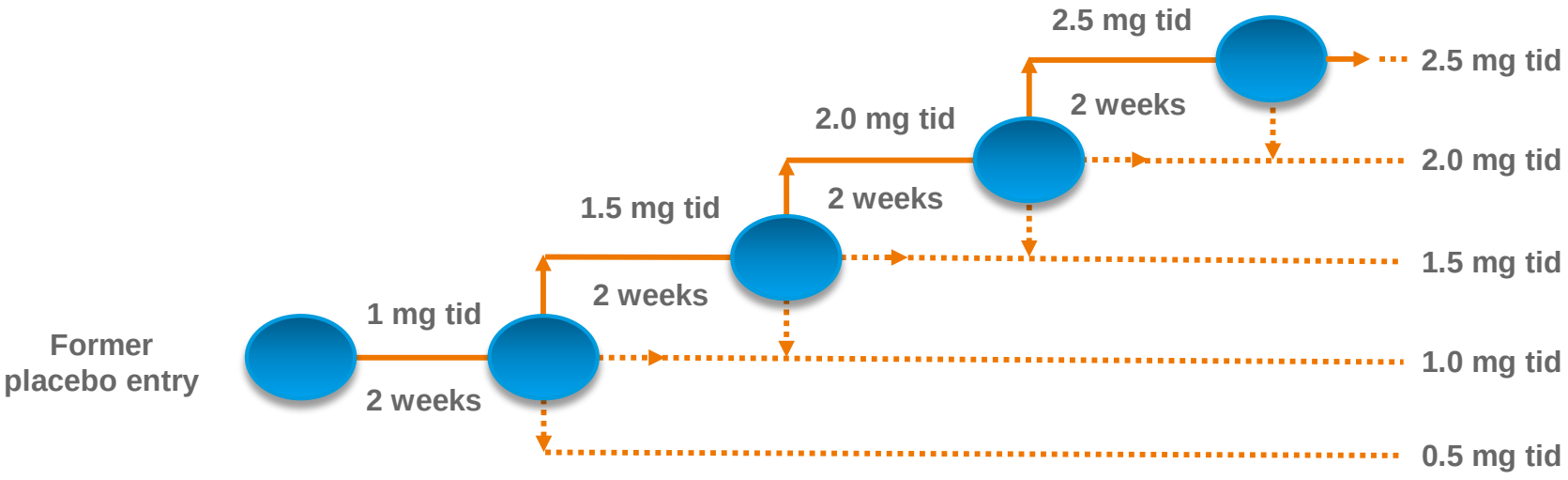
# CHEST-2 objectives

- **Outcomes**
  - **Primary outcomes**: Safety and tolerability
    - AEs, SAEs, blood pressure, heart rate, ECG, oxygen saturation
  - **Exploratory outcomes**: Efficacy
    - 6MWD, NT-proBNP level, WHO FC, Borg dyspnea score, QoL assessments, time to clinical worsening

ECG, electrocardiography; QoL, quality of life

# CHEST-2 dose-adjustment strategy

- Dose was adjusted every 2 weeks (to Week 8) according to the peripheral systolic blood pressure measured at trough before intake of the morning dose
  - ≥95 mmHg: increased dose by 0.5 mg
  - 90–94 mmHg: maintained dose
  - <90 mmHg without symptoms of hypotension: reduced dose by 0.5 mg
  - <90 mmHg with symptoms of hypotension: treatment discontinued for 24 hours and restarted at a 0.5 mg lower dose
  - Patients from CHEST-1 individually adjusted pretreatment arm continued on their optimum dose of riociguat while receiving sham dose adjustments



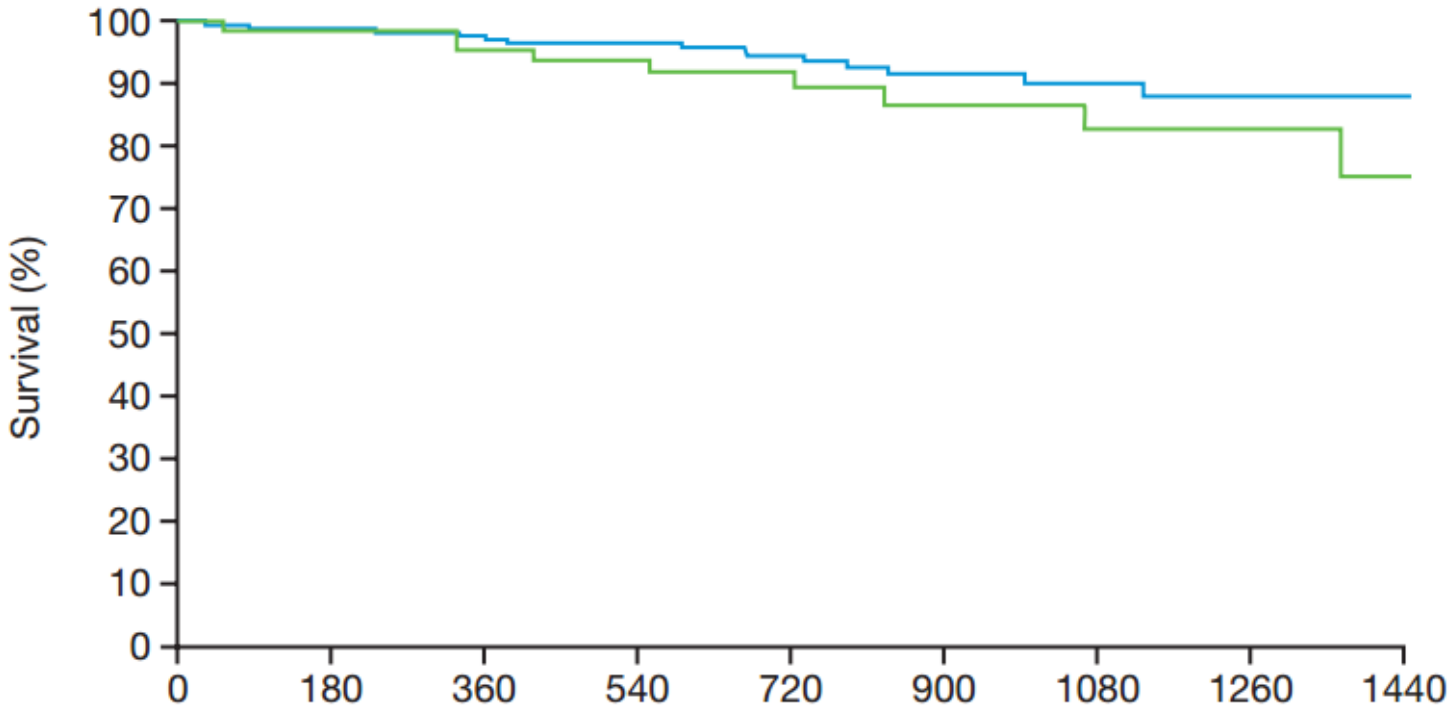
# Other exploratory efficacy endpoints

| Endpoint | Inoperable CTEPH | | | | | Persistent/recurrent PH after PEA | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Change from baseline at timepoint, months | | | | Baseline | Change from baseline at timepoint, months | | | |
| | | 6 | 12 | 18 | 24 | | 6 | 12 | 18 | 24 |
| **NT-proBNP, pg/mL** | 1624±2456 (n=154) | –471±1944 (n=147) | –601±1785 (n=137) | –332±1406 (n=100) | –351±1308 (n=60) | 1130±1208 (n=50) | –270±730 (n=47) | –133±770 (n=37) | +20±658 (n=26) | –194±816 (n=20) |
| **Borg dyspnea score** | 4.58±2.31 (n=172) | –1.04±2.44 (n=158) | –0.87±2.42 (n=150) | –0.84±2.50 (n=115) | –0.90±2.23 (n=73) | 4.13±2.23 (n=65) | –0.77±2.01 (n=60) | –0.51±2.06 (n=50) | –0.35±2.36 (n=36) | –0.05±1.75 (n=27) |
| **EQ-5D score** | 0.63±0.24 (n=170) | +0.11±0.25 (n=160) | +0.08±0.29 (n=150) | +0.10±0.25 (n=114) | +0.09±0.26 (n=71) | 0.68±0.27 (n=65) | +0.04±0.22 (n=61) | +0.06±0.26 (n=49) | +0.01±0.25 (n=32) | +0.02±0.26 (n=26) |

- In general, improvements were more pronounced in the inoperable CTEPH subgroup

Data are mean±SD unless otherwise stated
EQ-5D, EuroQol 5-Dimensions Self-Report Questionnaire

# Survival in the inoperable and persistent/recurrent subgroups




| Number of patients at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Inoperable CTEPH | 172 | 166 | 162 | 155 | 119 | 71 | 48 | 32 | 16 |
| Persistent/recurrent PH after PEA | 65 | 62 | 58 | 55 | 37 | 27 | 22 | 15 | 7 |

# Clinical worsening-free survival in the inoperable and persistent/recurrent subgroups