Effects of riociguat in treatment-naïve vs pretreated patients with pulmonary arterial hypertension: 2-year efficacy results from the PATENT-2 study

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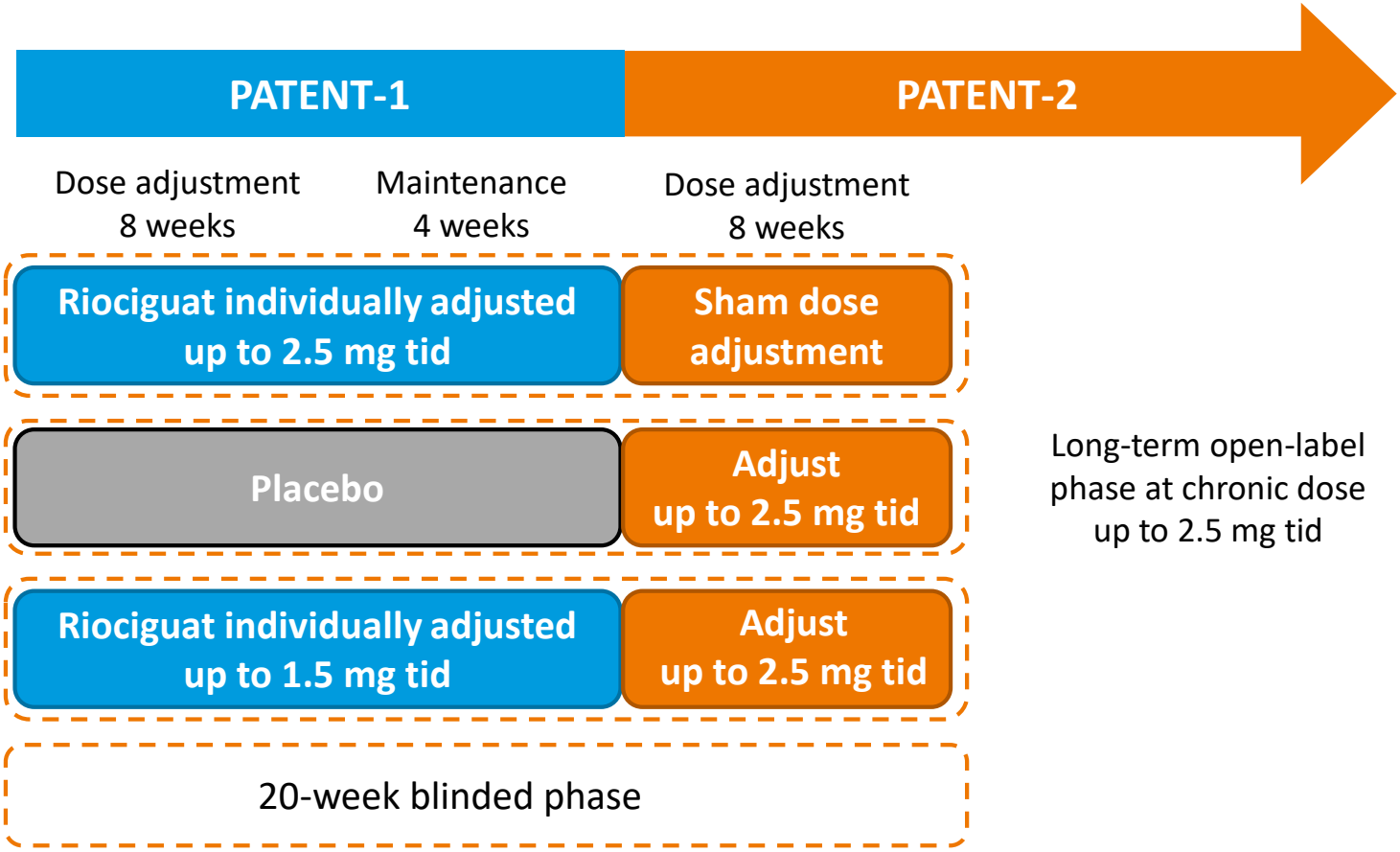
Introduction

- In the PATENT-1 study, the sGC stimulator riociguat was assessed in patients with PAH[1]
- After 12 weeks of treatment with riociguat, significant improvements were seen in:
  - Exercise capacity (6MWD)
  - Clinically relevant secondary endpoints, including hemodynamics, WHO FC, time to clinical worsening, Borg dyspnea score, and NT-proBNP levels
- Improvements in 6MWD and WHO FC persisted at 2 years in the PATENT-2 long-term extension[2]
- Here we compare the safety and efficacy of riociguat in the subgroups of treatment-naïve and pretreated patients using the final data-cut of PATENT-2 (March 2014), when most patients had received at least 2 years of riociguat treatment[2]

6MWD, 6-minute walking distance; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; sGC, soluble guanylate cyclase; WHO FC, World Health Organization functional class

1. Ghofrani HA, et al. N Engl J Med 2013;369:330–340;
2. Ghofrani HA, et al. Lancet Respir Med 2016;4:361–371

PATENT study design



- Patients with PAH who were treatment naïve or pretreated with ERAs or prostanoids entered PATENT-2 after completing PATENT-1 without ongoing riociguat-related SAEs

ERA, endothelin receptor antagonist; SAE, serious adverse event; tid, three times daily

Safety profile of riociguat in treatment-naïve and pretreated patients

AEs, n (%)	Treatment-naïve (n=197)	Pretreated (n=199)
AEs of special interest in >5% of overall population		
Hypotension	21 (11)	30 (15)
Syncope	11 (6)	27 (14)
Other AEs of interest		
Hemoptysis or pulmonary hemorrhage	18 (9)	12 (6)
Drug-related AEs	104 (53)	128 (64)
SAEs	103 (52)	135 (68)
Discontinuation due to AEs	14 (7)	31 (16)
Deaths	22 (11)	28 (14)

- AEs were generally more common in the pretreated subgroup compared with the treatment-naïve subgroup

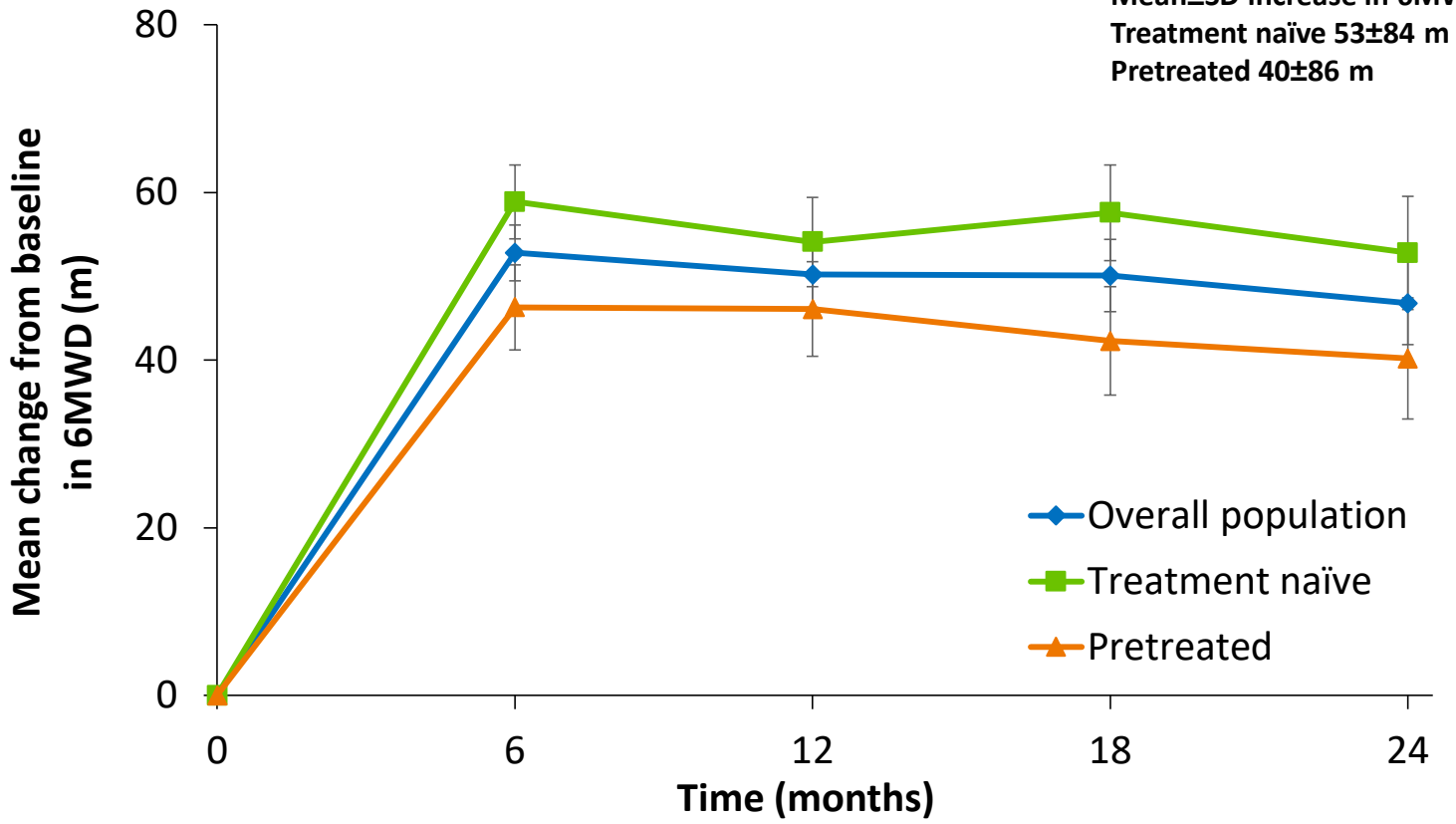
AE, adverse event

Most frequent AEs in treatment-naïve and pretreated patients

AEs, n (%)	Treatment-naïve (n=197)	Pretreated (n=199)
Any AE	190 (96)	198 (99)
AEs in >15% of overall population		
Nasopharyngitis	53 (27)	65 (33)
Dizziness	50 (25)	51 (26)
Peripheral edema	42 (21)	56 (28)
Cough	45 (23)	43 (22)
Diarrhea	28 (14)	56 (28)
Headache	29 (15)	53 (27)
Nausea	27 (14)	49 (25)
Vomiting	26 (13)	41 (21)
Dyspnea	25 (13)	39 (20)
Upper respiratory tract infection	43 (22)	21 (11)

Improvements in 6MWD were greater in treatment-naïve patients versus pretreated patients at 2 years

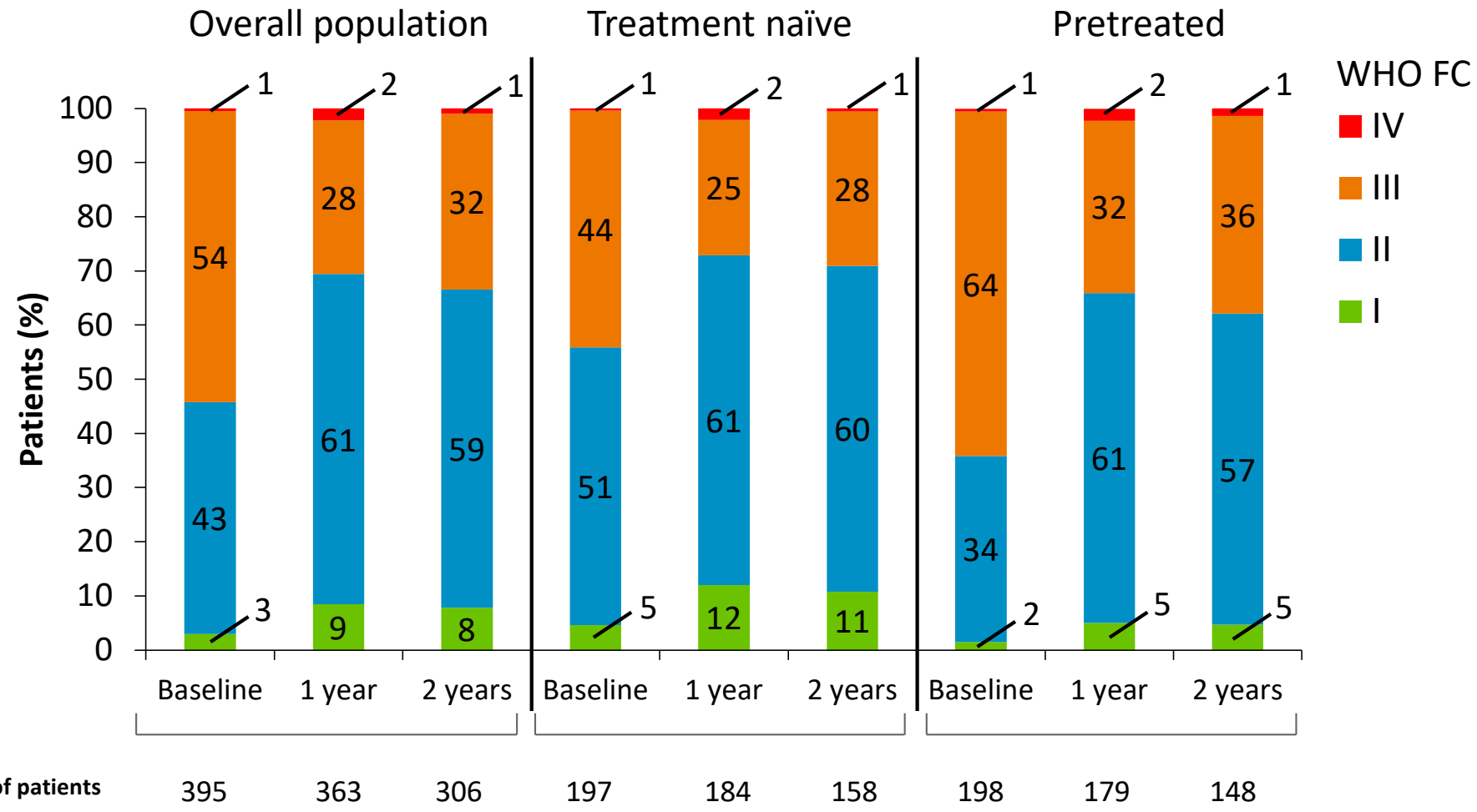
Mean±SD increase in 6MWD at 2 years:
Treatment naïve 53±84 m
Pretreated 40±86 m



No. of patients					
Overall population	396	366	351	329	296
Treatment naïve	197	189	179	169	154
Pretreated	199	177	172	160	142

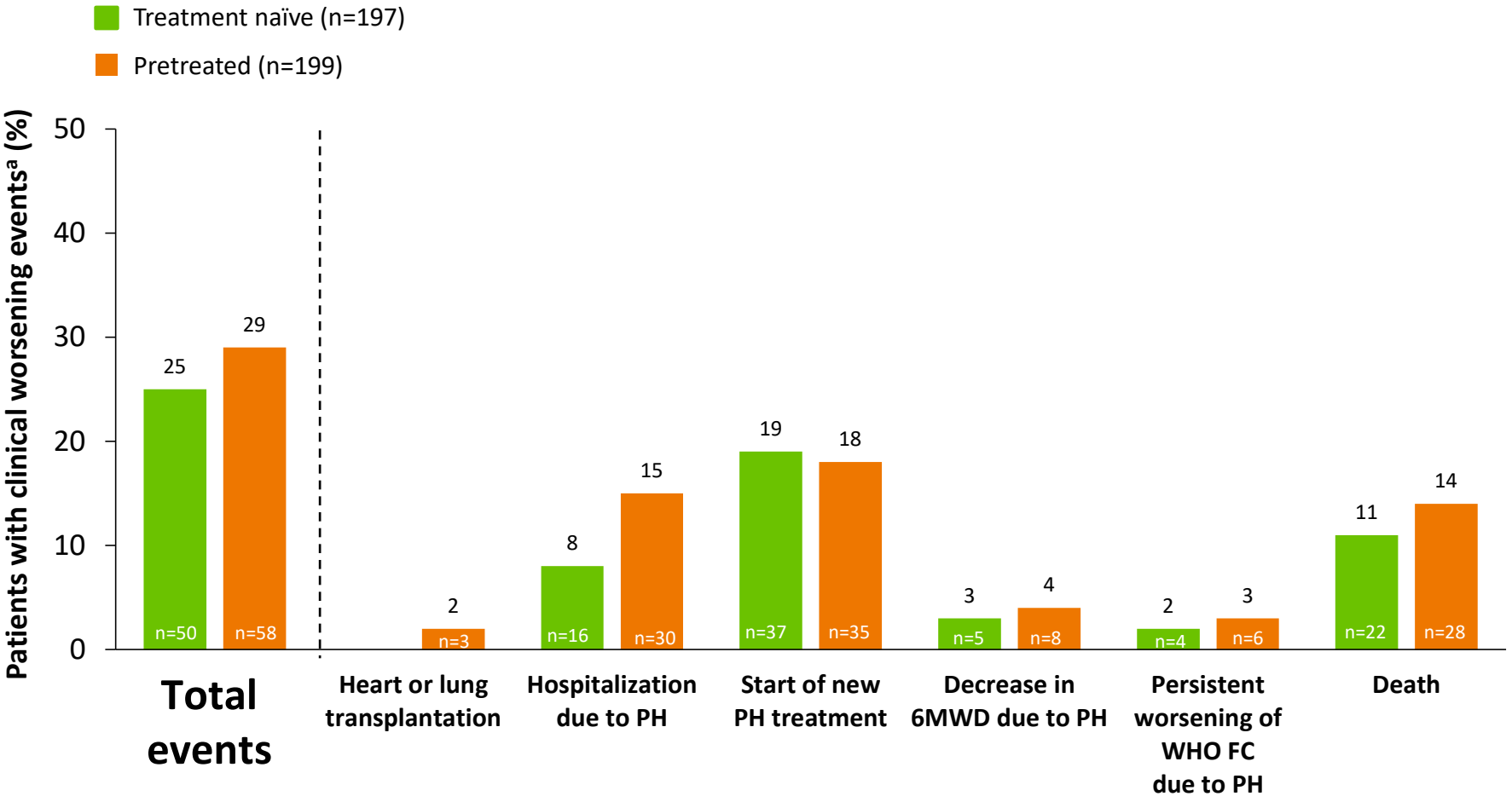
Graph shows mean±standard error of the mean; data are observed values
SD, standard deviation

Improvements in WHO FC were similar in pretreated and treatment-naïve patients



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; PH pulmonary hypertension

Conclusions

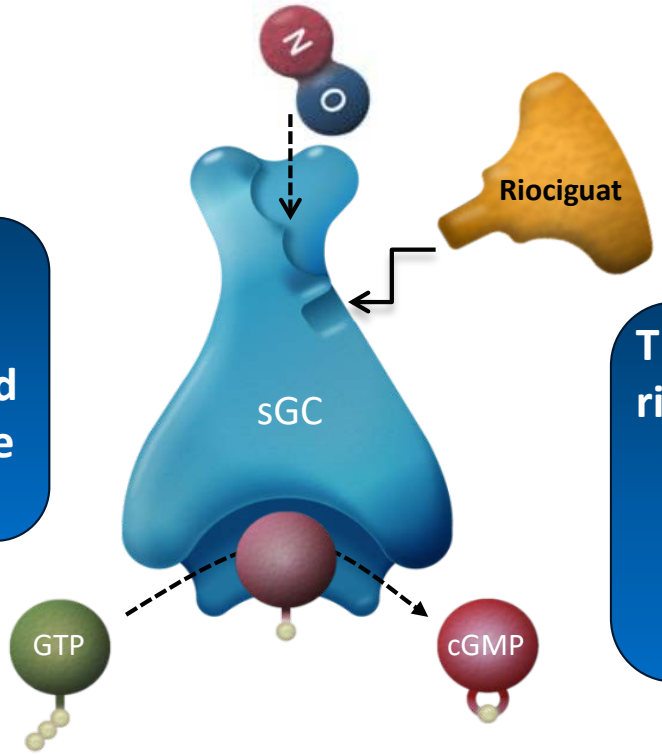
- Riociguat was well tolerated in treatment-naïve and pretreated patients with PAH
  - Syncope, discontinuation due to AEs, and hospitalization were more common in the pretreated subgroup compared with the treatment-naïve subgroup
  - No new safety signals were identified
- The overall frequency of clinical worsening events was similar in the treatment-naïve and pretreated subgroups
- Riociguat increased 6MWD and improved or stabilized WHO FC in both subgroups
- These data support the use of long-term treatment with riociguat as monotherapy or in combination with ERAs or prostanoids in patients with PAH

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

PATENT-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

PATENT study inclusion criteria

PATENT-1

- 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 prostanoid (oral, inhaled, or SC) for ≥3 months

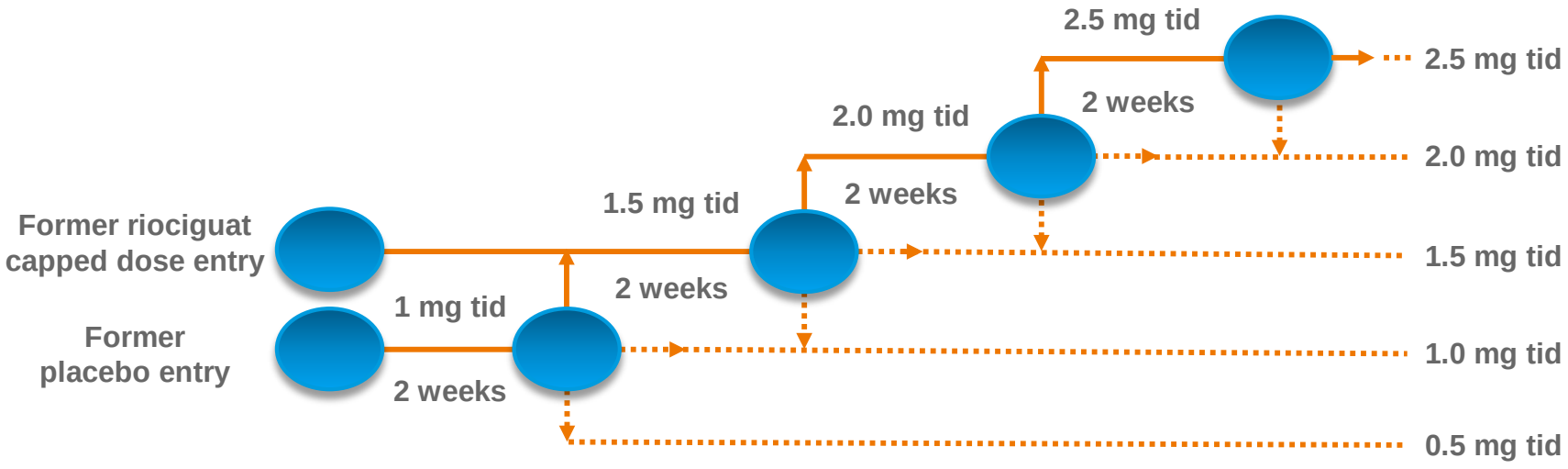
PATENT-2

- Completed 12 weeks of treatment in PATENT-1
- No ongoing SAEs from PATENT-1 considered related to study drug

mPAP, mean pulmonary artery pressure; PDE5i, phosphodiesterase type 5 inhibitor; PVR, pulmonary vascular resistance; SC, subcutaneous

PATENT-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 PATENT-1 individually adjusted pretreatment arm continued on their optimum dose of riociguat while receiving sham dose adjustments



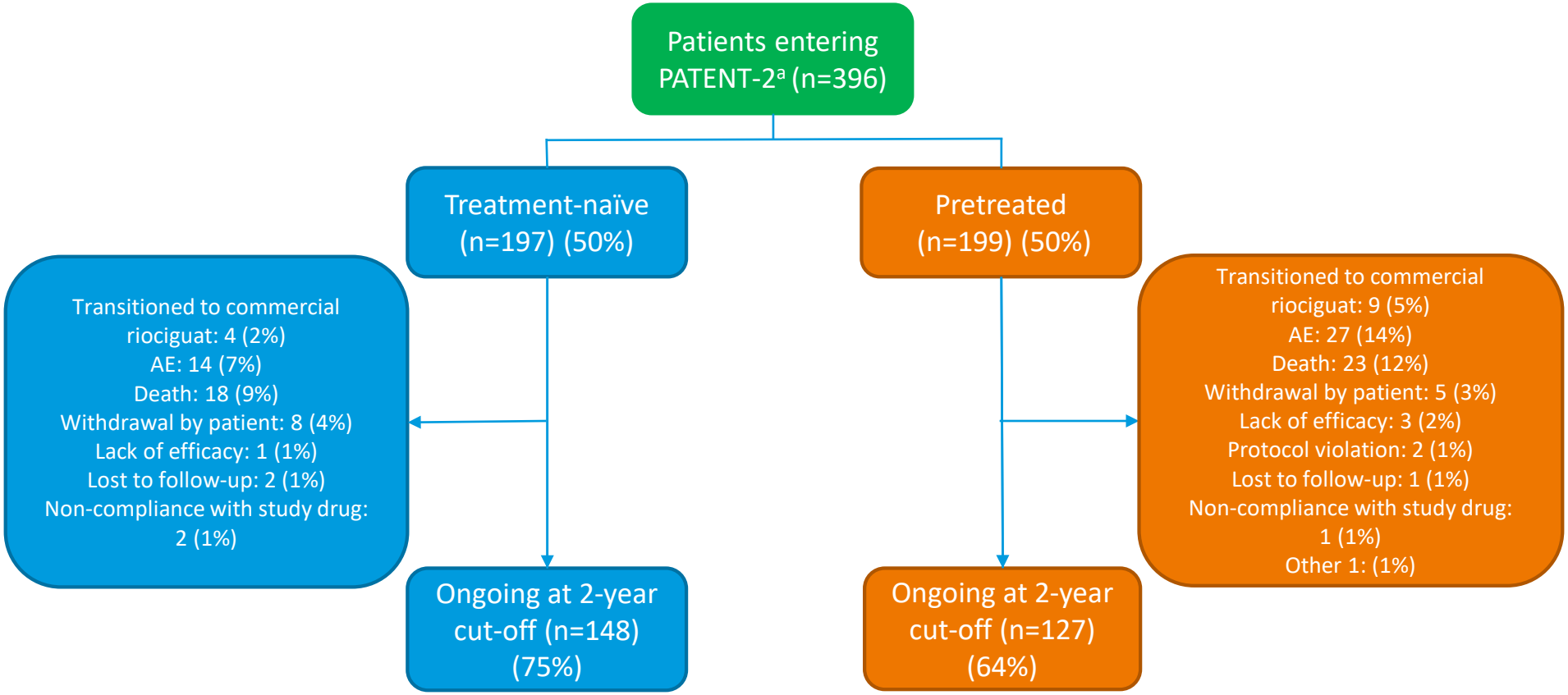
Baseline characteristics

Characteristic (at entry to PATENT-1)	Treatment-naïve (n=197)	Pretreated (n=199)
Age, years	47 (17)	53 (15)
Female, n (%)	153 (78)	164 (82)
PAH classification, n (%)		
Idiopathic	126 (64)	119 (60)
Familial	8 (4)	1 (1)
Connective tissue disease	34 (17)	60 (30)
Congenital heart disease	19 (10)	14 (7)
Portal PH	9 (5)	3 (2)
Anorexigen/amphetamine	1 (1)	2 (1)
6MWD, m	369 (68)	365 (66)
WHO FC I/II/III/IV, %	5/51/44/1[a]	2/34/64/1[a,b]
NT-proBNP, pg/mL	1209 (1891)[c]	912 (1152)[d]

- 396 patients entered PATENT-2; 197 (50%) were treatment naïve and 199 (50%) were pretreated

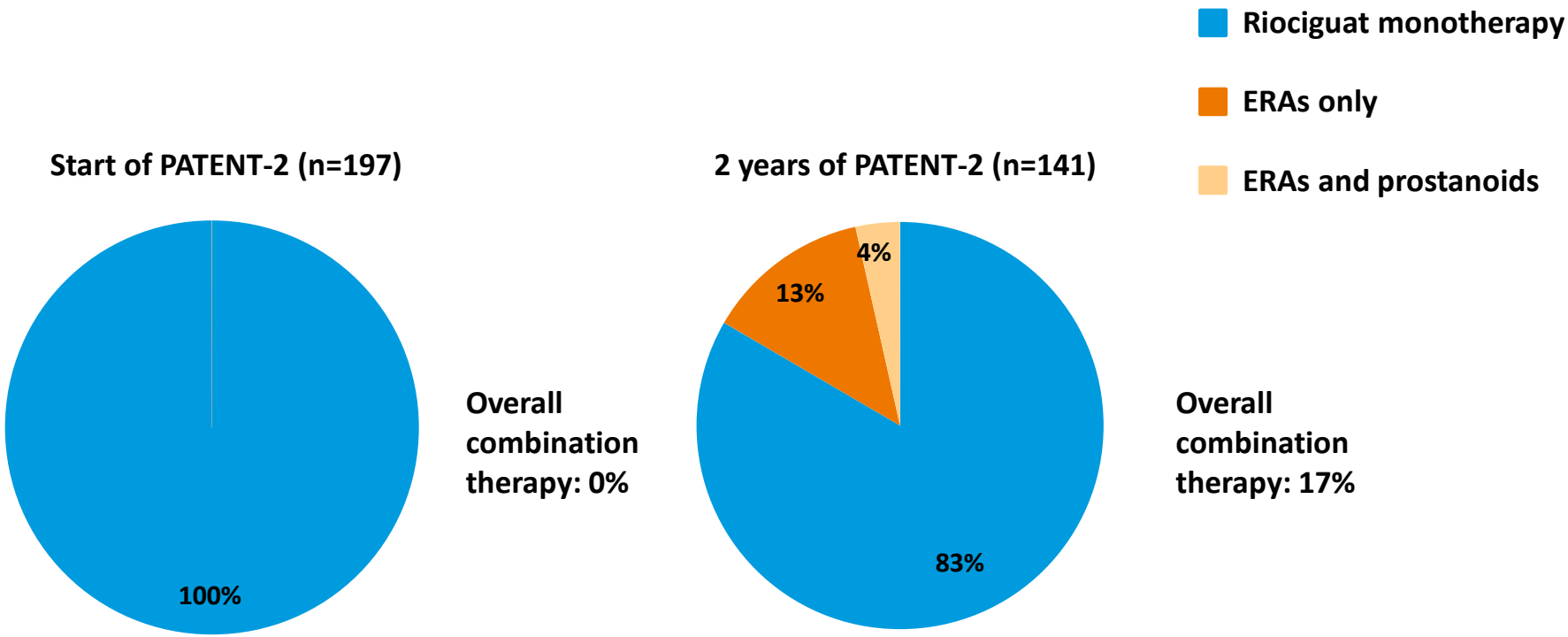
[a]Data do not add up to 100% due to rounding. [b]n=198. [c]n=181. [d]n=173. Data are mean (SD) unless otherwise stated

PATENT-2 patient disposition



[a]All patients received riociguat up to 2.5 mg tid in the long-term extension
Data are number of patients (%)

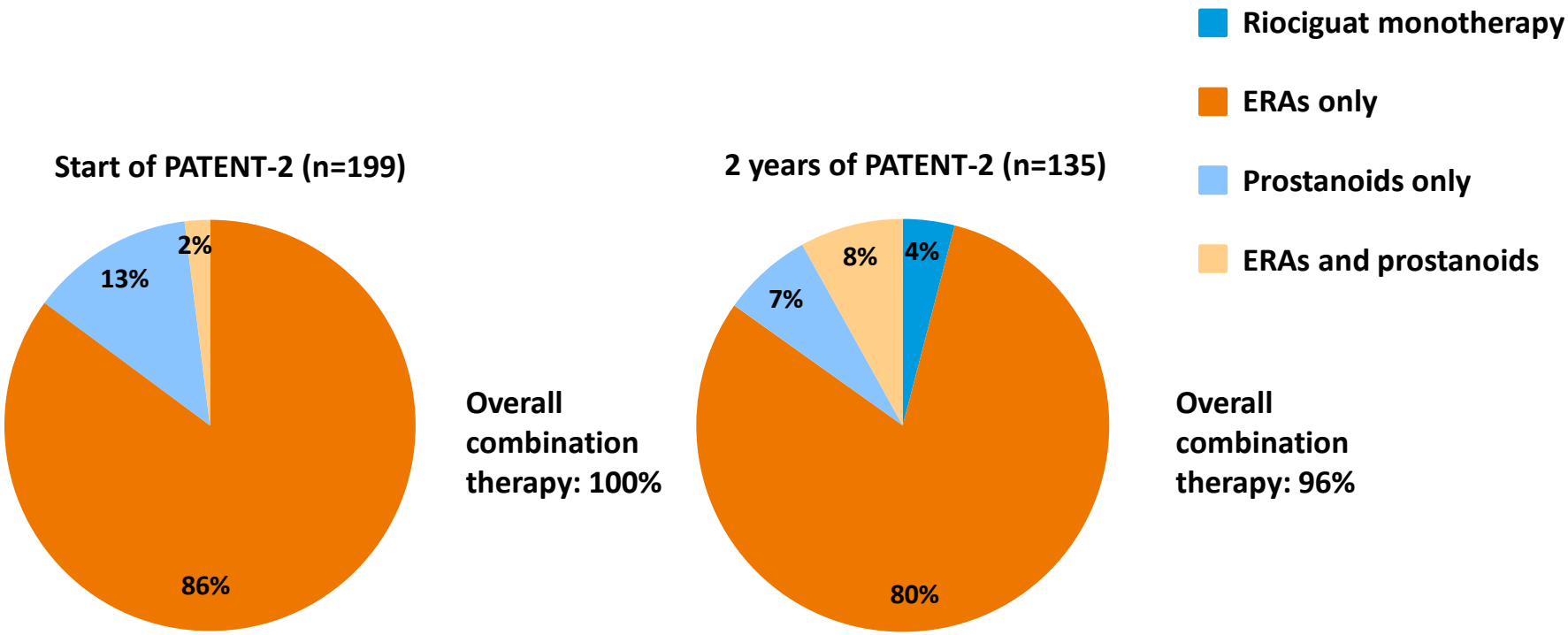
At 2 years, the majority of treatment-naïve patients remained on riociguat monotherapy



- At 2 years, 17% of patients in the treatment-naïve subgroup were receiving combination therapy

Percentages may not add up to 100% due to rounding

At 2 years, the majority of pretreated patients remained on combination therapy



- At 2 years, 4% of patients in the pretreated subgroup were receiving riociguat monotherapy

Percentages may not add up to 100% due to rounding

Other exploratory efficacy endpoints

Endpoint	Treatment-naïve subgroup					Pretreated subgroup				
	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	1209±1891 (n=181)	–482±1688 (n=174)	–386±2097 (n=166)	–510±1934 (n=138)	–291±1626 (n=104)	912±1152 (n=173)	–159±911 (n=160)	–210±879 (n=155)	–70±984 (n=122)	+19±1553 (n=92)
Borg dyspnea score	3.2±2.0 (n=197)	–0.6±1.7 (n=188)	–0.5±1.8 (n=177)	–0.3±1.8 (n=150)	–0.2±1.8 (n=115)	4.3±2.2 (n=199)	–0.5±1.8 (n=177)	–0.4±2.0 (n=169)	–0.4±2.3 (n=132)	–0.6±1.9 (n=98)
EQ-5D score	0.69±0.24 (n=195)	+0.08±0.22 (n=187)	+0.06±0.26 (n=176)	+0.06±0.24 (n=152)	+0.48±0.26 (n=115)	0.68±.0.23 (n=197)	+0.08±0.21 (n=181)	+0.09±0.19 (n=171)	+0.06±.0.22 (n=131)	+0.08±0.24 (n=102)

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