Riociguat for the treatment of patients with chronic thromboembolic pulmonary hypertension: Application of criteria for satisfactory clinical response to CHEST-1 and CHEST-2 populations

Gustavo A. Heresi,[1] Roblee Allen,[2] Harrison W. Farber,[3] Ekkehard Grünig,[4] Pavel Jansa,[5] Dennis Busse,[6] David Platt,[7] Hossein-Ardeschir Ghofrani[8]

[1]Cleveland Clinic, Cleveland, Ohio, USA; [2]Division of Critical Care and Pulmonary Medicine, University of California, Davis Medical Center, Sacramento, California, USA; [3]Pulmonary Center, Boston University School of Medicine, Boston, Massachusetts, USA; [4]Centre for Pulmonary Hypertension, Thoraxclinic, University Hospital Heidelberg, Heidelberg, Germany; [5]Clinical Department of Cardiology and Angiology of the First Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic; [6]Chrestos Concept GmbH & Co. KG, Essen, Germany; [7]Bayer HealthCare Pharmaceuticals, Whippany, New Jersey, USA; [8]University of Giessen and Marburg Lung Center, Giessen, Germany, member of the German Center for Lung Research (DZL); Department of Medicine, Imperial College London, London, UK

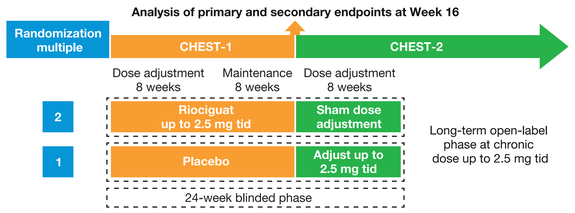
Background

- Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, debilitating, and life-threatening disease characterized by residual organized thrombi obstructing the pulmonary vasculature.[1]
- Pulmonary endarterectomy (PEA) is the treatment of choice for CTEPH and is potentially curative, but some patients are not eligible for PEA and others develop persistent/recurrent pulmonary hypertension (PH) after undergoing the procedure.[2,3]
- Riociguat, a soluble guanylate cyclase (sGC) stimulator, is the first drug to consistently demonstrate clinical efficacy in patients with CTEPH.[4]
  - In the 16-week, Phase III, placebo-controlled CHEST-1 study, riociguat significantly improved 6-minute walking distance (6MWD) and a range of secondary endpoints in patients with inoperable CTEPH or persistent/recurrent PH after PEA.[4]
  - These improvements were sustained at 2 years in the CHEST-2 open-label extension.[5]
- The satisfactory clinical response (SCR) endpoint has previously been applied to patients in the AIR and AMBITION studies.[6,7]
  - The SCR endpoint has never been applied to a database consisting exclusively of patients with CTEPH.
  - Here we present the results from an exploratory post hoc analysis which investigated the SCR outcome measure in patients with CTEPH in the CHEST studies.

Methods

Study design

- CHEST-1 was a 16-week, double-blind, placebo-controlled Phase III study.
  - Patients with inoperable CTEPH or persistent/recurrent PH after PEA received either placebo or riociguat individually adjusted from a starting dose of 1 mg three times daily (tid) to a maximum of 2.5 mg tid according to systolic blood pressure and signs and symptoms of hypotension (Figure 1).



tid, three times daily.

Figure 1. CHEST study design.

- Patients were eligible to enter the CHEST-2 open-label long-term extension study if they completed CHEST-1 without any ongoing riociguat-related serious adverse events.
- Upon entry into CHEST-2, patients underwent an 8-week, double-blind, dose-adjustment phase (Figure 1).
  - Patients originally randomized to riociguat continued on their optimum dose (up to 2.5 mg tid) while receiving sham dose adjustment.
  - Patients originally randomized to placebo were adjusted to their optimum dose of riociguat (up to 2.5 mg tid).
- Patients were permitted to receive endothelin receptor antagonists and prostanoids as possible add-on combination therapy during the main open-label phase of CHEST-2.
  - Specific or non-specific phosphodiesterase inhibitors and NO donors were not permitted.

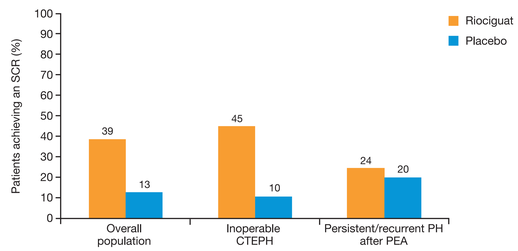
Statistical analyses

- The proportion of patients achieving an SCR was calculated post hoc at Week 16 of CHEST-1 and Week 12 of CHEST-2 (28 weeks after the start of CHEST-1) for observed cases without imputation.
- An SCR was defined as:
  - ≥10% improvement from baseline in 6MWD
  - Improvement to or maintenance of World Health Organization functional class (WHO FC) I/II
  - No clinical worsening events as defined in the study protocols of CHEST-1 and CHEST-2.
- Clinical worsening was defined as the first occurrence of any of the following events: death, heart/lung transplantation, rescue PEA, hospitalization due to worsening of PH, start of new specific PH treatment, persistent decrease of >15% from baseline in 6MWD, and persistent worsening of WHO FC.
- A Kaplan–Meier analysis was used to assess the effect of achieving components of the SCR endpoint on long-term clinical worsening-free survival in CHEST-2.
- Patients with missing 6MWD or WHO FC values were excluded from the analyses.

Results

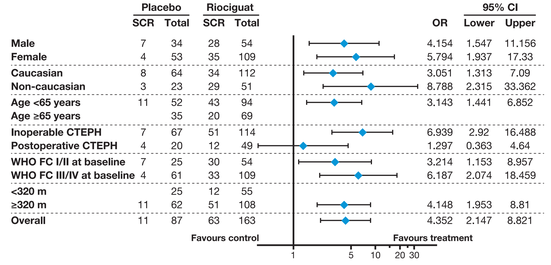
Satisfactory clinical response: CHEST-1

- SCR status at Week 16 was determined for 250 of the 261 patients enrolled in CHEST-1 (163 in the riociguat group and 87 in the placebo group).
- Overall, 39% of patients receiving riociguat achieved an SCR at Week 16 compared with 13% of patients receiving placebo (Figure 2).
  - As shown in Figure 3, the odds ratio (OR) of achieving an SCR with riociguat versus placebo was 4.4 (95% confidence interval 2.1–8.8).
  - This effect was consistent across various patient subgroups (Figure 3).
- In the inoperable subgroup, 45% of patients in the riociguat group achieved an SCR compared with 10% in the placebo group (Figure 2).
  - The effect was less pronounced in the persistent/recurrent subgroup (24% with riociguat vs 20% with placebo; Figure 2).



CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; SCR, satisfactory clinical response.

Figure 2. Number of patients achieving an SCR at Week 16 of CHEST-1.



CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; OR, odds ratio; SCR, satisfactory clinical response; WHO FC, World Health Organization functional class.

Figure 3. Forest plot of SCR at Week 16 in CHEST-1.

- The proportion of patients achieving each component of the SCR at Week 16 of CHEST-1 is shown in Table 1.

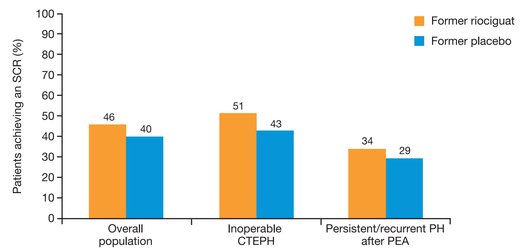
Table 1. Patients achieving individual components of the SCR at Week 16 of CHEST-1.

	Overall		Inoperable CTEPH		Persistent/recurrent PH after PEA	
Endpoint, n (%)	**Riociguat (n=173)**	**Placebo (n=88)**	**Riociguat (n=121)**	**Placebo (n=68)**	**Riociguat (n=52)**	**Placebo (n=20)**
≥10% improvement from baseline in 6MWD						
Yes	95 (55)	23 (26)	74 (61)	18 (26)	21 (40)	5 (25)
No	64 (37)	60 (68)	37 (31)	45 (66)	27 (52)	15 (75)
Unknown	14 (8)	5 (6)	10 (8)	5 (7)	4 (8)	0
Reduction to or maintenance of WHO FC I/II						
Yes	94 (54)	34 (39)	67 (55)	24 (35)	27 (52)	10 (50)
No	66 (38)	50 (57)	45 (37)	40 (59)	21 (40)	10 (50)
Unknown	13 (8)	4 (5)	9 (7)	4 (6)	4 (8)	0
Clinical worsening up to Day 112						
Yes	4 (2)	5 (6)	3 (2)	5 (7)	1 (2)	0
No	169 (98)	83 (94)	118 (98)	63 (93)	51 (98)	20 (100)

6MWD, 6-minute walking distance; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; SCR, satisfactory clinical response; WHO FC, World Health Organization functional class.

Satisfactory clinical response: CHEST-2

- SCR status at Week 12 of CHEST-2 was determined for 224 of the 237 patients who participated in CHEST-2 (147 former riociguat patients and 77 former placebo patients).
- Overall, 46% of former riociguat patients and 40% of former placebo patients achieved an SCR at Week 12 of CHEST-2 (Figure 4).
  - In the inoperable CTEPH subgroup, 51% of former riociguat patients and 43% of former placebo patients achieved an SCR at CHEST-2 Week 12.
  - In the persistent/recurrent subgroup, the proportions were 34% and 29%, respectively.



CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; SCR, satisfactory clinical response.

Figure 4. Number of patients achieving an SCR at Week 12 of CHEST-2.

- The proportion of patients achieving each component of the SCR at Week 12 of CHEST-2 is shown in Table 2.

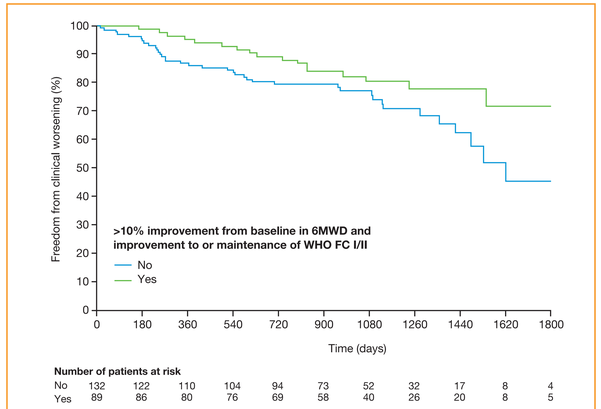
Table 2. Patients achieving individual components of the SCR at Week 12 of CHEST-2.

	Overall		Inoperable CTEPH		Persistent/recurrent PH after PEA	
Endpoint, n (%)	**Riociguat (n=155)**	**Placebo (n=82)**	**Riociguat (n=110)**	**Placebo (n=62)**	**Riociguat (n=45)**	**Placebo (n=20)**
≥10% improvement from baseline in 6MWD						
Yes	101 (65)	44 (54)	76 (69)	35 (56)	25 (56)	9 (45)
No	44 (28)	31 (38)	27 (25)	23 (37)	17 (38)	8 (40)
Unknown	10 (6)	7 (9)	7 (6)	4 (6)	3 (7)	3 (15)
Reduction to or maintenance of WHO FC I/II						
Yes	99 (64)	48 (59)	71 (65)	36 (58)	28 (62)	12 (60)
No	53 (34)	31 (38)	37 (34)	24 (39)	16 (36)	7 (35)
Unknown	3 (2)	3 (4)	2 (2)	2 (3)	1 (2)	1 (5)
Clinical worsening up to Day 84						
Yes	5 (3)	3 (4)	3 (3)	3 (5)	2 (4)	0
No	150 (97)	79 (96)	107 (97)	59 (95)	43 (96)	20 (100)

6MWD, 6-minute walking distance; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; SCR, satisfactory clinical response; WHO FC, World Health Organization functional class.

Association of SCR with long-term outcomes in CHEST-2

- Figure 5 shows long-term clinical worsening-free survival in patients achieving or not achieving components of the SCR (≥10% improvement from baseline in 6MWD and improvement to or maintenance of WHO FC I/II).
  - Patients achieving these components had improved clinical worsening-free survival in CHEST-2 compared with those not achieving these endpoints.



6MWD, 6-minute walking distance; SCR, satisfactory clinical response; WHO FC, World Health Organization functional class.

Figure 5. Kaplan–Meier plot showing effect on clinical worsening-free survival of achieving components of the SCR.

Conclusions

- Riociguat increased the proportion of patients who met SCR criteria compared with placebo at Week 16 in CHEST-1, with further increases observed during CHEST-2.
- The proportion of former placebo patients who achieved an SCR in CHEST-2 was similar to that observed for patients who had received riociguat from the start of CHEST-1.
- Further studies will be required to investigate the clinical relevance of SCR criteria in patients with CTEPH.

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