Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2)

Gérald Simonneau1, Andrea M. D’Armini2, Hossein-Ardeschir Ghofrani3,4, Friedrich Grimminger3, Marius M. Hoeper5, Pavel Jansa6, Nick H. Kim7, Chen Wang8, Martin Wilkins9, Arno Fritsch10, Neil Davie10, Pablo Colorado11 and Eckhard Mayer12

Affiliations: 1Assistance Publique–Hôpitaux de Paris, Service de Pneumologie, Hôpital Bicêtre, Université Paris-Sud, Laboratoire d’Excellence en Recherche sur le Médicament et Innovation Thérapeutique, and INSERM Unité 999, Le Kremlin-Bicêtre, France. 2Division of Cardiothoracic Surgery, Foundation “I.R.C.C.S. Policlinico San Matteo”, University of Pavia School of Medicine, Pavia, Italy. 3University of Giessen and Marburg Lung Center (UGMLC), Giessen, Germany, and Member of the German Center of Lung Research (DZL). 4Dept of Medicine, Imperial College London, London, UK. 5Clinic for Respiratory Medicine, Hannover Medical School, Hannover, Germany, and Member of the German Center of Lung Research (DZL). 6Clinical Dept of Cardiology and Angiology, First Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic. 7Division of Pulmonary and Critical Care Medicine, School of Medicine, University of California San Diego, San Diego, CA, USA. 8Beijing Institute of Respiratory Medicine, Beijing Chao Yang Hospital, Dept of Respiratory Medicine, Capital Medical University, Beijing Key Laboratory of Respiratory and Pulmonary Circulation Disorders, Beijing, China. 9National Institute for Health Research/Wellcome Trust Imperial Clinical Research Facility, Imperial Centre for Translational and Experimental Medicine, Imperial College London, London, UK. 10Global Clinical Development, Bayer HealthCare Pharmaceuticals, Wuppertal, Germany. 11Global Clinical Development, Bayer HealthCare Pharmaceuticals, Barcelona, Spain. 12Kerckhoff Heart and Lung Center, Bad Nauheim, Germany.

Correspondence: Gérald Simonneau, Assistance Publique–Hôpitaux de Paris, Service de Pneumologie, Hôpital Bicêtre, Université Paris-Sud, Laboratoire d’Excellence en Recherche sur le Médicament et Innovation Thérapeutique, and INSERM Unité 999, 78 Rue du Général Leclerc, Le Kremlin-Bicêtre, 94275, France. E-mail: gerald.simonneau@abc.ap-hop-paris.fr

ABSTRACT Riociguat is a soluble guanylate cyclase stimulator approved for the treatment of inoperable and persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH). In the 16-week CHEST-1 study, riociguat showed a favourable benefit–risk profile and improved several clinically relevant end-points in patients with CTEPH. The CHEST-2 open-label extension evaluated the long-term safety and efficacy of riociguat.

Eligible patients from CHEST-1 received riociguat individually adjusted up to a maximum dose of 2.5 mg three-times daily. The primary objective was the safety and tolerability of riociguat; exploratory efficacy end-points included 6-min walking distance (6MWD) and World Health Organization (WHO) functional class (FC).

Overall, 237 patients entered CHEST-2 and 211 (89%) were ongoing at this interim analysis (March 2013). The safety profile of riociguat in CHEST-2 was similar to CHEST-1, with no new safety signals. Improvements in 6MWD and WHO FC observed in CHEST-1 persisted for up to 1 year in CHEST-2. In the observed population at 1 year, mean ± SD 6MWD had changed by +51 ± 62 m (n=172) versus CHEST-1 baseline (n=237), and WHO FC had improved/stabilised/worsened in 47/50/3% of patients (n=176) versus CHEST-1 baseline (n=236).

Long-term riociguat had a favourable benefit–risk profile and apparently showed sustained benefits in exercise and functional capacity for up to 1 year.
Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (PH) caused by obstruction of the pulmonary vasculature by organised fibrotic thromboembolic material, leading to increased pulmonary vascular resistance (PVR), progressive PH and right ventricular failure [1–3]. Pulmonary endarterectomy (PEA) is the recommended treatment for CTEPH as it is potentially curative [4]. However, up to 40% of patients are considered technically inoperable and 17–31% of patients develop persistent or recurrent PH after undergoing PEA [5–8]. Until recently, no pharmacological therapies were approved for these patients.

PH is associated with endothelial dysfunction, impaired synthesis of nitric oxide (NO) and insufficient stimulation of the NO–soluble guanylate cyclase (sGC)–cyclic GMP (cGMP) pathway [9–11]. Riociguat, the first member of a new class of compounds called sGC stimulators, has a dual mode of action, sensitising sGC to endogenous NO by stabilising NO–sGC binding, and directly stimulating sGC via a different binding site, independently of NO. This leads to increased generation of cGMP [10–13].

Based on the results of the pivotal phase III CHEST-1 and PATENT-1 studies [14, 15], riociguat is the first drug to be approved for two separate PH indications: pulmonary arterial hypertension and inoperable or persistent/recurrent CTEPH [4, 16]. In the CHEST-1 study, riociguat significantly improved 6-min walking distance (6MWD) (primary end-point) with a least-squares mean difference of +46 m (95% CI 25–67 m; p<0.0001) compared with placebo at week 16. A number of secondary end-points were also significantly improved compared with placebo, including PVR (p<0.0001), N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (p<0.0001) and World Health Organization (WHO) functional class (FC) (p=0.003) [15]. In CHEST-1, there was a higher number of clinical worsening events in the placebo group versus the riociguat group (6% versus 2%, respectively), although this was not statistically significant. Riociguat showed a favourable benefit–risk profile, with the most frequently occurring serious adverse events (SAEs) in CHEST-1 being right ventricular failure (3% of patients in each group), syncope (2% in the riociguat group and 3% in the placebo group) and haemoptysis (2% of the riociguat group) [15].

Patients completing CHEST-1 were eligible to enter the CHEST-2 long-term extension study, in which all patients received open-label riociguat, for the assessment of the long-term safety and efficacy of riociguat in patients with CTEPH. Here we report the results from an interim analysis of CHEST-2 where the majority (76%) of patients had received ≥1 year of treatment.

Methods

Patients

Patients aged 18–80 years with technically inoperable CTEPH or persistent/recurrent PH following PEA were included in the CHEST study. Additional inclusion and exclusion criteria have been published previously [15], and included 6MWD 150–450 m, PVR ≥300 dyn·s·cm⁻⁵ and mean pulmonary artery pressure ≥25 mmHg. Patients were invited to participate in CHEST-2 after completing CHEST-1 without ongoing study drug-related SAEs. Patients who withdrew from CHEST-1 due to clinical worsening were not allowed to participate in CHEST-2. Patients who were allowed to receive endothelin receptor antagonists (ERAs) and prostanoids as add-on combination therapy during the open-label study phase of CHEST-2, if the investigator considered it to be necessary, but NO donors and specific or non-specific phosphodiesterase inhibitors were not allowed.

The study was carried out in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. The study protocol was approved by the ethics committees of all participating centres and all patients gave their written informed consent. The CHEST-1 and CHEST-2 studies are registered at ClinicalTrials.gov (identifiers NCT00855465 and NCT00910429, respectively).
Study design
CHEST-2 was a multicentre, open-label, single-group study conducted at 71 out of the 89 centres (across 25 out of the 26 countries) that participated in CHEST-1. The study consisted of an 8-week double-blind dose-adjustment phase, followed by the open-label study phase that will run until riociguat receives official approval and is commercially available. Following the approval of riociguat for the treatment of inoperable or persistent/recurrent CTEPH in the USA, Canada, Europe and Japan, some patients are now transitioning to commercially available riociguat.

Patients in CHEST-1 were randomised to receive either placebo or riociguat adjusted from a starting dose of 1 mg three-times daily up to a maximum of 2.5 mg three-times daily for 16 weeks [15]. Patients in the former riociguat group started CHEST-2 at the riociguat dose they received at the end of CHEST-1, while former placebo patients started CHEST-2 at 1 mg three-times daily. During the 8-week double-blind dose-adjustment phase of CHEST-2, patients in the former placebo group were individually adjusted up to a maximum of 2.5 mg three-times daily according to systolic blood pressure (SBP) and symptoms of hypotension, and patients in the former riociguat group continued on the dose they were receiving at the end of CHEST-1 while receiving sham titration. During the open-label study phase, investigators could adjust the riociguat dose (up to a maximum dose of 2.5 mg three-times daily) according to the patient’s need, considering SBP, side-effects and progression of underlying CTEPH.

Assessment
The primary objective of the study was to assess the safety and tolerability of long-term riociguat treatment. Safety parameters included adverse events (AEs) and laboratory variables. Exploratory efficacy end-points included 6MWD, NT-proBNP, WHO FC, time to clinical worsening, Borg dyspnoea score, EuroQol 5 Dimensions (EQ-5D) questionnaire and the Living with Pulmonary Hypertension (LPH) questionnaire. Assessments took place at entry to CHEST-2, at 2, 4, 6, 8 and 12 weeks, and every 3 months thereafter. Patients who stopped study medication had a safety follow-up visit 30 days after discontinuation.

Analysis
All variables were analysed descriptively in this open-label, non-comparative study. Baseline refers to the start of CHEST-1.

At week 12 of CHEST-2, missing data were imputed according to last observation carried forward (LOCF), except in cases of death or clinical worsening without subsequent visit, where the following rules were used: 6MWD, worst possible value (0 m); WHO FC, worst possible score (IV) for cases of clinical worsening without subsequent visit and worst possible value plus one (V) for cases of death; Borg dyspnoea score, worst possible value (10); EQ-5D and LPH questionnaires, worst possible score. Worst possible values were not imputed for NT-proBNP.

In addition, the following exploratory missing data sensitivity analyses were performed at 1 year: LOCF, without worst case value imputation, for 6MWD; LOCF, with worst case plus one (V) imputation for cases of death, for WHO FC; and mixed model for repeated measures (MMRM) analysis for 6MWD. The MMRM was applied with baseline value, visit, former treatment group, the interaction of visit and baseline, and the interaction of visit and former treatment group as fixed effects and an unstructured covariance matrix for the observations of one patient.

Rates of survival and clinical worsening at 1 year were estimated using a Kaplan–Meier analysis, in which patients were censored if they had not reached 1 year of treatment or if they had withdrawn without experiencing an event. In addition, worst-case analyses were performed at 1 year for clinical worsening (assuming that a patient dropping out experienced clinical worsening immediately after drop-out); and survival (assuming that a patient dropping out died immediately after drop-out).

Results
Patients
Of the 243 patients who completed CHEST-1, 237 (98%) entered CHEST-2 (fig. 1). Patient characteristics were well balanced across the groups at CHEST-1 baseline (table 1); 73% of patients had inoperable CTEPH and 27% had persistent/recurrent PH following PEA. At the March 2013 data cut-off, 211 patients (89%) were receiving ongoing treatment and 179 (76%) had received &gt;1 year of treatment. Mean treatment duration was 83 weeks (median 75 weeks) and cumulative treatment exposure was 378 patient-years.

At the end of the 8-week double-blinded dose-adjustment phase, most patients in the former riociguat and placebo groups were receiving riociguat 2.5 mg three-times daily (82% and 90%, respectively) (online supplementary fig. S1). This was sustained for up to 1 year, when 90% of patients were receiving riociguat.
2.5 mg three-times daily. During the open-label study phase of CHEST-2, 23 patients received at least one up-titration of riociguat dose and 13 patients received at least one down-titration.

At the start of CHEST-2, all patients were receiving riociguat monotherapy. Of patients treated for 1 year in CHEST-2, 145 (92%) out of 157 were continuing to receive monotherapy and 12 (8%) patients were receiving additional PH-specific medication (eight (5%) were receiving ERAs and four (3%) were receiving prostanoids). No patient required additional treatment with both an ERA and prostanoid at 1 year.

Safety

The most common AEs in CHEST-2 are shown in table 2. Hypotension was reported in 6% of patients and syncope in 7%. Compared with the initial 16-week CHEST-1 study, lower exposure-adjusted rates per 100 patient-years were seen in the long-term extension phase for the most frequent AEs and AEs of special interest.

TABLE 1 Patient characteristics at CHEST-1 baseline

<table>
<thead>
<tr>
<th></th>
<th>Former riociguat</th>
<th>Former placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>155</td>
<td>82</td>
<td>237</td>
</tr>
<tr>
<td>Age years</td>
<td>59 ± 14</td>
<td>59 ± 12</td>
<td>59 ± 13</td>
</tr>
<tr>
<td>Female</td>
<td>104 (67)</td>
<td>49 (60)</td>
<td>153 (65)</td>
</tr>
<tr>
<td>CTEPH classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inoperable</td>
<td>110 (71)</td>
<td>62 (76)</td>
<td>172 (73)</td>
</tr>
<tr>
<td>Persistent/recurrent</td>
<td>45 (29)</td>
<td>20 (24)</td>
<td>65 (27)</td>
</tr>
<tr>
<td>6MWD m</td>
<td>345 ± 82</td>
<td>360 ± 71</td>
<td>351 ± 78</td>
</tr>
<tr>
<td>WHO FC (I/II/III/IV)</td>
<td>2/31/65/3 ⁹</td>
<td>0/31/67/2 ³</td>
<td>1/31/65/3 ³</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, n (%) or %, unless otherwise stated. CTEPH: chronic thromboembolic pulmonary hypertension; 6MWD: 6-min walking distance; WHO: World Health Organization; FC: functional class. ⁹: data do not add up to 100% due to rounding; ³: n=81; ³: n=236.
interest (online supplementary table S1). Drug-related AEs were reported in 46% of patients; the most common were dizziness (10%), dyspepsia (8%) and hypotension (5%).

SAEs were reported in 42% of patients and drug-related SAEs in 5%. The most common drug-related SAEs were syncope (2%) and hypotension (1%), which were resolved in all cases. The exposure-adjusted rate of haemoptysis/pulmonary haemorrhage AEs was 2.9 per 100 patient-years in CHEST-2 versus 7.8 per 100 patient-years in the riociguat group of CHEST-1. The exposure-adjusted rate of haemoptysis/pulmonary haemorrhage SAEs was 1.1 cases per 100 patient-years in CHEST-2 compared with 5.9 cases per 100 patient-years in the riociguat group of CHEST-1. No AEs or SAEs of haemoptysis/pulmonary haemorrhage were reported in the placebo group of CHEST-1. Two of the SAEs were graded as severe, but none were considered study drug-related by the investigators. Of the patients who experienced an SAE in CHEST-2, one had a previous history of pulmonary bleeding prior to the CHEST study (requiring bronchial artery embolisation to be carried out twice) and one had an episode of haemoptysis during CHEST-1. One (0.4%) case was fatal and, of the remaining cases, none led to riociguat discontinuation and all were resolved or resolving at cut-off. All patients with haemoptysis/pulmonary haemorrhage were receiving anticoagulants. Warfarin was discontinued in one patient and one patient underwent bronchial artery embolisation.

There were 13 deaths during CHEST-2, none of which were considered to be study drug-related by the investigators.

Exploratory analyses

6MWD

The reported differences in 6MWD relate to different numbers of patients and should therefore be considered as exploratory. Improvements in 6MWD in the riociguat group of CHEST-1 were sustained at week 12 and year 1 of CHEST-2 (fig. 2). In the former riociguat group, mean ± SD 6MWD had changed from CHEST-1 baseline by +50 ± 59 m at week 16 of CHEST-1 (n=154) and by +61 ± 59 m at week 12 of CHEST-2 (n=145; total 28 weeks). In the former placebo group, little change in 6MWD was observed at week 16 of CHEST-1 (+8 ± 63 m; n=81); however, a change of +51 ± 64 m (n=75) was observed at week 12 of CHEST-2 following transition to riociguat, which is comparable to the former riociguat group (fig. 2).

At 1 year of CHEST-2, 6MWD had changed by +59 ± 58 m for the former riociguat group (n=114), +37 ± 69 m in the former placebo group (n=58) and +51 ± 62 m in the overall population (n=172) (fig. 2).
In the overall population, mean $\pm SD$ 6MWD was 409 $\pm$ 96 m ($n=172$) at 1 year, compared with 351 $\pm$ 78 m ($n=237$) at baseline. Missing data sensitivity analyses, using different imputation methods, showed slightly lower improvements in 6MWD compared with observed values (online supplementary table S2). This was due to patients who dropped out tending to have a lower 6MWD. However, the overall interpretation of the study results was not affected.

**NT-proBNP**

The decreases in NT-proBNP in the riociguat groups of CHEST-1 were sustained for up to 1 year in CHEST-2 (table 3). Patients in the placebo group of CHEST-1 showed a similar decrease in NT-proBNP following transition to riociguat in CHEST-2. At 1 year in the overall population, NT-proBNP changed by $-416 \pm 1321$ pg·mL$^{-1}$ ($n=149$) versus baseline ($n=204$).

**WHO FC**

At 1 year, WHO FC had improved/stabilised/worsened in 50/45/4%, respectively, of patients in the former riociguat group ($n=117$), 39/59/2% of patients in the former placebo group ($n=59$) and 47/50/3% of patients in the overall population ($n=176$) (fig. 3). The proportion of patients in the overall population in WHO FC I/II/III/IV at 1 year was 14/54/31/1% ($n=177$), respectively, compared with 1/31/65/3% ($n=236$) at baseline.

Similar to 6MWD, missing data sensitivity analyses showed slightly reduced improvements in WHO FC compared with observed values (online supplementary table 2), but the overall interpretation of study results was not affected.

**Survival and clinical worsening**

Overall, 16% of patients experienced a clinical worsening event during CHEST-2 (table 4). The estimated rate of clinical worsening-free survival at 1 year was 88% (95% CI 83–92%) (fig. 4a). Using a worst-case analysis, in which patients who dropped out were assumed to have experienced clinical worsening, the rate of clinical worsening-free survival at 1 year was 86% (95% CI 80–90%).
### TABLE 3 Change from CHEST-1 baseline in NT-proBNP, Borg dyspnoea score, EQ-5D score and LPH score during CHEST-1 and CHEST-2

<table>
<thead>
<tr>
<th></th>
<th>Former riociguat</th>
<th></th>
<th>Former placebo</th>
<th></th>
<th>Total population</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>CHEST-1 week 16</td>
<td>CHEST-2 week 12</td>
<td>CHEST-2 1 year</td>
<td>CHEST-1 week 16</td>
<td>CHEST-2 week 12</td>
<td>CHEST-2 1 year</td>
</tr>
<tr>
<td>Borg dyspnoea score#</td>
<td>-1.05 ± 2.26 [154]</td>
<td>-1.00 ± 2.36 [145]</td>
<td>-0.80 ± 2.41 [113]</td>
<td>-0.06 ± 2.15 [81]</td>
<td>-0.70 ± 1.93 [75]</td>
<td>-0.57 ± 1.98 [58]</td>
</tr>
<tr>
<td>EQ-5D score*</td>
<td>+0.10 ± 0.23 [152]</td>
<td>+0.13 ± 0.24 [146]</td>
<td>+0.12 ± 0.29 [113]</td>
<td>-0.03 ± 0.26 [79]</td>
<td>+0.07 ± 0.23 [75]</td>
<td>+0.01 ± 0.30 [58]</td>
</tr>
<tr>
<td>LPH score</td>
<td>-9.3 ± 16.3 [152]</td>
<td>-13.2 ± 16.7 [138]</td>
<td>-5.0 ± 15.0 [79]</td>
<td>10.8 ± 18.9 [67]</td>
<td></td>
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</tbody>
</table>

Data are presented as mean ± SD [n]. NT-proBNP: N-terminal prohormone of brain natriuretic peptide; EQ-5D: EuroQol 5 Dimensions; LPH: Living with Pulmonary Hypertension. #: the Borg dyspnoea scale ranges from 0 to 10, with 0 representing no dyspnoea and 10 maximal dyspnoea; *: Scores on the EQ-5D self-report questionnaire range from -0.6 to 1.0, with higher scores indicating a better quality of life; #: Scores on the LPH questionnaire [an adaptation of the Minnesota Living with Heart Failure Questionnaire] range from 0 to 105, with higher scores indicating worse quality of life; 1: CHEST-2 week 8 data are shown for LPH score.
The estimated overall survival rate at 1 year of CHEST-2 was 97% (95% CI 93–98%) (fig. 4b). Using a worst-case analysis, where patients who dropped out were assumed to have died, the rate of survival at 1 year was 93% (95% CI 88–96%).

Quality of life

The improvement in Borg dyspnoea score seen in the former riociguat group at the end of CHEST-1 (n=154) was maintained in CHEST-2 at week 12 (n=145) and year 1 (n=113), while patients in the former placebo group showed minimal change at the end of CHEST-1 (n=81), with improved scores after the switch to riociguat in CHEST-2 at week 12 (n=75) and year 1 (n=58) (table 3). Likewise, improvement in EQ-5D questionnaire score seen in the former riociguat group at the end of CHEST-1 (n=153) was maintained in CHEST-2 at week 12 (n=147) and year 1 (n=114), while patients in the former placebo group showed no improvement during CHEST-1 (n=80), but showed moderate improvement after the switch to riociguat in CHEST-2 at week 12 (n=76) and year 1 (n=59). A similar trend was observed for LPH, although this end-point was not measured beyond week 8 of CHEST-2 (table 3).

Discussion

The results of CHEST-2 support the findings from CHEST-1 and suggest that riociguat is an effective treatment for improving exercise capacity and functional capacity in patients with inoperable or

<table>
<thead>
<tr>
<th>TABLE 4 Clinical worsening events during CHEST-2</th>
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<tbody>
<tr>
<td><strong>Subjects n</strong></td>
</tr>
<tr>
<td>Subjects n</td>
</tr>
<tr>
<td>Patients with clinical worsening*</td>
</tr>
<tr>
<td>PEA</td>
</tr>
<tr>
<td>Hospitalisation due to PH</td>
</tr>
<tr>
<td>Start of new PH treatment</td>
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<tr>
<td>Decrease in 6MWD due to PH</td>
</tr>
<tr>
<td>Persistent worsening of WHO FC due to PH</td>
</tr>
<tr>
<td>Death</td>
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</tbody>
</table>

Data are presented as n [%], unless otherwise stated. The mean treatment duration was 83 weeks. PEA: pulmonary endarterectomy; PH: pulmonary hypertension; 6MWD: 6-min walking distance; WHO: World Health Organization; FC: functional class. *: one patient can experience more than one type of event.
persistent/recurrent PH. The AE profile of riociguat in CHEST-2 was similar to that seen in CHEST-1 [15], including episodes of haemoptysis. The majority of patients were receiving the maximum 2.5 mg three-times daily dose of riociguat at 1 year and changes in dose were infrequent during the open-label phase of the study, further supporting the long-term tolerability of this treatment. Furthermore, improvements in 6MWD, WHO FC and other exploratory efficacy end-points seen at the end of CHEST-1 [15] were apparently sustained for up to 1 year in CHEST-2.

PEA remains the recommended treatment for CTEPH as it is potentially curative in the majority of patients. Despite being an invasive procedure, the mortality rates of PEA are low: 7% and 9% at 1 and 2 years post-surgery, respectively [7, 17]. However, there is a significant unmet medical need for effective therapies in patients who are considered technically inoperable or who develop persistent/recurrent PH after undergoing PEA [5, 7, 8]. Riociguat is the only approved pharmacological therapy for such patients [4] and is the first to show significant and sustained improvements in exercise capacity.

Haemoptysis and pulmonary haemorrhage are known complications of CTEPH. A previous single-centre survey found that five (6%) out of 79 patients with CTEPH had experienced haemoptysis. The majority of patients were receiving the maximum 2.5 mg three-times daily dose of riociguat at 1 year and changes in dose were infrequent during the open-label phase of the study, further supporting the long-term tolerability of this treatment. Furthermore, improvements in 6MWD, WHO FC and other exploratory efficacy end-points seen at the end of CHEST-1 [15] were apparently sustained for up to 1 year in CHEST-2.

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the former riociguat group by the 1-year cut-off. This highlights the importance of initiating the appropriate treatment as early as possible.

Long-term extension studies provide vital information regarding the long-term safety and tolerability of a drug; however, their lack of a control group and open-label nature in combination with patient withdrawals and the different lengths of time patients have been treated do not allow evidence-based messages regarding efficacy to be derived. In CHEST-2, patients were also allowed to receive concomitant PH medication during the open-label phase. Although the use of concomitant therapies at 1 year was low (8%), this may have affected the AE profile and contributed to the improvement in efficacy parameters. Pulmonary haemodynamics were not assessed in the CHEST-2 study, and so it is unclear whether the improvements in PVR and other haemodynamic parameters persisted beyond the 16-week CHEST-1 study. However, improvements in NT-proBNP, a marker of right ventricular function, apparently persisted for up to 1 year.

In conclusion, long-term treatment with riociguat showed a favourable benefit–risk profile in patients with inoperable CTEPH or persistent/recurrent PH after PEA. As in CHEST-1, cases of haemoptysis/pulmonary haemorrhage were observed in the CHEST-2 long-term extension. Although caution is required when interpreting open-label long-term extension studies, improvements in 6MWD and WHO FC were maintained for up to 1 year of treatment, with a survival rate of 97% (worst-case analysis: 93%) and a rate of clinical worsening-free survival of 88% at 1 year (worst-case analysis: 86%). These results support the use of riociguat as a long-term treatment for patients with inoperable or persistent/recurrent CTEPH.

References