ABSTRACT
Stimulators of soluble guanylate cyclase (sCG) are novel pharmacological agents that directly stimulate sGC. Ongoing research on sGC stimulators led to the development of the more potent and more specific sGC stimulator, riociguat.
Recently, the US Food and Drug Administration has approved riociguat to treat pulmonary arterial hypertension in adults. Support for the approval of riociguat comes from the recently published PATENT-1 (Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1) study.
BACKGROUND

Pulmonary arterial hypertension (PAH) is associated with the impairment of the nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway, supporting a role for therapeutic interventions which target this pathway.1–2

Until recently, the only practical therapeutic strategy to enhance the NO–sGC–cGMP pathway was the use of phosphodiesterase-5 (PDE-5) inhibitors, such as sildenafil, tadalafil, and vardenal to slow cGMP degradation. The clinical benefits associated with the PDE-5 inhibitor have led to interest in testing whether other agents that modulate NO signaling might be similarly beneficial in PAH. This is important considering the finding that up to 60% of patients with PAH do not respond to therapy with the PDE-5 inhibitor sildenafil, with some indication that pulmonary cGMP production is markedly impaired.3–4

Stimulators of sCG are novel pharmacological agents that directly stimulate sGC, both independently of NO and in synergy with NO. Ongoing research on sGC stimulators led to the development of the more potent and more specific sGC stimulator, riociguat.5

Recently, the US Food and Drug Administration has approved riociguat to treat PAH in adults. Support for approval of riociguat comes from the recently published PATENT-1 (Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1) study.6

SOLUBLE GUANYLATE CYCLASE AS A THERAPEUTIC TARGET IN PAH

sGC is a dimeric, heme-containing, redox-sensitive enzyme that catalyzes the synthesis of the second messenger cGMP, which produces (through a number of downstream mechanisms) numerous biological effects, including vasorelaxation and inhibition of fibrosis, smooth muscle proliferation, apoptosis, leukocyte recruitment, and platelet aggregation.5–8

NO binds to sGC only when the heme group on sGC is in the reduced ferrous state. Notably, binding of NO to the reduced heme group leads to an approximately 200-fold increase in the conversion of GTP to cGMP.9 Alternatively, oxidation of this heme group results in its dissociation from the enzyme and the generation of NO-insensitive sGC.10

In the presence of an intact heme-moiety, the sGC is a constitutively active enzyme that basally releases cGMP.11 However in PAH, although the total sGC expression is increased, alteration of the redox state of sGC through oxidative stress may lead to reduced levels of the NO-sensitive form of sGC.12

sGC agonists are divided in two different categories according to their mechanism of action5–13:

- **sGC stimulators** sensitize sGC to NO by stabilizing the binding site on sGC. Accordingly, action of sGC stimulators is dependent on the presence of a reduced heme (heme-dependent compounds such as riociguat)
- **sGC activators** preferentially and effectively activate sGC when it is in an oxidized (heme-independent compounds such as cinaciguat)

Riociguat is the first drug approved in the new class of sGC stimulators. Riociguat acts through a dual mechanism: (1) direct stimulation of sGC in a NO independent fashion, and (2) by sensitization of sGC to low endogenous NO levels.14 In experimental studies, riociguat stimulated recombinant sGC up to 73-fold, and in the presence of a NO-releasing agent, increased the activity of sGC 112-fold above baseline.15 Pre-clinical studies with sGC stimulators have shown vasodilatory, antiproliferative, antifibrotic, and antiinflammatory effects.5–16

PATENT-1

PATENT-16 is a double-blind, randomized, placebo-controlled trial of 443 patients with PAH at 124 centers in 30 countries. Patients were randomly assigned in 2:4:1 ratio to; placebo, riociguat in individually adjusted doses up to 2.5 mg three times daily (2.5 mg maximum group), or riociguat in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg maximum group). The 1.5-mg maximum group was included for exploratory purposes (to provide information about lower riociguat doses), and the data from that group were not included in the efficacy analyses.

The primary endpoint was change from baseline to the end of week 12 in the 6-minute walk distance (6MWD). Secondary endpoints included pulmonary vascular resistance changes, N-terminal prohormone brain-type natriuretic peptide (NT-proBNP), WHO functional class, time to clinical
worsening, Borg scores, EuroQoL 5-dimensional Classification Component scores, and Living with Pulmonary Hypertension scores.

At week 12, 6MWD had increased from baseline by a mean of 30 m in the 2.5 mg–maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% confidence interval: 20 to 52; \( P < 0.001 \)).

Significant benefits were seen in the 2.5 mg–maximum group, as compared with the placebo group, with respect to a range of secondary end points including pulmonary vascular resistance (\( P < 0.001 \)), NT-proBNP (\( P < 0.001 \)), WHO functional class (\( p = 0.003 \)), time to clinical worsening (\( p = 0.005 \)), and score on the Borg dyspnea scale (\( p = 0.002 \)).

Notably, patients who were receiving endothelin-receptor antagonists or non-intravenous prostanoids were permitted into the study and, accordingly, half of patients were on background therapy for PAH: 44% with endothelin-receptor antagonists and 6% with nonintravenous prostanoids. Pre-specified subgroup analysis showed that riociguat improved the 6MWD in patients who had not received other PAH-targeted therapies and also in those who had been on endothelin-receptor antagonists or prostanoids.

Concerning the safety profile, riociguat was well tolerated with a discontinuation rate of 3% in the 2.5 mg–maximum group versus 7% in the placebo group. Syncope occurred less frequently in the 2.5-mg maximum (1%) compared to placebo (4%). The 2.5 mg maximum group had increased rates of hypotension (10%) and anemia (8%) compared to placebo group (2% for each), though without statistical significance.

WHAT HAVE WE LEARNED?

Both PDE-5 inhibitors and sGC stimulators target the NO-sGC-cGMP pathway. From a mechanistic point of view, sGC stimulators may have several advantages over PDE-5 inhibitors:

1. The therapeutic action of PDE-5 inhibitors is dependent on baseline NO availability (which is typically reduced in PAH). In contrast, owing to its NO-independent mode of action, sGC stimulators are effective even when NO production is markedly reduced.
2. PDE-5 inhibitors acts by prevention of cGMP degradation; accordingly in diseases where cGMP levels are low (as in PAH), the effectiveness of PDE-5 inhibitors is expected to be markedly limited. Furthermore, when PDE-5 is inhibited, the activity of other PDEs may compensate for it.
3. In PAH, sGC is upregulated in small pulmonary arteries (as a compensatory mechanism) with increased opportunity for enhanced therapeutic actions of sGC stimulators.

Compared with other PAH-targeted therapies, the position of riociguat within the therapeutic armamentarium in the management of PAH depends on several factors including: efficacy, safety, suitability for use in drug combination, drug-drug interaction, number of daily doses, and cost.

1. Efficacy: In the PATENT-1 trial, the overall difference in the 6MWD with riociguat as compared with placebo, was 36 m at 12 weeks. This change in 6MWD is consistent with the increases observed in previous studies (22.4 m; 95% confidence interval: 17.4–27.5 m). In comparison with PDE-5 inhibitors, this change in 6MWD is less than that observed with sildenafil in the SUPER trial, where the mean placebo-corrected treatment on 6MWD was 45 m, 46 m, and 50 m for patients receiving 20, 40, and 80 mg of sildenafil, respectively. On the other hand, the improvement in 6MWD reported in PATENT-1 is close to that reported with tadalafil in the PHIRST trial, where tadalafil in 40 mg was associated with 33 m increase in 6MWD relative to placebo. Improvement in WHO functional class in PATENT-1 is modest where 21% of patients moved to lower class. In SUPER trial, the proportions of patients with an improvement of at least one functional class were 7%, 36%, and 42% for patients receiving 20, 40, and 80 mg of sildenafil, respectively. In the PHIRST trial, no significant differences in the proportions of patients with and without improvement of WHO functional class were observed with tadalafil compared with placebo.

Importantly, many variables should be considered when comparing changes in 6MWD or WHO functional class among different studies (e.g., population characteristics, baseline 6MWD and WHO functional class, duration of study, proportion of patients on background therapy). For example, in the PHIRST study, about half of patients were receiving bosentan as a background therapy, while in SUPER background therapy was not permitted. This is important since the use of background effective therapy may reduce the ability to demonstrate a statistically significant difference in 6MWD or WHO functional class between the placebo and the active treatment groups.
2. **Safety**: Riociguat was well tolerated and had a favorable safety profile. Two adverse events appear to be common among patients receiving the highest tolerated dose of riociguat: hypotension (10%) and anemia (8%). The risk of hypotension should be minimized by a gradual individual dose titration to the highest tolerated dose (in PATENT-1, riociguat was titrated over 8 weeks), and by contraindicating concomitant use with other drugs affecting the NO-sGC-cGMP pathway (e.g., PDE-5 inhibitors, nitrates). The apparent increased risk of bleeding has been addressed by means of a prominent warning and a description of bleeding events in the adverse reactions section of the Product Monograph.

3. **Drug-drug interaction**: So far, the interaction potential of riociguat with other drugs is virtually unknown. Recent in vitro study suggests that riociguat is a P-glycoprotein substrate and might therefore act as a victim drug when co-administered with strong P-glycoprotein inducers or inhibitors.20

4. **Use in combination therapy**: There is a growing trend to combine drugs that target multiple pathologic pathways in an attempt to increase efficacy and optimize outcomes in PAH patients. In one retrospective analysis, 56% of patients required additional therapy within 2 years.21 Half of patients in PATENT-1 were on background therapy for PAH with significant improvement in the 6MWD in PAH-drug-therapy-naive patients as well as patients treated with combination therapy. Endothelin receptor antagonists were the most common drug class combined with riociguat. The combination between riociguat and PDE-5 inhibitor is contraindicated. PATENT-plus trial investigated the effects of riociguat on supine systolic blood pressure in patients receiving sildenafil over 12 weeks. In this study, riociguat was associated with a high rate of discontinuation due to hypotension with no evidence that this combination exerts a beneficial effect.22

Preserving right ventricular (RV) function is one of the current targets of PAH therapy.23 The significant reduction of NT-proBNP in PAH patients receiving riociguat may denote a favorable effect on RV performance. However, the precise mechanisms underlying this positive effect remain uncertain. Possible mechanisms may include: reduction of RV afterload induced by pulmonary vasodilatation; reversing remodeling of pulmonary vasculature mediated by antiproliferative and antifibrotic effect; or direct effect on the RV. This possibility is supported by the results of experiments in a mouse model of chronic RV pressure overload, in which riociguat treatment reduced the collagen content of the RV and improved the RV ejection fraction.24

One of the major limitation of PAH trials is the short duration. Accordingly, long-term open-label extension study for patients who completed PATENT-1 was performed (PATENT-2).25 After 1 year of treatment, 6MWD further improved by 48 m over the original baseline of PATENT-1, WHO functional class also continued to improve and 68% of the overall cohort were in functional class I/II after 1 year of treatment.

In conclusion, riociguat, the first drug approved in the new class of sGC stimulators, represents an advance within the available therapeutic armamentarium for PAH with an efficacy that is expected to be comparable to PDE-5 inhibitors. Since combination therapy is gaining more ground in the management strategy of patients with PAH, large-scale and long term studies with clinical endpoints should be planned in order to further evaluate the role of the combination between riociguat and other PAH-targeted therapies with special emphasis on endothelin receptor antagonists.

**REFERENCES**


