RIOCIGUAT FOR THE TREATMENT OF INOPERABLE OR PERSISTENT/RECURRENT CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH): A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY (CHEST-1)

G Simonneau,[1] HA Ghofrani,[2,3] F Grimminger,[2] MM Hoeper,[4] NH Kim,[5] E Mayer,[6] N Davie,[7] J Pena,[8] MR Wilkins.[3]

[1]University Paris-Sud, France; [2]University of Giessen and Marburg Lung Center, Germany; [3]Imperial College London, UK; [4]Hannover Medical School, Germany; [5]UCSD School of Medicine, USA; [6]Kerckhoff Heart and Lung Center, Germany; [7]Bayer HealthCare, Germany; [8]Bayer HealthCare, USA.

Objective: Riociguat, a soluble guanylate cyclase (sGC) stimulator, has a dual mode of action, directly stimulating sGC independently of nitric oxide (NO) and increasing the sensitivity of sGC to endogenous NO, thus restoring the NO–sGC–cyclic guanosine monophosphate pathway. Here, we present results from CHEST-1, which investigated the efficacy and safety of riociguat in CTEPH patients (pts).

Methods: In this Phase III, multicenter study, 261 pts with inoperable (assessed by an independent adjudication committee) or persistent/recurrent CTEPH after pulmonary endarterectomy were treated with placebo (pbo) or riociguat, individually adjusted up to 2.5 mg three times daily. The primary outcome was change from baseline in 6-minute walking distance (6MWD) vs pbo after 16 weeks. Secondary endpoints included change in pulmonary vascular resistance (PVR), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), World Health Organization functional class (WHO FC), time to clinical worsening (TTCW), safety and tolerability.

Results: Riociguat significantly improved 6MWD by a least-squares (LS) mean difference of +46 m (95% CI: 25 to 67; $p<0.0001$) vs pbo at Week 16. Significant improvements in PVR (LS mean difference: –246 dyn·s/cm^5 [–303 to –190]; $p<0.0001$) and NT-proBNP (LS mean difference: –444 ρg/mL [–843 to –45]; $p<0.0001$) were also evident at Week 16. WHO FC improved/stabilized/worsened in 33/62/5% and 15/78/7% of riociguat and pbo pts, respectively ($p=0.003$). TTCW showed a trend in favor of riociguat that was not statistically significant. Riociguat had a good safety profile; the most common serious adverse events

were right ventricular failure (3% in each group) and syncope (2% and 3% in the riociguat and pbo groups, respectively).

Conclusions: Riociguat was well tolerated and significantly improved 6MWD and several secondary endpoints in pts with inoperable or persistent/recurrent CTEPH. CHEST-1 is the first pbo-controlled trial to consistently show clinical efficacy in CTEPH.