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Title: An interim analysis of the phase III riociguat long-term extension study in CTEPH (CHEST-2)

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Body: Background In the 16-wk CHEST-1 study, riociguat, a novel sGC stimulator, was well tolerated in CTEPH patients (pts) and significantly improved 6-min walking distance (6MWD) and WHO functional class (FC) vs placebo (pbo). Objectives The CHEST-2 open-label extension assessed the long-term safety and efficacy of riociguat. Methods Pts with inoperable CTEPH or persistent/recurrent PH after pulmonary endarterectomy were eligible to enter CHEST-2 after completion of CHEST-1 without ongoing riociguat-related serious AEs. The primary endpoints were safety and tolerability. Secondary endpoints included change in 6MWD and FC. Results Of 233 pts entering CHEST-2, 194 were eligible for this interim analysis (cut-off May 2012; median treatment duration ~1 y). Riociguat was well tolerated during CHEST-2; 1% of pts withdrew due to AEs. CHEST-1 baseline (BL) 6MWD was 351 m in riociguat pts and 365 m in pbo pts, increasing by 51 m and 4 m, respectively at the end of CHEST-1. After 12 wks of CHEST-2, 6MWD

increased by 63 m in former riociguat pts and 35 m in former pbo pts, vs CHEST-1 BL. After 1 y (overall cohort; n=93), change in 6MWD was 48 m. The number of pts with FC I/II/III/IV at CHEST-1 BL was 2/44/80/3 in the riociguat arm and 0/20/42/2 in the pbo arm. At the end of CHEST-1, FC was improved/stable/worsened in 35/61/4% of riociguat pts and 14/83/3% of pbo pts vs CHEST-1 BL. After 12 wks of CHEST-2, FC was improved/stable/worsened in 41/56/3% of former riociguat pts and 38/58/5% of former pbo pts, vs CHEST-1 BL. Preliminary data suggest improvement in FC for up to 1 y. Conclusions Riociguat has a good long-term safety profile and is the first therapy to show sustained benefits in 6MWD and FC in CTEPH pts.