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Safety, Efficacy, and Tolerability of RAD001 in Patients With Lymphangioleiomyomatosis

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Rationale: Lymphangioleiomyomatosis (LAM) is a rare, progressive cystic lung disorder of women, associated with inappropriate activation of the mammalian target of rapamycin complex (mTORC) signaling. RAD001 (everolimus) is an oral, selective mTORC1 inhibitor. We report findings from an interim analysis of a 26-week study of the safety and efficacy of RAD001 in women with LAM.

Methods: This was a multicenter, open-label, nonrandomized, within-patient multiple dose-escalation study of RAD001 in women with LAM. Patients received 2.5 mg once daily for 4 weeks, followed by 5 mg/day for 4 weeks, and 10 mg/day for 18 weeks thereafter. Dose titration was based on safety and tolerability. The primary efficacy endpoint was change from baseline in forced vital capacity (FVC), with forced expiratory volume in 1 second (FEV_1) a key secondary endpoint. Other endpoints included safety and tolerability (primary), 6-minute walking distance (6-MWD), serum biomarkers, and pharmacokinetics.

Results: 24 patients (of 24 planned) have been enrolled. Data for efficacy were available for 18 women at 26 weeks. The mean change from baseline in FEV_1 was an increase of 120 mL (95% CI, 2 to 238) and the mean change from baseline in FVC was an increase of 15 mL (95% CI, −135 to 165) after 26 weeks. The 6-MWD increased by 68.3 meters (95% CI, 9.5 to 127.1). There were increases from baseline in residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC), and reductions in serum vascular endothelial growth factor D and collagen IV. There were no improvements in diffusing capacity for carbon monoxide (DLco) or arterial saturation. Systemic exposure to RAD001 increased proportionally from a dose of 2.5 mg to 10 mg. Greater than 75% of patients experienced adverse events (AEs) at every dose level. Common AEs, experienced by more than 10% of patients, included mouth ulceration, headache, nausea, stomatitis and fatigue. There were 7 serious AEs, with 2 suspected to be related to study drug. Four patients were withdrawn due to AEs, with 2 suspected to be related to study drug.

Conclusions: In patients with LAM, RAD001 treatment was associated with improvements in FEV_1, FVC, and 6-MWD. AEs were frequent and consistent with the known toxicity profile of mTORC1 inhibitors. Treatment with RAD001 may be useful in selected patients with LAM.

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