HDACi, CS014, dose-dependently reverses vascular remodeling in a preclinical model of pulmonary arterial hypertension

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Summary

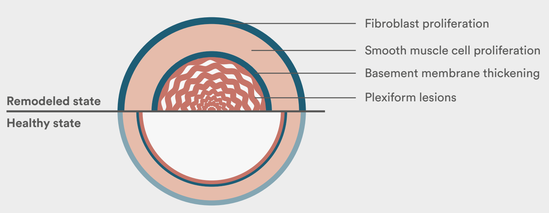
In the Sugen/hypoxia rat model of pulmonary arterial hypertension (PAH), CS014, a novel drug candidate with HDAC inhibition properties, showed significant efficacy in reversing vascular remodeling. Oral administration of CS014 for three weeks led to a robust, dose-dependent improvement in pulmonary arteriolar structure, including marked reductions in vascular occlusion, intimal proliferation, plexiform lesions, and fibrosis.

CS014 achieved approximately a 50% reduction in overall vascular occlusion compared to vehicle controls at plasma exposures above 250 hr·µg/mL. These findings indicate that CS014 effectively reverses key pathological features of PAH, demonstrating strong potential as a therapeutic agent for vascular remodeling diseases.

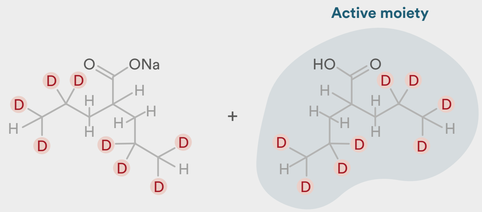
Introduction

- PAH is a severe rare disease of the pulmonary microvasculature.[1]
- Characterized by pulmonary vasoconstriction, thickening of pulmonary artery walls, muscularization of pulmonary arterioles, capillary rarefaction, in situ thrombosis, and the appearance of plexiform lesions.[1]
- Symptoms include dyspnea, limited exercise capacity, fainting, chest pain.[2]
- PAH generally progresses to right ventricular failure, with median survival of ~7 years in treated patients.[1]
- HDAC inhibitors (HDACi) postulated beneficial effect in severe cardiopulmonary diseases, including PAH.
- CS014, a novel HDACi, a precision-deuterated valproic acid (VPA).

Pathophysiological changes in small pulmonary arteries



CS014 structure



Aim

Assess effects of CS014 on a preclinical model of PAH, the Sugen/hypoxia rat.

Methods

Controls PAH animal model

Sugen 5416 (20 mg/kg, single dose, SC) to rats followed by hypoxia (10% O_2) for 3 weeks. A control group received vehicle and was maintained at normoxia.

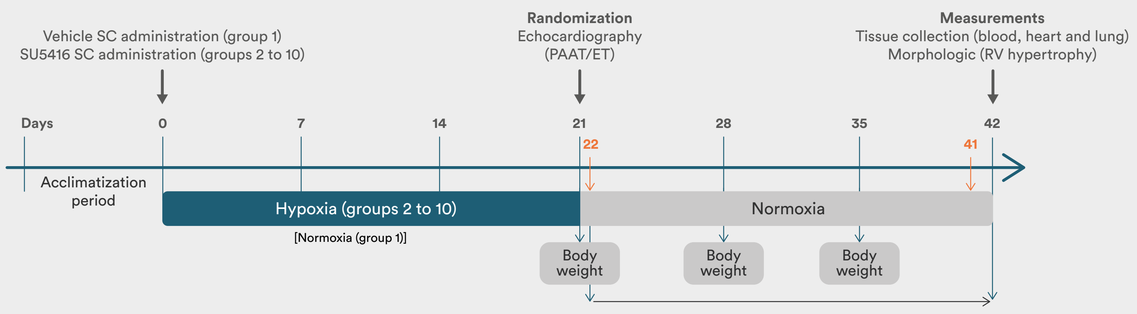
CS014 Dosing

Rats returned to normoxia orally dosed for 3 weeks, with either vehicle control or CS014 at doses of 20, 40, 75, 150 or 300 mg/kg/day, n=8-10/group.

PK

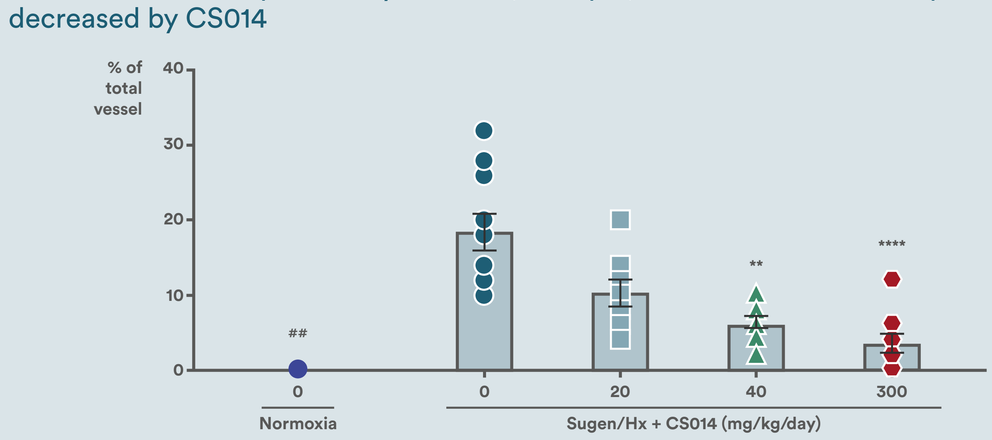
PK profiles were obtained in parallel groups of animals (n=3/group). Plasma protein binding was determined using rapid equilibrium dialysis.

Protocol

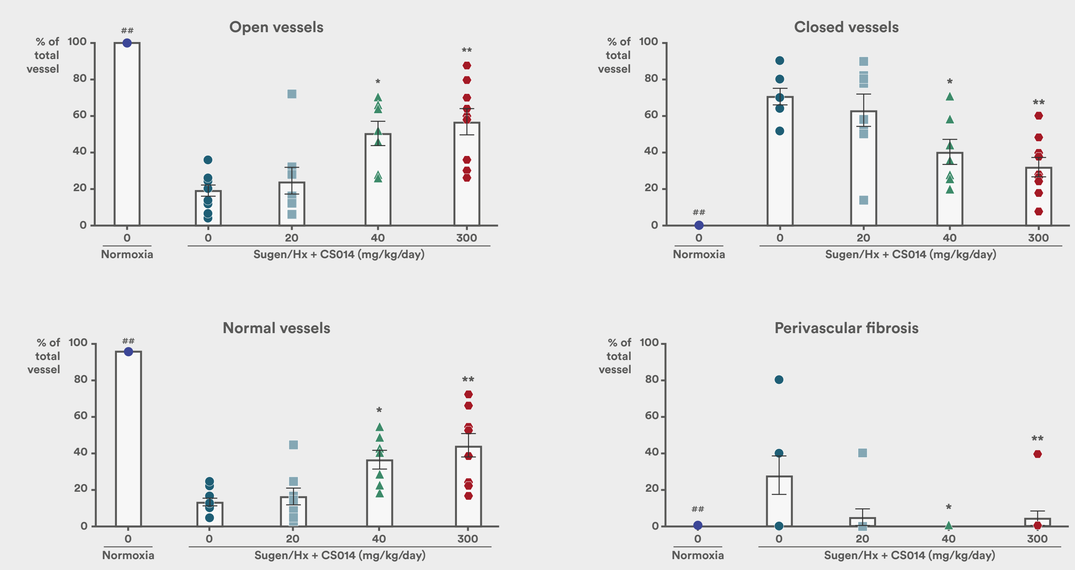


Results

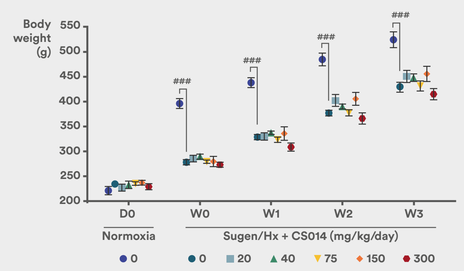
Plexiform lesions in pulmonary arteries (< 100 µm) of PAH model dose-dependently decreased by CS014



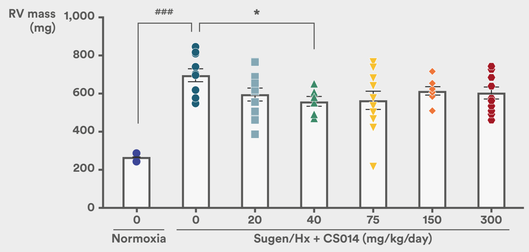
Reversal of pulmonary vascular remodeling by CS014 in PAH model



Body weight gain decreased in PAH model



CS014 modestly reversed severe right ventricular hypertrophy in a PAH model

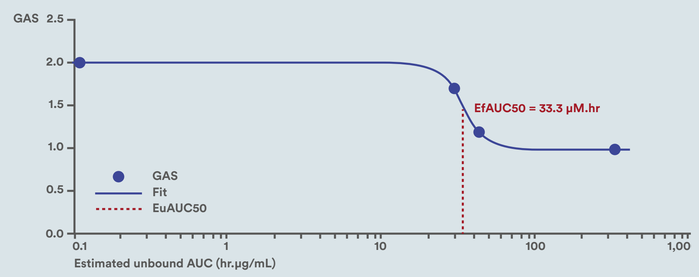


#p<0.05; ##p<0.01; ###p<0.001; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001. vs Sugen/Hx + CS014 0 mg/kg/day

Conclusion

CS014 treatment for 3 weeks decreased perivascular fibrosis and dose-dependently ameliorated pulmonary arteriolar vascular remodeling, including reduction in plexiform lesions, in the Sugen/hypoxia rat model of PAH.

Global arterial score (GAS), which reflects the extent of vascular occlusion, versus estimated unbound CS014 exposures.



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References:
1. Humbert, Marc, et al. The Lancet Respiratory Medicine 11.9 (2023): 804-819.
2. Highland, Kristin B., et al. Health and quality of life outcomes 19.1 (2021): 202.

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