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CS014, a Novel HDACi Inhibitor, Demonstrates Preclinical Efficacy in Pulmonary Vascular Disease and Clinical Safety in FIH Trial

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Summary

- In the Sugen/hypoxia rat model of pulmonary arterial hypertension (PAH), CS014, a novel HDAC inhibitor, demonstrated significant efficacy in reversing pulmonary vascular remodeling. Oral administration of CS014 for three weeks led to a robust, dose-dependent improvement in small pulmonary artery histopathology, including marked reductions in vascular occlusion, plexiform lesions, and fibrosis.
- A Phase 1 first-in-human (FIH) trial was performed to assess safety, tolerability and PK parameters of single and multiple oral doses of CS014 in healthy volunteers. CS014 was safe and well-tolerated, based on reported adverse events (AEs), vital signs, ECG measurements, safety laboratory parameters, and physical examination findings.
- Analysis of PK data showed that the estimated unbound exposures in humans exceeded those needed to achieve the reversal of pulmonary vascular remodeling and fibrosis in the preclinical PAH model.

Introduction

- HDAC inhibitors (HDACi) have been postulated to have beneficial effect in severe cardiopulmonary diseases, including PAH.
- CS014, a novel precision deuterated valproic acid (VPA) and histone deacetylase (HDAC) inhibitor is being developed for rare pulmonary diseases characterized by vascular remodeling and fibrosis. These include idiopathic pulmonary fibrosis (IPF), pulmonary hypertension associated with interstitial lung disease (PH-ILD), and PAH.

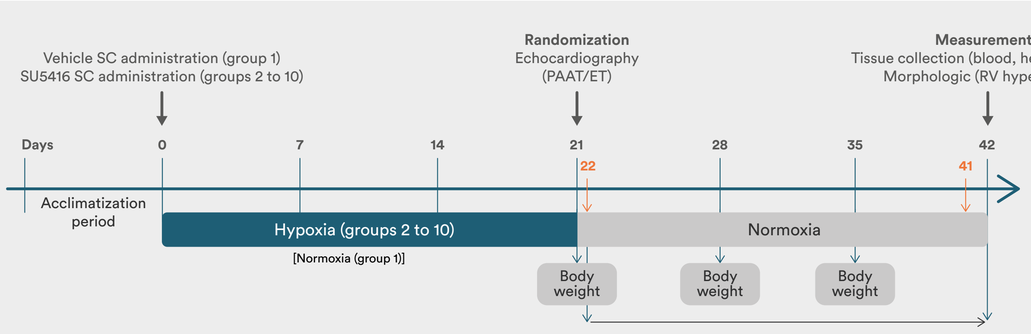
Objectives

- Evaluate the potential of CS014 to ameliorate pulmonary vascular remodeling and fibrosis in the Sugen/hypoxia rat model.
- Assess safety, tolerability and PK parameters of CS014 in a first-in-human (FIH) study.

Methods

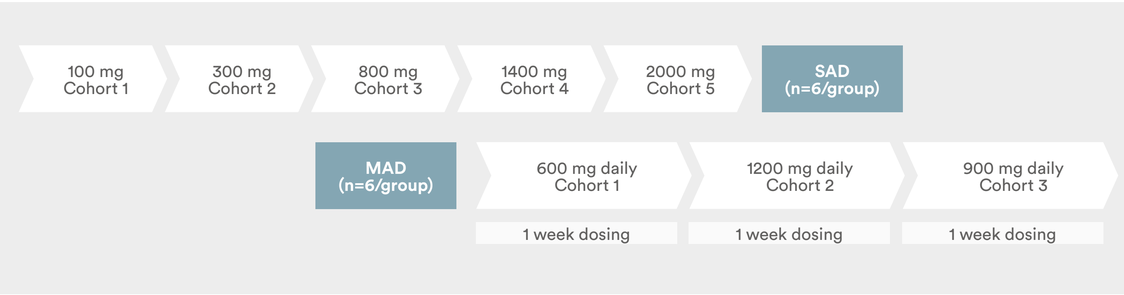
Nonclinical PAH rat model

- Sugen 5416 (20 mg/kg, single dose, SC) followed by hypoxia (10% O2) for 3 weeks. A control group received vehicle and was maintained at normoxia.
- 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 profiles were obtained in parallel groups of animals (n = 3/group). Plasma protein binding was determined using rapid equilibrium dialysis.



First-in-human clinical trial

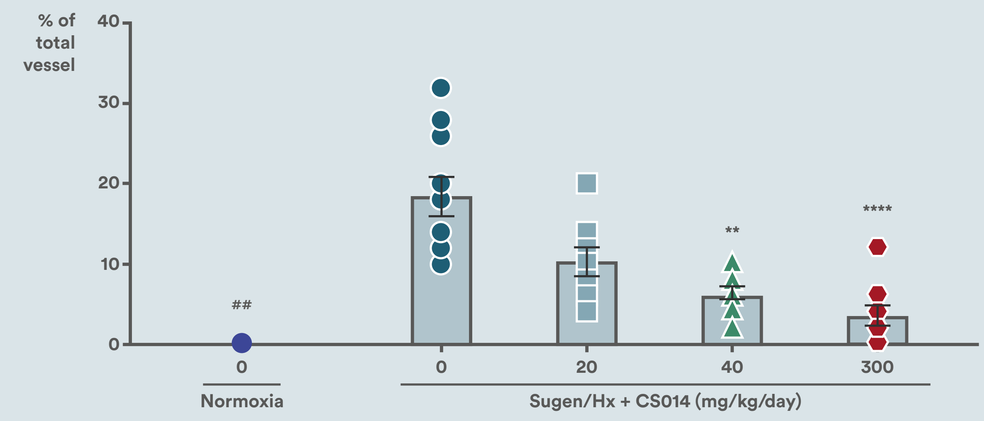
- Healthy adults (34–65 years) were assigned to single (SAD, n=30) or multiple (MAD, n=18) oral doses of CS014.
- Primary endpoint: Safety and tolerability.
- Secondary endpoints: PK parameters.



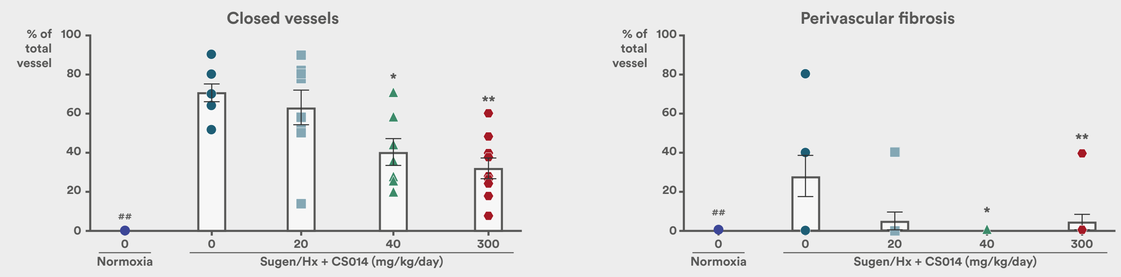
Results

- Rat model: CS014 induced a robust, dose-dependent amelioration of vascular remodeling with reduced arteriolar vessel occlusion, reductions of plexiform lesions and fibrosis.
- FIH trial: CS014 was safe and well-tolerated at all doses. All adverse reactions were mild and fully resolved. Additionally, CS014 induced no clinically significant changes in objective safety measurements, such as vital signs, safety laboratory, and ECG.

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

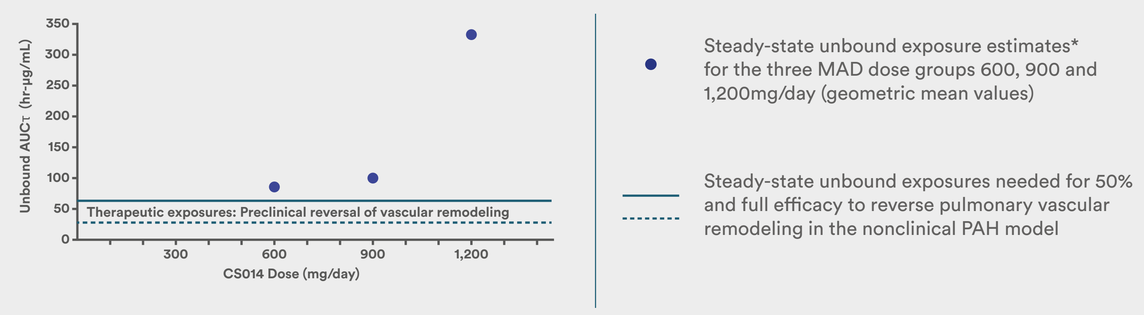


#p<0.05; ##p<0.01; ###p<0.001; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001. vs Sugen/Hx + CS014 0 mg/kg/day

MAD safety summary: CS014 treatment had few treatment-related adverse events, all mild in nature and fully resolved

System organ class – Preferred term	CS014 600 mg (N=6) n (%)	m	CS014 900 mg (N=6) n (%)	m	CS014 1200 mg (N=6) n (%)	m	Total (N=18) n (%)	m
Total	**0**	**0**	**3 (50%)**	**9**	**3 (50%)**	**13**	**6 (33%)**	**22**
Gastrointestinal disorders	**0**	**0**	**3 (50%)**	**8**	**2 (33%)**	**10**	**5(28%)**	**18**
Dyspepsia	0	0	1 (17%)	1	0	0	1 (5.6%)	1
Eructation	0	0	0	0	1 (17%)	3	1 (5.6%)	3
Feces discolored	0	0	1 (17%)	1	0	0	1 (5.6%)	1
Gastroesophageal reflux disease	0	0	1 (17%)	6	0	0	1 (5.6%)	6
Nausea	0	0	0	0	2 (33%)	6	2 (11%)	6
Vomiting	0	0	0	0	1 (17%)	1	1 (5.6%)	1
Nervous system disorders	**0**	**0**	**0**	**0**	**1 (17%)**	**3**	**1 (5.6%)**	**3**
Headache	0	0	0	0	1 (17%)	3	1 (5.6%)	3
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (17%)**	**1**	**0**	**0**	**1 (5.6%)**	**1**
Epistaxis	0	0	1 (17%)	1	0	0	1 (5.6%)	1

FIH doses exceeded exposure levels needed for reversal of pulmonary vascular remodeling and were safe and well-tolerated



*Plasma protein binding determined using a rapid equilibrium dialysis in selected plasma samples from all volunteers in the 1400 mg SAD cohort. The model was then used to estimate unbound exposures for all MAD cohorts.

Conclusions

The results presented support further development of CS014 for the treatment of severe cardiovascular and pulmonary diseases characterized by vascular remodeling and fibrosis.

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