Safety, tolerability, and pharmacokinetics of the novel HDAC inhibitor CS014: a first-in-human trial

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CS014 is being developed for rare and severe cardiopulmonary diseases involving vascular remodeling and fibrosis

- Several rare diseases involving the **remodeling of pulmonary vasculature**, including pulmonary arterial hypertension (PAH)
- Small pulmonary arteries: **fibrosis**, **vasoconstriction**, **thickening** of walls, **muscularization**, endothelial **cell proliferation**, and in situ **thrombosis**[1]
- Symptoms include **dyspnea**, **chest pain**, **fainting**, **limited daily activities** and severely impaired **quality of life**[2]
- PAH generally progresses to **right ventricular failure**
- Median **survival** of treated patients **~7 years**[1]

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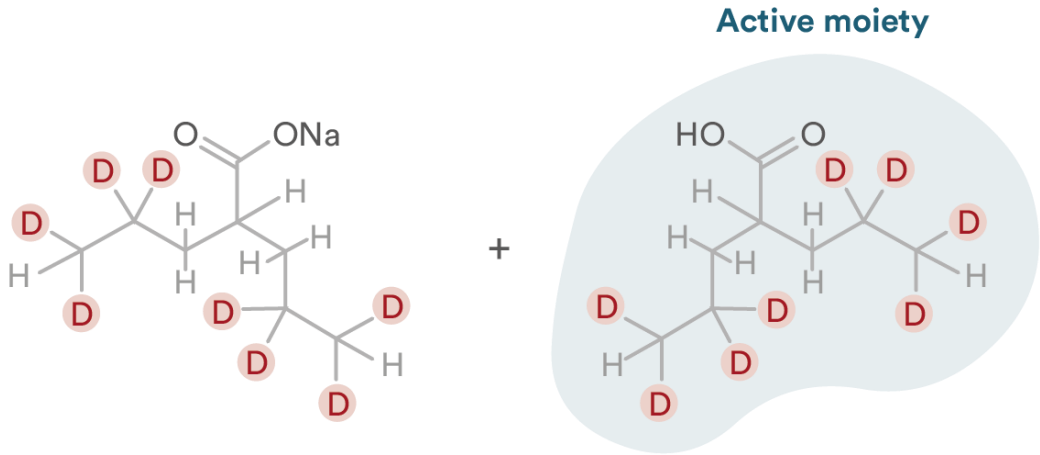
1. Humbert, Marc, et al. *The Lancet Respiratory Medicine* 11.9 (2023): 804-819.
2. Highland, Kristin B., et al. *Health and quality of life outcomes* 19.1 (2021): 202.

CS014, a novel HDAC inhibitor with a molecular structure based upon valproic acid

- **Histone deacetylase inhibitors (HDACi),** including valproic acid (VPA), have been postulated to have **beneficial effects in severe cardiopulmonary diseases**, including PAH
- **CS014**, a novel precision deuterated VPA with equal HDAC inhibition potency compared to VPA, is under evaluation for the **treatment of serious rare cardiovascular and pulmonary diseases**

CS014 Structure



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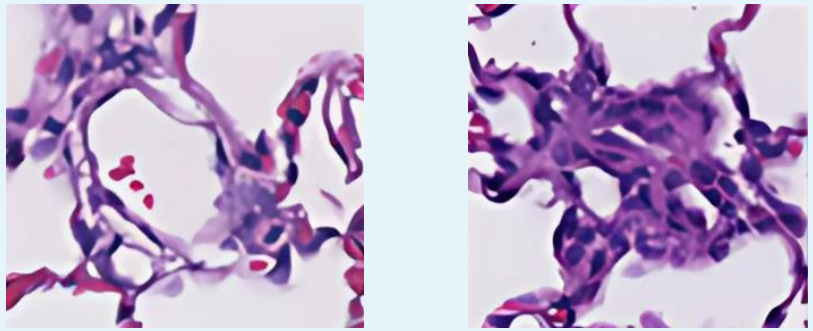
Preclinical data in a PAH rat model – Dose-dependent reversal of pulmonary vascular remodeling

Cross sections of arteries (<100 µm)

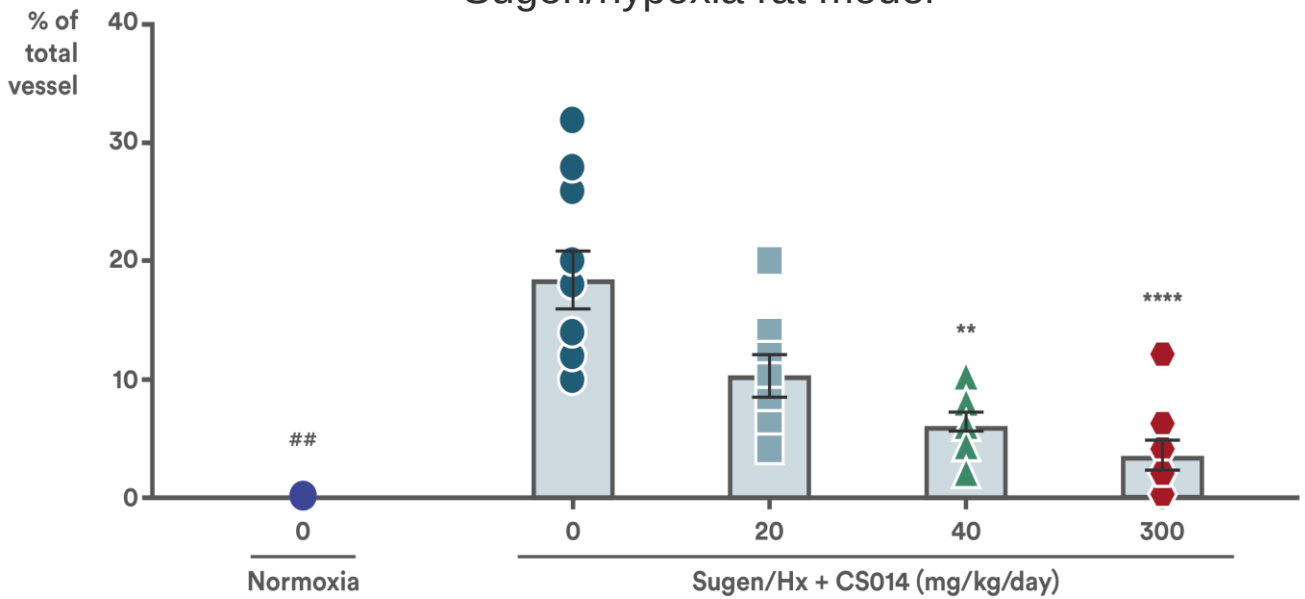
Healthy **Plexiform lesions**



CS014 also reduced small artery-associated fibrosis

Reduced incidence of plexiform lesions in small pulmonary arteries (<100µm) (%)

Sugen/hypoxia rat model



Presented in poster 258 – Wednesday, December 17, at 13:10

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CS014-001 Phase I: First-in-human, single- and multiple-dose study (SAD/MAD) in healthy volunteers

Primary endpoint:
Safety and tolerability

Secondary endpoints:
PK properties

SAD:
30 participants,
5 cohorts

MAD:
18 participants,
3 cohorts

Volunteers' characteristics:

Part	Gender	Age (years)
SAD	♀: n=26 ♂: n=4	34 – 64
MAD	♀: n=12 ♂: n=6	47 – 65

100mg Cohort 1 → 300mg Cohort 2 → 800mg Cohort 3 → 1400mg Cohort 4 → 2000mg Cohort 5 → **SAD (n=6/group)**

MAD (n=6/group) → 600mg daily Cohort 1 → 1200mg daily Cohort 2 → 900mg daily Cohort 3

1 week dosing | *1 week dosing* | *1 week dosing*

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

	CS014 600 mg (N=6)		CS014 900 mg (N=6)		CS014 1200 mg (N=6)		Total (N=18)	
System organ class Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**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

CS014-001_MAD: Data based on Full analysis set. An AE is considered treatment-related when the causality assessment is probable or possible. N: Number of participants in the dose cohort. Percentages are based on N. n: number of participants with events. m: number of events.

CS014 induced no clinically significant changes in objective safety measurements

- Physical examination
- Safety ECGs (including no QT prolongation)
- Vital signs
- Safety laboratory (clinical chemistry, hematology, coagulation)

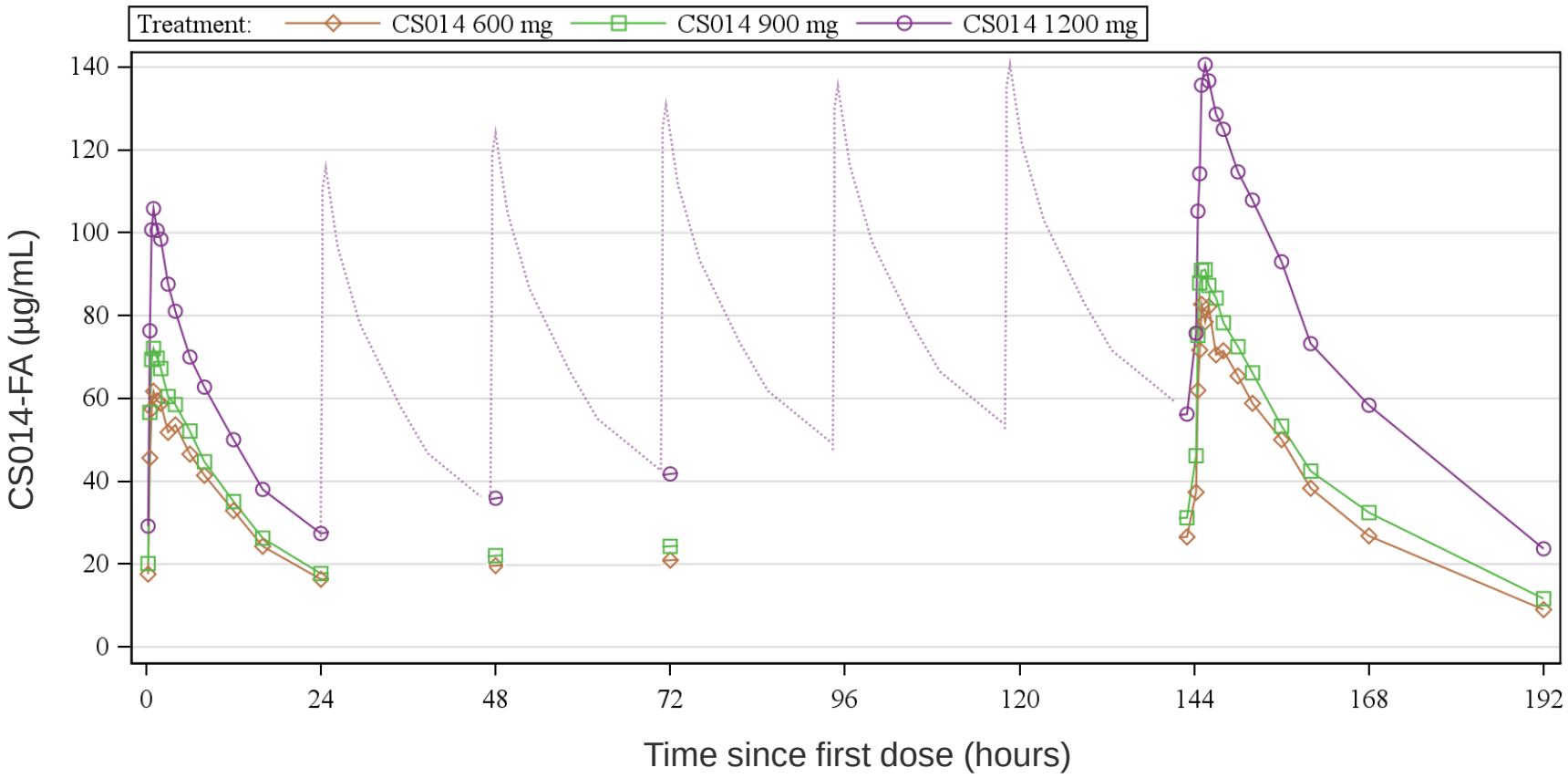
All volunteers completed the study

No serious adverse events (SAEs), no safety signals raised

All treatment-related AEs mild and fully resolved

CS014 first-in-human trial reveals well-defined pharmacokinetics

Total plasma concentrations



- **CS014-FA rapidly absorbed**
- **Plasma accumulation** upon repeated dosing and **increased exposure with increasing dose**
- **Steady-state** by **Day 7**
- Mean **$T_{1/2}$** at steady state increased with dose: **~15 to 20h**

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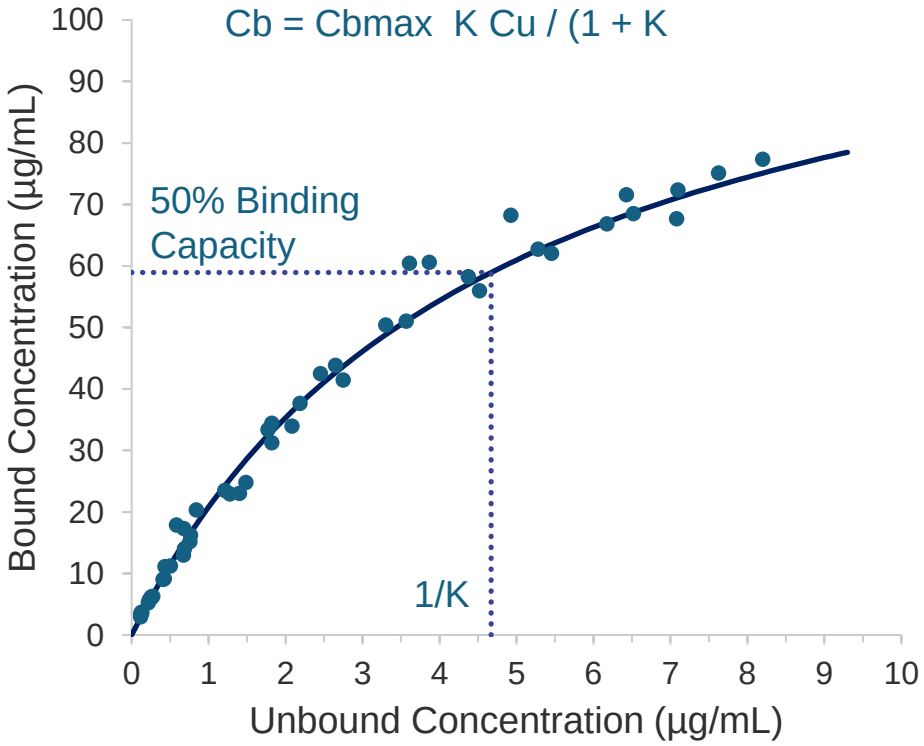
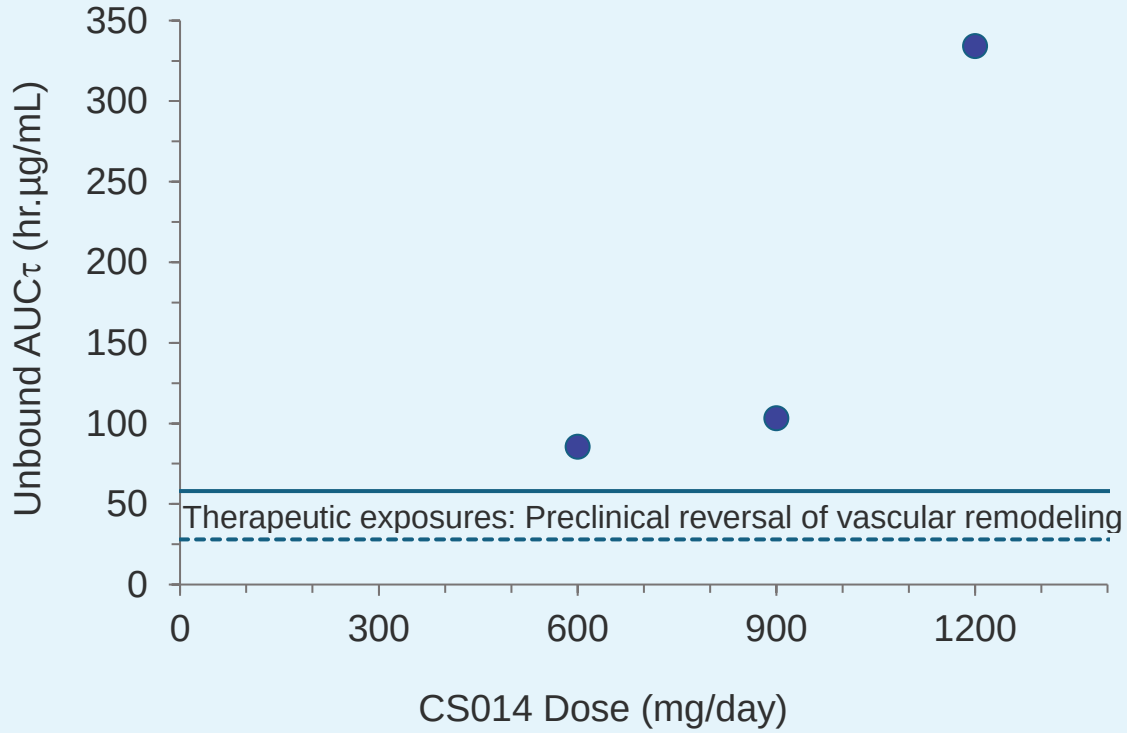
CS014 plasma protein binding: non-linear and concentration-dependent



- Plasma protein binding determined using a **rapid equilibrium device** in selected plasma samples from all volunteers in 1400 mg SAD cohort
- Single site binding model fitted to bound (Cb) and unbound (Cu) data at equilibrium
- Model used to **estimate unbound exposures for all MAD cohorts**

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



- Steady-state **unbound exposure estimates for the three MAD dose groups**, 600, 900, and 1200mg/day (geometric mean values)
- Steady-state **unbound exposures needed for 50% and full efficacy** to reverse pulmonary vascular remodeling in a preclinical disease (PAH) model

Conclusion

- In this Phase 1 trial, single and multiple oral doses of **CS014** in healthy volunteers were **safe and well tolerated**, based on reported AEs, vital signs, ECG measurements, safety laboratory parameters, and physical examination findings
- **PK properties**, including plasma protein binding, were **well-defined**
- Estimated **unbound exposures** exceeded those needed to achieve the **reversal of pulmonary vascular remodeling and fibrosis** in a preclinical PAH model
- These **results support further clinical evaluation of CS014** in patients with severe cardiovascular and pulmonary diseases involving pulmonary vascular remodeling and fibrosis, e.g., pulmonary arterial hypertension, idiopathic pulmonary fibrosis, and pulmonary hypertension due to interstitial lung disease

For more information:

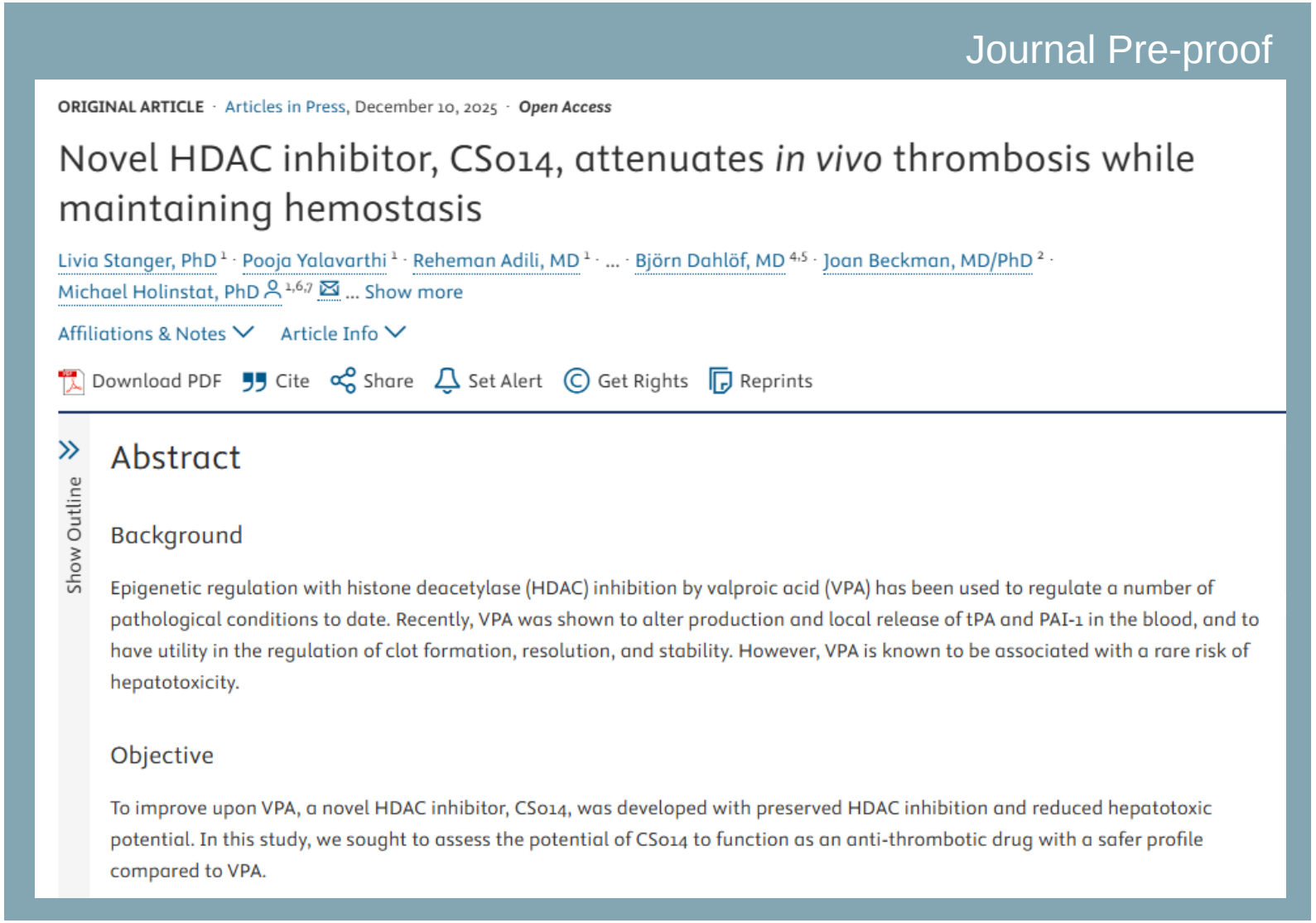
Read CS014's first manuscript

Journal of Thrombosis and Haemostasis

December 2025

Access here >

Journal Pre-proof



ORIGINAL ARTICLE · Articles in Press, December 10, 2025 · *Open Access*

Novel HDAC inhibitor, CSo14, attenuates *in vivo* thrombosis while maintaining hemostasis

Livia Stanger, PhD [1] · Pooja Yalavarthi [1] · Reheman Adili, MD [1] · ... · Björn Dahlöf, MD [4,5] · Joan Beckman, MD/PhD [2] · Michael Holinstat, PhD [1,6,7] ... Show more

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Show Outline

Abstract

Background

Epigenetic regulation with histone deacetylase (HDAC) inhibition by valproic acid (VPA) has been used to regulate a number of pathological conditions to date. Recently, VPA was shown to alter production and local release of tPA and PAI-1 in the blood, and to have utility in the regulation of clot formation, resolution, and stability. However, VPA is known to be associated with a rare risk of hepatotoxicity.

Objective

To improve upon VPA, a novel HDAC inhibitor, CSo14, was developed with preserved HDAC inhibition and reduced hepatotoxic potential. In this study, we sought to assess the potential of CSo14 to function as an anti-thrombotic drug with a safer profile compared to VPA.

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Thank you for your attention!

Questions?

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Cereno Scientific is pioneering treatments to enhance and extend life. The company's innovative pipeline offers disease-modifying drug candidates to empower people suffering from rare cardiovascular and pulmonary diseases to live life to the full.

The company is headquartered in GoCo Health Innovation City, in Gothenburg, Sweden, and has a US subsidiary; Cereno Scientific Inc. based in Kendall Square, Boston, Massachusetts, US. Cereno Scientific is listed on the Nasdaq First North (CRNO B).

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