Investigation of efficacy, safety and optimal dose of CS1 in subjects with pulmonary arterial hypertension: a prospective, randomized, multicenter, parallel-group phase II study

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Background and rationale

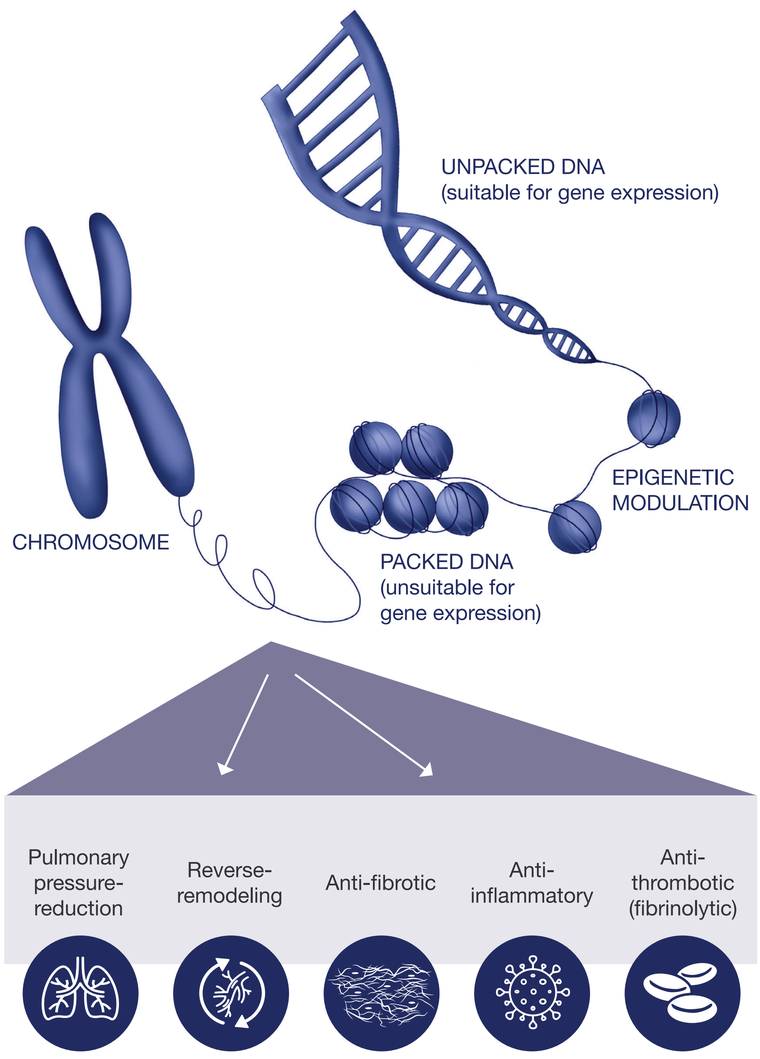
Pulmonary arterial hypertension (PAH) is a rare disease characterized by pulmonary vascular remodeling with endothelial dysfunction, smooth muscle cell proliferation, fibrosis and in situ thrombosis resulting in increased pulmonary arterial pressure, right ventricular failure and death. PAH currently has poor prognosis, unsatisfactory treatments and an unacceptable long-term survival rate. There is a large unmet need for new disease-modifying therapy.

CS1 is an advanced controlled-release formulation of valproic acid, with a putative multi-fold mechanism of action: pulmonary pressure reducing, reverse vascular remodeling, antifibrotic, anti-inflammatory and antithrombotic, mediated by epigenetic modulation via histone deacetylase inhibition (HDACi). Phase I clinical trial results have demonstrated good safety and tolerability, alongside favourable pharmacokinetics, correlated with a significant reduction in PAI-1 levels and improved clot lysis times, with no increased bleeding risk.[1]

Objectives

This innovative phase II trial aims to demonstrate CS1's safety, tolerability, pharmacokinetics, dose and exploratory efficacy in PAH through an optimized trial design utilizing cutting-edge technology for monitoring pulmonary arterial pressure and pulmonary/RH hemodynamics, via Abbott's CardioMEMS™ device. The one or two most well tolerated and efficacious doses will be selected for a follow-on Phase IIb/III study.

CS1: an HDAC inhibitor with a multi-fold epigenetic mechanism of action



Optimizing clinical trial design[2]

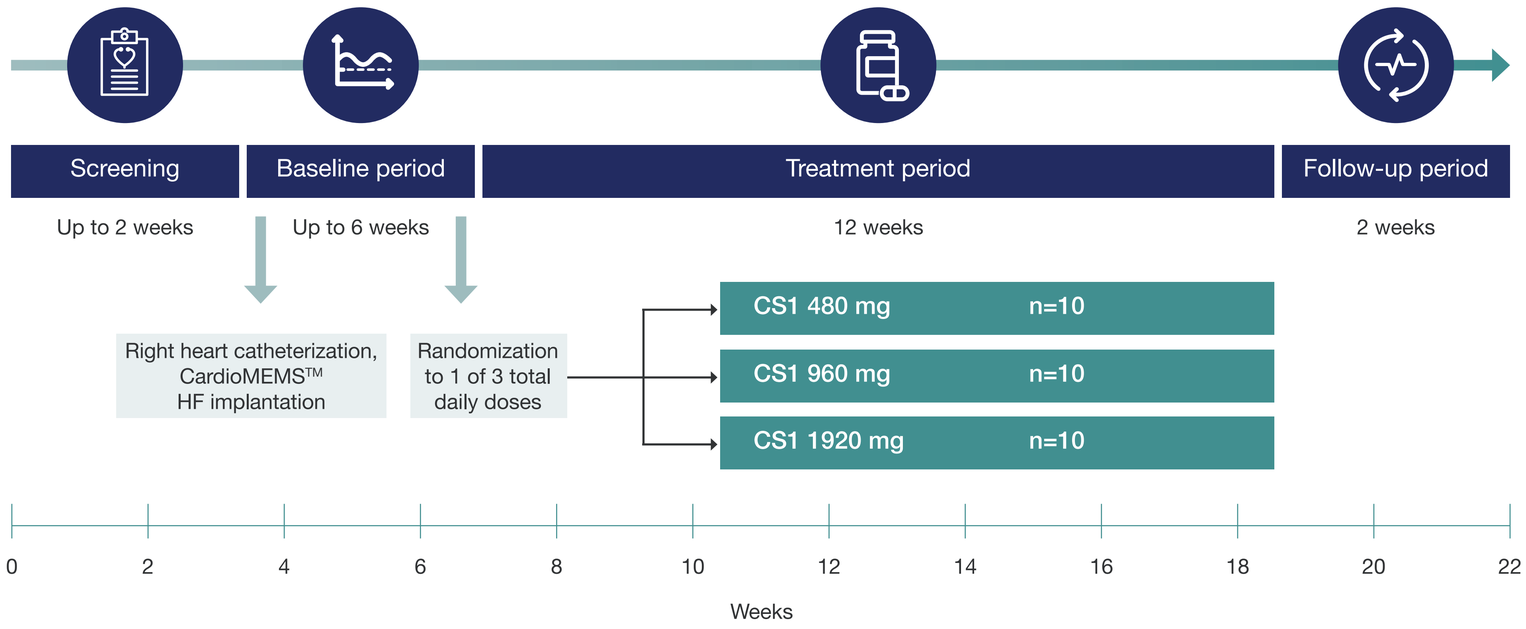
A task force convened to review clinical trial design and novel therapies for PAH for the 6th World Symposium on Pulmonary Hypertension made the following recommendations on optimizing the design of Phase II trials in patients with PAH:

- Trials should include both mechanistic and biological disease markers in order to better assess responses to treatment
- Subject groups should be more homogenous
- Risk tools should be employed as an enrichment strategy for phenotyping a heterogenous group
- Change in risk should be utilized as an exploratory efficacy marker to determine their predictability as future clinical endpoints
- Novel biomarkers (e.g. serum, genomic, metabolic and patient-reported outcomes) should be utilized as exploratory endpoints to determine their predictability as future clinical endpoints

Study population

The study population comprises 30 patients at 10 different US sites, with NYHA/WHO FC II or III PAH class I (male and female, aged 18-80 years, BMI 18-40 kg/m^2) with limited exercise capacity, on stable mono or dual combination therapy, and at intermediate/high risk (REVEAL Risk Score 2.0) of clinical worsening.

Study design



Primary and secondary endpoints[3-5]

The primary endpoint is safety and tolerability. Secondary, exploratory variables include all standard efficacy endpoints for this patient group, together with pharmacokinetics and calculated validated risk scores, REVEAL 2.0 and REVEAL Lite 2. Novel endpoints include actigraphy and CardioMEMS™-derived systolic, diastolic and mean pulmonary artery pressures, calculated total pulmonary resistance and stroke volume index, alongside sophisticated imaging modalities, including cardiac MRI in sync with CardioMEMS™ and standardized echocardiography, to assess changes in morphology and function of the left and right ventricles.

Primary endpoint

Safety and tolerability as measured by:

- AEs
- Adverse events of special interest (AESIs)
- Serious adverse events (SAEs)
- Adverse device effects (ADEs) related to the CardioMEMS™ HF system incl. unexpected serious adverse device effects (USADEs)
- Laboratory parameter abnormalities
- Change in vital signs
- Bleedings
- Change in ECG parameters

Secondary exploratory endpoints

Change from baseline and difference between doses

- **Pulmonary vascular resistance, cardiac/ pulmonary hemodynamics from RHC**
- **RRS 2,0**
- **REVEAL lite 2**
- **Pharmacokinetics**
- **6MWD**
- **Actigraphy**
- Need for additional therapy
- NYHA/WHO FC
- Quality of life (SYMPACT)
- Minnesota Living with HF Q
- Hospitalizations; PAH related and other
- CV morbidity and mortality; PAH related/other
- eGFR
- NT-pro-BNP, ST2, PAI-1
- Other biomarkers TBD (Biobank)
- **From CardioMEMS™**
  - sPAP, dPAP, mPAP
  - Other calculated RV variables and TPR
- **Echocardiography**
  - Morphology and function left ventricle
  - Morphology and function right ventricle
- **MRI in sync with CardioMEMS™**
  - Morpholgy and function left ventricle
  - Morphology and function right ventricle

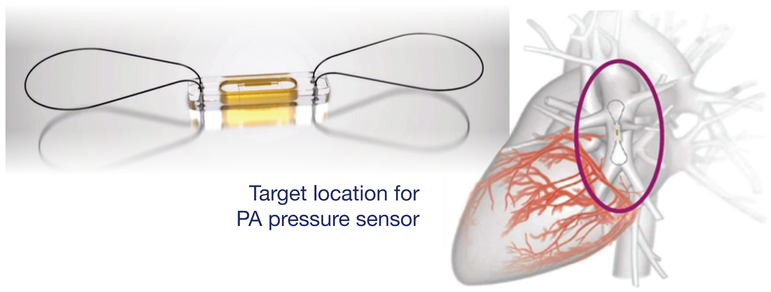
Pre- and post-dose plasma concentrations of VPA at visits 4, 5 and 9 (end of treatment) will also be analyzed.

Use of CardioMEMS™ to remotely and continuously monitor pulmonary arterial blood pressure

The CardioMEMS™ HF System (Abbott Inc.) is an ambulatory implantable hemodynamic monitoring system, indicated for wirelessly monitoring pulmonary artery pressure and heart rate in patients with severe heart failure.[6] CardioMEMS™ has been evaluated long term (up to 4 years) in patients with PAH and right heart failure NYHA class III-IV, demonstrating safety and feasibility in monitoring the efficacy of therapy for PAH.[7]

There are several benefits in using CardioMEMS™ for the Phase II study of CS1, notably it:

- provides useful information for monitoring the efficacy of the therapy, including on the function of the right ventricle
- enables a smaller-size patient population in the study
- can help inform dosing for later clinical studies of CS1 in PAH.



Target location for PA pressure sensor

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Cereno Scientific

Summary

This innovative Phase II clinical trial is designed to evaluate the HDACi CS1, an epigenetic modulator with disease-modifying potential, at three doses for the treatment of PAH. The primary endpoint is safety and tolerability. Secondary exploratory endpoints include established risk scores and pulmonary/RH hemodynamics, assessed via the CardioMEMS™ system, alongside all standard endpoints for PAH studies. The one or two best tolerated and most efficacious doses will be selected for follow-on Phase IIb/III study.

References

1. Bergh N, et al. (2019). A first in class treatment for thrombosis prevention. a phase I study with CS1, a new controlled release formulation of sodium valproate. *J Cardio Vasc Med* 5: 1–12.
2. Sitbon O, et al. (2019). Clinical trial design and new therapies for pulmonary arterial hypertension. *Eur Resp J*, 53(1).
3. Benza RL, et al. (2019). Predicting survival in patients with pulmonary arterial hypertension: The REVEAL Risk Score Calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. *Chest*, 156(2), 323–337.
4. Benza RL, et al. (2021). Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. *Chest*, 159(1), 337–346.
5. Benza RL, et al. (2018). REVEAL risk scores applied to riociguat-treated patients in PATENT-2: Impact of changes in risk score on survival. *J Heart Lung Transplant* 37(4), 513–519.
6. Abraham WT, et al. (2016). Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: Complete follow-up results from the CHAMPION randomised trial. *The Lancet*, 387(10017), 453–461.
7. Benza RL, et al. (2019). Monitoring pulmonary arterial hypertension using an implantable hemodynamic sensor. *Chest*, 156(6), 1176–1186.

Acknowledgements

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ABBREVIATIONS: 6MWD: 6-minute walking distance; ADE: adverse device effect: AE: adverse event; AESI: adverse event of special interest; BMI: body mass index; CV: cardiovascular; dPAP: diastolic pulmonary artery pressure; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; HDAC: histone deacetylase; HDACi: histone deacetylase inhibition; HF: heart failure; MRI: magnetic resonance imaging; mPAP: mean pulmonary artery pressure; NYHA/WHO FC New York Heart Association/World Health Organization functional classification; NT-pro BNP: N-terminal prohormone brain natriuretic peptide; PAH: pulmonary arterial hypertension; PAI-1: plasminogen activator inhibitor -1; PAP: pulmonary artery pressure; RH: right heart; RHC: right heart catheterization; RRS: REVEAL risk score; SAE: serious adverse event; sPAP: systolic pulmonary artery pressure; TPR: total pulmonary resistance; USADE: unexpected serious adverse device effect; VPA: valproic acid