Inhibition of Cardiac Fibrosis and Pro-Fibrotic Collagen Hormone Endotrophin by VS-041, a Novel Drug Candidate for Heart Failure with Preserved Ejection Fraction

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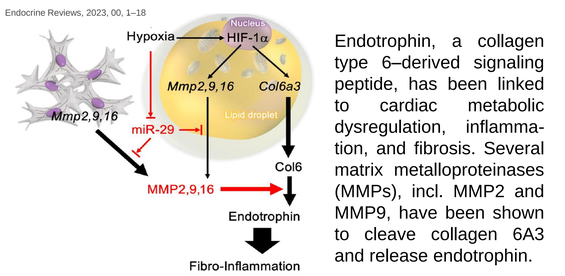
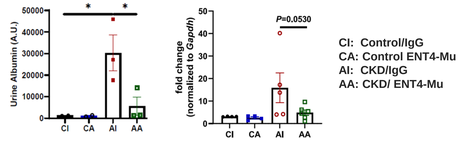
Background: Endotrophin and HFpEF

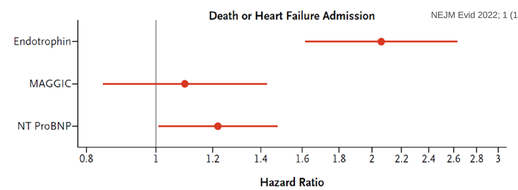


Endotrophin, a collagen type 6–derived signaling peptide, has been linked to cardiac metabolic dysregulation, inflammation, and fibrosis. Several matrix metalloproteinases (MMPs), incl. MMP2 and MMP9, have been shown to cleave collagen 6A3 and release endotrophin.

Inhibition of endotrophin signaling with neutralizing mAb (ENT4-Mu) has been shown to be an efficacious approach in preclinical models of CKD, liver cirrhosis, and adipose tissue fibrosis.

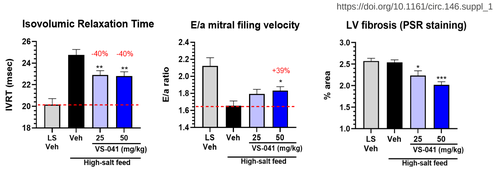


Baseline plasma endotrophin levels in heart failure with preserved ejection fraction (HFpEF) patients were shown to be strongly and independently associated with increased risk of poor outcomes (death or HF-admissions).



VS-041 is a drug candidate for HFpEF that inhibits key MMPs implicated in cardiac fibrosis and diastolic dysfunction. Previously, VS-041 improved diastolic parameters and reduced left ventricle (LV) fibrosis in the Dahl Salt Sensitive rat model of HFpEF.

https://doi.org/10.1161/circ.146.suppl_1.13724

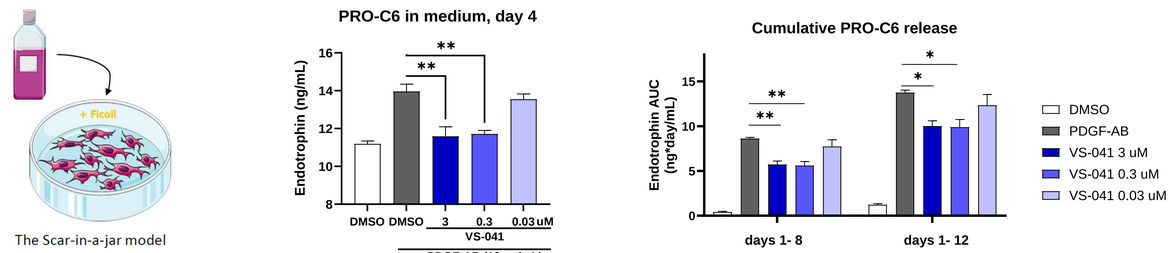


Hypothesis

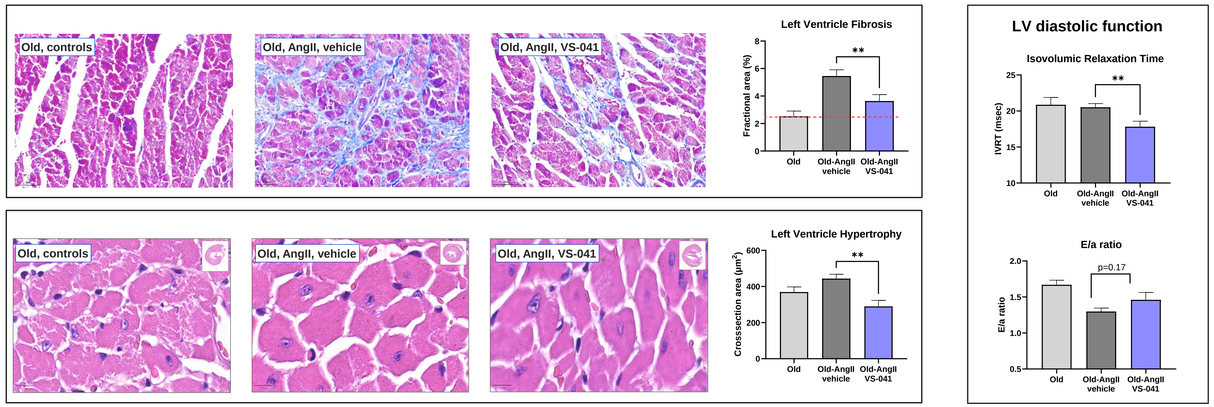
Inhibition of endotrophin release by VS-041 could contribute to its anti-fibrotic mechanism and serve as a potential biomarker of MMP inhibition (target engagement) in patients.

Results

VS-041 Inhibits Release of Endotrophin (PRO-C6) from Cultured Human Primary Cardiac Fibroblasts



VS-041 Reduces Cardiac Fibrosis and LV Hypertrophy, and Improves Diastolic Function in Old C57BL/6 Mice Infused with Angiotensin II



Methods

The effect of VS-041 on production of endotrophin was investigated in a “Scar-in-a-Jar” model using primary human cardiac fibroblasts isolated from adult healthy ventricles. Fibroblasts were treated with 10 ng/mL platelet-derived growth factor (PDGF) AB in the presence of 0.03, 0.3, or 3 μM VS-041, or DMSO control. The concentration of endotrophin in the medium was assessed via the ELISA nordicPRO-C6™ (Nordic Bioscience A/S).

The anti-fibrotic activity of VS-041 was also tested in a model of extensive cardiac fibrosis in16-months old C57BL/6 mice exacerbated by angiotensin II infusion at 1 mg/kg/day for 28 days. Oral treatment with VS-041 at 75 mg/kg BID resulted in a 62% reduction (p<0.01) of LV fibrosis and hypertrophy as assessed by morphometry of Masson trichrome and H&E stained sections. VS-041 also improved the diastolic echocardiography parameters IVRT and E/a ratio.

Acknowledgements

European Funds Smart Growth

Republic of Poland

European Union European Regional Development Fund

Project co-funded by European Regional Development Fund and Polish National Centre for Research and Development:

(**POIR.01.01.01-00-1210/19-01**).

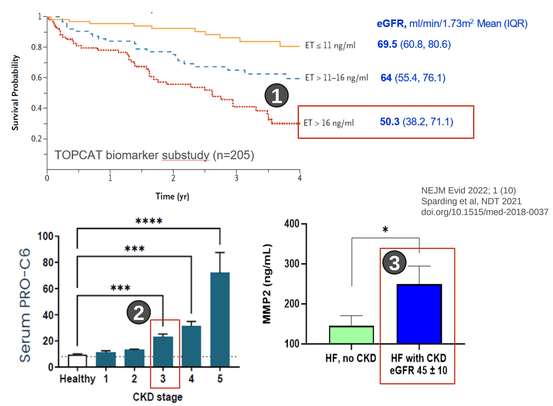
Summary & Development Status

- The production of endotrophin by fibroblasts is diminished by VS-041, therefore, this plasma level change should be explored as a biomarker of *in vivo* MMP inhibition by VS-041.
- VS-041 demonstrated a robust efficacy in mouse model of HFpEF (~62% decrease in LV fibrosis and improvement in diastolic function).
- Inhibition of endotrophin release by VS-041 could be causatively linked to reduction of cardiac fibrosis and potentially translate into improved clinical outcomes in HFpEF patients.
- **Phase 1 clinical trial in healthy participants is ongoing.**
- **The exploratory 4-week phase 1c biomarker study in HFpEF patients with stage 3a CKD (eGFR 60-44 ml/min/1.73m²) is planned in 1H 2025.**

Patient selection rationale:

1. Highest risk of poor outcomes
2. Elevated plasma endotrophin (Pro-C6)
3. Elevated plasma MMP2

All-cause death or heart failure–related hospital admission, by baseline endotrophin (ET) level and eGFR



Financial Disclosure

AP, JPB, BP, MK, JV, WB, CJL are employees and/or shareholders of Vasa Therapeutics. YMM and FG are employees and/or shareholders of Nordic Bioscience A/S.

AHA 2024 Poster #Sa2170

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