

VS-041, a narrow-spectrum, matrix metalloproteinase (MMP) inhibitor and novel drug candidate for heart failure with preserved ejection fraction (HFpEF), demonstrates target engagement and is safe and well-tolerated in healthy participants

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# Disclosures and affiliations

All authors are employees and/or shareholders of Vasa Therapeutics

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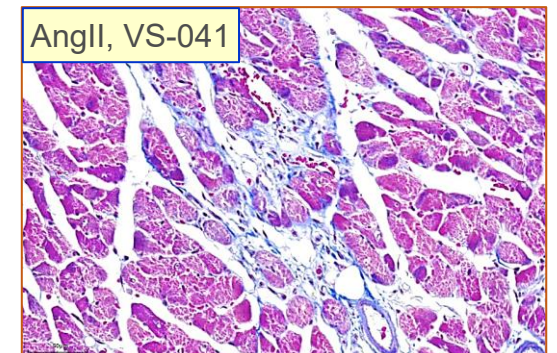
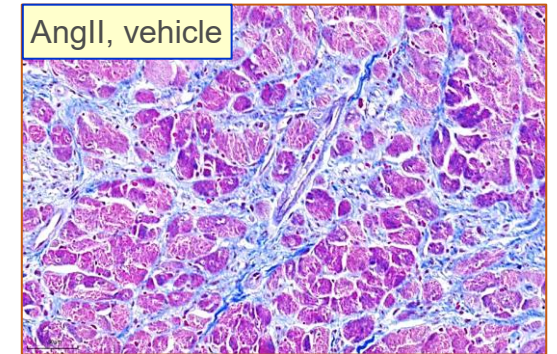
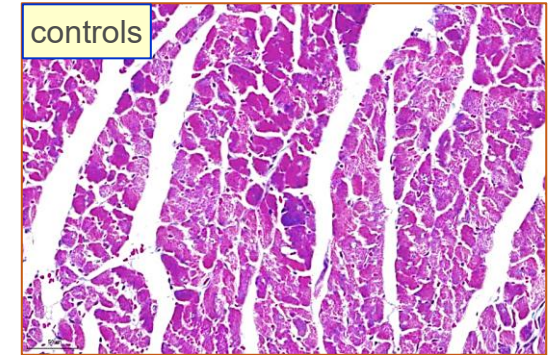
# Introduction

## VS-041:

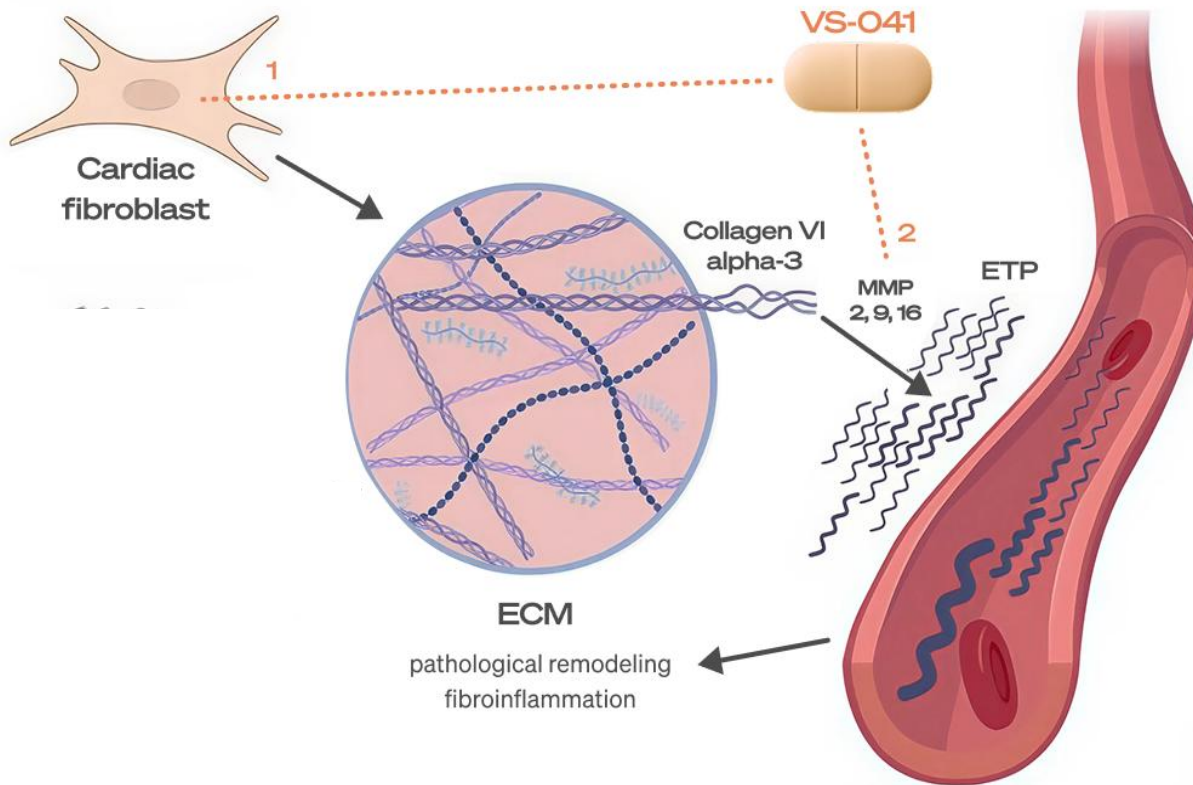
- inhibits key matrix metalloproteinases (MMPs) implicated in HFpEF
- reduces cardiac fibrosis and improves diastolic function in HFpEF models
- inhibits formation of endotrophin in ex-vivo cardiac fibroblasts

## Endotrophin:

- is cleaved from collagen VI $\alpha$ 3 by MMP2, 9 and 16
- independently drives cardiac fibroinflammation
- is a biomarker of poor outcome in HFpEF patients



# VS-041: Unique dual mechanism of action



## Objectives of Phase 1

- single- and multiple- ascending dose (SAD/MAD) safety, tolerability and pharmacokinetics (PK) study in healthy participants
- estimation of target engagement by VS-041 (suppression of MMP2 and 9 activity in clinical plasma samples)

# Methods

VS-041-01 was a randomized, double-blind placebo-controlled SAD and MAD trial in healthy participants:

- ▶ Cohorts were to enroll 8 participants, randomized 3:1 active:placebo
- ▶ VS-041 was administered orally once or twice daily
- ▶ MAD cohort patients received VS-041 daily for 7 days
- ▶ Safety and tolerability were assessed
- ▶ Serum samples were obtained for PK modeling

A novel ex-vivo assay of MMP2 and MMP9 activity was performed in human plasma enriched with MMP2 and MMP9, utilizing a fluorescein-labeled gelatin conjugate as physiological and specific substrate.

# Results: VS-041 Safety and Tolerability

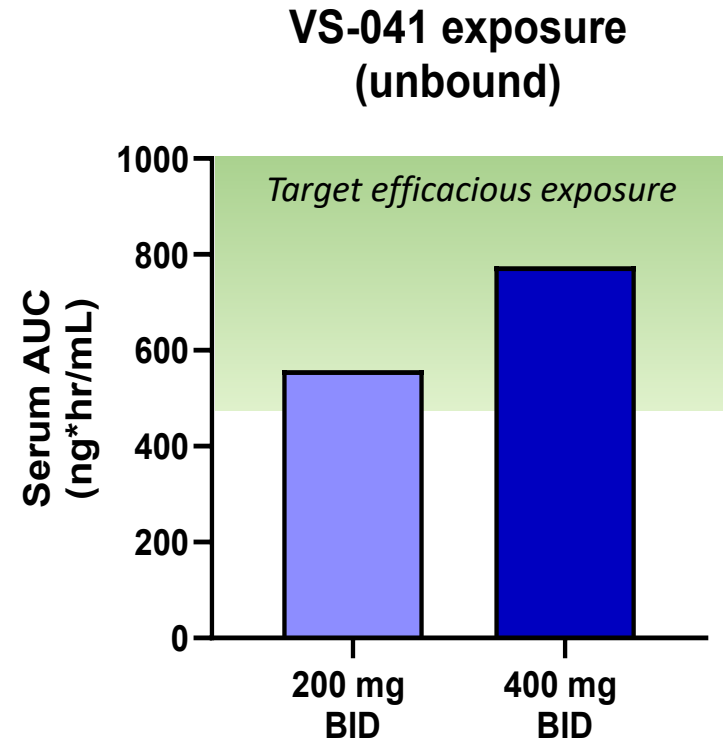
Treatment-emergent Adverse Events (TEAEs) in  $\geq 1$  VS-041 MAD participants:

MedDRA Preferred Term	Placebo n (%)	50 mg BID n (%)	200 mg QD n (%)	400 mg QD n (%)	400 mg BID n (%)
<b>Any TEAE</b>	<b>3 (37.5)</b>	<b>3 (50.0)</b>	<b>2 (33.3)</b>	<b>5 (83.3)</b>	<b>2 (33.3)</b>
Medical device site reaction	0	1 (16.7)	0	2 (33.3)	0
Fatigue	0	0	1 (16.7)	0	1 (16.7)
Viral upper respiratory tract infection	0	0	1 (16.7)	1 (16.7)	0
Catheter site bruise	0	1 (16.7)	0	0	0
Cyst rupture	0	0	0	0	1 (16.7)
Ear infection	0	0	0	1 (16.7)	0
Nasopharyngitis	0	0	0	1 (16.7)	0
Thermal burn	0	0	0	0	1 (16.7)
Decreased appetite	0	0	1 (16.7)	0	0
Myalgia	0	0	1 (16.7)	0	0
Cough	0	1 (16.7)	0	0	0

# Results: VS-041 Pharmacokinetics

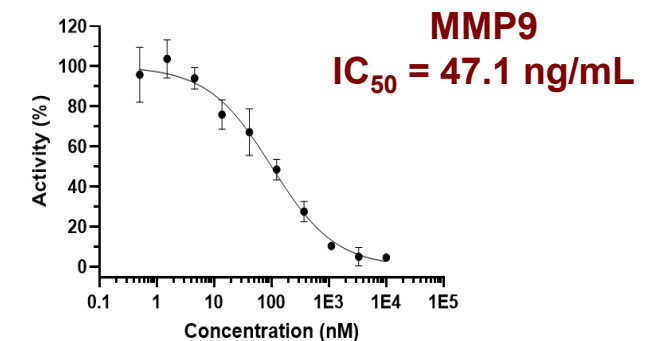
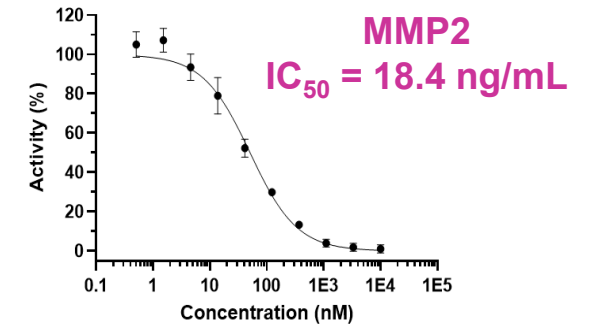
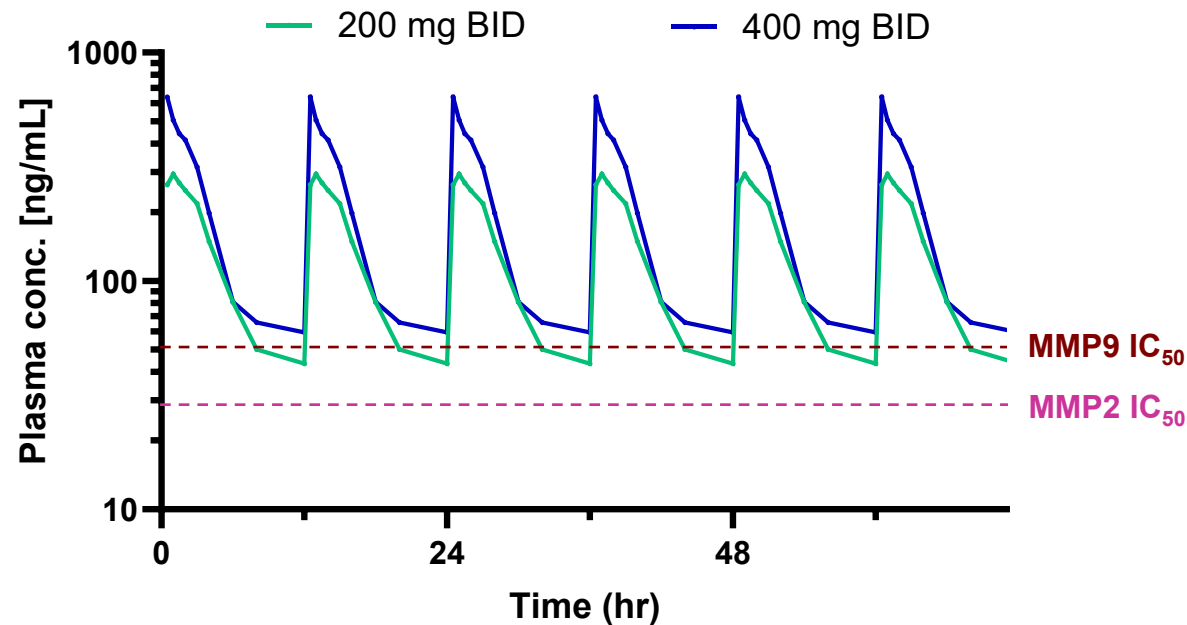
## VS-041 demonstrated:

- ▶ dose dependent increases in exposure,
- ▶ steady state was achieved within 2 days with no accumulation
- ▶ terminal half-life ranged between 6-9 hours
- ▶ serum levels achieved were within target range of the estimated minimally efficacious dose



# Results: VS-041 Ex-vivo target engagement

- ▶ The gelatinolytic activity in human plasma enriched with MMP2 & 9 was inhibited by VS-041 in a concentration-dependent manner
- ▶ **Minimum concentration of VS-041 is expected to remain at or above the  $IC_{50}$  of MMP2 and MMP9 inhibition in serum**



# Conclusions

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- ▶ VS-041 is safe and well tolerated at doses that effectively inhibit key MMPs implicated in the pathophysiology of HFpEF
- ▶ VS-041 has the potential to inhibit the release of endotrophin, a mediator of fibroinflammation and biomarker of poor outcomes in HFpEF

VS-041 is currently being evaluated in a Proof-of-Mechanism study in participants with HFpEF and elevated levels of serum endotrophin

**NCT07219511**

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