

Reduced cardiac stress and inflammatory proteomic signatures in obstructive and nonobstructive HCM following EDG-7500 treatment in CIRRUS-HCM

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Conclusions

- In CIRRUS-HCM, EDG-7500 administration was associated with reductions in NT-proBNP and coordinated proteomic changes in pathways linked to myocardial stress, inflammation, and atrial fibrillation risk biology across obstructive and nonobstructive HCM.
- These exploratory findings support a potential mechanistic basis for the observed clinical and hemodynamic improvements observed in HCM patients treated with EDG-7500.

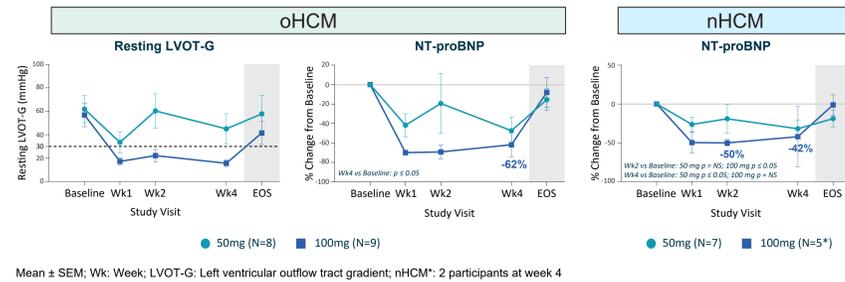


Background

Hypertrophic cardiomyopathy (HCM) is a genetically mediated myocardial disorder caused by sarcomeric protein mutations. HCM is classified into two phenotypes: obstructive (oHCM) is characterized by left ventricular outflow obstruction (LVOT-G) due to septal hypertrophy during systole and diastolic dysfunction, and nonobstructive (nHCM) lacks outflow obstruction but still exhibits diastolic dysfunction. EDG-7500 is an investigational cardiac sarcomere modulator in development to improve myocardial relaxation in both oHCM and nHCM and relieve LVOT-G in oHCM. In the Phase II CIRRUS HCM trial (NCT06347159), EDG-7500 reduced NT-proBNP levels, a myocardial wall stress marker, lowered LVOT-G in oHCM, and improved symptoms and functional status across both subtypes¹ (below).

We hypothesized that reductions in NT-proBNP would be accompanied by beneficial changes in other proteins and pathways linked to cardiac stress.

CIRRUS-HCM Phase II, Effects of EDG-7500 Treatment:



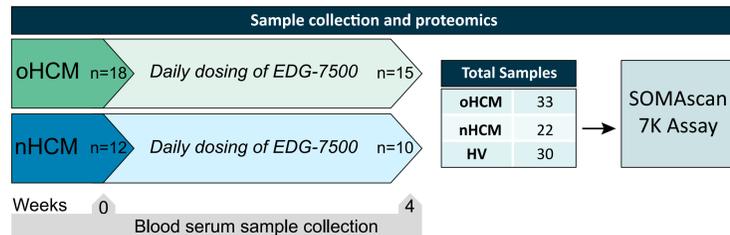
Methods

Serum proteomics were profiled using the SOMAscan 7K platform in oHCM (n=18) and nHCM (n=12) patients at baseline and after 4 weeks of EDG-7500 treatment (oHCM n=15; nHCM n=10). Healthy volunteer (HV) serum samples were also included (n=30).

Given the exploratory nature of this study, analyses were conducted without adjustment for clinical multiplicity. Directional consistency in protein abundance was observed despite the limited sample sizes.

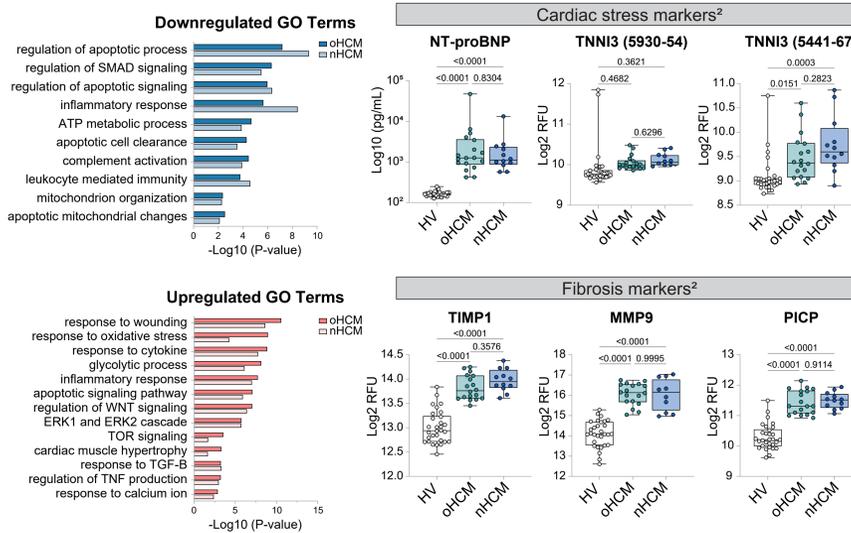
Baseline Characteristics			
	oHCM	nHCM	HV
# of participants	18	12	30
Age (mean years ± SD)	62 ± 12.8	58.75 ± 12.8	43.57 ± 13.3
Male, n (%)	6 (33.3%)	6 (50%)	27 (90%)
Female, n (%)	12 (66.7%)	6 (50%)	3 (10%)
LVOT-G (mean mmHg ± SD)	58.7 ± 29.6	N/A	
LVEF (mean % ± SD)	65.4 ± 3.6	60.7 ± 5.9	
NYHA Class I, n (%)	1 (5.5%)	0	
NYHA Class II, n (%)	11 (61.1%)	7 (58.3%)	
NYHA Class III, n (%)	6 (33.3%)	5 (41.7%)	
NYHA Class IV, n (%)	0	0	

HV: Healthy Volunteers; LVOT-G: Left ventricular outflow tract gradient; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association Functional Classification

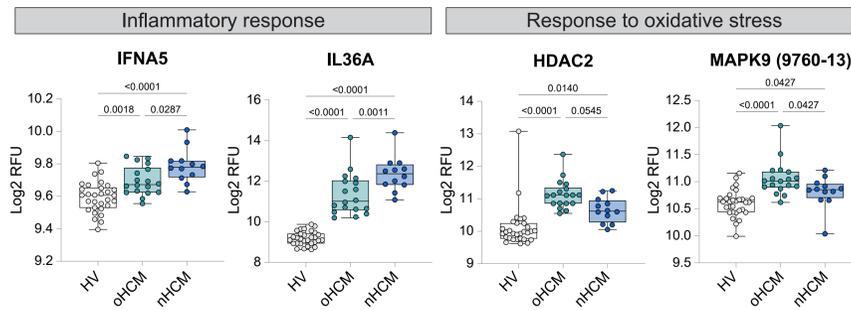


Results: Baseline

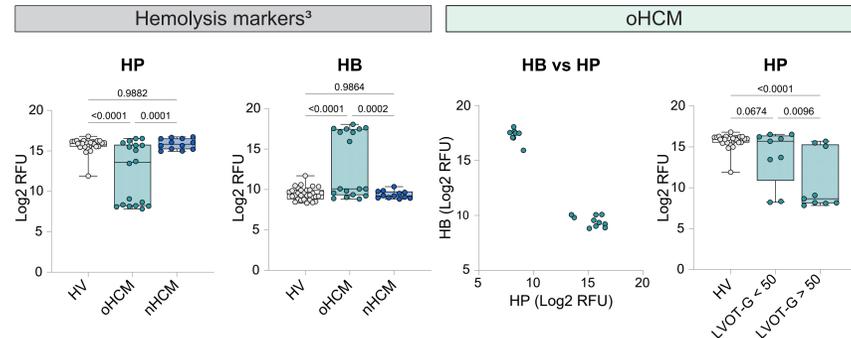
oHCM and nHCM show enrichment of inflammation, hypertrophy, and metabolism gene ontology (GO) terms, and similar levels of cardiac stress and fibrosis markers



Inflammatory response and oxidative stress proteins are differentially regulated in oHCM and nHCM

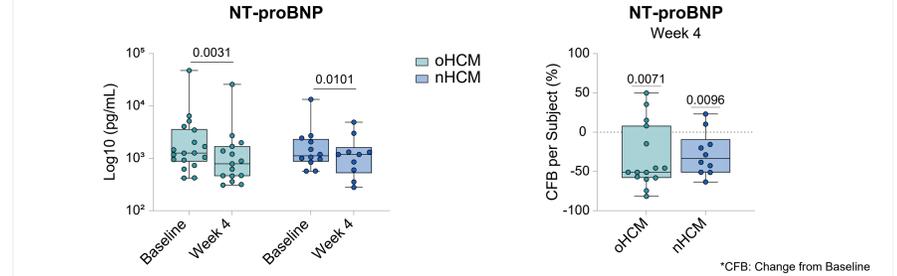


oHCM shows dysregulation of hemolysis that correlates with baseline LVOT-G

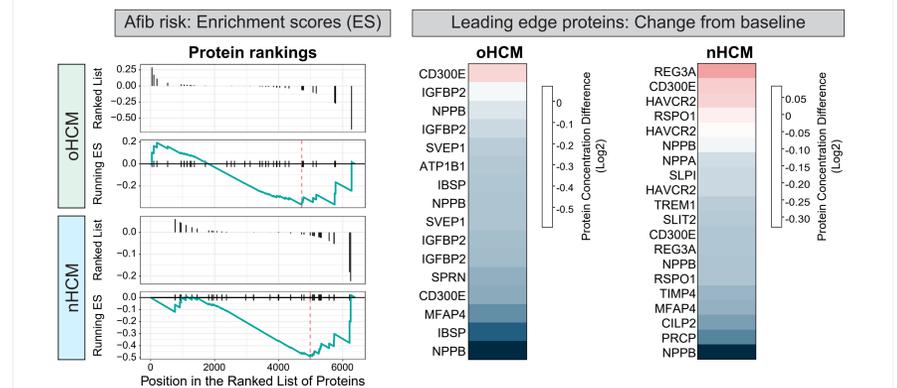


Results: Post-treatment

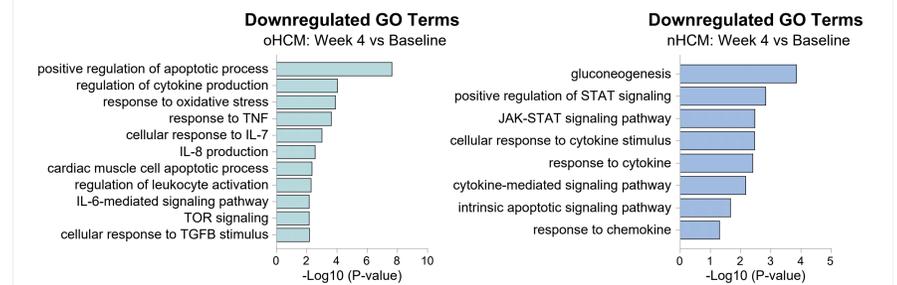
NT-proBNP levels decrease after 4 weeks of treatment



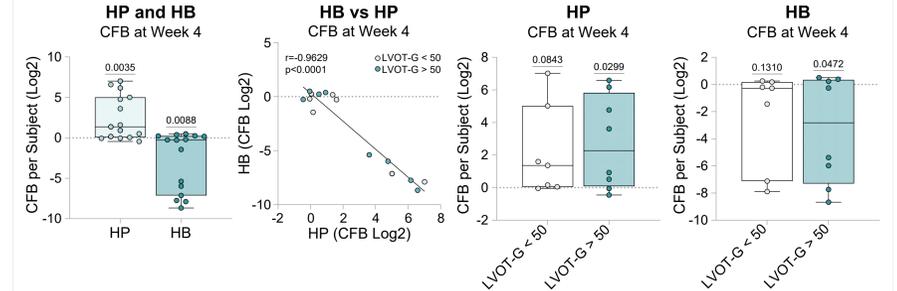
Gene set enrichment analysis reveals negative enrichment of protein sets previously associated with atrial fibrillation (Afib) risk⁴



Proteins related to inflammatory pathways are downregulated



Haptoglobin and Hemoglobin are significantly changed in oHCM patients with greater baseline LVOT-G



References

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Disclosures

Luuli N. Tran, Ben Barthel, Aylin Tugcu, Christopher Dufton, Alan Russell, and Robert O. Blaustein[†] are shareholders and employees of Edgewise Therapeutics. EDG-7500 is an investigational agent that is not approved for use by any regulatory authority in any territory.

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Abbreviations

Afib, atrial fibrillation; CFB, change from baseline; GO, Gene Ontology; HP, Haptoglobin; HV, healthy volunteers; HB, Hemoglobin; LVOT-G, left ventricular outflow tract gradient; LVEF, left ventricular ejection fraction; nHCM, nonobstructive hypertrophic cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; oHCM, obstructive hypertrophic cardiomyopathy; RFU, relative fluorescence units; SEM, standard error of the mean