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AMBER-HFpEF: Assessment of CK-586 in a Multicenter, Blinded Evaluation of Safety and Tolerability Results in HFpEF

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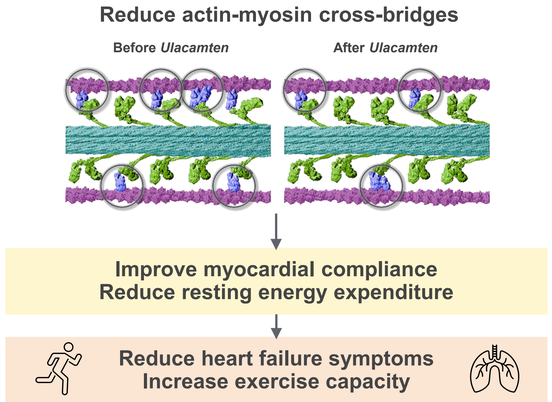
BACKGROUND

Individuals with heart failure with preserved ejection fraction (HFpEF) and normal to hypercontractile function (defined as left ventricular ejection fraction [LVEF] ≥60%) have limited capacity to augment stroke volume with exercise, dyspnea on exertion, poor clinical outcomes, and few treatment options.

Ulacamten (CK-4021586) is a small molecule allosteric cardiac myosin inhibitor (CMI), with a distinct binding site compared with other CMIs, in development as a chronic oral treatment for patients with HFpEF and LVEF ≥60%. Phase 1 studies demonstrated tolerability and safety of *ulacamten* in healthy individuals across a wide range of doses.[1]

Assessment of CK-586 in a **M**ulti-Center, **B**linded **E**valuation of Safety and Tolerability **R**esults in HFpEF **(AMBER-HFpEF; NCT06793371)** is a Phase 2a multicenter, randomized, double-blind, placebo-controlled dose-finding study testing the hypothesis that *ulacamten* will safely improve myocardial compliance and exercise capacity in adults with symptomatic HFpEF and LVEF ≥60%.

Figure 1. Therapeutic Hypothesis

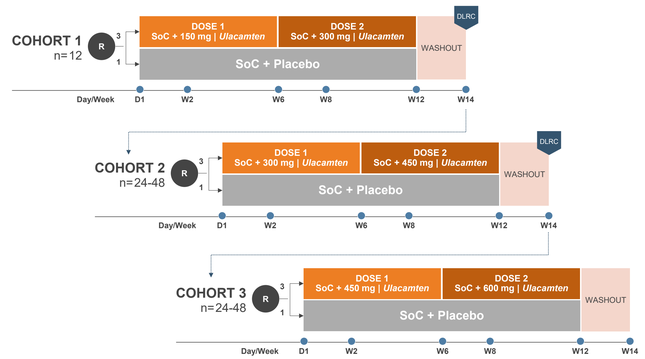


Potential clinical efficacy observed in non-obstructive hypertrophic cardiomyopathy with the CMI aficamten[2] suggests this mechanism might also benefit patients with HFpEF and hypercontractility.

STUDY DESIGN

- Phase 2a, multicenter, randomized, double-blind, placebo-controlled, dose-finding trial in adults with symptomatic HFpEF and LVEF ≥60%.
- Patients randomized 3:1 (*ulacamten*: placebo) in 3 sequential dose escalation cohorts.
- Patients randomized to *ulacamten* will receive 2 doses over a 12-week treatment period.
- Dose adjustments driven by blinded, site-read echocardiograms (echos).
- Dose Level Review Committee will evaluate unblinded data to ensure acceptable safety and guide enrollment.
- 60 patients will be enrolled across the 3 cohorts from 24 centers in the United States.
- Randomization will be stratified according to patients with LVEF ≤65% vs >65%.
- Enrollment of patients with atrial fibrillation is limited to up to 10% of each cohort.

Figure 2. Study Design Schema and Schedule of Activities



	SCREENING	DOSE 1					DOSE 2				WASHOUT	
STUDY VISITS	D −42 to D −1	D1	W2			W6	W8			W12		W14
Echo	X	X	X			X	X			X		X
Stress Echo		X								X		
ECG	X	X	X			X	X			X		X
NT-proBNP	X	X	X			X	X			X		X
KCCQ/NYHA	X	X	X			X	X			X		X
EQ-5D-5L	X	X				X				X		X
Ulacamten PK			X			X	X			X		

ELIGIBILITY CRITERIA

Key Inclusion Criteria

- 40–85 years old inclusive, diagnosed with HFpEF.
- Screening Echo with LVEF ≥60%, plus
  - Left atrial volume index ≥34 mL/m^2, ***and***
  - LV wall thickness ≥11 mm ***or*** E/e′ ≥13.
- NYHA class II or III at screening.
- Screening NT-proBNP ≥300 pg/mL (or ≥900 pg/mL with atrial fibrillation).
- Receiving diuretics (loop, thiazide, or MRA) treatment at a stable dose for ≥30 days. Patients on beta-blockers, ACE/ARB or ARNI or SGLT2 inhibitors, must be on stable doses ≥4 weeks (GLP-1 agonists for 24 weeks).
- Body mass index <40 kg/m^2.

Key Exclusion Criteria

- Significant valvular heart disease (moderate-severe stenosis or regurgitation).
- Known or suspected infiltrative or storage disorder (eg, Noonan syndrome, Fabry disease, amyloidosis).
- Patients with evidence of substantial LVH (MWT ≥15mm) on cardiac imaging must have cardiac amyloid excluded (EMB or technetium-pyp scan).
- History of LV systolic dysfunction (LVEF <45%).
- Paroxysmal or permanent atrial fibrillation requiring rhythm restoring treatment (unless anticoagulated and adequately rhythm controlled for >6 months).
- Any significant condition that would prevent completing an exercise test.

ENDPOINTS

Primary Endpoints

- Incidence of early drug discontinuation.
- Incidence of adverse events.
- Incidence of LVEF <40%.

Secondary Endpoints

- Change from baseline in NT-proBNP at Weeks 6 and 12.
- Change from baseline in LVEF at Weeks 6 and 12.
- Pharmacokinetic (PK) parameters for *ulacamten.*
- Relationship of PK to pharmacodynamic parameters (NT-proBNP and LVEF).

Exploratory Endpoints

- Change from baseline at Weeks 6 and 12 in:
  - NYHA class.
  - KCCQ-CSS.
  - E/A, E/e′, and left atrial volume index.
  - EQ-5D-5L.
- Change from baseline at Week 12 in:
  - Systolic functional reserve on stress echo.
  - Exercise time.

SUMMARY

The development strategy for *ulacamten* represents an important step in the targeted therapy of HFpEF and is intended to enable the evaluation of a cardio-specific drug with a mechanism of action targeting the underlying pathophysiology. The AMBER-HFpEF trial is currently open and enrolling participants.

CONTACT INFORMATION
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REFERENCES
1. Lutz J, et al. A First-in-Human, Single and Multiple Ascending Dose Study of CK-40121586, a Novel Cardiac Myosin Inhibitor. Poster presented at American College of Clinical Pharmacology (ACCP), September 8-16, 2024, Bethesda, MD, USA.
2. Masri A, et al. Eur J Heart Fail. 2024;26(9):1993-1998.

ACKNOWLEDGMENTS
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ABBREVIATIONS
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; CMI, cardiac myosin inhibitor; DLRC, Dose Level Review Committee; Echo, echocardiogram; ECG, electrocardiogram; EMB, endomyocardial biopsy; GLP-1, glucagon-like peptide-1; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MWT, maximal wall thickness; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; PK, pharmacokinetics; pyp, pyrophosphate; SGLT-2, sodium-glucose cotransporter 2; SoC, standard of care.

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