Multicenter Exercise Tolerance Evaluation of *Omecamtiv Mecarbil* Related to Increased Contractility in Heart Failure (METEORIC-HF)

A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Effect of *Omecamtiv Mecarbil* on Exercise Capacity in Subjects With Heart Failure With Reduced Ejection Fraction and Decreased Exercise Tolerance

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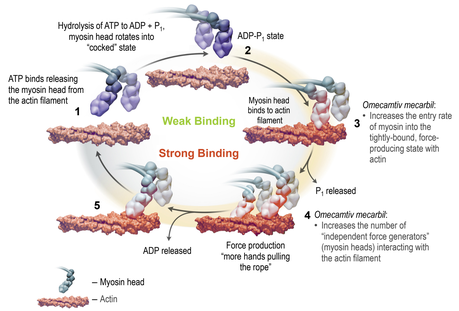
Background

- Heart failure with reduced ejection fraction (HFrEF) is a progressive disorder marked by cardiac systolic dysfunction and punctuated by frequent recurrent hospitalizations and ultimately death
- Close to 6 million adults in the United States have heart failure, and ~50% die within 5 years of diagnosis[1]
- Few therapies have demonstrated improvements in exercise capacity. Currently, only angiotensin-converting-enzyme inhibitors (ACEi) have product labels that describe a positive effect on exercise capacity in patients with HFrEF
- A new class of medications for chronic HFrEF aims to directly improve myocardial contractility, as there is a clinical need for agents that improve cardiac performance with a favorable safety profile[2]
- *Omecamtiv mecarbil* is a novel small molecule classified as a cardiac myosin activator that increases cardiac contractility by selectively and directly activating the enzymatic domain of the cardiac myosin heavy chain, the force-generating motor protein of the cardiac sarcomere, without increasing cardiac myocyte intracellular calcium[3,4]
  - This stabilizes the lever arm of myosin in a primed position prior to contraction, increasing the number of myosin molecules able to bind actin and generate force when systole starts

Omecamtiv Mecarbil Mechanism of Action



Source: Ahmad et al. *Eur J Heart Fail.* 2019. doi:10.1002/ejhf.1557. [Epub ahead of print]

- *Omecamtiv mecarbil* increases stroke volume, decreases filling pressures, and improves ventricular volumes without increasing the rate of left ventricular pressure development or heart rate, and without noticeable effect upon myocardial oxygen uptake, blood pressure, or coronary blood flow[3–5]
- *Omecamtiv mecarbil* has been evaluated in 10 Phase 1 studies, four Phase 2a studies in participants with chronic HF, one Phase 2b study in participants with acutely decompensated HFrEF, and two Phase 2b studies in participants with chronic HFrEF
- The Phase 2b COSMIC-HF trial demonstrated that *omecamtiv mecarbil* oral formulation was well tolerated and the pharmacokinetic (PK)-based dose adjustment approach successfully prevented overexposure[5]
  - Secondary objectives showed decreases in cardiac dimensions and volumes, N-terminal-prohormone B-type natriuretic peptide (NT-proBNP), and heart rate
  - Overall serious and nonserious adverse events profile was similar to the placebo group
- GALACTIC-HF is an ongoing Phase 3 study in participants with chronic HFrEF receiving standard of care (SoC)

Study Purpose

- To assess the effect of *omecamtiv mecarbil* on exercise capacity following 20 weeks of treatment

Study Objectives

Primary

- To evaluate the effect of treatment with *omecamtiv mecarbil* compared with placebo on change in peak oxygen uptake (pVO_2) on cardiopulmonary exercise testing (CPET) from baseline to Week 20

Secondary

- To evaluate effect of treatment with *omecamtiv mecarbil* compared with placebo on:
  - Change in exercise capacity, as measured by the change in total workload during CPET from baseline to Week 20
  - Change in ventilatory efficiency (VE), as measured by change in ventilation/carbon dioxide output (VCO_2) slope during CPET from baseline to Week 20
  - Change in average daily activity units measured over a 2-week period from baseline to Weeks 18–20 as determined using accelerometry

Exploratory Objectives

- To evaluate effect of treatment with *omecamtiv mecarbil* compared with placebo on:
  - Change in oxygen uptake efficiency slope (VO_2/logVE slope), ventilatory threshold, VO_2 recovery kinetics, percent predicted pVO_2, and exercise duration from baseline to Week 20
  - Change in average daily activity units from baseline to Weeks 6–8 and Weeks 12–14
  - Change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score and its subdomains from baseline to Week 20

Key Inclusion Criteria

- Male or female, ≥ 18 to ≤ 85 years of age
- History of chronic HF, defined as requiring continuous treatment with medications for HF for a minimum of 3 months before screening
- New York Heart Association class II or III at screening
- Left ventricular ejection fraction ≤ 35%
- Ambulatory without assistance
- On maximally tolerated HF SoC therapies consistent with regional clinical practice guidelines, if not contraindicated and according to investigator judgment of the participant's clinical status; beta-blocker dose must be stable for 30 days prior to randomization
- NT-proBNP level ≥ 200 pg/mL
- Peak VO_2 ≤ 75% of the predicted normal value with respiratory exchange ratio (RER) ≥ 1.05 on a screening CPET, confirmed by a CPET core laboratory

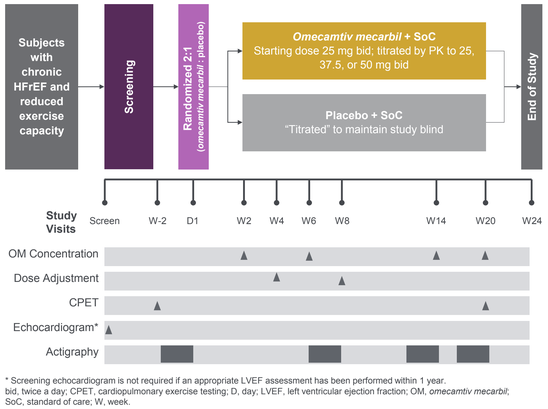
Key Exclusion Criteria

- Paroxysmal atrial fibrillation or flutter documented within the previous 6 months, direct-current (DC) cardioversion or ablation procedure for atrial fibrillation within 6 months, or plan to attempt to restore sinus rhythm within 6 months of randomization
  - Participants with persistent atrial fibrillation and no sinus rhythm documented in the prior 6 months are permitted
- Requires assistance to walk or use of mobility assistive devices such as motorized devices, wheelchairs, or walkers
  - Use of canes for stability while ambulating is acceptable if the subject is deemed capable of performing CPET
- Ongoing or planned enrollment in cardiac rehabilitation
- Severe uncorrected valvular heart disease
- Major medical event or procedure within 3 months prior to randomization, including hospitalization, surgery, renal replacement therapy, cardiac procedure, or episodes of decompensated HF that require intravenous HF treatment
- Chronotropic incompetence (including inadequate pacemaker rate response) during CPET at screening, defined as a maximum heart rate < 60% of the maximum predicted heart rate

Study Design

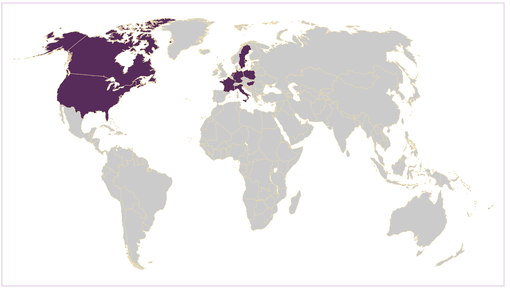
- METEORIC-HF is a Phase 3, randomized, placebo-controlled, double-blind, parallel group, multicenter study for oral *omecamtiv mecarbil* in participants with HFrEF
- The study aims to enroll 270 patients in up to 80 clinical sites across nine countries in North America and Europe for 20 weeks of treatment with follow-up at Week 24, providing 90% power to detect a change in peak VO_2 with a two-sided type I error of 0.05
- Randomization will be stratified based on the RER on the baseline CPET (< 1.15, ≥ 1.15) and persistent atrial fibrillation at screening (Y/N)
- Participants are screened and randomized in a 2:1 ratio (*omecamtiv mecarbil* to placebo) into two treatment arms for 20 weeks:
  - **Arm 1:** Oral *omecamtiv mecarbil* started at 25 mg twice daily (bid); titrated to 25, 37.5, or 50 mg bid based on PK-guided dosing regimen determined by periodic blood testing
  - **Arm 2:** Oral placebo titrated to maintain study blinding
- At study visit Week 2 and Week 6, a predose blood sample will be collected for all participants to guide dose adjustment
- Both treatment arms are given in conjunction with SoC treatment for HF
- Investigational product will be administered orally bid, under fasted or fed conditions, and must be swallowed whole

Trial Overview



* Screening echocardiogram is not required if an appropriate LVEF assessment has been performed within 1 year.
bid, twice a day; CPET, cardiopulmonary exercise testing; D, day; LVEF, left ventricular ejection fraction; OM, *omecamtiv mecarbil*; SoC, standard of care; W, week.

METEORIC-HF Study Participating Countries



References

1. Benjamin EJ, et al. *Circulation*. 2019;139:e56–e528; **2.** Hasenfuss G, Teerlink JR. *Eur Heart J*. 2011;32:1838–1845; **3.** Malik FI, et al. *Science*. 2011;331:1439–1443; **4.** Planelles-Herrero VJ, et al. *Nat Commun*. 2017;8:190; **5.** Teerlink JR, et al. *Lancet*. 2016;388:2895–2903.

Disclosures

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Additional Information

www.amgentrials.com (Study ID: CY 1031)

www.clinicaltrials.gov (Identifier: NCT03759392)

Omecamtiv mecarbil is being developed under a collaboration between Amgen and Cytokinetics, with funding and strategic support from Servier. Efficacy and safety have not been established.

To obtain a PDF of this poster: Scan the QR code OR http://bit.ly/2KEN8Oh No personal information is stored

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