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A Multicenter, Double-blind, Randomized, Placebo-controlled Trial to Assess Efficacy and Safety of Omecamtiv Mecarbil in Patients with Symptomatic Heart Failure with Severely Reduced Ejection Fraction

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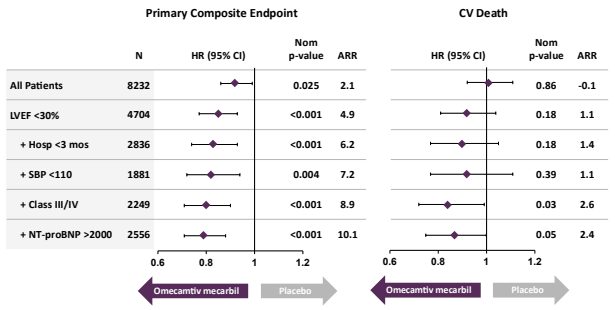
BACKGROUND

Omecamtiv mecarbil is a selective cardiac myosin activator (myotrope) that improves cardiac function by increasing myocardial contractility and systolic ejection time.

The Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (**GALACTIC-HF, NCT02929329**) clinical trial showed a statistically and clinically significant reduction in heart failure (HF) outcomes among patients with symptomatic HF and reduced ejection fraction (HFrEF) treated with omecamtiv mecarbil.[1]

Prespecified subgroup analyses demonstrated patients with LVEF <30% experienced the greatest benefit.[2] The potential benefit from omecamtiv mecarbil was further concentrated in patients with common markers of high-risk HFrEF, (including higher baseline NT-proBNP), worse symptoms, more recent hospitalization, or lower blood pressure (**Figure 1**).

Figure 1. GALACTIC-HF: Treatment benefit in subgroups of increased risk



Confirmation of Omecamtiv Mecarbil Efficacy Trial in Heart Failure **(COMET-HF; NCT06736574)** expands on the results from GALACTIC-HF. It is designed to evaluate the effect of omecamtiv mecarbil on risk of HF outcomes in patients with severe symptomatic HFrEF (LVEF <30%, NT-proBNP ≥1000 pg/mL, and HF event within <6 months).

STUDY DESIGN

- Phase 3, randomized, multicenter, double-blind, placebo-controlled trial in patients with symptomatic HFrEF.
- 1800 patients will be randomized 1:1 to omecamtiv mecarbil or placebo (**Figure 2**). The study will be completed when ~850 primary endpoint events have occurred to give ≥90% power to detect a 20% RRR in the primary endpoint.
- Patients will receive omecamtiv mecarbil 25 mg BID x 2 weeks (run-in phase) to assess adherence and tolerance (**Figure 3**).
- Patients randomized to omecamtiv mecarbil will have dose assigned (25 mg, 37.5 mg, or 50 mg BID) based on the plasma concentration obtained after run-in phase.

Figure 2. Study overview

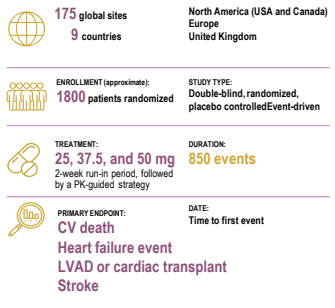
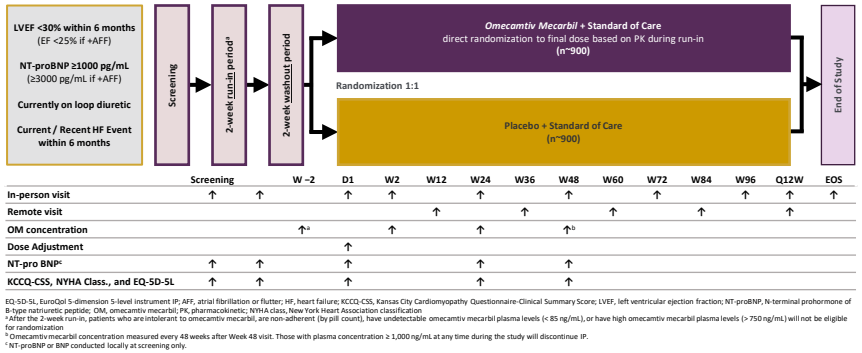


Figure 3. Study design schema



EQ-5D-5L, EuroQol 5-dimension 5-level instrument IP; AFF, atrial fibrillation or flutter; HF, heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; OM, omecamtiv mecarbil; PK, pharmacokinetic; NYHA class, New York Heart Association classification
[a] After the 2-week run-in, patients who are intolerant to omecamtiv mecarbil, are non-adherent (by pill count), have undetectable omecamtiv mecarbil plasma levels (< 85 ng/mL), or have high omecamtiv mecarbil plasma levels (> 750 ng/mL) will not be eligible for randomization
[b] Omecamtiv mecarbil concentration measured every 48 weeks after Week 48 visit. Those with plasma concentration ≥ 1,000 ng/mL at any time during the study will discontinue IP.
[c] NT-proBNP or BNP conducted locally at screening only.

ELIGIBILITY CRITERIA

Key Inclusion Criteria	Key Exclusion Criteria
History of chronic HFrEF, defined as requiring treatment for HF for ≥3 months prior to screening	AFF on screening ECG and currently taking digoxin
Currently hospitalized with the primary reason of HF or HF event within 6 months prior to screening	Receiving IV inotropes or IV vasopressors ≤3 days prior to screening
Patients without AFF on screening ECG: • LVEF <30% within 6 months of screening • NT-proBNP ≥1000 pg/mL (BNP ≥300)	Receiving mechanical hemodynamic support or mechanical ventilation ≤7 days prior to screening
Patients with AFF on screening ECG: • LVEF <25% within 6 months of screening • Elevated NT-proBNP ≥3000 pg/mL (BNP ≥900) • Not currently taking digoxin	eGFR <20 mL/min/1.73 m^2 or receiving dialysis at screening
Established on standard of care therapies for HFrEF for ≥30 days prior to screening	Receiving treatment in another investigational device or drug study or within 30 days of ending such investigational treatment
Receiving oral loop diuretics	Previously received omecamtiv mecarbil

Eligibility is based on local labs, local echo, and clinical history.

ENDPOINTS

Primary Endpoints

- Time to first event of CV death, HF event*, LVAD implantation or cardiac transplantation, stroke.

* HF event defined as an urgent, unscheduled clinic/office/emergency department visit or hospital admission with a primary diagnosis of HF

Secondary Endpoints

- Time to first event of CV death or HF event.
- Time to the first HF hospitalization.
- HF outcomes in severe HFrEF group (NYHA III-IV, hospitalization within 3 months): CV death, HF event, LVAD implantation or cardiac transplantation, stroke.
- Time to irreversible morbidity or mortality: CV death, LVAD implantation or cardiac transplantation, stroke.
- Time to CV death.
- Time to first event of stroke.
- Time to all-cause death.

Safety Endpoints

- CV death, nonfatal stroke, nonfatal myocardial infarction, unstable angina, hospitalization, HF hospitalization.
- Incidence of any AEs leading to drug discontinuation, serious AEs, and AEs of special interest.

SUMMARY

Building on findings from GALACTIC-HF, COMET-HF is designed to determine whether omecamtiv mecarbil can further reduce heart-failure events in patients with severe systolic dysfunction – a population with substantial unmet therapeutic need.

REFERENCES: 1. Teerlink JR, et al. Eur J Heart Fail 2020;22(11):2160-71. **2.** Teerlink JR, et al. J Am Coll Cardiol 2021;78(2):97-108.

ABBREVIATIONS: ARR, absolute risk reduction; AE, adverse event; AFF, atrial fibrillation or flutter; BID, twice daily; BNP, brain natriuretic peptide; CV, cardiovascular; echo, echocardiogram; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol 5-dimension 5-level instrument; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PK, pharmacokinetic; RRR, relative risk reduction.

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