The Effect Of Omecamtiv Mecarbil In Hospitalized Patients As Compared With Outpatients

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BACKGROUND

- In the GALACTIC-HF trial, omecamtiv mecarbil (OM), compared with placebo, reduced the risk of the composite endpoint of cardiovascular death or worsening HF events in patients with heart failure with reduced ejection fraction (HFrEF).
- By design, 25% of patients in GALACTIC-HF were enrolled during hospitalization for worsening HF.
- Hospitalized patients often have lower blood pressure, worse kidney function, may be harder to treat with conventional therapy, and are at higher risk than outpatients.
- The safety and effectiveness of novel therapies for HF are rarely examined after initiation in hospitalized patients. Comparison of the effect of OM in hospitalized patients, as compared with outpatients, was a pre-specified subgroup analysis.

METHODS

- Eligible patients were in NYHA class II-IV with an LVEF ≤35% and had elevated natriuretic peptide levels.
- Patients were randomized either as an inpatient during a hospitalization for worsening HF or as an outpatient, within one year of a worsening HF event (hospitalization or emergency department [ED] visit).
- Key exclusions were systolic BP <85mmHg, eGFR <20 mL/min/1.73m^2 and, in hospitalized patients, the use of inotropes or vasopressors within 72 hours and use of IV vasodilators or diuretics within 12 hours of screening.
- The primary outcome was a composite of cardiovascular death or a worsening HF event (defined as hospitalization for HF or an urgent ED or clinic visit).

RESULTS

- Of the 8232 patients analyzed, 2084 (25%) were hospitalized at the time of randomization. Of those randomized as an outpatient (n=6148), the most recent worsening HF event was a hospitalization in 5669 (92%), an ED visit in 458 (7%) and unknown in 21 (0.3%).
- Compared with outpatients, hospitalized patients were more frequently in a higher (worse) NYHA class, in atrial fibrillation, had lower systolic blood pressure and eGFR, and had higher heart rate and concentrations of NT-proBNP.
- Fewer inpatients, compared with outpatients, were taking a renin angiotensin system inhibitor, with or without a neprilysin inhibitor, or a beta-blocker at baseline. Conversely, use of mineralocorticoid receptor antagonists was more common in inpatients as compared with outpatients.

Cardiovascular outcomes according to randomization setting

- The rate (per 100 person-years [PY]) of the primary outcome was higher in hospitalized patients (placebo group = 38.3/100 PY) than in outpatients (23.1/100 PY); adjusted hazard ratio (HR) 1.21 (95%CI 1.12, 1.31).
- Among the patients randomized as outpatients, there was a stepwise gradient in risk, with those randomized within 3 months of a worsening HF event at the highest risk (placebo group = 26.6/100 PY) as compared with those 9-12 months post-event (19.0/100 PY); adjusted HR 1.20 (95%CI 1.01, 1.42), p for trend = 0.008 – ***Figure 1.***
- The rates of the individual components of the primary composite outcome were similarly greater in hospitalized patients as compared with outpatients – ***Central Figure***.

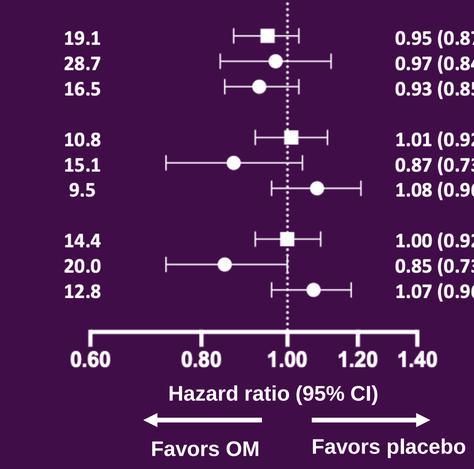
Efficacy of omecamtiv mecarbil by randomization setting

- The effect of OM versus placebo on the primary outcome was similar in hospitalized patients (HR 0.89, 95%CI 0.78, 1.01) and outpatients (HR 0.94, 95%CI 0.86, 1.02) (interaction p = 0.51 – ***Central Figure***).

GALACTIC-HF

In GALACTIC-HF, omecamtiv mecarbil reduced the risk of cardiovascular death or worsening HF when initiated in hospitalized patients and in outpatients

	Omecamtiv mecarbil Rate /100PY	Placebo Rate/100PY	HR (95% CI)	Interaction p-value
Primary Outcome				
All patients	24.2	26.3	0.92 (0.86, 0.99)	
Inpatient	34.1	38.3	0.89 (0.78, 1.01)	0.51
Outpatient	21.5	23.1	0.94 (0.86, 1.02)	
First Heart Failure Event				
All patients	18.7	20.3	0.93 (0.86, 1.00)	
Inpatient	28.7	30.2	0.95 (0.82, 1.09)	0.64
Outpatient	15.9	17.6	0.91 (0.83, 1.01)	
Heart Failure Hospitalization				
All patients	18.0	19.1	0.95 (0.87, 1.03)	
Inpatient	27.8	28.7	0.97 (0.84, 1.12)	0.66
Outpatient	15.3	16.5	0.93 (0.85, 1.03)	
Cardiovascular Death				
All patients	10.9	10.8	1.01 (0.92, 1.11)	
Inpatient	13.3	15.1	0.87 (0.73, 1.04)	0.055
Outpatient	10.2	9.5	1.08 (0.96, 1.21)	
All-Cause Death				
All patients	14.4	14.4	1.00 (0.92, 1.09)	
Inpatient	17.2	20.0	0.85 (0.73, 1.00)	0.02
Outpatient	13.5	12.8	1.07 (0.96, 1.18)	



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Cytokinetics

FIGURE 1 – PRIMARY OUTCOME BY RANDOMIZATION SETTING AND RANDOMIZED TREATMENT

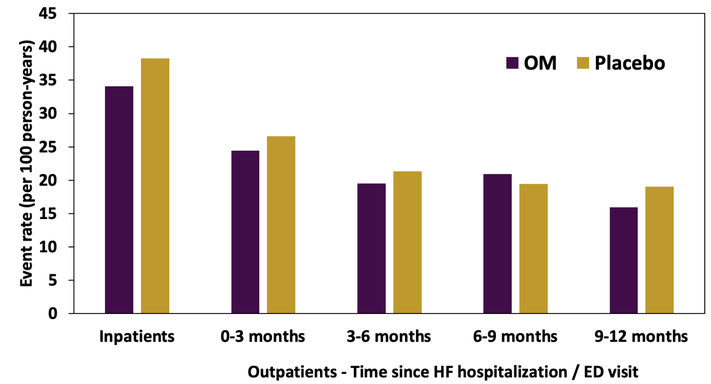
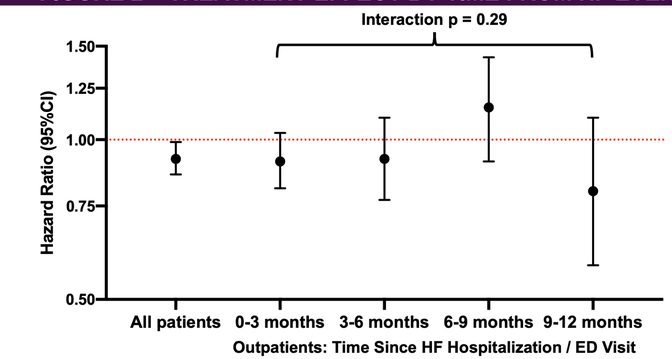


FIGURE 2 – TREATMENT EFFECT BY TIME FROM HF EVENT



- Applying the overall treatment effect (HR 0.92) resulted in a number needed to treat of 33 and 38 over 3 years in inpatients and outpatients, respectively.
- In patients randomized as outpatients, there was no modification of treatment effect on the primary outcome by time from most recent outpatient worsening HF event to randomization when examined as a categorical variable in 3-month groups (Interaction p = 0.29 – ***Figure 2***) or as a continuous variable (Interaction p = 0.78).
- There was no heterogeneity of treatment effect on time-to-first non-fatal worsening HF event (interaction p = 0.64) – ***Central Figure***.
- There was a greater effect of OM, as compared with placebo, in reducing the risk of cardiovascular death (interaction p = 0.055) and all-cause death (interaction p = 0.02) in hospitalized patients as compared with outpatients – ***Central Figure***.

Safety of omecamtiv mecarbil by randomization setting

- Treatment-emergent serious adverse events occurred more frequently in patients randomised as inpatients, as compared with outpatients, but did not differ significantly between the treatment groups.
- The changes in systolic blood pressure at week 2 and creatinine at week 12 were similar in hospitalized patients and outpatients and were not different between OM and placebo.

CONCLUSION

- In GALACTIC-HF, hospitalized HFrEF patients had a higher rate of the primary outcome than outpatients.
- OM reduced the risk of the primary outcome both when initiated in hospitalized patients and in outpatients.
- In hospitalized patients and outpatients, the initiation of OM was safe and well tolerated.

DISCLOSURE INFORMATION

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