Effect of Omecamtiv Mecarbil in Patients With Heart Failure With Reduced Ejection Fraction and **Atrial Fibrillation/Flutter: Results from COSMIC-HF**

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INTRODUCTION

 Omecamtiv mecarbil (OM) is a novel selective cardiac myosin activator under investigation as a potential treatment for heart failure with reduced ejection fraction

OM increases the entry rate of myosin

Mechanochemical Cycle of Myosin^{1,2}



MVO₂ = myocardial oxygen consumption

- Atrial fibrillation/flutter (AF) is a common comorbidity in patients with heart failure (HF)⁴
- Prevalence increases by HF severity (4% in NYHA Class I to 40% in Class IV)

OBJECTIVES

- To characterize, in patients with and without atrial fibrillation or flutter, the effects of omecamtiv mecarbil (OM) at 20 weeks on change from baseline in:
- Systolic ejection time (SET)
- Stroke volume
- Left ventricular end-diastolic (systolic) diameter (LVEDD, LVESD)
- Heart rate
- N-terminal pro-B-type natriuretic peptide (NT-proBNP)

METHODS

Study Design

- COSMIC-HF (NCT01786512) was a multicenter, randomized, placebo-controlled, double-blind phase 2 study that enrolled patients with:
- Stable, optimally-treated chronic heart failure (HF)
- New York Heart Association (NYHA) class II or III
- Left ventricular ejection fraction (LVEF) $\leq 40\%$
- N-terminal pro B-type natriuretic peptide (NT-proBNP) \geq 200 pg/mL (\geq 1200 pg/mL with atrial fibrillation or flutter)
- Patients receiving chronic antiarrhythmics (except amiodarone) were excluded
- OM and placebo groups were compared on the basis of presence/absence of AF
- Here we present data for the OM PK-guided titration group versus placebo group



RESULTS

Table 1. Baseline Demographics

• 21% of patients had atrial fibrillation/flutter (AF) at randomization, which was used as a stratification factor

		AF		No AF	
		OM 25 – >50 mg		OM 25 – >50 mg	
	Placebo	PK-based titration	Placebo	PK-based titration	
	n = 32	n = 32	n = 117	n = 117	
Age, years, mean (SD)	65.8 (9.9)	70.3 (8.8)	63.1 (9.6)	60.6 (11.5)	
Sex, male, %	71.9	87.5	82.1	82.9	
Systolic blood pressure (mmHg), mean (SD)	117.4 (13.1)	116.5 (14.3)	119.9 (14.9)	118.9 (16.5)	
Heart rate (bpm), mean (SD)	72.9 (12.3)	69.2 (11.5)	67.6 (9.7)	69.6 (12.1)	
HF Characteristics					
NYHA Class II, %	65.6	71.9	71.8	71.8	
Ischemic heart disease, %	56.3	84.4	60.7	63.2	
Years from HF diagnosis, mean (SD)	9.5 (9.2)	9.3 (6.7)	7.6 (6.4)	7.2 (6.4)	
HF hospitalization in prior year, %	31.3	21.9	23.9	26.5	
Comorbidities, %					
Myocardial infarction	50.0	62.5	56.4	53.0	
Percutaneous coronary intervention	40.6	46.9	41.9	41.0	
Coronary artery bypass grafting	15.6	50.0	19.7	20.5	
Hypertension	71.9	78.1	66.7	71.8	
Stroke	18.8	9.4	6.8	9.4	
Diabetes	46.9	28.1	39.3	39.3	
HF Medications, %					
Angiotensin converting enzyme inhibitor (ACE	l) 65.6	65.6	72.6	65.0	
Angiotensin II receptor blocker (ARB)	34.4	21.9	21.4	28.2	
Beta blocker (BB)	100.0	90.6	97.4	98.3	
Mineralocorticoid receptor antagonist (MRA)	65.6	40.6	57.3	69.2	
Diuretics	90.6	87.5	82.1	90.6	
Echocardiographic Variables					
Stroke volume, mL, mean (SD)	51.3 (13.3)	51.0 (14.0)	52.4 (15.4)	52.8 (15.1)	
SET, msec, mean (SD)	280.7 (30.7)	297.7 (28.5)	303.5 (37.2)	299.1 (33.9)	
LVEDD, cm, mean (SD)	6.3 (0.9)	6.0 (0.8)	6.2 (1.0)	6.4 (0.9)	
LVESD, cm, mean (SD)	5.4 (0.9)	5.1 (0.7)	5.3 (1.0)	5.5 (0.9)	
NT-proBNP, pg/mL, median (Q1,Q3)	2941 (1717, 5394)	2998 (1687, 4356)	1322 (647, 2483)	1564 (687, 2457)	

Abbreviations: LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; SET, systolic ejection time

Figure 1. COSMIC-HF: Overall Effects of Omecamtiv Mecarbil

LS, Least squares; SE, standard error

Table 2. Effects of Omecamtiv Mecarbil in Patients With HFrEF, With and Without AF

Placebo-corrected change from baseline at 20 weeks in OM PK-titration group						
Prespecified Secondary Endpoints	AF, n = 32 LS mean (95% CI)	No AF, n = 117 LS mean (95% CI)	Interaction (p-value)			
SET (msec)	27 (13, 41)	24 (17, 32)	0.69			
Stroke volume (mL)	6.6 (-0.6, 13.8)	3.0 (-0.4, 6.5)	0.38			
LVEDD (mm)	-1.1 (-3.3, 1.1)	-1.3 (-2.4, -0.1)	0.90			
LVESD (mm)	-2.1 (-4.5, 0.4)	-1.6 (-2.9, -0.3)	0.75			
HR (bpm)	-7.8 (-13.8, -1.7)	-2.0 (-4.2, 0.1)	0.08			
NT-proBNP (pg/mL)	-187 (-2216, 1842)	-1022 (-1597, -448)	0.43			

P-values are post-hoc, nominal and unadjusted for multiple comparisons; Doppler-derived stroke volume Abbreviations: CI. confidence interval; HR, heart rate.

Figure 2. Effects of Omecamtiv Mecarbil on Change in Left Ventricular Diameter, Cardiac Function, Heart Rate, and NT-proBNP in Patients With and Without AF

Table 3. Summary of Adverse Events

	AF		No AF	
	Placebo (n = 32)	OM 25 – >50 mg PK-based titration (n = 30)	Placebo (n = 117)	OM 25 – >50 mg PK-based titration (n = 116)
Treatment-emergent AEs, n (%)	21 (65.6)	19 (63.3)	70 (59.8)	76 (65.5)
Serious AEs	4 (12.5)	8 (26.7)	26 (22.2)	24 (20.7)
Leading to discontinuation	1 (3.1)	5 (16.7)	11 (9.4)	7 (6.0)
Cardiac AEs, n (%)	4 (12.5)	8 (26.7)	32 (27.4)	23 (19.8)
Cardiac failure	3 (9.4)	3 (10.0)	10 (8.5)	5 (4.3)
Acute cardiac failure	0 (0)	0 (0)	1 (0.9)	3 (2.6)
Congestive cardiac failure	0 (0)	3 (10.0)	3 (2.6)	1 (0.9)
Angina pectoris	0 (0)	0 (0)	3 (2.6)	1 (0.9)
Ventricular tachycardia	0 (0)	1 (3.3)	2 (1.7)	3 (2.6)
Adjudicated events, n	2	8	23	19
Death	0	0	4*	3*
MI	0	0	1	0
Hospitalization for HF	2	5	9	5
Troponin I (ng/mL), change from baseline to week 20, median (Q1, Q3)	0.00 (–0.01, 0.01	0.02) (0.01, 0.03)	0.00 (-0.01, 0.00)	0.00 (0.00, 0.02)

*In the placebo group, 2 of the 4 deaths were cardiovascular (2 sudden cardiac deaths); in the OM group, 2 of the 3 deaths were cardiovascular (1 sudden cardiac death, 1 due to other CV cause)

CONCLUSION

- Overall, COSMIC-HF showed that omecamtiv mecarbil, a novel selective cardiac myosin activator, improved measures of cardiac systolic function and decreased ventricular volumes, heart rate, and NT-proBNP over 20 weeks of treatment
- Results for the OM fixed-dose and PK-guided titration groups were qualitatively similar
- The effects of omecamtiv mecarbil on the above parameters did not differ statistically according to the presence or absence of AF at baseline
- Overall, the pattern of AEs did not appear markedly different between treatment arms, regardless of the presence of AF at baseline
- Findings are limited by relatively small subgroup size and differences
- The phase 3 study GALACTIC-HF (NCT02929329) will examine the effects of omecamtiv mecarbil on CV death and HF hospitalization, including approximately 25% of patients with AF at baseline
- Chronic HF patients on standard-of-care therapy with LVEF \leq 35%, NYHA II-IV, HF hospitalization or ED visit within 12 months, elevated natriuretic peptide
- N≈8,000 patients, primary endpoint of CV death and HF hospitalization; powered for CV death

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DISCLOSURES

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