The Effect of the Cardiac Myosin Activator, Omecamtiv Mecarbil, on Right Ventricular Structure and Function in Chronic Systolic Heart Failure (COSMIC-HF)

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BACKGROUND

- Systolic heart failure (HF) is associated with poor prognosis; mortality and morbidity remain high despite improvements in interventions.
- Right ventricular (RV) dysfunction and pulmonary hypertension (PH) are common in left-sided HF
- RV dysfunction and PH are associated with clinical symptoms and worse prognosis in patients with HF.
- A target for treatment of systolic HF is to improve myocardial contractility.[1]
- Omecamtiv mecarbil (OM) is a novel therapy that increases cardiac contractility *(Figure 1)*, increases stroke volume, decreases filling pressures, and improves ventricular volumes.[2]
- COSMIC-HF was a Phase 2 clinical trial in patients with chronic heart failure that showed OM improved left ventricular (LV) function and decreased LV volumes.[3]

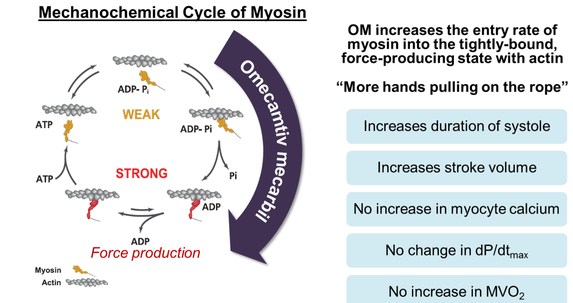
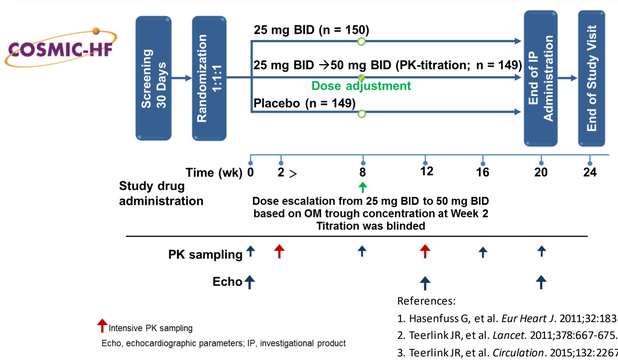


Fig 1: Omecamtiv Mecarbil (OM), Selective Cardiac Myosin Activator

METHODS



References:
1. Hasenfuss G, et al. *Eur Heart J*. 2011;32:1838-1845.
2. Teerlink JR, et al. *Lancet.* 2011;378:667-675.
3. Teerlink JR, et al. *Circulation*. 2015;132:2267-2285.

Fig 2: COSMIC-HF Expansion Phase Study Design

AIM

- Increasing contractility through pharmacologic intervention has an unknown effect on RV structure and function in patients with HF.
- We sought to determine the effect of OM vs. placebo on measures of RV structure and function in patients with HF.

METHODS

Patient population (N = 448)

– Aged 18–85 years with chronic HF (New York Heart Association [NYHA] class II/III)
– Treated with stable, optimal medical therapy ≥ 4 weeks
– N-terminal of prohormone brain natriuretic peptide (NT-proBNP) ≥ 200 pg/mL (≥ 1200 pg/mL if atrial fibrillation at presentation)
– Left ventricular ejection fraction (LVEF) ≤ 40%

Treatment *(Figure 2)*: patients were randomized 1:1:1 to receive

– Placebo
– 25 mg OM BID
– 25 mg OM BID with PK-guided uptitration to 50 mg OM BID

Analysis

– Echocardiograms were obtained at baseline, Week 12, and Week 20
– In this analysis, measures of RV structure and function was compared between patients from the OM PK titration group (n = 149) and the placebo group (n = 149)

RESULTS

	Placebo (n = 149)	25 mg BID (n = 150)	OM Titration Group (n = 149)
Age — years	64±10	63 ±10	63 ±12
Men — no. (%)	119 (80)	127 (85)	125 (84)
White Race — no. (%)	136 (91)	142 (95)	140 (94)
Ejection Fraction — % ± SD	29.3±7.4	29.3±7.5	29.0±7.3
RV end-diastolic area (EDA) — cm^2 ± SD	25.3±8.5	24.6±7.9	25.9±8.0
RV end-systolic area (ESA) — cm^2 ± SD	14.5± 5.6	14.5±6.6	15.4±6.4
TAPSE — cm ± SD	1.67±0.52	1.72±0.48	1.63±0.47
RVOT-VTI — cm ± SD	12.7±3.3	12.8±3.7	12.9±3.8
RV Systolic Ejection Time (SET) — msec ± SD	314.5±29.3	316.3±34.1	312.8±26.2
PASP— mmHg ± SD	35.1±12.5	34.5±10.0	34.4±10.1
TAPSE/PASP ratio — cm/mmHg ± SD	0.05±0.02	0.05±0.02	0.05±0.02
RVOT-VTI/PASP-ratio — cm/mmHg ± SD	0.39±0.17	0.40±0.19	0.40±0.16
HF characteristics:			
Ischemic heart disease — no. (%)	89 (60)	97 (65)	101 (68)
NYHA class II/III — no. (%)	105 (70)/ 44 (30)	102 (68)/ 48 (32)	107 (72)/ 42 (28)
Co-morbidities:			
Persistent A Fib/Flutter — no. (%)	33 (22)	28 (19)	24 (16)
Diabetes mellitus — no. (%)	61 (41)	70 (47)	55 (37)
Hypertension — no. (%)	101 (68)	94 (63)	109 (73)
Laboratory variables:			
Troponin I — ng/mL, median (Q1, Q3)	0.025 (0.016, 0.041)	0.022 (0.016, 0.039)	0.022 (0.016, 0.042)
NT-proBNP — pg/mL, median (Q1, Q3)	1719 (699, 3242)	1538 (634, 3427)	1719 (881, 3060)
eGFR — mL/min/1.73m^2 ± SD	65±19	63±19	65±19

Table 1: Baseline characteristics

RESULTS

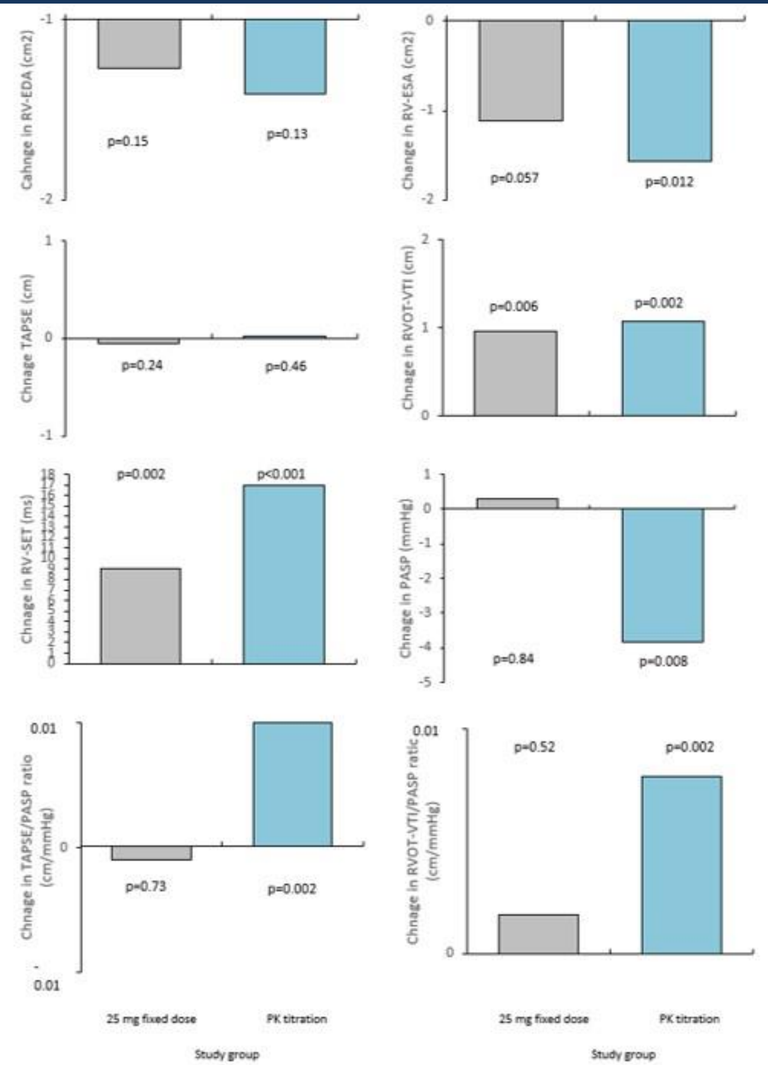


Fig 3: LS means for week 20 were calculated from repeated measure models which assessed the treatment differences vs. placebo and included the stratification factor of presence or absence of atrial fibrillation/flutter at randomization, baseline value, visit, and the treatment group by visit interaction as covariates. Grey bar: 25 mg fixed dose; Blue bar: PK titration.

CONCLUSION

In patients with chronic HF and reduced LV systolic function, 20 weeks of OM treatment was associated with improvement in several measures of RV function together with improvement in measures of RV pulmonary arterial coupling.

DISCLOSURES

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