

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

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for the COSMIC-HF Investigators**

Background and Objectives

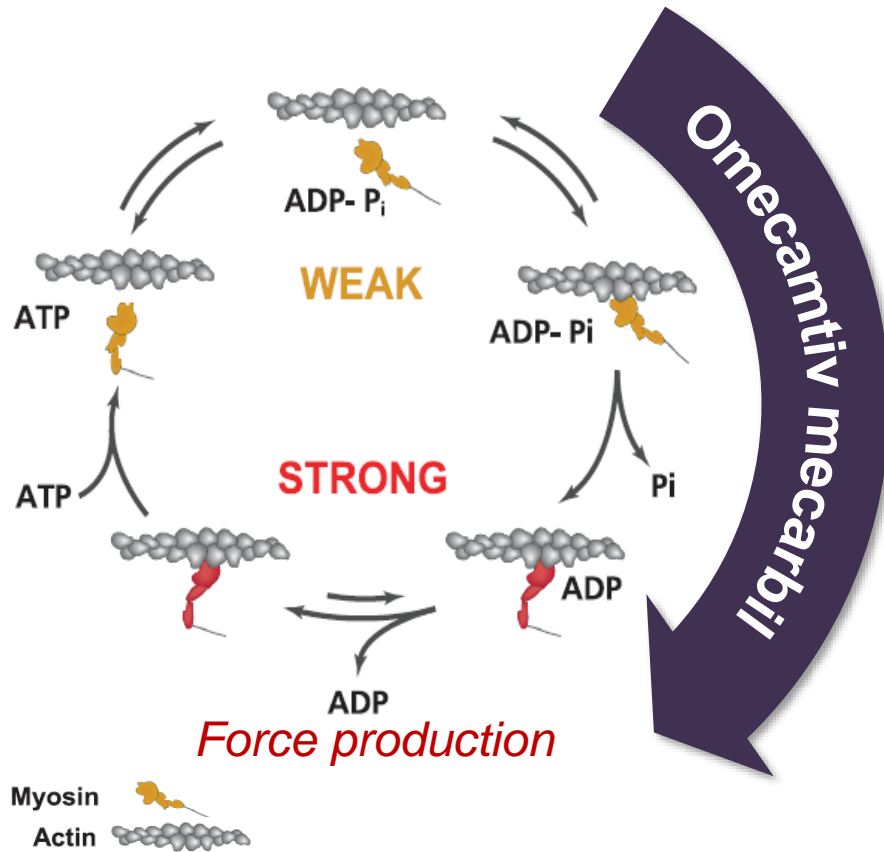
- Measures of diastolic function (e.g., LV filling velocities¹, E/e'², left atrial size³, restrictive filling pattern⁴ and measures of LA function⁵) are important prognosticators in HFrEF, independent and incremental to LVEF
- Omecamtiv mecarbil improves systolic function in patients with chronic HFrEF. The effect of omecamtiv mecarbil on diastolic function is not well-studied.

- **Primary Objective**
 - In this post-hoc analysis, to determine the effect of chronic therapy with OM on diastolic function in patients with heart failure (HF)

1. Pinamonti B, et al. *J Am Coll Cardiol.* 1993; 22:808–815.
2. Hirata K, et al. *Am J Cardiol.* 2009; 103:1275–1279.
3. Rossi A, et al. *Eur J Heart Fail.* 2009;11:929–936.
4. Somaratne JB, et al. *J Card Fail.* 2007;13:346–352.
5. Modin D, et al. *J Card Fail.* *J Card Fail.* 2019;25:87–96.

Background: Omecamtiv Mecarbil (OM) is a Novel Selective Cardiac Myosin Activator

Mechanochemical Cycle of Myosin



Data show OM increases the entry rate of myosin into the tightly-bound, force-producing state with actin

“More hands pulling on the rope”

Increases duration of systole

Increases stroke volume

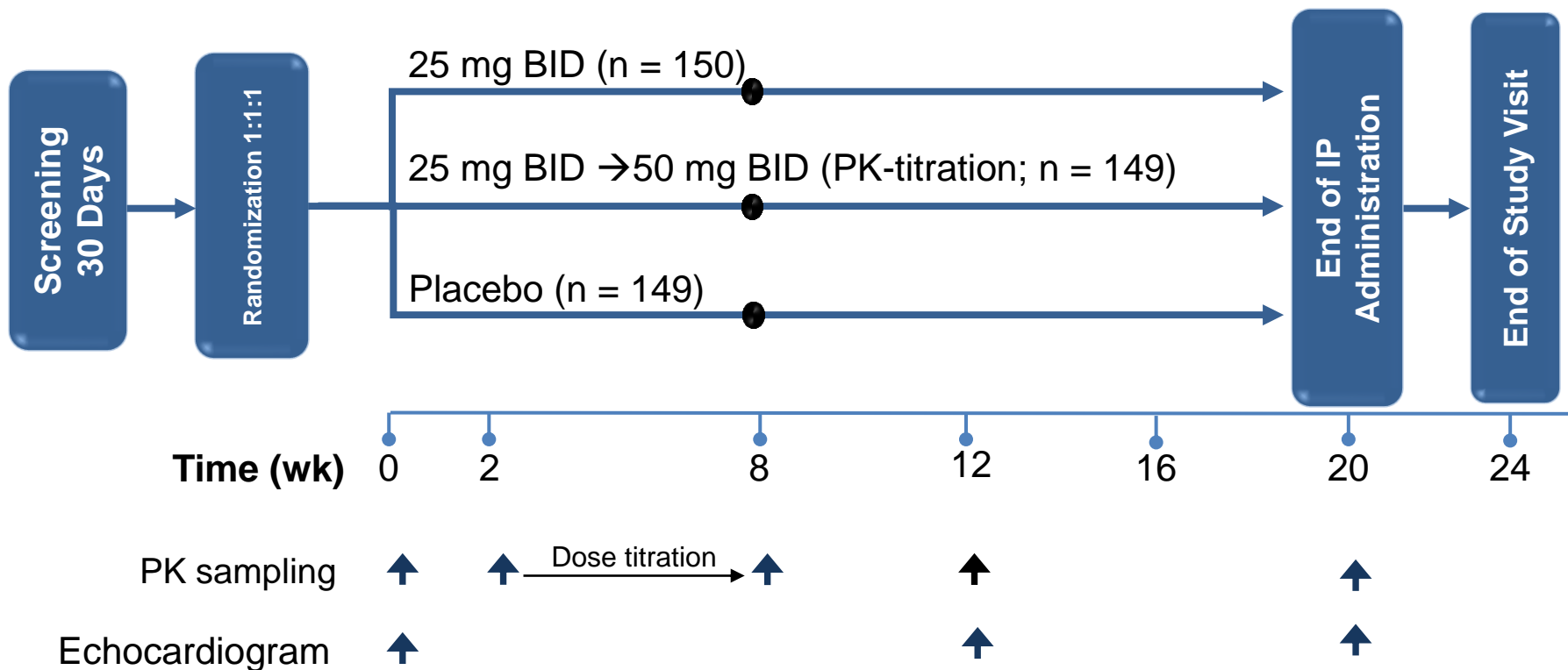
No increase in myocyte calcium

No change in dP/dt_{max}

No increase in MVO_2

COSMIC-HF: Study schema

History of chronic HFrEF (LVEF \leq 40%)
 NYHA class II or III
 Treated with stable, optimal HF Rx
 NT-proBNP \geq 200 pg/mL



Key Baseline Characteristics

448 Patients Enrolled	Placebo (n = 149)	OM 25 mg BID (n = 150)	PK Titration (n = 149)
Demographics			
Age (years), mean (SD)	64 (10)	63 (10)	63 (12)
Male, %	80	85	84
White, %	91	95	94
Disease characteristics			
Ischemic heart disease, %	60	65	67
LVEF (%), mean (SD)	29 (7)	29 (8)	29 (7)
NYHA class II, %	70	68	72
NYHA class III, %	30	32	28
Persistent atrial fibrillation or flutter, %	22	19	16
Diabetes mellitus, %	41	47	37
NT-proBNP (pg/mL), median	1719	1538	1719
eGFR (mL/min/1.73m ²), mean (SD)	65 (19)	63 (19)	65 (19)
Concomitant medications, %			
ACEi and/or ARB	94	95	92
Beta-blockers	98	97	97
MRAs	59	58	63

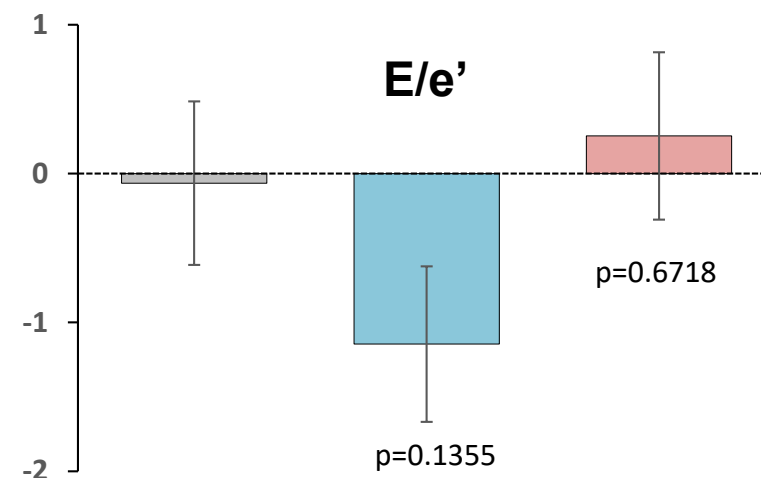
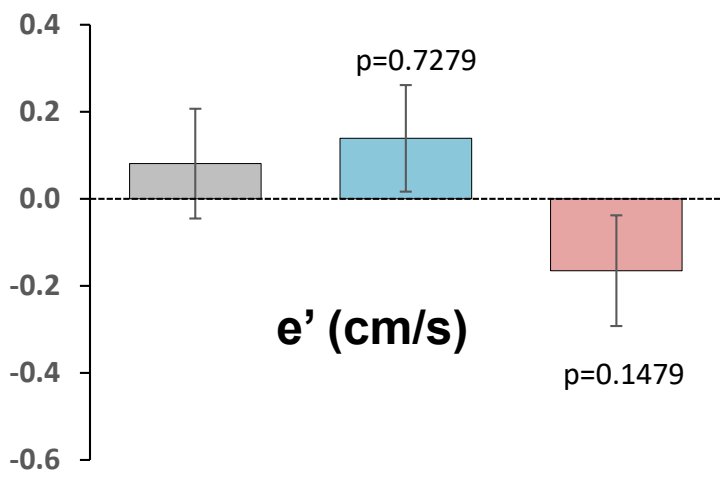
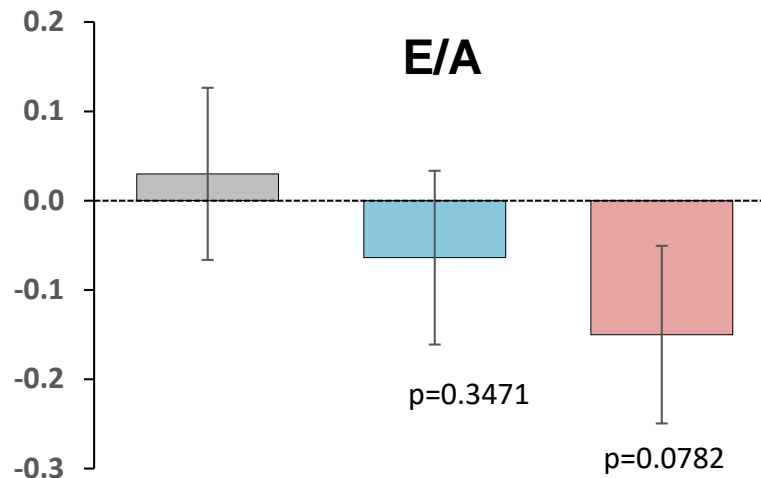
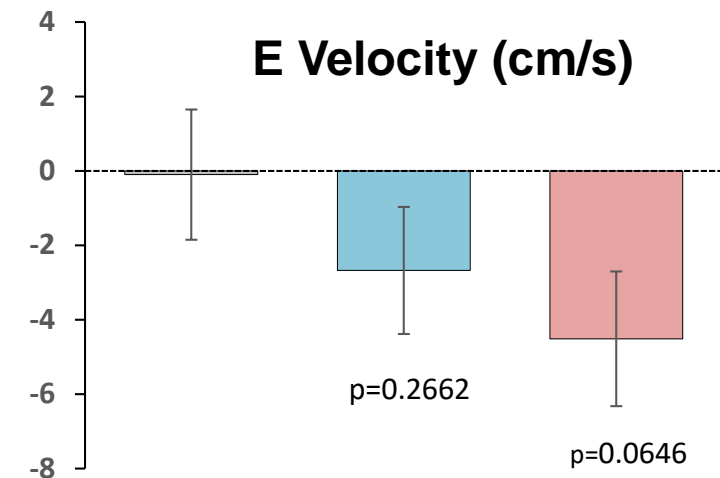
Key Baseline Diastolic Echo Parameters

	Placebo (n = 149)	OM 25 mg BID (n = 150)	PK Titration (n = 149)
Maximal LA volume (mL)	83 (34)	78 (36)	79 (29)
Minimal LA volume (mL)	57 (31)	53 (34)	54 (28)
LAVI (mL/m ²)	42 (17)	40 (17)	40 (14)
Minimal LA volume/BSA (mL/m ²)	29 (16)	27 (16)	27 (14)
LAEF (%)	34 (14)	36 (13)	35 (13)
E (m/s)	5.6 (1.9)	5.6 (1.6)	5.5 (1.7)
E/A ratio	1.4 (1.0)	1.3 (0.8)	1.4 (1.1)
E/e'	14 (7)	14 (9)	14 (8)
IVRT (ms)	100 (2)	105 (2)	101 (2)
TRV (m/s)	2.7 (0.5)	2.7 (0.5)	2.7 (0.4)

BSA, body surface area; EF, ejection fraction; IVRT, isovolumic relaxation time; LAVI, left atrial volume index; SD, standard deviation; TRV, tricuspid regurgitation velocity

Effect of OM on diastolic function

Least squares mean (SE) changes from baseline to Week 20



Placebo

25 mg fixed dose
Study group

PK titration

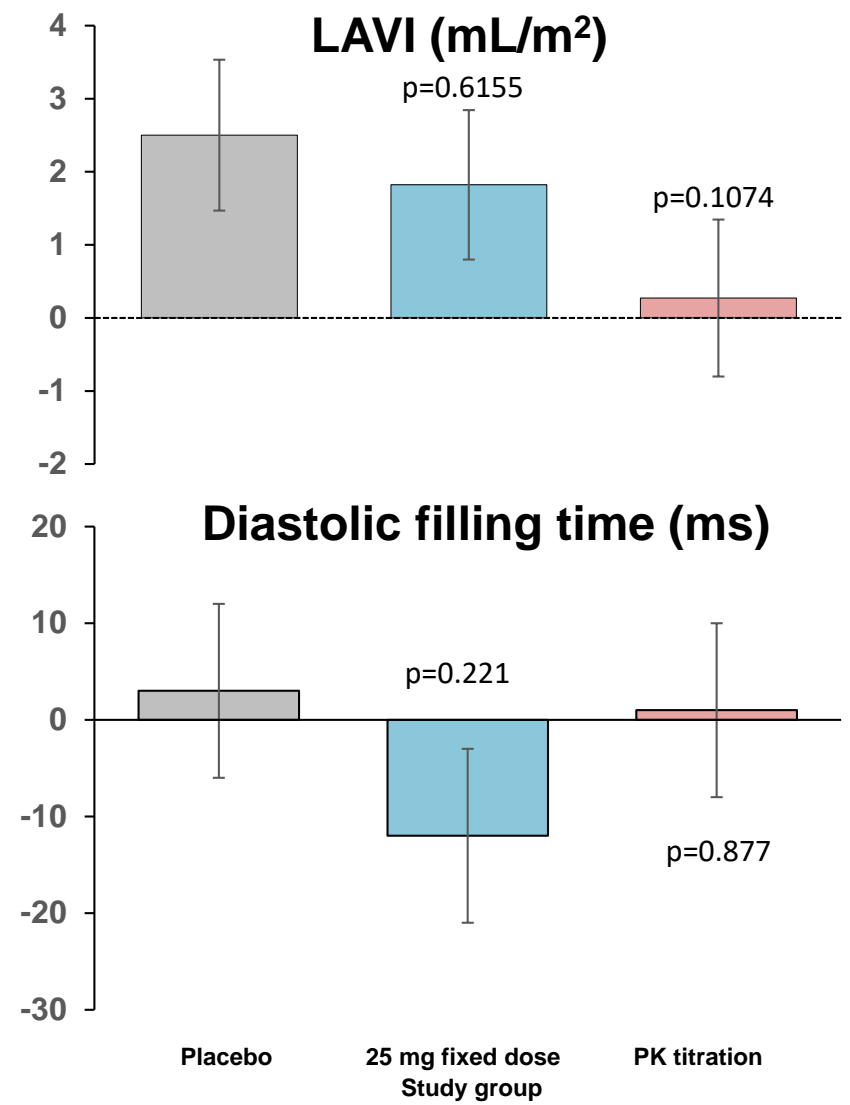
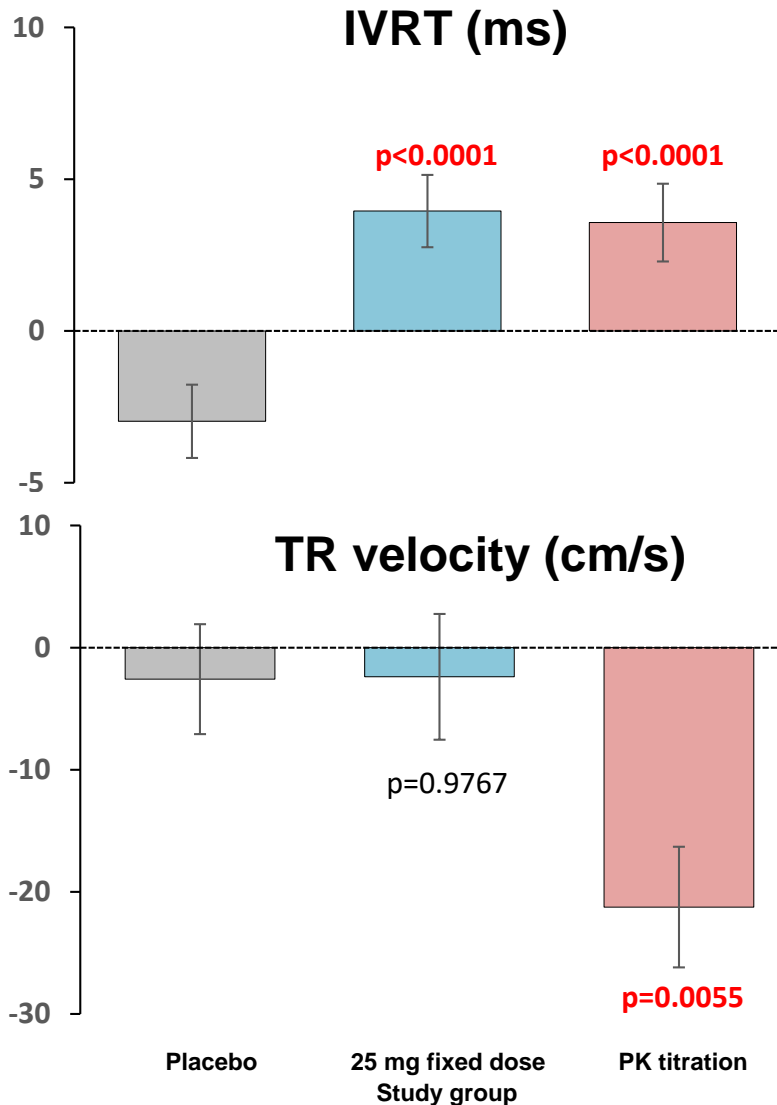
Placebo

25 mg fixed dose
Study group

PK titration

Effect of OM on diastolic function (cont'd)

Least squares mean (SE) changes from baseline to Week 20



Conclusions

- In patients with HFrEF who received omecamtiv mecarbil, a post-hoc analysis demonstrated:
 - Systolic ejection time increased, as previously reported
 - Diastolic filling time was not prolonged, diastolic parameters were stable
 - IVRT increased modestly, and pulmonary pressures (estimated by TRV) improved in the PK group
- Omecamtiv mecarbil improved measures of left ventricular systolic function and size, and did not appear to worsen diastolic function
- The impact of omecamtiv mecarbil on cardiovascular outcomes is being assessed in GALACTIC-HF

Thank you for the attention

- Thank you to the sponsors, the investigators and all of the patients

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