Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): Improved Contractility and Evolution of Ventricular Remodelling Through Time

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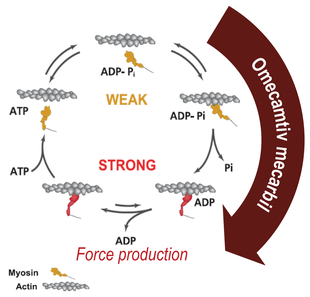
BACKGROUND

- Heart failure (HF)
  - A progressive disorder most commonly marked by cardiac systolic dysfunction
  - Has a natural history punctuated by frequent, recurrent hospitalization and ultimately death
- While several interventions reduce the rate of HF hospitalizations and improve mortality, mortality and morbidity still remain high.
- A target for treatment of systolic HF is to improve myocardial contractility.[1]
- Omecamtiv mecarbil (OM) is a novel therapy that increases cardiac contractility, increases stroke volume, decreases filling pressures, and improves ventricular volumes.[2]
- OM does so by increasing the left ventricular systolic ejection time, without increasing the rate of left ventricular pressure development or heart rate, and without noticeable effect upon myocardial oxygen uptake, blood pressure, or coronary blood flow.[3-7]

Mechanochemical Cycle of Myosin[4]



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

"More hands pulling on the rope"

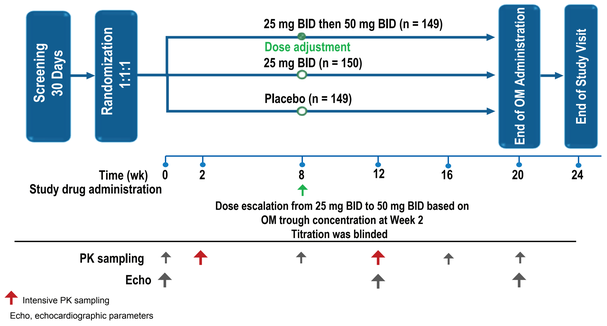
- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt_{max}
- No increase in MVO_2

ADP, adenosine diphosphate; ATP, adenosine triphosphate; MVO_2, myocardial oxygen consumption

COSMIC-HF

- The **C**hronic **O**ral **S**tudy of **M**yosin Activation to **I**ncrease **C**ontractility in **H**eart **F**ailure (COSMIC-HF; NCT01786512) tested the hypothesis that administration of oral OM for 20 weeks would result in effective and well-tolerated plasma concentrations that would:
  - Improve ventricular systolic function
  - Decrease ventricular dimensions
  - Reduce evidence of neurohormonal activation

COSMIC-HF Expansion Phase Study Design



OBJECTIVE

- As it is unknown whether pharmacologically increasing contractility is sufficient to produce favourable ventricular remodelling in patients with HF, we sought to determine the effect of OM vs. placebo on measures related to cardiac volumes and function

METHODS

- Patients (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: 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, patients from the OM PK titration group (n = 149) were compared with the placebo group (n = 149)

RESULTS

Baseline Patient Characteristics

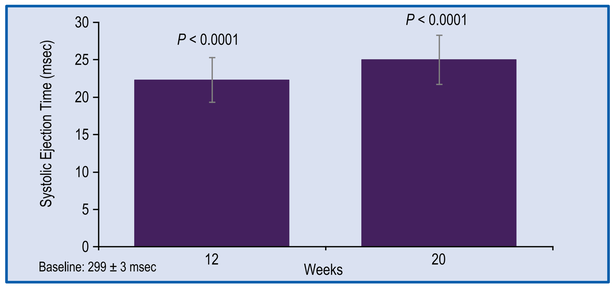
	Placebo (n = 149)	All PK Titration (n = 149*)
Demographics		
Age (years), mean (SD)	64 (10)	63 (12)
Male, %	80	84
White, %	91	94
Disease characteristics		
Ischemic heart disease, %	60	68
LVEF (%), mean (SD)	29 (7)	29 (7)
NYHA class II, %	70	72
NYHA class III, %	30	28
Persistent atrial fibrillation or flutter, %	22	16
Diabetes mellitus, %	41	37
Laboratory parameters		
Troponin I (ng/mL), median (Q1, Q3)	0.025 (0.016, 0.041)	0.022 (0.016, 0.042)
NT-proBNP (pg/mL), median (Q1, Q3)	1719 (699, 3242)	1719 (881, 3060)
eGFR (mL/min/1.73m^2), mean (SD)	65 (19)	65 (19)
Concomitant medications, %		
ACE inhibitors	71	65
ARBs	24	27
Beta-blockers	98	97
MRAs	59	63
Diuretics other than MRAs	84	90

*Includes 3 patients who did not receive OM

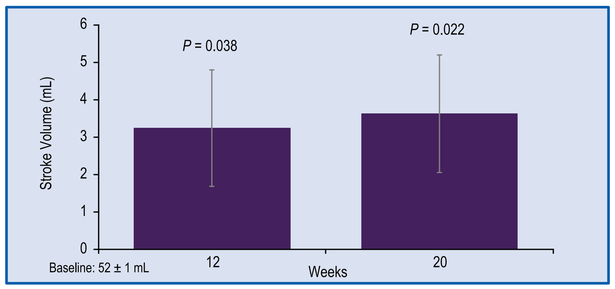
ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; MRA, mineralcorticoid receptor blocker; Q1, Q3, 1st and 3rd quartiles; SD, standard deviation

RESULTS

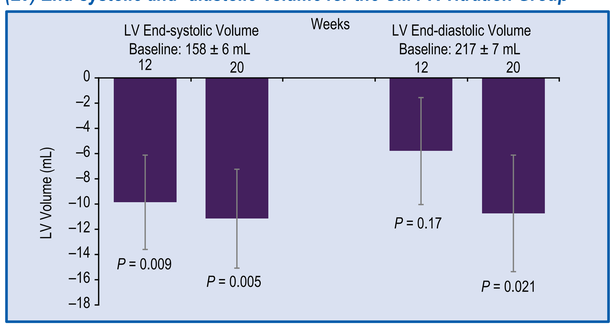
Placebo-corrected LS Mean (SE) Change from Baseline in Systolic Ejection Time for the OM PK Titration Group



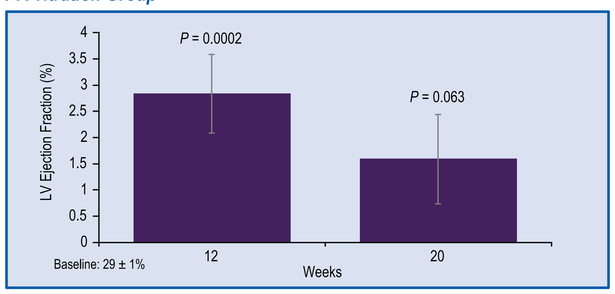
Placebo-corrected LS Mean (SE) Change from Baseline in Stroke Volume for the OM PK Titration Group



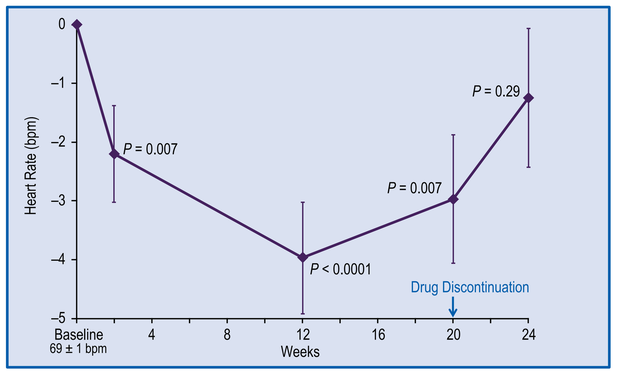
Placebo-corrected LS Mean (SE) Change from Baseline in Left Ventricular (LV) End-systolic and -diastolic Volume for the OM PK Titration Group



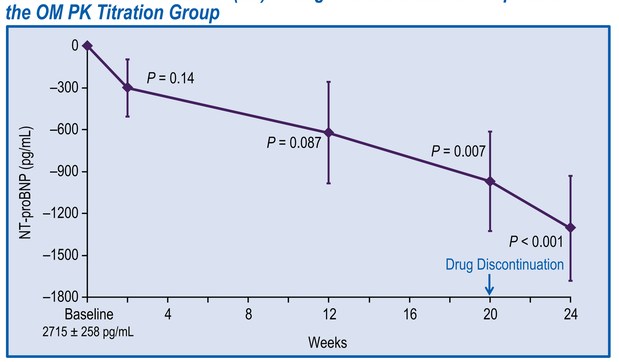
Placebo-corrected LS Mean (SE) Change from Baseline in LVEF for the OM PK Titration Group



Placebo-corrected LS Mean (SE) Change from Baseline in Heart Rate for the OM PK Titration Group



Placebo-corrected LS Mean (SE) Change from Baseline in NT-proBNP for the OM PK Titration Group



CONCLUSIONS

- These data from COSMIC-HF indicate OM produced a sustained increase in LV systolic function in patients with chronic HF with reduced ejection fraction.
- Decreases in diastolic volume and in NT-proBNP during treatment accumulated over time and suggest favourable ventricular remodelling and a progressive reduction in myocardial wall stress.
- The magnitude of cardiac effects observed in this trial may potentially translate into improvements in clinical outcomes.

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DISCLOSURES

John R. Teerlink: research grants from Amgen, Bayer, Cytokinetics, Mast Therapeutics, Novartis, Trevena; consultant to Amgen, Cytokinetics, Mast Therapeutics, Novartis, Trevena; **G. Michael Felker**: research grants from Amgen, Roche Diagnostics, Novartis, Otsuka, NHLBI; consultant for Amgen, Novartis, Roche Diagnostics, Singulex, Trevena, Celladon, Bristol Meyers Squibb, Merck, Medtronic; **John J.V. McMurray**: employer has been paid by Cytokinetics/Amgen; advisory board: Cytokinetics, Amgen; **Scott D. Solomon**: none; **Maria Laura Monsalvo, James Johnston, Narimon Honarpour**: employees of Amgen, Inc; **Fady I. Malik**: employee of Cytokinetics, Inc.

This study was funded by Amgen, Inc in collaboration with Cytokinetics, Inc. Amgen provided editorial support for the creation of this poster.