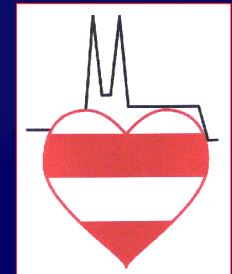
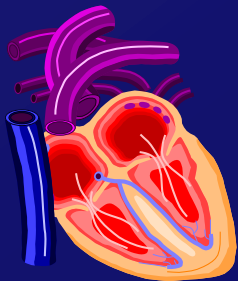


# STUDIE COSMIC

L. Špinarová

BRNO



**Chronic Oral Study of Myosin  
Activation to Increase Contractility  
in Heart Failure (COSMIC-HF):  
Results from a Double-blind, Randomized,  
Placebo-controlled, Multicenter Study**

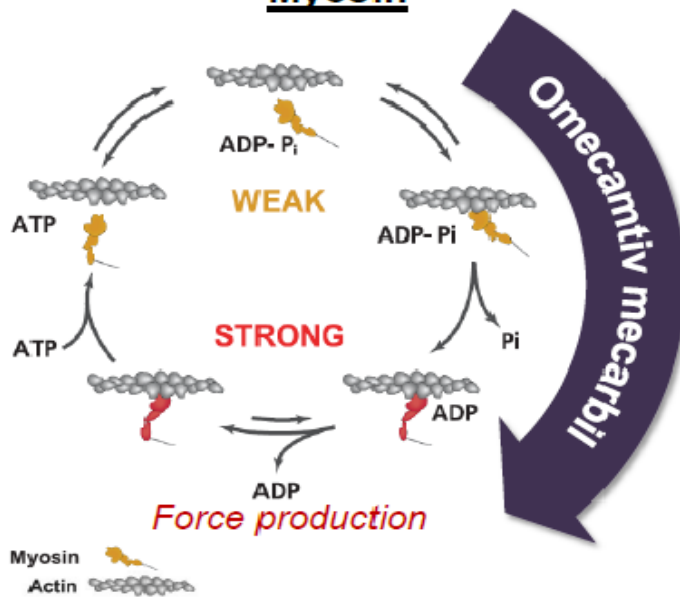
**John R. Teerlink,<sup>1</sup> G. Michael Felker,<sup>2</sup> John J. V. McMurray,<sup>3</sup>  
Scott D. Solomon,<sup>4</sup> Maria Laura Monsalvo,<sup>5</sup> Jason Legg,<sup>5</sup>  
Fady I. Malik,<sup>6</sup> Narimon Honarpour<sup>5</sup>  
for the COSMIC-HF Investigators**

# Mechanismus účinku

COSMIC-HF

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

### Mechanochemical Cycle of Myosin



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

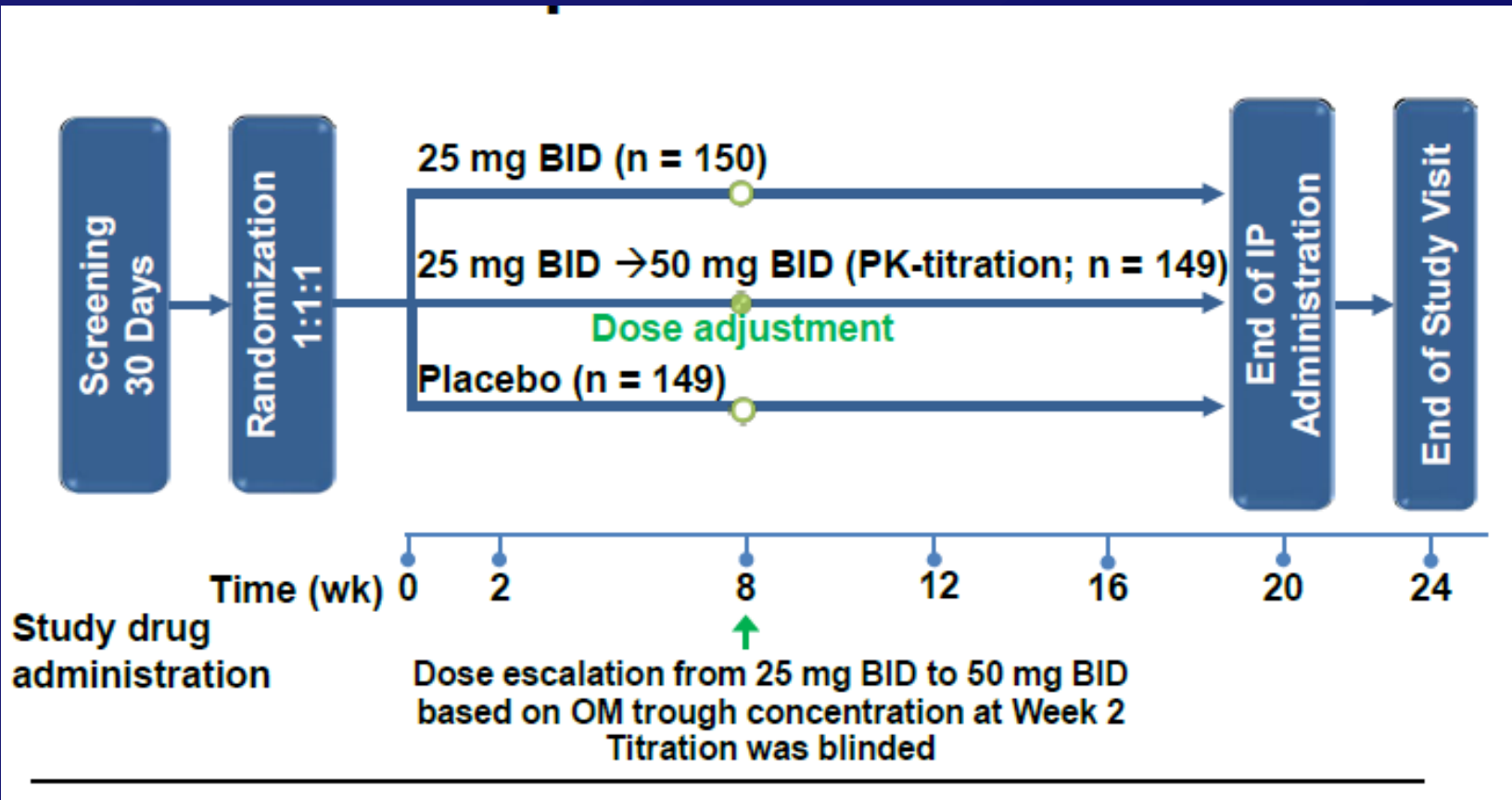
No change in  $dP/dt_{max}$

No increase in  $MVO_2$

# CÍLE STUDIE

- To evaluate the safety and tolerability of the oral formulation
- To measure changes in SET, stroke volume, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), and heart rate (HR) over 20 weeks of oral dosing
- To evaluate the effect over 20 weeks of oral dosing on N-terminal pro-B-type natriuretic peptide (NT-proBNP)

# DESIGN STUDIE



# VSTUPNÍ KRITÉRIA

COSMIC-HF

## Key Inclusion and Exclusion Criteria

- **Key Inclusion Criteria**

- $\geq 18$  and  $\leq 85$  years of age
- History of chronic HF
- Treated with stable, optimal heart failure therapy
- NYHA class II or III
- LVEF  $\leq 40\%$
- NT-proBNP  $\geq 200$  pg/mL ( $\geq 1200$  pg/mL if AFib at screening)

- **Key Exclusion Criteria**

- NYHA class IV
- Severe uncorrected valvular heart disease
- Acute MI, unstable angina, or persistent angina at rest within 30 days prior to randomization
- Systolic BP  $> 160$  mmHg or  $< 90$  mmHg, or diastolic BP  $> 90$  mmHg, or HR  $> 110$  bpm or HR  $< 50$  bpm at screening
- eGFR  $< 30$  mL/min/1.73 m<sup>2</sup> at screening

# VSTUPNÍ CHARAKTERISTIKA

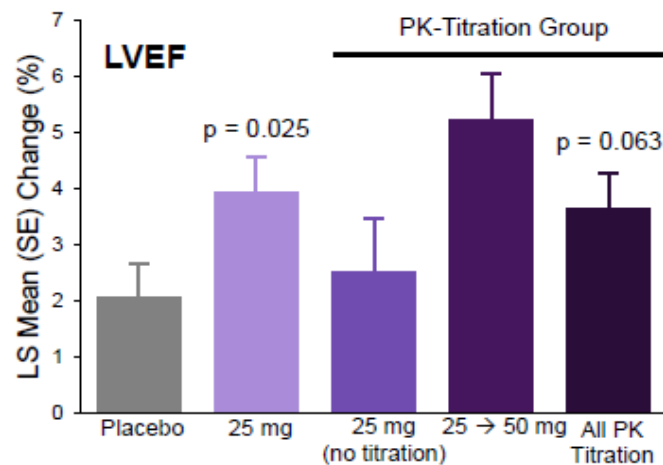
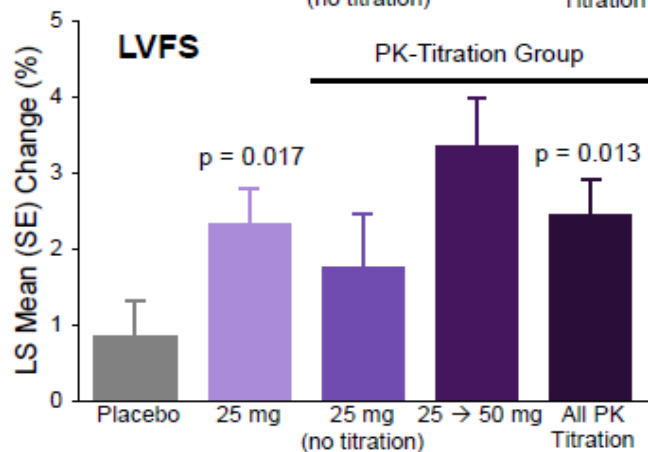
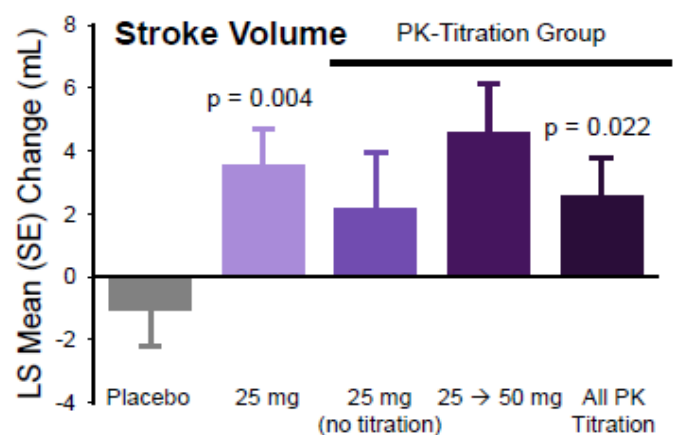
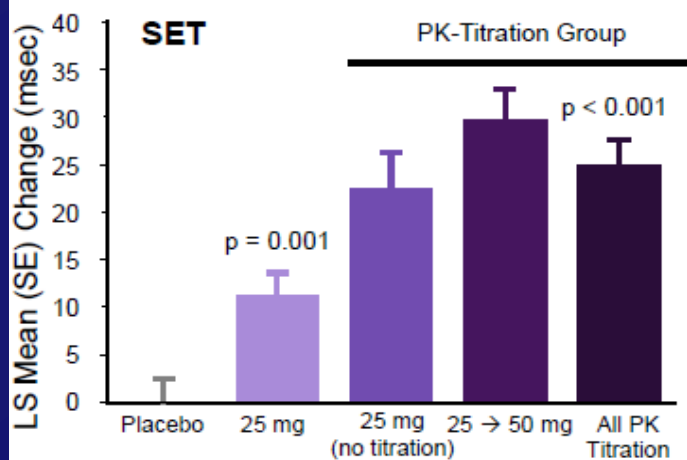
448 Patients Enrolled	Placebo (n = 149)	OM 25 mg BID (n = 150)	All PK Titration (n = 149)
<b>Demographics</b>			
Age (years), mean (SD)	64 (10)	63 (10)	63 (12)
Male, %	80	85	84
White, %	91	95	94
<b>Disease characteristics</b>			
Ischemic heart disease, %	60	65	67
LVEF (%), mean (SD)	29 (7)	29 (8)	29 (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

# VSTUPNÍ CHARAKTERISTIKA

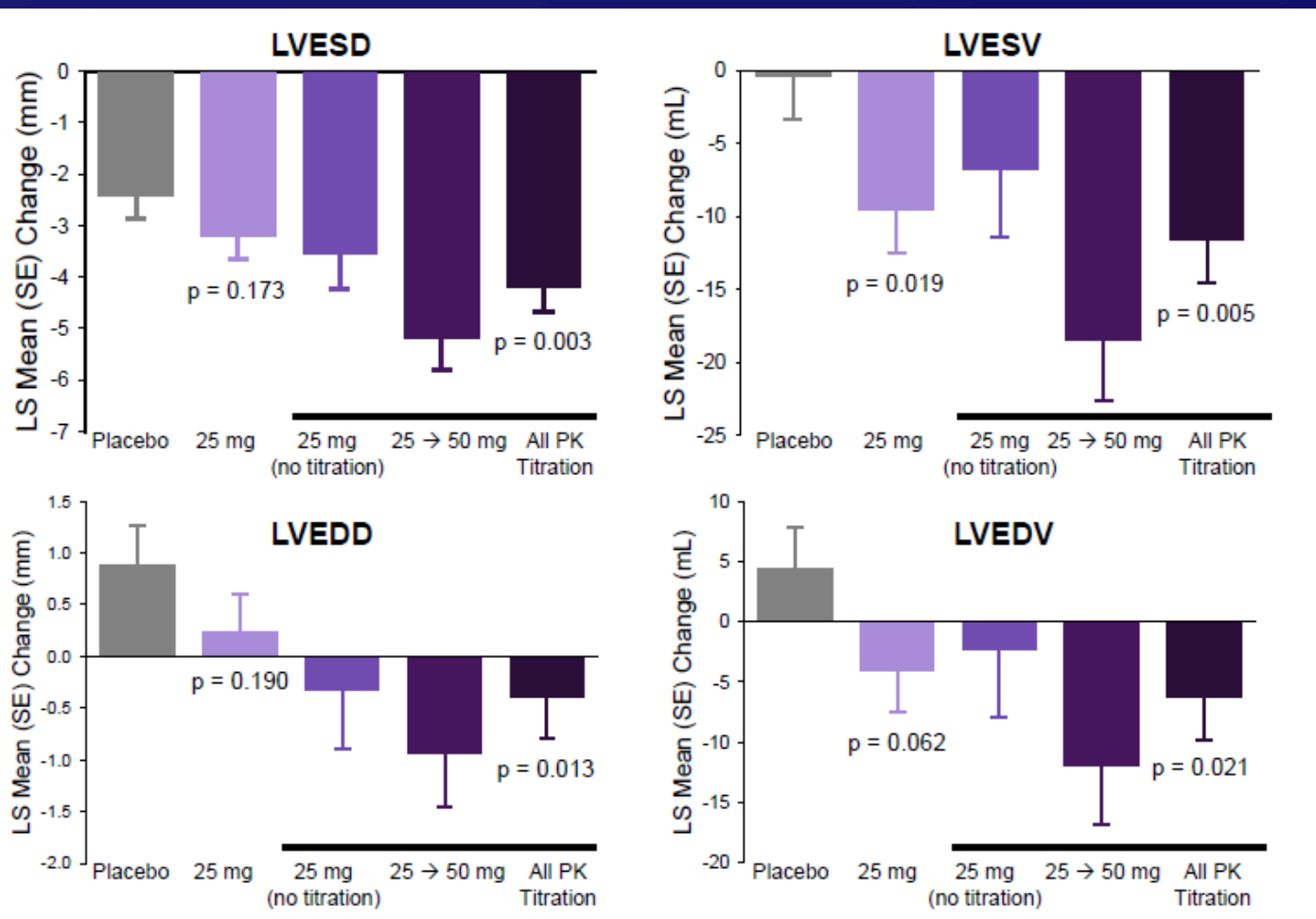
	Placebo (n = 149)	OM 25 mg BID (n = 150)	All PK Titration (n = 149)
<b>Laboratory parameters</b>			
Troponin I (ng/mL), median (Q1, Q3)	0.025 (0.016, 0.041)	0.022 (0.016, 0.039)	0.022 (0.016, 0.042)
NT-proBNP (pg/mL), median (Q1, Q3)	1719 (699, 3242)	1538 (634, 3427)	1719 (881, 3060)
eGFR (mL/min/1.73m <sup>2</sup> ), mean (SD)	65 (19)	63 (19)	65 (19)
<b>Concomitant medications, %</b>			
ACE inhibitors	71	69	65
ARBs	24	28	27
Beta-blockers	98	97	97
MRAs	59	58	63
Diuretics other than MRAs	84	85	90



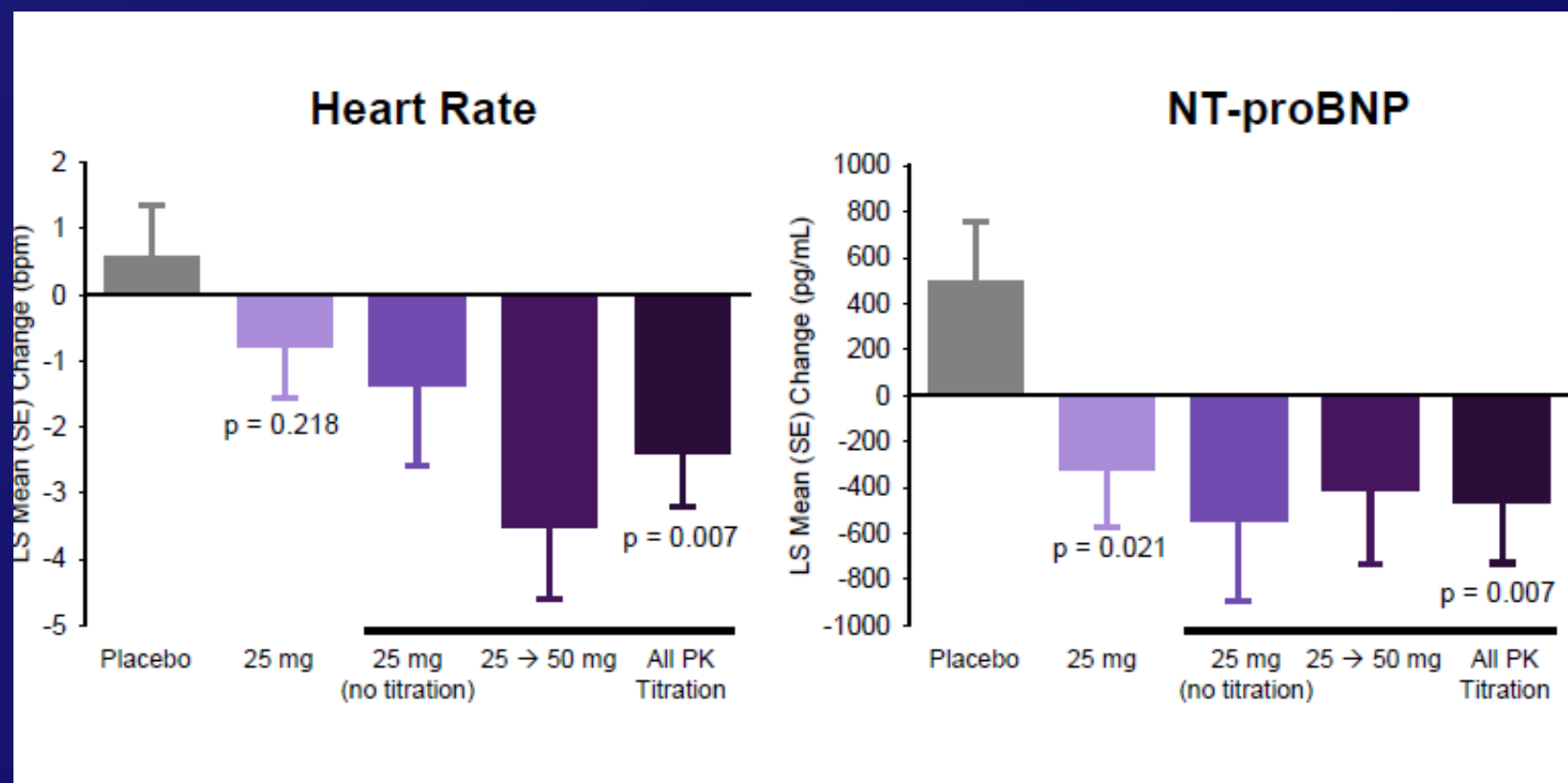
# VÝSLEDKY



# VÝSLEDKY



# VÝSLEDKY



# TROPONIN

Troponin I (ng/mL)	Placebo (n = 149)	25 mg (n = 150)	PK-guided titration arm			Pooled OM (n = 296)
			25 mg (n = 58)	50 mg (n = 78)	All PK Titration (n = 146) <sup>a</sup>	
	<b>Baseline</b>					
Median	0.025	0.022	0.024	0.021	0.025	0.022
Q1, Q3	0.016, 0.041	0.016, 0.039	0.016, 0.034	0.016, 0.046	0.016, 0.042	0.016, 0.040
	<b>Change to Week 20</b>					
Median	0.000	0.001	0.006	0.007	0.006	0.004
Q1, Q3	-0.007, 0.004	0.000, 0.012	0.000, 0.022	0.000, 0.024	0.000, 0.024	0.000, 0.019
	<b>Change to Week 24</b>					
Median	0.000	0.000	0.001	0.000	0.000	0.000
Q1, Q3	-0.006, 0.008	-0.002, 0.009	-0.002, 0.016	-0.005, 0.005	-0.003, 0.010	-0.003, 0.009

# KLINICKÉ PŘÍHODY

n (%)	Placebo (n = 149)	25 mg (n = 150)	PK-guided titration arm			Pooled OM (n = 296)
			25 mg (n = 58)	50 mg (n = 78)	All PK Titration (n = 146) <sup>a</sup>	
<b>Hospitalization</b>	24 (16)	24 (16)	10 (17)	11 (14)	26 (18)	50 (17)
Heart failure	11 (7)	9 (6)	4 (7)	5 (6)	10 (7)	19 (6)
MI	1 (1)	-	-	-	1 (1)	1 (< 1)
Unstable angina	-	1 (1)	-	-	-	1 (< 1)
Chest pain (non-MI/UA)	1 (1)	2 (1)	2 (3)	-	2 (1)	4 (1)
Other categories	15 (10)	14 (9)	5 (9)	7 (9)	15 (10)	29 (10)
<b>MI (nonfatal)</b>	1 (1)	-	-	-	-	-
Investigator-reported	1 (1)	-	-	-	-	-
CEC-reported	-	-	-	-	-	-
Total MI	2 (1)	-	-	-	1 (1)	1 (< 1)
<b>Death</b>	4 (3)	1 (1)	1 (2)	1 (1)	3 (2)	4 (1)
CV Death	2 (1)	1 (1)	1 (2)	1 (1)	2 (1)	3 (1)

# NEŽÁDOUCÍ ÚČINKY

n (%)	Placebo (n = 149)	25 mg (n = 150)	PK-guided titration arm			Pooled OM (n = 296)
			25 mg (n = 58)	50 mg (n = 78)	All PK Titration (n = 146) <sup>a</sup>	
<b>Any AE</b>	91 (61)	92 (61)	35 (60)	53 (68)	95 (65)	187 (63)
<b>Most-common<sup>b</sup></b>						
Dyspnea	8 (5)	11 (7)	5 (9)	6 (8)	13 (9)	24 (8)
Fatigue	4 (3)	14 (9)	5 (9)	3 (4)	9 (6)	23 (8)
Dizziness	6 (4)	8 (5)	5 (9)	4 (5)	10 (7)	18 (6)
Cardiac failure	13 (9)	5 (3)	2 (3)	5 (6)	8 (5)	13 (4)
Nasopharyngitis	5 (3)	8 (5)	2 (3)	3 (4)	5 (3)	13 (4)
<b>Leading to study discontinuation</b>	12 (8)	8 (5)	5 (9)	1 (1)	12 (8)	20 (7)
<b>SAEs</b>	30 (20)	35 (24)	12 (21)	15 (19)	32 (22)	68 (23)

# KARDIÁLNÍ ZÁVAŽNÉ NEŽÁDOUCÍ ÚČINKY

n (%)	Placebo (n = 149)	25 mg (n = 150)	PK-guided titration arm			Pooled OM (n = 296)
			25 mg (n = 58)	50 mg (n = 78)	All PK Titration (n = 146) <sup>a</sup>	
<b>Cardiac SAEs</b>	19 (13)	18 (12)	7 (12)	7 (9)	17 (12)	35 (12)
Cardiac failure	4 (3)	3 (2)	1 (2)	3 (4)	5 (3)	8 (3)
Cardiac failure acute	1 (1)	3 (2)	1 (2)	2 (3)	3 (2)	6 (2)
Cardiac failure congestive	3 (2)	3 (2)	2 (3)	-	3 (2)	6 (2)
Angina pectoris	-	3 (2)	1 (2)	-	1 (1)	4 (1)
Ventricular tachycardia	1 (1)	2 (1)	1 (2)	-	1 (1)	3 (1)

# ZÁVĚR

- **Efficacy**

- Improvements in SET, stroke volume, and LVEF
- Decreases in cardiac dimensions and volumes
- Decreases in HR and NT-proBNP

- **Safety**

- Overall SAE profile and tolerability similar to placebo
- Small increase in troponin I without imbalance in cardiac adverse events