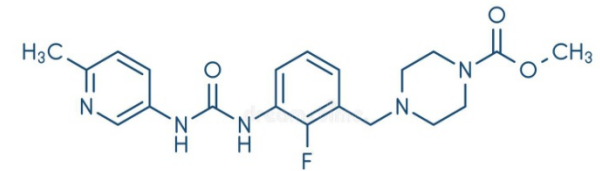




ΔΗΜΟΚΡΙΤΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΡΑΚΗΣ
DEMOCRITUS UNIVERSITY OF THRACE

GALACTIC HF



omecamtiv mecarbil

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure

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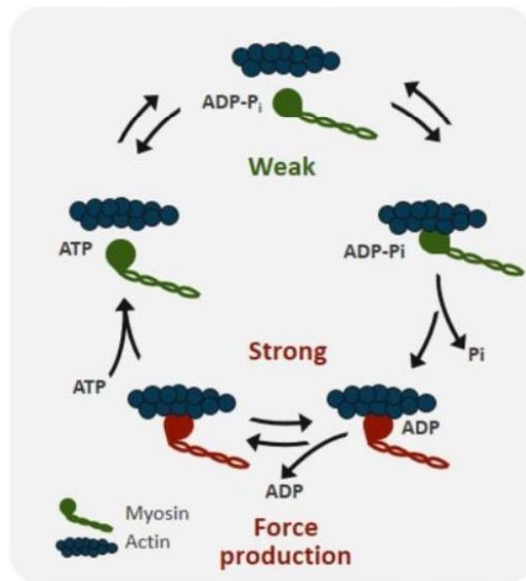


No conflict of interests

Omecamtiv Mecarbil MOA

Novel Selective Cardiac Myosin Activator

Mechanochemical Cycle of Myosin



Omecamtiv mecarbil 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

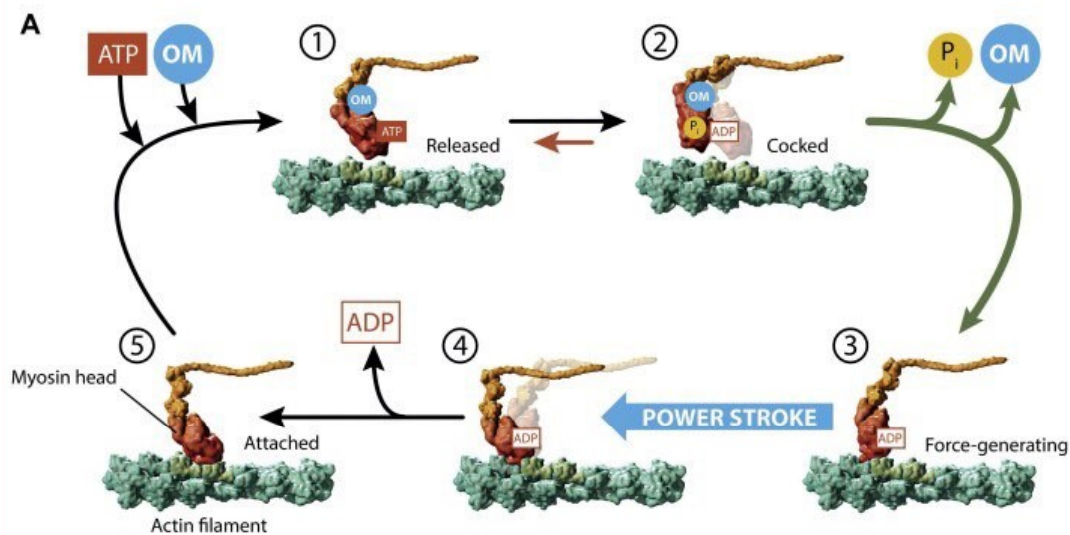
Increases stroke volume

No increase in myocyte calcium

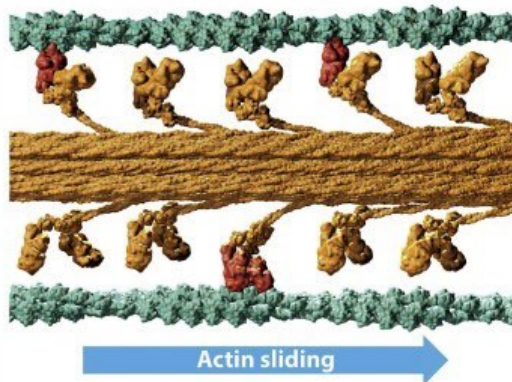
No change in dp/dt_{max}

No increase in MVO_2

CENTRAL ILLUSTRATION: Mechanism of Action of Omecamtiv Mecarbil



B BEFORE OMECANTIV MECARBIL



C AFTER OMECANTIV MECARBIL

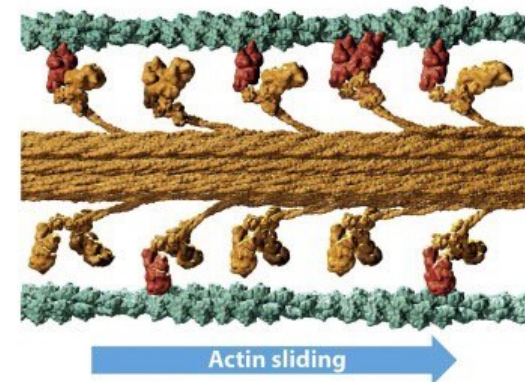


TABLE 2 Selected Clinical Studies With Omecamtiv Mecarbil

Trial (Phase), Year(s) (Ref. #)	Subjects	Dose (Route)	Design	Endpoints	Major Outcomes
NCT01380223 (I), 2005-2006 (10)	Young, healthy, 85% white, male subjects in 4 successive cohorts of 8 (n = 34)	0.005-1.0 mg/kg/h for 6 h (IV)	Double-blind, placebo-controlled, dose-escalating, crossover, single-center trial	1. Maximum infusion dose tolerated in ≥ 8 subjects for 6 h. 2. Safety, tolerability, pharmacokinetics, pharmacodynamics.	1. Maximum tolerated infusion 0.5 mg/kg/h. 2. Dose-dependent linear increase in SET ($r^2 = 0.99$), with increased LVEF, FS, and SV. $t_{1/2} = 17.1$ -21.0 h. Cardiac ischemia in some participants at plasma concentrations $>1,200$ ng/mL.
NCT00624442 (II), 2007-2009 (11)	Stable HF, 87% male, 64% ischemic, HFrEF, LVEF $\leq 40\%$ or LVEF $\leq 30\%$ in cohort 4 (n = 45)	Loading 0.125-1.0 mg/kg/h; Maintenance 0.0625-0.5 mg/kg/h (IV)	Double-blind, placebo-controlled, dose-escalating, crossover, multicenter international trial	1. Safety and tolerability for 2, 24, and 72 h. 2. Establish tolerated range of pharmacologically active plasma concentrations.	1. Cardiac ischemia at plasma concentrations $>1,300$ ng/mL. 2. Dose-dependent increases in SET, FS, LVEF, SV, and CO; decreased HR, QTc, LVESV, LVEDV, and standing SBP and DBP.
NCT00682565 (II), 2008 (13)	Stable HF, 80% male, ischemic HFrEF with LVEF $\leq 35\%$ and angina (n = 94)	Loading 24-48 mg/h for 2 h, then maintenance 6-11 mg/h for 18 h (IV)	Double-blind, placebo-controlled, randomized, multicenter study	1. Safety and tolerability exercise during infusion; proportion stopping ETT due to angina at earlier stage than baseline. 2. Duration of exercise, angina, ECG changes.	1. Only 1 patient (receiving placebo) stopped ETT early due to angina. 2. No statistical difference in time to angina, exercise duration, or ischemic ECG changes.
NCT01786512 ATOMIC-AHF (Iib), 2013-2015 (14)	Acute HFrEF, 77% male, 88% white, 62% ischemic, with LVEF $\leq 40\%$, dyspnea and elevated BNP (n = 613)	Loading 7.5-20 mg/h for 4 h, then maintenance 1.5-4 mg/h for 44 h (IV)	Double-blind, placebo-controlled, dose-escalating, randomized international multicenter trial	1. Dyspnea relief by 7-point Likert-type scale at 6, 24, and 48 h without worsening HF or death. 2. Safety and tolerability, biomarkers, hospital length of stay, 30-day morbidity, and mortality.	1. No benefit for dyspnea relief at 6, 24, or 48 h vs. pooled placebo; improved dyspnea in third cohort vs. paired placebo. 2. No benefit for 30-day death or worsening HF, length of stay, or NT-proBNP; increased SET and SBP; decreased HR and LVESD.
NCT01300013 COSMIC-HF (Iib), 2011-2015 (15)	Expansion phase: stable HF, 83% male, $>90\%$ white, HFrEF with LVEF $\leq 40\%$ and elevated NT-proBNP (n = 448)	25 mg twice-daily or PK-guided titration to 50 mg twice daily (oral)	Double-blind, placebo-controlled, dose-escalating, randomized, multicenter, international trial	1. Pharmacokinetics of modified release dosing over 20 weeks. 2. Safety and tolerability, echocardiographic, and biomarker changes over 20 weeks.	1. Modified release allowed titration to 50 mg twice daily in 60% of patients. 2. Increased SET and SV and decreased HR, LVESV, LVEDV, and NT-proBNP; asymptomatic small increased troponin at 20 weeks: 0.001 ng/mL with 25 mg and 0.006 ng/mL with 25-50 mg twice daily.

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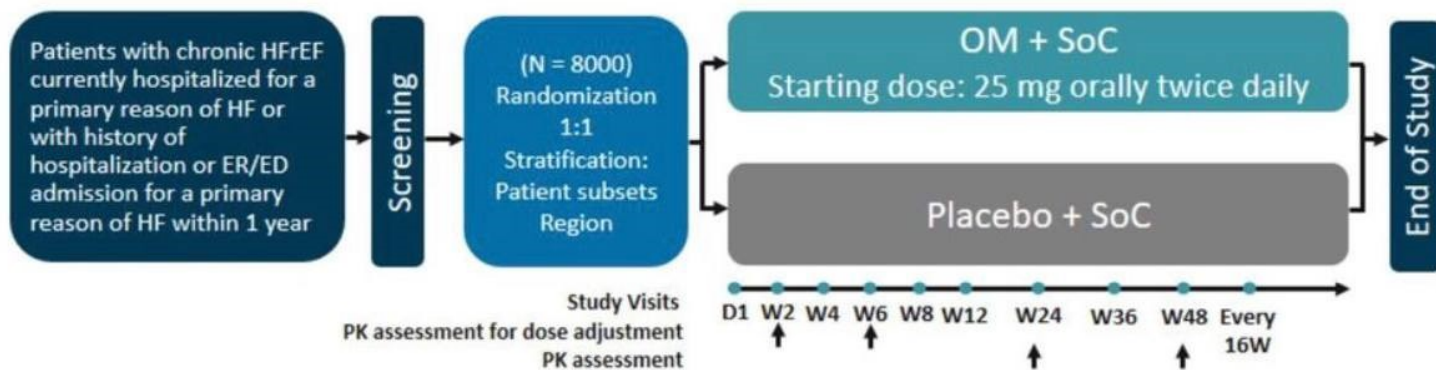
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**Cardiac Myosin Activation with Omecamtiv Mecarbil
in Systolic Heart Failure**

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GALACTIC-HF Study Design



- Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter, CV outcomes study for oral OM in patients with HFrEF
 - Approximately 25% or more of the total planned enrollment will include patients who are hospitalized at randomization
 - Enrollment of patients with AF will be limited to 20% of each enrollment setting

INCLUSION CRITERIA

- *Patients 18-85 years of age with chronic HF symptoms*
- *New York Heart Association class II, III, or IV symptoms*
- *Left ventricular EF (LVEF) $\leq 35\%$*
- *N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 400 pg/ml (AF ≥ 1200 pg/ml)*
- *BNP ≥ 125 pg/ml (AF ≥ 375 pg/ml)*
- *Guidelines-based therapy for HF*
- *HHF or ED visit within 1 year before screening*

EXCLUSION CRITERIA

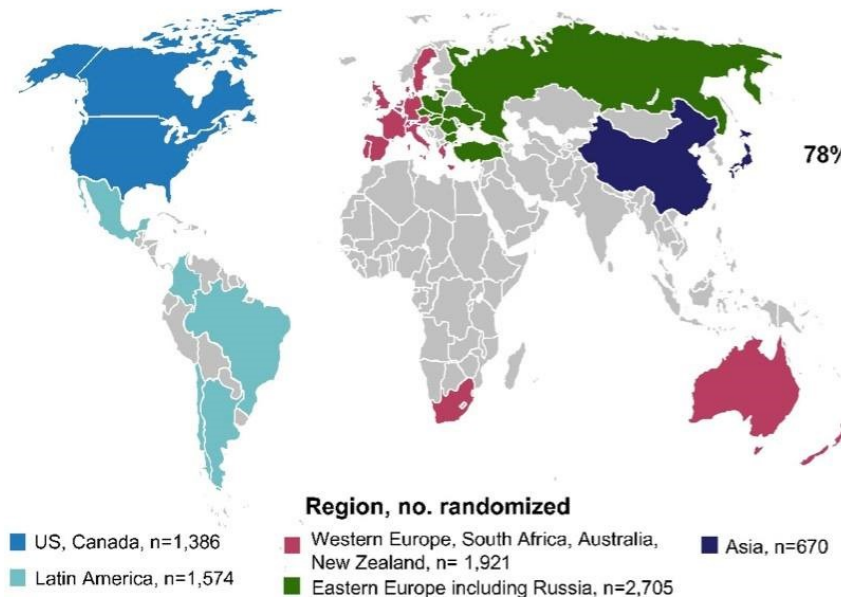
- *Hemodynamic instability requiring mechanical support or intravenous medication (within last 12 hours before randomization)*
- *Systolic blood pressure <85 mm Hg*
- *Estimated glomerular filtration rate <20 ml/min/1.73 m²*
- *Recent acute coronary syndrome or cardiovascular procedure 3 months before triage*

CENTRAL ILLUSTRATION: Baseline Characteristics of GALACTIC-HF, Phase 3 Trial of Omecamtiv Mecarbil in Patients With HFrEF

GALACTIC-HF: Multicenter, randomized, double-blind, placebo-controlled, event-driven trial

- Assess effects of omecamtiv mecarbil, a novel, selective cardiac myosin activator, on clinical outcomes in both inpatients and outpatients with HFrEF
- *Primary efficacy outcome:* Time to CV death or HF event, whichever occurs first

Enrolled 8,256 Patients With HFrEF



Baseline Characteristics

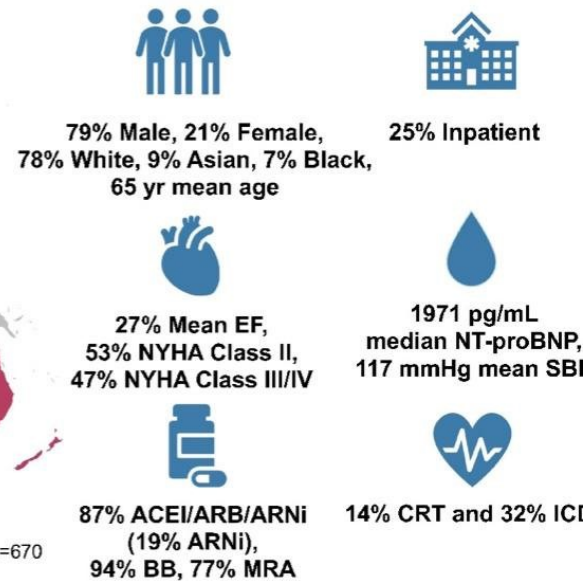
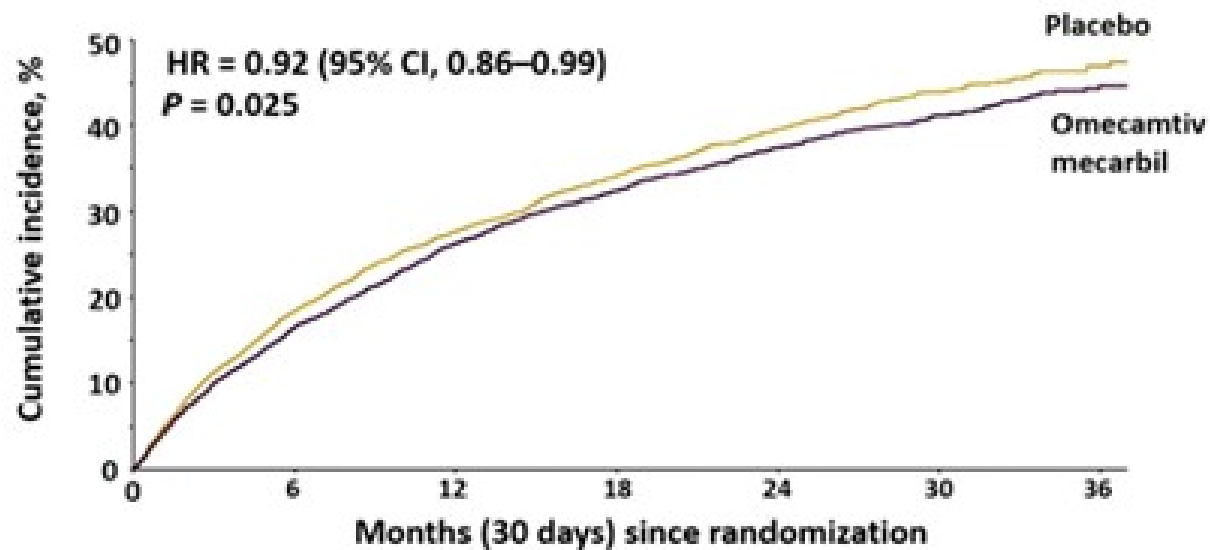


Table 2. Primary and Secondary Cardiovascular Outcomes.*

Variable	Omecamtiv Mecarbil (N=4120)		Placebo (N=4112)		Hazard Ratio or Difference (95% CI)†	P Value
	Value	Events	Value	Events		
		<i>no./100 patient-yr</i>		<i>no./100 patient-yr</i>		
Primary composite outcome — no. (%)‡	1523 (37.0)	24.2	1607 (39.1)	26.3	0.92 (0.86 to 0.99)	0.03
Cardiovascular death as first event	346 (8.4)		371 (9.0)			
Hospitalization for heart failure as first event	1107 (26.9)		1133 (27.6)			
Urgent outpatient visit for heart failure as first event	70 (1.7)		103 (2.5)			
Secondary outcomes						
Cardiovascular death — no. (%)	808 (19.6)	10.9	798 (19.4)	10.8	1.01 (0.92 to 1.11)	0.86§
Change in KCCQ total symptom score at wk 24						0.03§
Inpatients	23.7±0.7	NA	21.2±0.7	NA	2.5 (0.5 to 4.5)	
Outpatients	5.8±0.3	NA	6.3±0.3	NA	-0.5 (-1.4 to 0.5)	
First hospitalization for heart failure — no. (%)	1142 (27.7)	18.0	1179 (28.7)	19.1	0.95 (0.87 to 1.03)	NA
Death from any cause — no. (%)	1067 (25.9)	14.4	1065 (25.9)	14.4	1.00 (0.92 to 1.09)	NA
Exploratory outcome						
Heart-failure event — no. (%)	1177 (28.6)	18.7	1236 (30.1)	20.3	0.93 (0.86 to 1.00)	NA

Primary Composite Endpoint

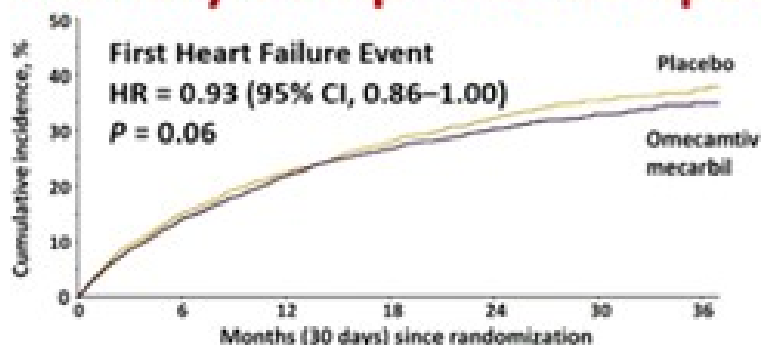
Time to First Heart Failure Event or Cardiovascular Death



Patients at risk, n

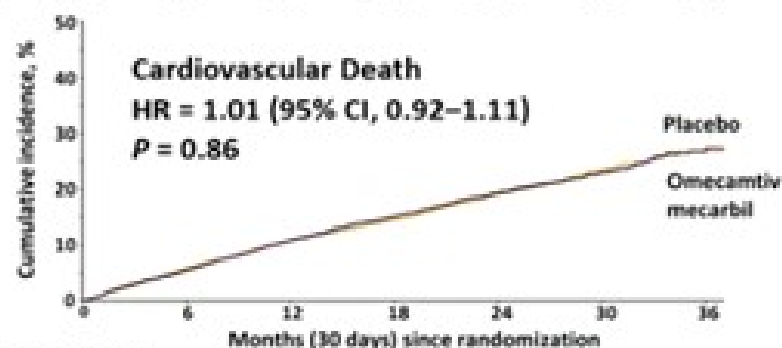
Placebo	4112	3310	2889	2102	1349	647	141
Omecamtiv mecarbil	4120	3391	2953	2158	1430	700	164

Primary Composite Components and KCCQ TSS



Patients at risk, n

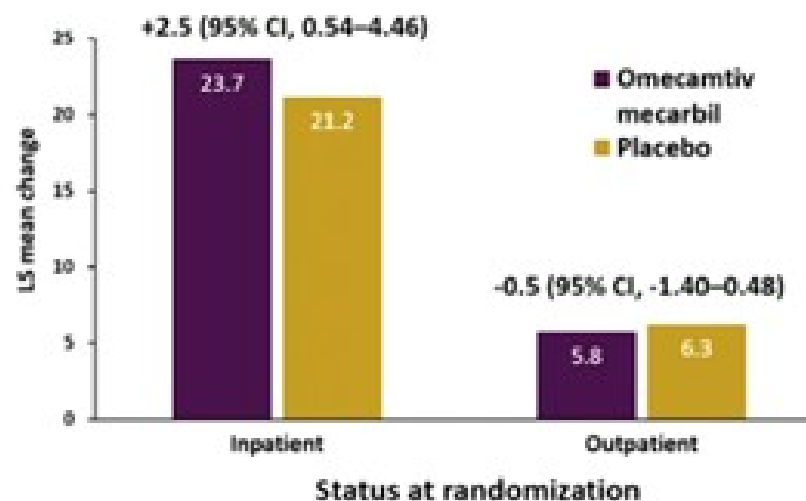
	0	6	12	18	24	30	36
Placebo	4112	3309	2889	2102	1348	647	141
OM	4120	3391	2953	2156	1430	699	164

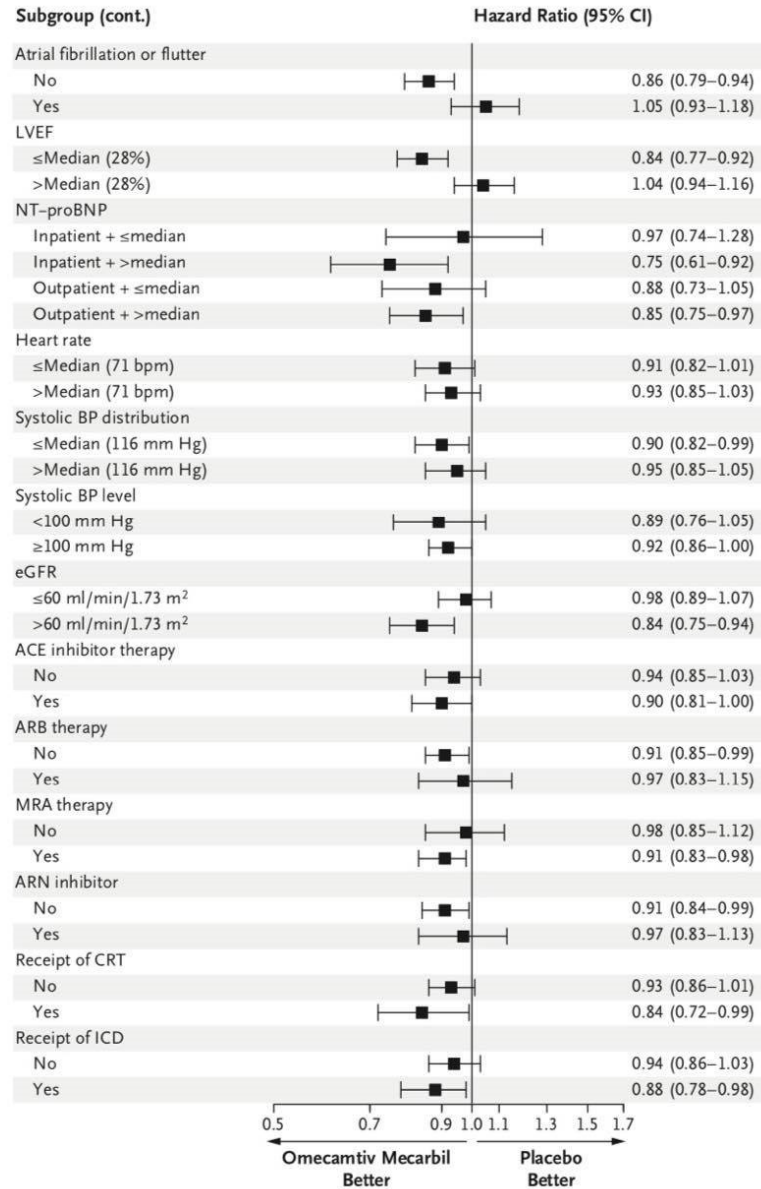
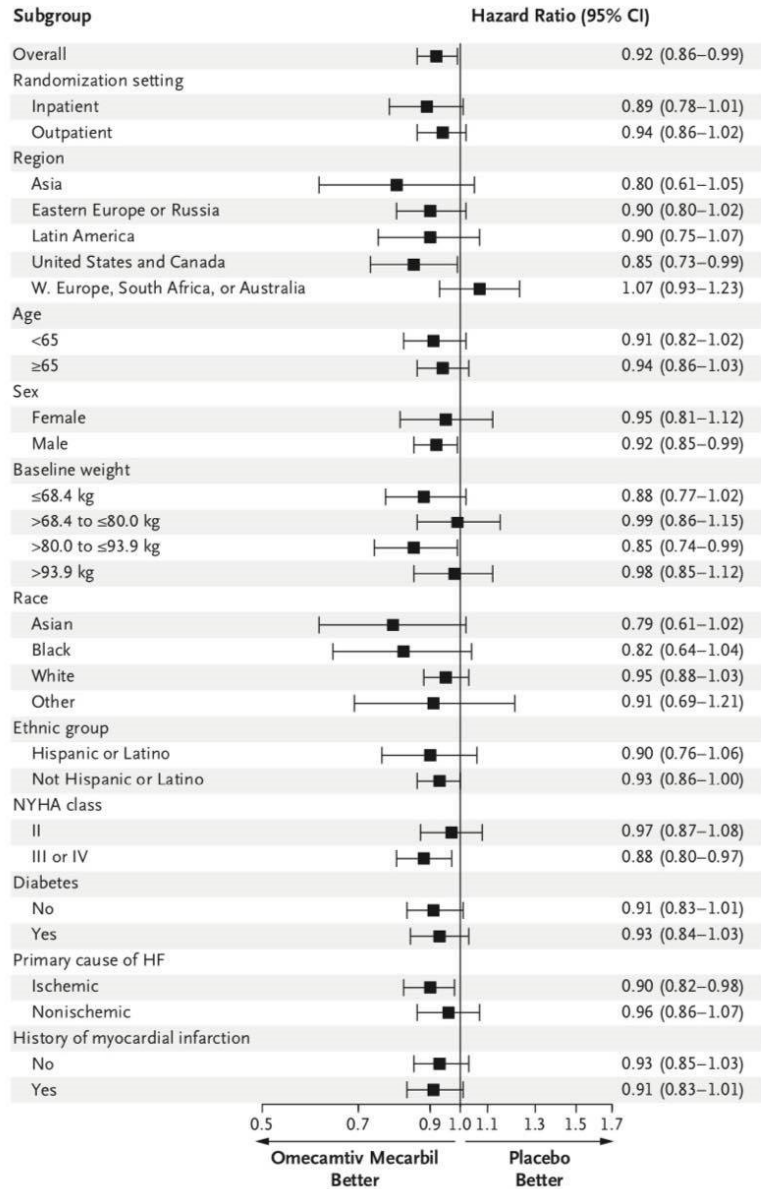


Patients at risk, n

	0	6	12	18	24	30	36
Placebo	4112	3821	3560	2722	1788	885	201
OM	4120	3838	3556	2710	1838	903	224

**Change in Kansas City Cardiomyopathy Questionnaire
Total Symptom Score from Baseline to Week 24**
Joint test P = 0.028





Primary Outcome: Subgroup Results

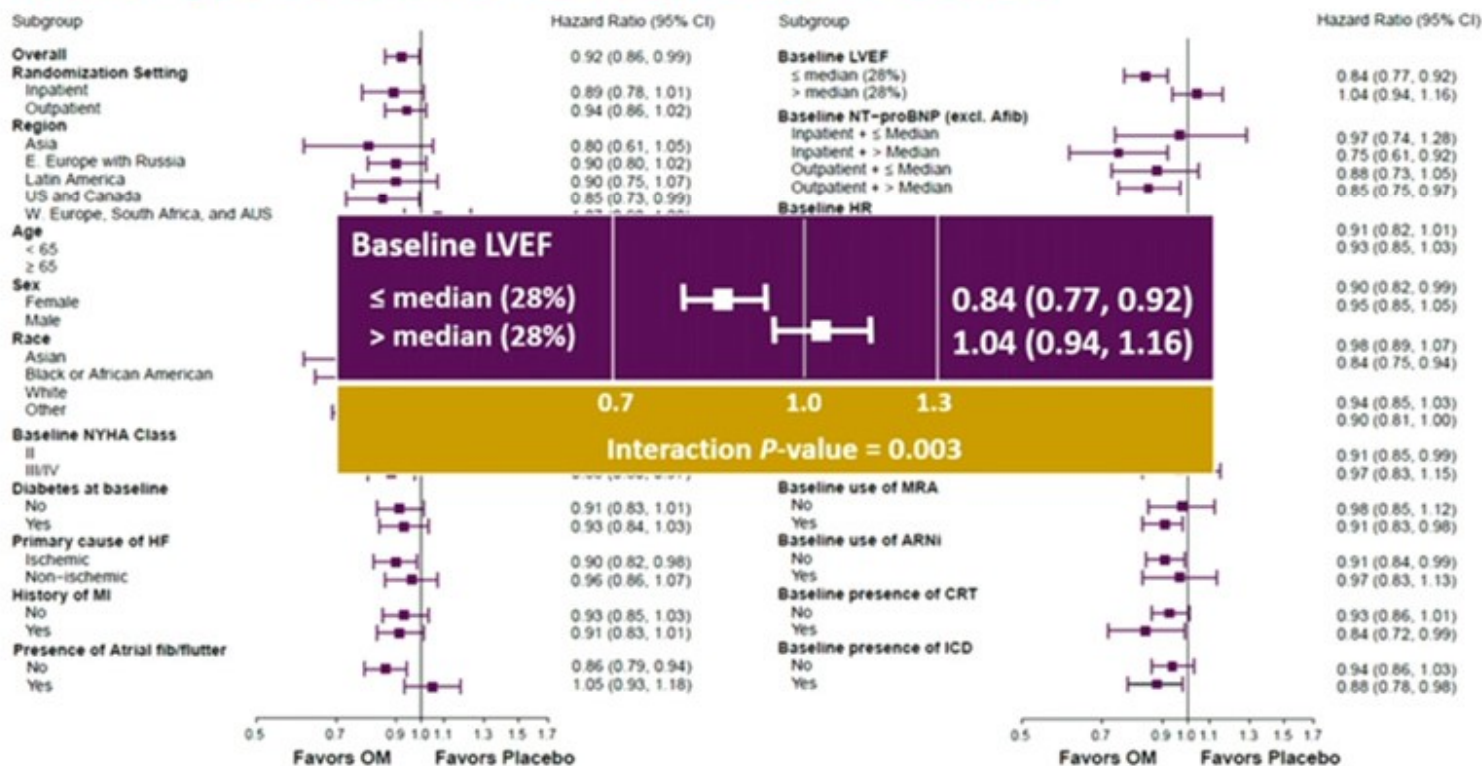
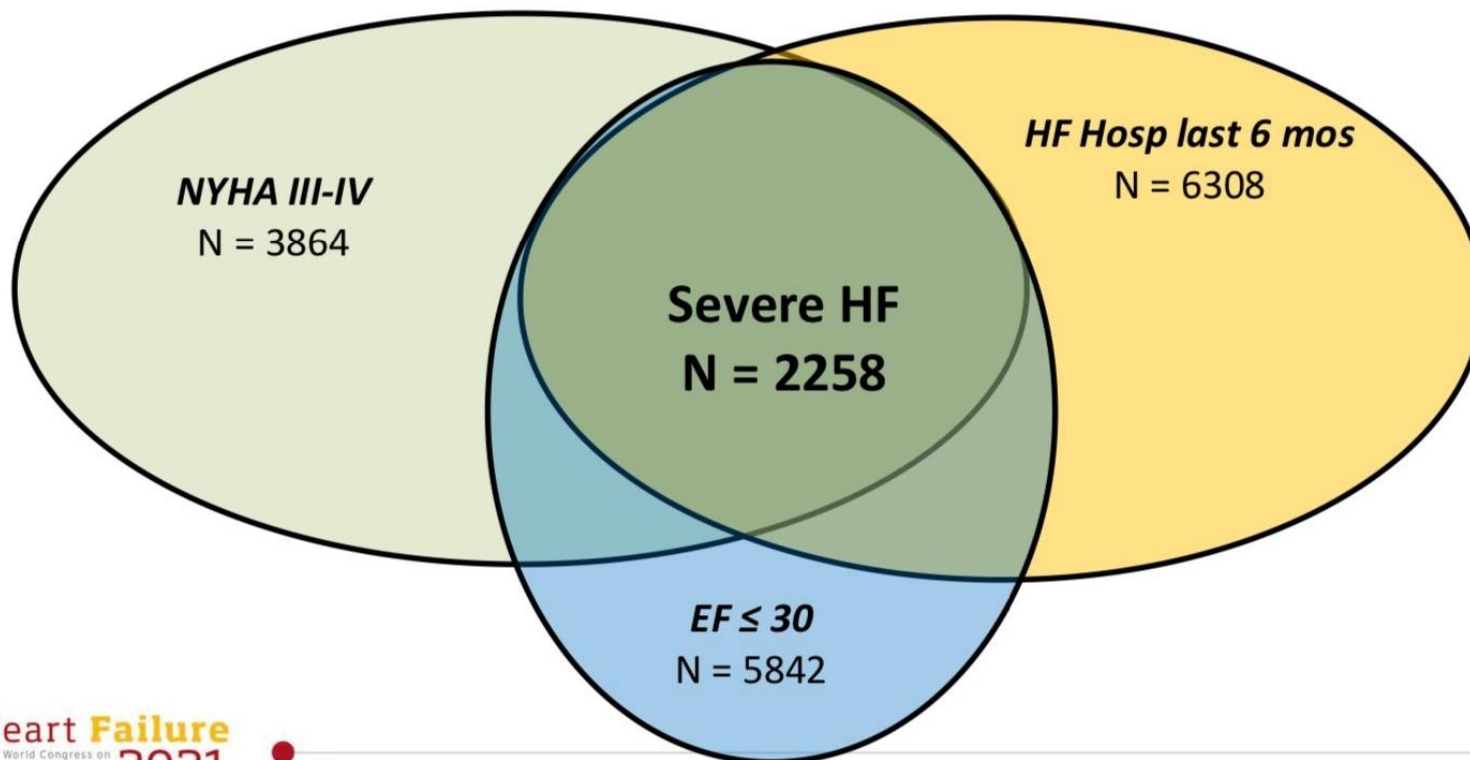


TABLE 2 Clinical Outcomes

Outcome by EF Quartiles	Omecamtiv Mecarbil		Placebo		HR (95% CI)	ARR (per 100 patient-yrs)
	n/N (%)	Rate (per 100 patient-yrs)	n/N (%)	Rate (per 100 patient-yrs)		
Primary outcome					Interaction p = 0.013	
EF ≥33%	298/892 (33)	20.5	280/858 (33)	20.0	0.99 (0.84-1.16)	-0.4
EF 29%-32%	375/1,015 (37)	23.8	356/1,011 (35)	22.4	1.11 (0.96-1.28)	-1.4
EF 23%-28%	393/1,086 (36)	24.0	449/1,124 (40)	27.2	0.85 (0.74-0.97)	3.3
EF ≤22%	457/1,127 (41)	28.3	522/1,119 (47)	35.6	0.83 (0.73-0.95)	7.4
First HF event					Interaction p = 0.004	
EF ≥33%	236/892 (26)	16.2	208/858 (24)	14.9	1.04 (0.86-1.25)	-1.3
EF 29%-32%	286/1,015 (28)	18.2	269/1,011 (27)	16.9	1.13 (0.96-1.33)	-1.3
EF 23%-28%	304/1,086 (28)	18.5	345/1,124 (31)	20.9	0.84 (0.72-0.98)	2.4
EF ≤22%	351/1,127 (31)	21.7	414/1,119 (37)	28.3	0.81 (0.70-0.93)	6.6
First HF hospitalization					Interaction p = 0.004	
EF ≥33%	228/892 (26)	15.5	201/858 (23)	14.3	1.03 (0.85-1.24)	-1.2
EF 29%-32%	279/1,015 (27)	17.6	251/1,011 (25)	15.5	1.19 (1.01-1.42)	-2.1
EF 23%-28%	295/1,086 (27)	17.8	327/1,124 (29)	19.6	0.86 (0.74-1.01)	1.8
EF ≤22%	340/1,127 (30)	20.9	400/1,119 (36)	26.9	0.82 (0.71-0.94)	6.1
CV death					Interaction p = 0.14	
EF ≥33%	153/892 (17)	9.0	136/858 (16)	8.4	1.06 (0.84-1.33)	-0.6
EF 29%-32%	196/1,015 (19)	10.5	162/1,011 (16)	8.5	1.26 (1.02-1.55)	-2.0
EF 23%-28%	207/1,086 (19)	10.8	235/1,124 (21)	11.8	0.88 (0.73-1.07)	1.0
EF ≤22%	252/1,127 (22)	13.0	265/1,119 (24)	14.1	0.96 (0.80-1.14)	1.1
All-cause death					Interaction p = 0.38	
EF ≥33%	200/892 (22)	11.8	189/858 (22)	11.7	0.98 (0.80-1.20)	-0.1
EF 29%-32%	260/1,015 (26)	13.9	226/1,011 (22)	11.9	1.19 (0.99-1.42)	-2.0
EF 23%-28%	278/1,086 (26)	14.4	315/1,124 (28)	15.8	0.89 (0.76-1.05)	1.4
EF ≤22%	329/1,127 (29)	17.0	335/1,119 (30)	17.8	0.98 (0.84-1.14)	0.8

CI = confidence interval; CV = cardiovascular; EF = ejection fraction; HF = heart failure; HR = hazard ratio.

Criteria for Severe Heart Failure Classification



Safety

	Omecamtiv	Placebo		Relative risk (95% CI)
Severe Heart Failure	n=1079	n=1132		
Any treatment-emergent serious adverse event	742 (67.3%)	790 (68.8%)	p=0.43	0.98 (0.92, 1.03)
AE: ventricular tachyarrhythmia	80 (8.0%)	86 (8.1%)	p=0.89	0.98 (0.73, 1.31)
Positively Adjudicated MI	42 (3.8%)	29 (2.5%)	p=0.08	1.51 (0.95, 2.40)
First Stroke	18 (1.6%)	31 (2.7%)	p=0.08	0.60 (0.34, 1.07)
Not Severe Heart Failure	n=2959	n=2920		
Any treatment-emergent serious adverse event	1631 (54.2%)	1645 (55.7%)	p=0.26	0.97 (0.93, 1.02)
AE: ventricular tachyarrhythmia	210 (7.9%)	218 (8.4%)	p=0.58	0.95 (0.79, 1.14)
Positively Adjudicated MI	80 (2.7%)	89 (3.0%)	p=0.41	0.88 (0.66, 1.19)
First Stroke	58 (1.9%)	81 (2.7%)	p=0.037	0.70 (0.50, 0.98)

Tolerability

Variable	Week 0		Week 24		Ratio or Difference	p-value
	OM	Placebo	OM	Placebo		
Severe HF						
Systolic BP (mm Hg)	114.0±15.3	113.5±14.7	116.7±17.3	116.0±17.7	0.6 (-0.7, 2.0)	p=0.35
HR (beats/min)	74.5±12.7	74.1±12.3	71.2±12.3	73.0±12.8	-1.9 (-2.9, -0.8)	p<0.001
Potassium (mmol/L)	4.53±0.57	4.56±0.56	4.52±0.57	4.56±0.58	-0.03 (-0.08, 0.02)	p=0.27
Creatinine (mg/dl)	1.39±0.50	1.36±0.48	1.37±0.55	1.38±0.56	-0.01 (-0.04, 0.02)	p=0.53
Not Severe HF						
Systolic BP (mm Hg)	117.1±15.4	117.9±15.4	118.4±16.8	119.6±17.9	-0.7 (-1.5, 0.1)	p=0.07
HR (beats/min)	71.7±12.0	71.6±11.9	69.6±11.3	71.0±11.6	-1.4 (-2.0, -0.9)	p<0.001
Potassium (mmol/L)	4.57±0.51	4.57±0.51	4.56±0.51	4.55±0.52	0.01 (-0.02, 0.03)	p=0.58
Creatinine (mg/dl)	1.27±0.45	1.28±0.45	1.29±0.49	1.28±0.48	0.01 (-0.00, 0.03)	p=0.14

CONCLUSIONS

- Reduced the risk of the of the primary endpoint of time to first HF event or CV death
- Was well-tolerated with regard to blood pressure, renal function, and potassium homeostasis
- The treatment effect of omecamtiv mecarbil increased with decreasing LVEF
- No difference in serious AEs compared to placebo group

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Cardiac myosin activator

The GALACTIC-HF study assessed the efficacy and safety of the cardiac myosin activator, omecamtiv mecarbil, in HFrEF patients, enrolling patients in both the inpatient and outpatient settings. The primary endpoint of a first HF event or CV death was reduced by 8%. There was no significant reduction in CV mortality. Currently, this drug is not licensed for use in HF. However, in the future it may be able to be considered, in addition to standard therapy for HFrEF to reduce the risk of CV mortality and hospitalization for HF.¹⁵⁹

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Diagnostic and management strategies of RV failure.

Efficacy and safety of hydralazine isosorbide in non-African American patients with HF and also in African American patients on GDMT including SGLT2i and ARNi.

Efficacy and safety of vericiguat in patients with HFrEF and markedly elevated natriuretic peptide levels.

Efficacy and safety of omecamtiv mecarbil in patients with stage D (advanced HF) HFrEF.

Table 3

Baseline characteristics and treatments in GALACTIC-HF, EMPEROR-Reduced, VICTORIA, DAPA-HF and PARADIGM-HF trials

	GALACTIC- HF <i>(n = 8256)</i>	EMPEROR- Reduced <i>(n = 3730)</i>	VICTORIA <i>(n = 5050)</i>	DAPA-HF <i>(n = 4744)</i>	PARADIGM- HF <i>(n = 8442)</i>
Demographics					
Age (years), mean (SD)	64.5 (11.3)	66.9 (11.0)	67.3 (12.2)	66.4 (11)	63.8 (11.4)
Female sex, <i>n</i> (%)	1756 (21.3)	893 (23.9)	1208 (23.9)	1109 (23.4)	1832 (22.0)
Race, <i>n</i> (%)					
White	6421 (77.8)	2629 (70.5)	3239 (64.2)	3333 (70.3)	5544 (65.7)
Asian	710 (8.6)	672 (18.0)	1132 (22.4)	1116 (23.5)	1509 (17.9)
Black or African American	562 (6.8)	257 (6.9)	249 (4.9)	226 (4.8)	428 (5.1)

Thank you

