HFSA 2021
ANNUAL SCIENTIFIC MEETING
SEPT 10-13 + Denver, CO + Virtual

Effect of Omecamtiv Mecarbil in Black Patients with Heart Failure and Reduced Ejection Fraction

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on behalf of the GALACTIC-HF Investigators

Background

- Black patients are broadly under-represented in biomedical research including pivotal clinical trials in heart failure (HF)
- Heterogeneity of treatment effect according to race is known for some HF treatments, such hydralazine/isosorbide, and has been a point of uncertainty for others key medications such as angiotensin converting enzyme (ACE) inhibitors and beta-adrenergic antagonists.
- In the **GALACTIC-HF** trial, omecamtiv mecarbil reduced the risk of a composite of first heart failure event or cardiovascular death in patients with heart failure and reduced ejection fraction (HFrEF)
- **Omecamtiv mecarbil** is a first-in-class myosin activator that augments cardiac sarcomere function by facilitating the actin-myosin interaction resulting in an increase in contractile force

Objectives

- Describe efficacy and safety of omecamtiv mecarbil in self-identified Black patients
- Compare the efficacy and safety omecamtiv mecarbil in self-identified Black patients to White patients

Trial Design

Hypothesis: Selectively improving cardiac function with the cardiac myosin activator, omecamtiv mecarbil, will improve clinical outcomes in patients with HFrEF

Screening:
- Chronic HF, NYHA II-IV
- LVEF ≤35%
- Elevated BNP/ NTproBNP
- Managed with Standard HF therapies
- Currently hospitalized for HF (Inpatients)
  OR
  Urgent ED visit or hospitalization for HF within 1 year prior to screening (Outpatients)
- SBP ≥85 mmHg;
  eGFR ≥20 mL/min/1.73m^2

Randomization (1:1)

Stratification
- Inpatient or outpatient
- Region

Omecamtiv Mecarbil + Standard HF Therapy
Starting dose: 25 mg PO BID; Pharmacokinetic-guided dose selection (25, 37.5 or 50 mg PO BID)

Placebo + SoC

End of Study

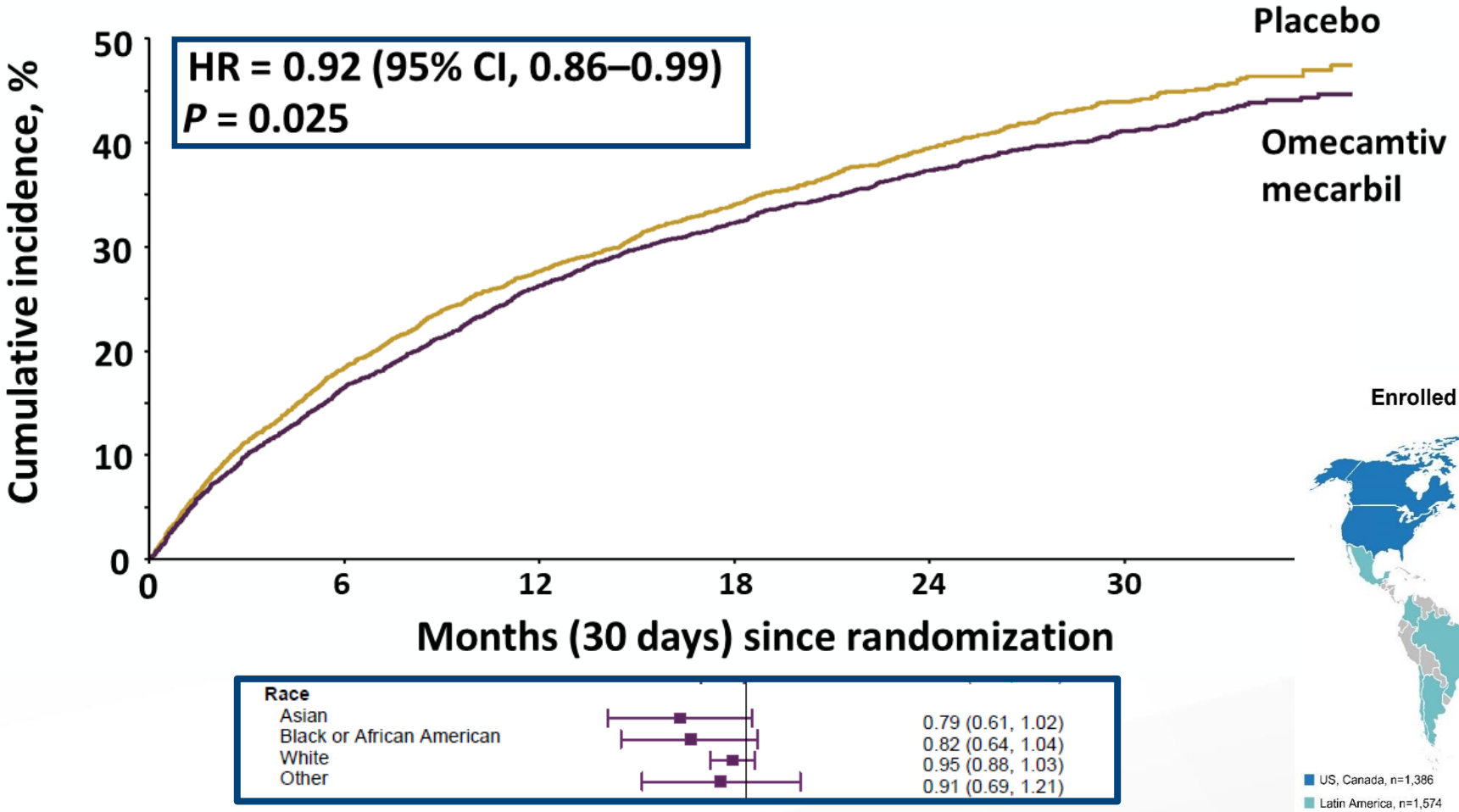
Study Visits: D1 W2 W4 W6 W8 W12 W24 W36 W48 Q16W

Pharmacokinetic assessment for dose adjustment

Multicenter, international, randomized, double-blind, placebo-controlled, event-driven Phase 3 study

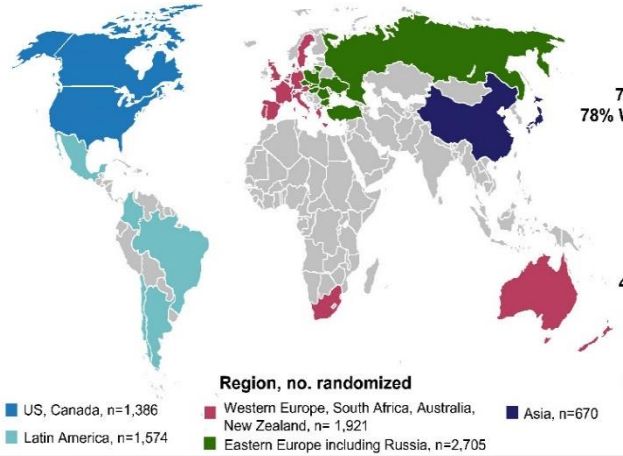
GALACTIC-HF Primary Results

Time to First Heart Failure Event or Cardiovascular Death



Variable	Relative Risk or Difference (95% CI)
Vital signs, laboratory values:	
Systolic BP, mmHg, mean (SD)	-0.1 (-0.9, 0.6)
Heart rate, bpm, mean (SD)	-1.6 (-2.2, -1.0)
Potassium, mmol/L, mean (SD)	0.00 (-0.03, 0.03)
Creatinine, mg/dL, mean (SD)	0.01 (-0.01, 0.02)
NT-proBNP, pg/mL, median (Q1, Q3)	0.90 (0.86, 0.94)
Cardiac troponin I, ng/mL, median (Q1, Q3)	0.004 (0.003, 0.005)

Enrolled 8,256 Patients With HFrEF



Baseline Characteristics

79% Male, 21% Female, 78% White, 9% Asian, 7% Black, 65 yr mean age

25% Inpatient

27% Mean EF, 53% NYHA Class II, 47% NYHA Class III/IV

1971 pg/mL median NT-proBNP, 117 mmHg mean SBP

87% ACEI/ARB/ARNi (19% ARNi), 94% BB, 77% MRA

14% CRT and 32% ICD

Teerlink JR, *et al. N Engl J Med* 2021;384:105-116.
Teerlink JR, *et al. Eur J Heart Fail* 2020;22:2160-2171

Statistical Analysis and Outcomes

Two-part analysis:

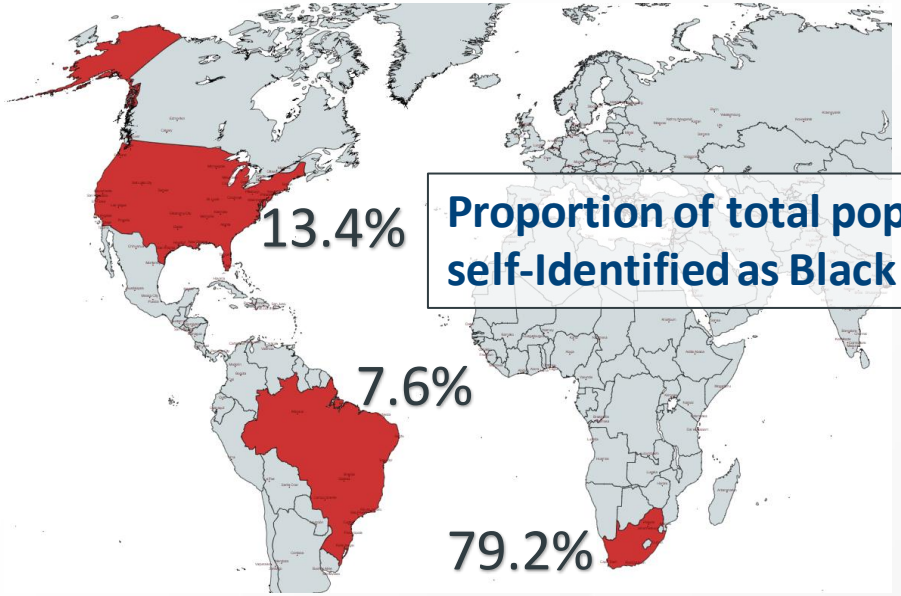
- Efficacy and safety of omecamtiv mecarbil in **all Black participants** in the trial
- Comparison of treatment effect in Black patients to White patients - **restricted to countries contributing ≥10 Black patients**
  - To mitigate potential national / regional confounding.

- Primary composite endpoint:
  - Time to first HF event* or CV death, whichever occurs first
- Secondary endpoints:
  - Time to CV death
  - Time to first HF hospitalization
- Vital signs/ Biomarkers
- Safety endpoints

*HF event is defined as an urgent clinic visit, emergency department visit, or hospitalization for subjectively and objectively worsening heart failure leading to treatment intensification beyond changed oral diuretic therapy.

Black Patient enrollment in GALACTIC-HF

- A total of **562** self-identified Black patients were enrolled in the trial
- Most (95%) were from U.S. (n=357), Brazil (n=100), and South Africa (n=78)
- This accounted for **29%, 21%** and **45%** of national enrollment, respectively.



Black Patient Enrollment in Recent Heart Failure Clinical Trials

Trial	Total Black Patients (%)	U.S. Black Patients (%)
GALACTIC-HF [1,2]	562 (6.8%)	357 (29%)
PARADIGM [3,4]	428 (5.1%)	111 (26%)
EMPEROR-reduced [5,6]	257 (6.9%)	100 (23.5%)*
VICTORIA [7]	249 (4.9%)	
DAPA-HF [8,9]	226 (4.8%)	121 (17.9%)*
PARAGON [10]	102 (2.2%)	

1. Teerlink JR, *et al. N Engl J Med* 2021;384:105-116.
2. Teerlink JR, *et al. Eur J Heart Fail* 2020;22:2160-2171.
3. McMurray JJ et al. *N Engl J Med* 2014;371:993-1004.
4. Lewis EF, et al. *J Cardiac Fail* 2016;22:S9-S10.
5. Lam CSP *et al. Eur Heart J* 2021.
6. Packer M *et al. N Engl J Med* 2020;383:1413-1424.
7. Armstrong PW *et al. N Engl J Med* 2020;382:1883-1893.
8. McMurray JJV, *et al. N Engl J Med* 2019;381:1995-2008.
9. Docherty KF, et al. *JACC HF, in press*
10. Solomon SD *et al. N Engl J Med* 2019;381:1609-1620.

*North America

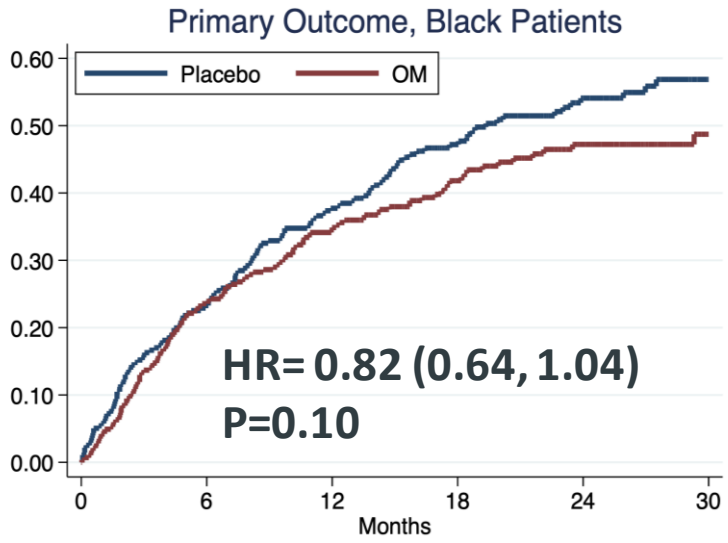
Baseline Characteristics of Black Patients in GALACTIC-HF

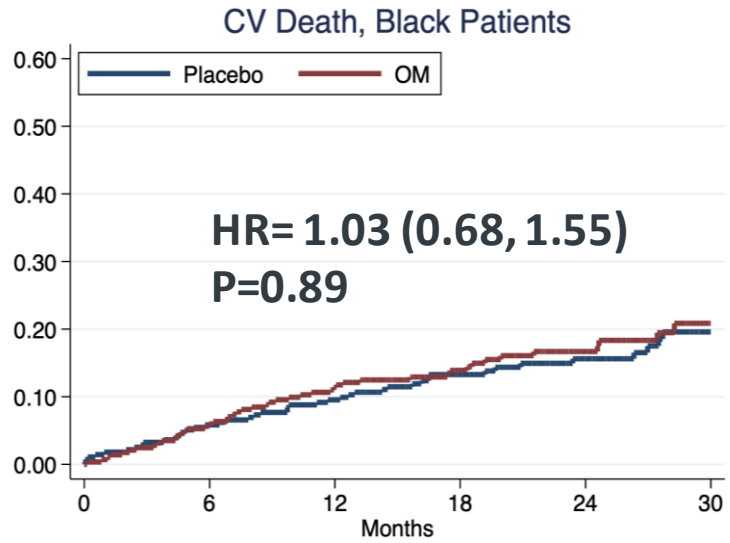
	Omecamtiv Mecarbil n=285	Placebo n=277
Demographics		
Age - yr	58.9 ± 12.3	57.2 ± 12.2
Sex, Female	100 (35.1%)	89 (32.1%)
Randomization Setting: In-patient	54 (18.9%)	51 (18.4%)
Geographic Region		
Latin America	57 (20.0%)	53 (19.1%)
US And Canada	181 (63.5%)	178 (64.3%)
Western Europe/South Africa/Australasia	47 (16.5%)	46 (16.6%)
Clinical Characteristics		
Atrial Fibrillation or Flutter at Screening	36 (12.6%)	39 (14.1%)
Hypertension Hx	239 (83.9%)	222 (80.1%)
Type 2 diabetes mellitus	142 (49.8%)	120 (43.3%)
History of stroke	33 (11.6%)	28 (10.1%)
Ischemic heart failure etiology	84 (29.5%)	75 (27.1%)
LVEF - %	24.3 ± 6.5	23.3 ± 6.7
NYHA Classification		
Class II	160 (56.1%)	149 (53.8%)
Class III-IV	125 (43.9%)	128 (46.2%)

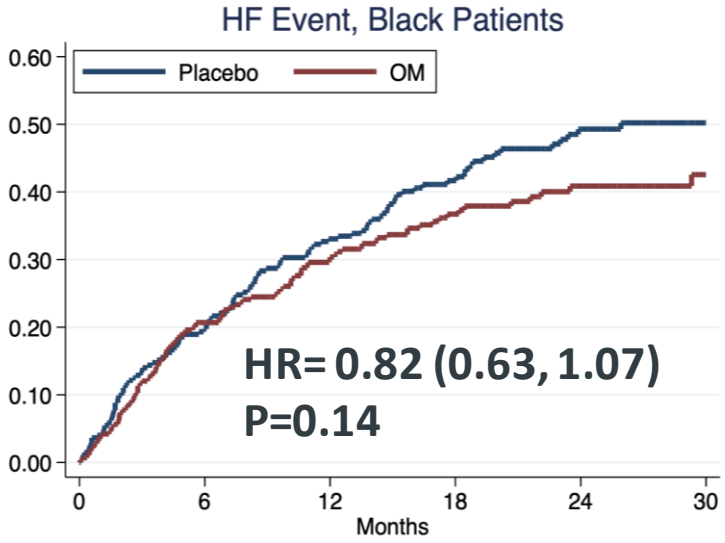
	Omecamtiv Mecarbil n=285	Placebo n=277
SBP — mmHg	116.8 ± 15.5	117.7 ± 16.2
Heart rate — beats/min	76.0 ± 14.0	75.3 ± 12.8
NT-proBNP — pg/mL	1854 [832, 3971]	1984 [905, 3919]
Cardiac Troponin I — ng/L	32 (13, 59)	31 (14, 63)
eGFR — mL/min/1.73m2	64.8 [49.4, 83.9]	65.3 [51.9, 84.8]
Baseline BMI (kg/m2)	31.0 ± 9.0	30.6 ± 8.6
Heart Failure Therapies		
ACEi, ARB or ARNi	242 (84.9%)	242 (87.4%)
ARNi	72 (25.3%)	65 (23.5%)
BB	267 (93.7%)	273 (98.6%)*
MRA	212 (74.4%)	192 (69.3%)
SGLT2 Inhibitors	4 (1.4 %)	3 (1.1 %)
Digitalis glycosides	51 (17.9%)	48 (17.3%)
Cardiac Resynchronization Therapy	33 (11.6%)	25 (9.0 %)
Implantable Cardioverter Defibrillator	105 (36.8%)	106 (38.3%)

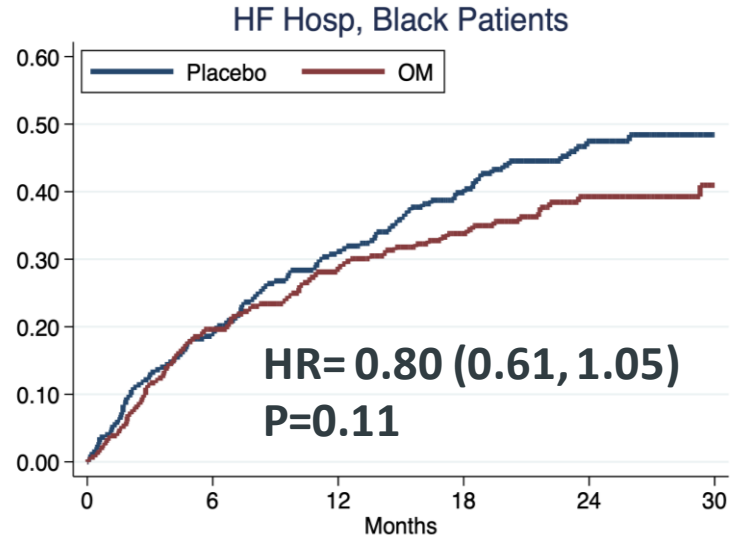
* p=0.003

Primary Outcome and Components in all Black Patients









Primary Outcome Events:

- OM: 124/285 (44%) vs. Placebo: 144/277 (52%)
- OM: 33.3 vs. Placebo: 41 events/ 100 pt-years
- **Saved 7.7 events/ 100 pt-years**
- **NNT 13**

Biomarker and Safety Outcomes in all Black Patients

Biomarker	Week 0		Week 24		Ratio or Difference	p-value
	OM	Placebo	OM	Placebo		
Systolic BP (mm Hg)	116.8±15.5	117.7±16.2	121.3±19.7	119.0±20.5	+3.5 (0.3, 6.7)	0.031
Heart rate (BPM)	76.0±14.0	75.3±12.8	71.8±12.9	73.9±12.4	-2.0 (-4.1, 0.0)	0.05
Potassium (mmol/L)	4.39±0.57	4.40±0.53	4.33±0.50	4.38±0.58	-0.05 (-0.14, 0.04)	0.32
Creatinine (mg/dl)	1.37±0.50	1.36±0.49	1.37±0.54	1.41±0.58	-0.00 (-0.06, 0.05)	0.88
NT-proBNP (pg/ml)	1854 (832, 3971)	1984 (905, 3919)	1028 (374, 2552)	1361 (490, 3166)	0.81 (0.66, 0.99)	0.040
Troponin I (ng/L)	32 (13, 59)	31 (14, 63)	36 (13, 67)	26 (11, 56)	1.15 (1.01, 1.30)	0.040

Safety Event	OM n=284	Placebo n=275	Relative Risk (95% CI)	p-value
Any treatment-emergent serious adverse event	181 (63.7%)	189 (68.7%)	0.93 (0.82, 1.04)	0.21
Ventricular tachyarrhythmia	17 (6.5 %)	18 (7.0 %)	0.92 (0.49, 1.75)	0.81
Torsade / QT	13 (5.0 %)	15 (5.9 %)	0.85 (0.41, 1.74)	0.65
SAE ventricular arrhythmia leading to treatment	12 (4.2 %)	9 (3.3 %)	1.29 (0.55, 3.02)	0.55
First Major Cardiac Ischemic Event	15 (5.3 %)	14 (5.1 %)	1.04 (0.51, 2.11)	0.92
First Stroke	9 (3.2 %)	10 (3.6 %)	0.87 (0.36, 2.11)	0.76

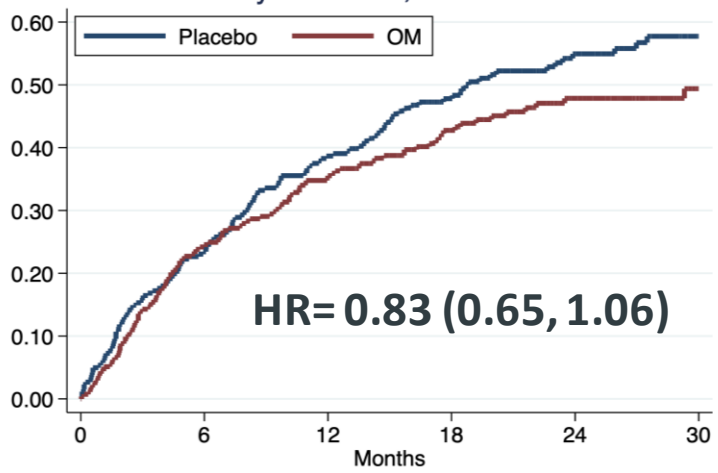
Baseline Characteristics in Black and White Patients from Brazil, South Africa and the U.S.

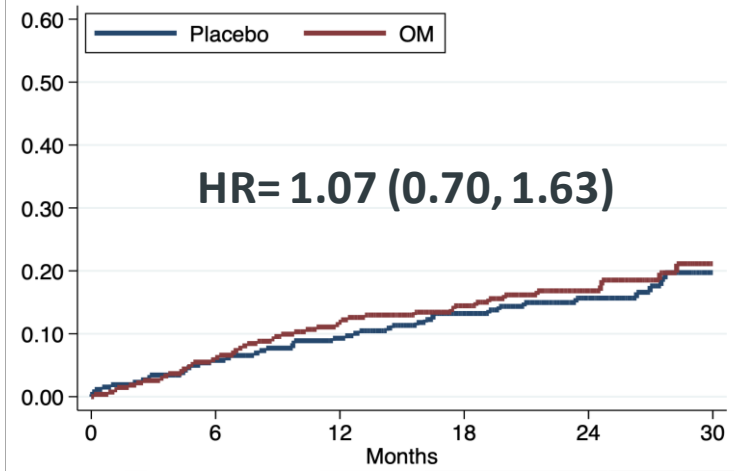
	Black Patients n=535	White Patients n=1129	p
Age - years	58.0 ± 12.4	65.0 ± 11.4	p<0.001
Sex, Female	181 (33.8%)	270 (23.9%)	p<0.001
Geographic Region			p<0.001
Brazil	100 (18.7%)	288 (25.5%)	
U.S.	357 (66.7%)	820 (72.6%)	
South Africa	78 (14.6%)	21 (1.9 %)	
Setting: In-patient	97 (18.1%)	179 (15.9%)	0.24
Clinical Characteristics			
Atrial Fib/Flutter at Screening	72 (13.5%)	237 (21.0%)	p<0.001
Hypertension Hx	443 (82.8%)	821 (72.7%)	p<0.001
Type 2 diabetes mellitus	250 (46.7%)	504 (44.6%)	0.42
History of stroke	59 (11.0%)	107 (9.5 %)	0.32
Ischemic etiology	151 (28.2%)	618 (54.7%)	p<0.001
LVEF - %	23.9 ± 6.6	25.0 ± 6.6	0.001
NYHA Classification			0.79
Class II	289 (54.0%)	592 (52.4%)	
Class III-IV	246 (46%)	537 (47.6%)	

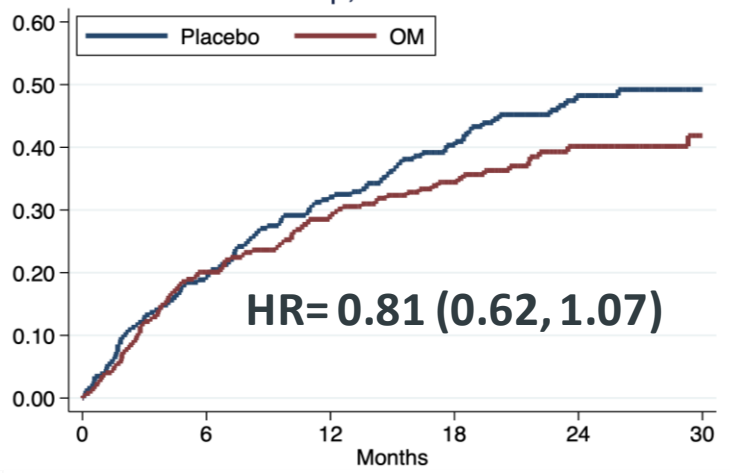
	Black Patients n=535	White Patients n=1129	p
Outpatient	75.0 [51.0, 91.7]	71.9 [52.1, 89.6]	0.42
Inpatient	41.7 [25.0, 58.3]	40.6 [21.9, 67.7]	0.82
SBP — mmHg	117.3 ± 15.7	114.0 ± 16.4	p<0.001
Heart rate — beats/min	75.8 ± 13.2	73.2 ± 12.1	p<0.001
NT-proBNP — pg/mL	1849 [852, 3852]	1930 [903, 4234]	0.32
Troponin I — ng/L	31 [13, 61]	26 [12, 48]	0.004
eGFR — mL/min/1.73m2	65.3 [51.0, 84.1]	56.1 [43.1, 70.2]	p<0.001
Heart Failure Therapies			
ACEi, ARB or ARNi	458 (85.6%)	886 (78.5%)	p<0.001
ARNi	128 (23.9%)	289 (25.6%)	0.46
BB	513 (95.9%)	1047 (92.7%)	0.013
MRA	382 (71.4%)	610 (54.0%)	p<0.001
SGLT2 Inhibitors	7 (1.3 %)	29 (2.6 %)	0.10
Digitalis glycosides	97 (18.1%)	199 (17.6%)	0.80
Resynchronization	55 (10.3%)	211 (18.7%)	p<0.001
Implantable Defibrillator	200 (37.4%)	538 (47.7%)	p<0.001

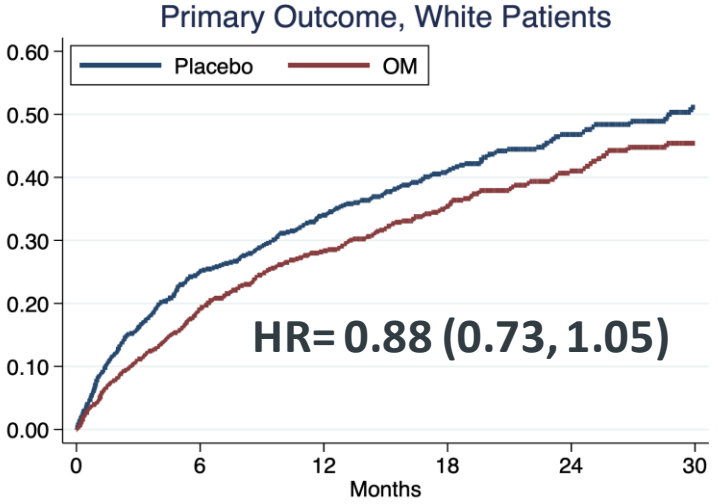
Primary Outcome and Components in Black and White Patients (Brazil, South Africa, and U.S. only)

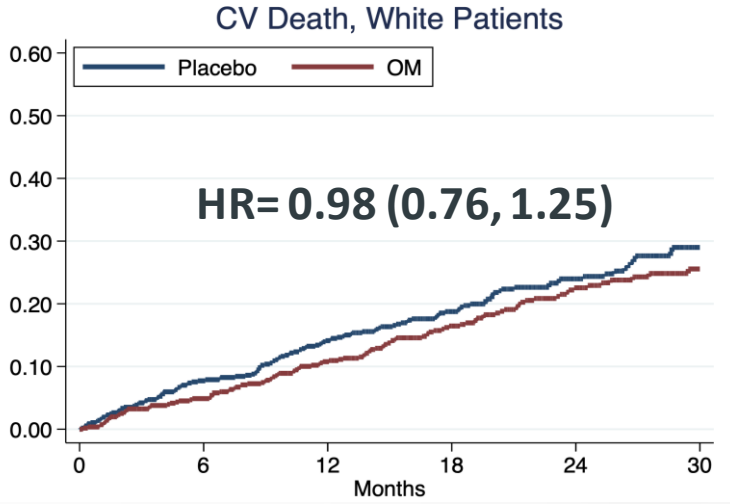
All P = NS for Interaction

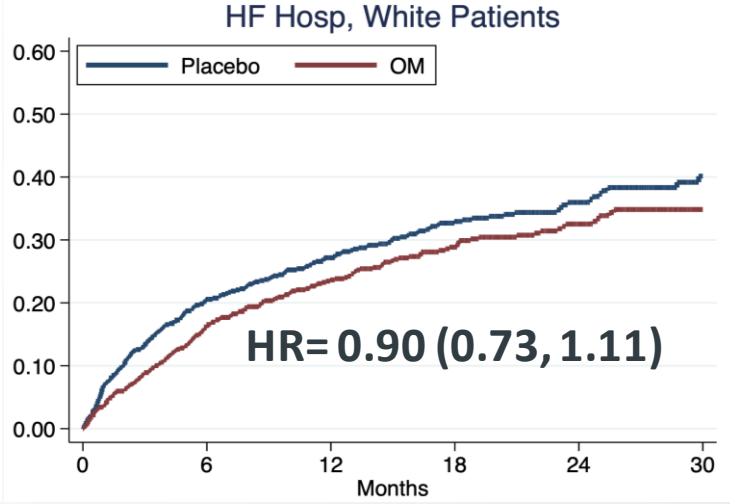












Biomarker and Safety Outcomes in Black Patients compared to White Patients (Brazil, South Africa, and U.S. only)

Biomarker	Black Patients		White Patients		Interaction
	Diff (95% CI)	P	Diff (95% CI)	P	p
Systolic BP (mm Hg)	+3.4 (0.2, 6.7)	0.039	-0.7 (-2.6, 1.3)	0.49	0.02
Heart rate (BPM)	-2.3 (-4.4, -0.2)	0.032	-2.2 (-3.6, -0.9)	0.001	0.95
Potassium (mmol/L)	-0.03 (-0.12, 0.06)	0.51	0.05 (-0.02, 0.11)	0.14	0.16
Creatinine (mg/dl)	-0.00 (-0.06, 0.06)	0.92	-0.00 (-0.05, 0.05)	0.89	0.87
NT-proBNP (pg/ml) [Ratio]	0.84 (0.68, 1.03)	0.09	0.81 (0.72, 0.91)	p<0.001	0.76
Troponin I (ng/L) [Ratio]	1.14 (1.00, 1.29)	0.06	1.24 (1.13, 1.36)	p<0.001	0.25

Safety Event	Black Patients (n=595)		White Patients (n=1129)		Interaction
	Diff (95% CI)	P	Diff (95% CI)	P	p
Any treatment-emergent SAE	0.93 (0.82, 1.04)	0.21	0.99 (0.95, 1.03)	0.57	0.47
Ventricular tachyarrhythmia	0.92 (0.49, 1.75)	0.81	1.01 (0.85, 1.21)	0.89	0.83
Torsade / QT	0.85 (0.41, 1.74)	0.65	0.93 (0.74, 1.16)	0.53	0.95
SAE Ventricular arrhyth. leading to treatment	1.29 (0.55, 3.02)	0.55	1.00 (0.76, 1.32)	0.99	0.36
First Major Cardiac Ischemic Event	1.04 (0.51, 2.11)	0.92	1.05 (0.85, 1.31)	0.64	0.69
First Stroke	0.87 (0.36, 2.11)	0.76	0.75 (0.53, 1.06)	0.11	0.30

Limitations

- Limitations inherent in sub-group analyses
- Despite strong enrollment of Black patients this analysis is still underpowered to examine death or hospitalization within minority race groups
- We did not compare to other race group (Asian patients) or examine treatment effect by ethnicity (Hispanic vs. non-Hispanic)
- The many baseline characteristic differences by race should be noted when interpreting comparisons across these groups

Conclusions

- GALACTIC-HF enrolled more Black patients than other recent HF trials
  - The proportion of enrollment in the U.S. and Brazil were both more than double the population proportion reported in national census.
- In Black patients, treatment with omecamtiv mecarbil resulted in a trend towards reduction in the primary endpoint by 18% (HR= 0.82 [0.64, 1.04]).
  - Parallel to the overall study results, this beneficial trend was driven by fewer HF events in the OM arm (HR=0.82) with no apparent impact on CVD (HR=1.03)
- Compared to White patients, Black patients had statistically similar overall benefit from treatment with omecamtiv mecarbil
  - Estimates reflect a numerically larger reduction in hospitalization (HR=0.81 compared to 0.90)
  - There was a statistically significant increase in systolic blood pressure in Black patients (+3.4 mmHg, p=0.039) that was not seen in White patients.
  - Similar safety and tolerability profile

Acknowledgements

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945 Site Investigators in 35 Countries!!

Thank you for your attention

GALACTIC-HF

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