Cytokinetics

Omecamtiv Mecarbil

Cardiovascular and Renal Drugs Advisory Committee

NDA 216401
13 December 2022

Introduction

Rachel E. Melman, MBS

Senior Director, Regulatory Affairs
Cytokinetics

Overview

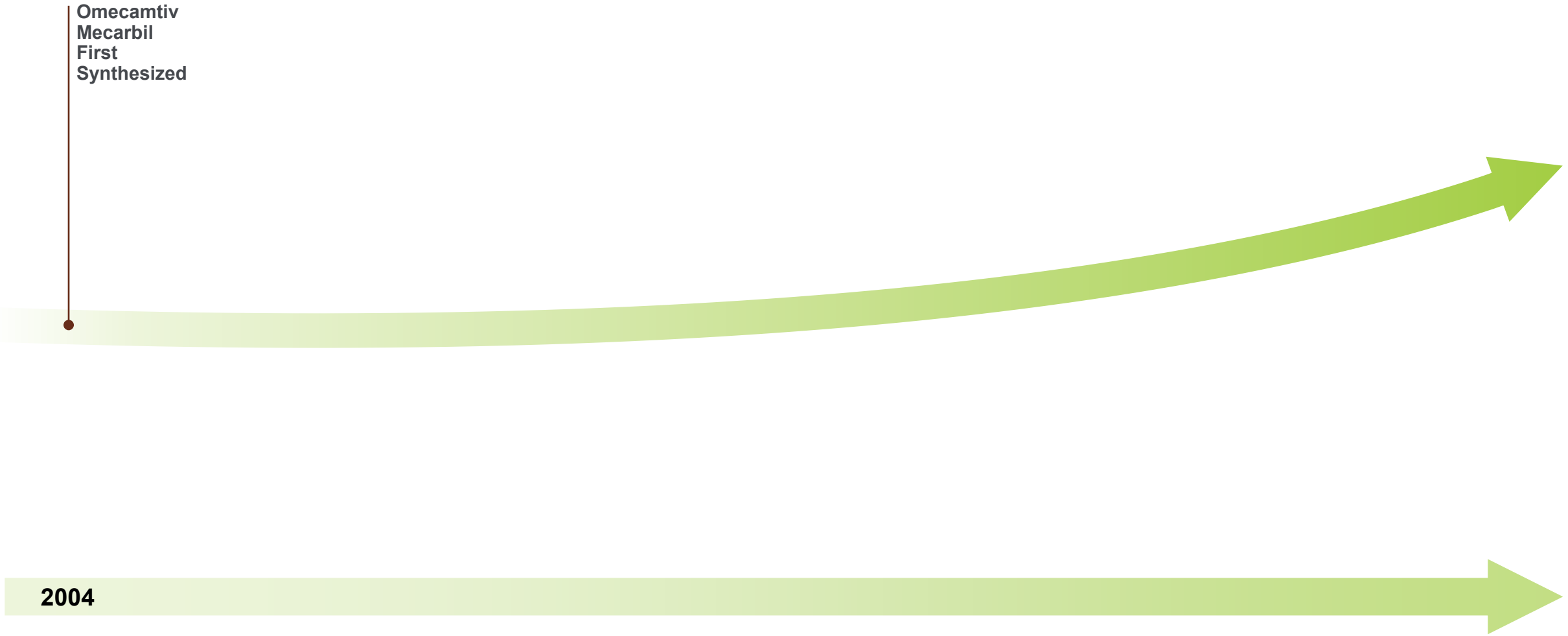
- **Despite advances in guideline-directed medical therapy (GDMT), patients with HFrEF remain at high risk for adverse outcomes**
- **Omecamtiv mecarbil can address a continued unmet medical need in heart failure with reduced ejection fraction (HFrEF)**
- **Omecamtiv mecarbil is the first therapy designed to treat heart failure by directly targeting the contractile mechanisms of cardiac muscle**
- **GALACTIC-HF met its pre-specified primary outcome**
  - Treatment effect increased for patients with higher risk
  - Safety profile was similar to that of the placebo group

Indication Proposed in the NDA

Omecamtiv mecarbil is a cardiac myosin activator indicated to reduce the risk of cardiovascular death and heart failure events in patients with symptomatic chronic heart failure with reduced ejection fraction. Benefits are increasingly evident the lower the left ventricular ejection fraction (LVEF).

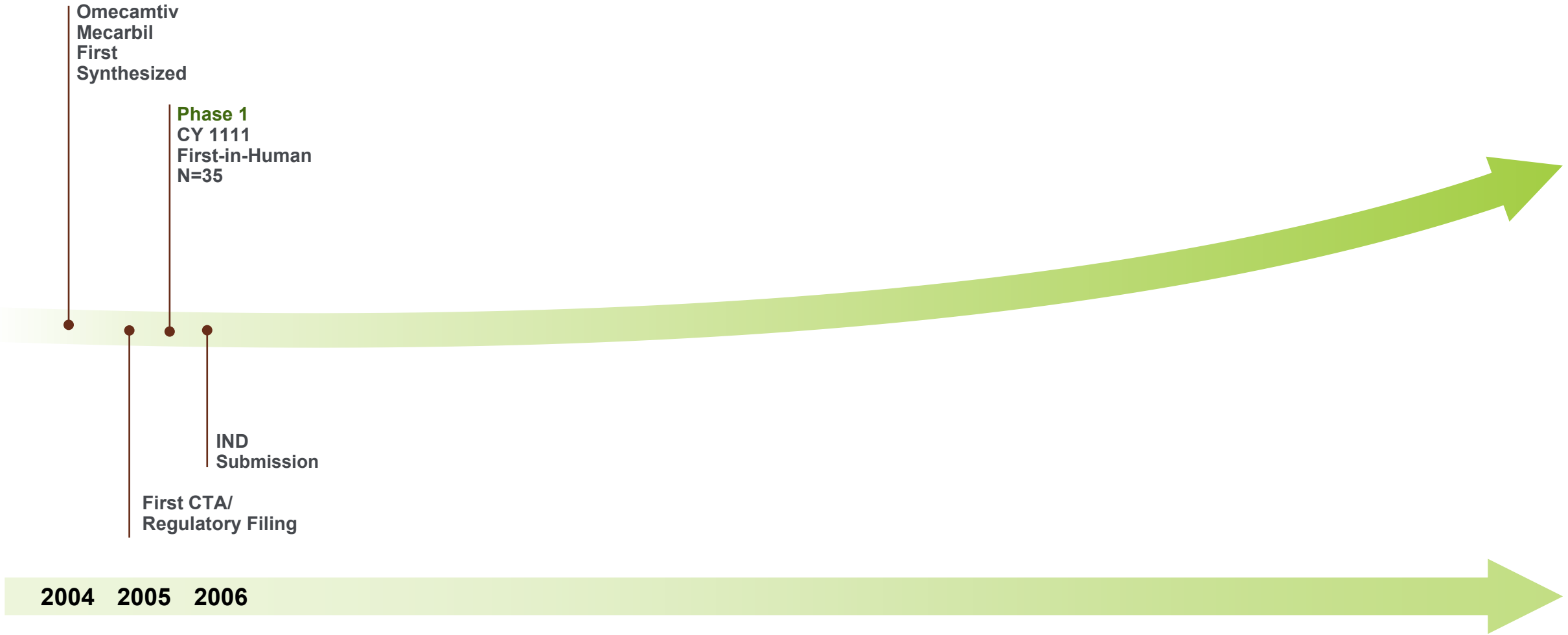
Cytokinetics Recommendation:
Focus labeling on patients who derive the greatest benefit

Regulatory and Program History



Regulatory and Program History

Completed studies enrolling over 10,300 participants



Note: not all studies are included

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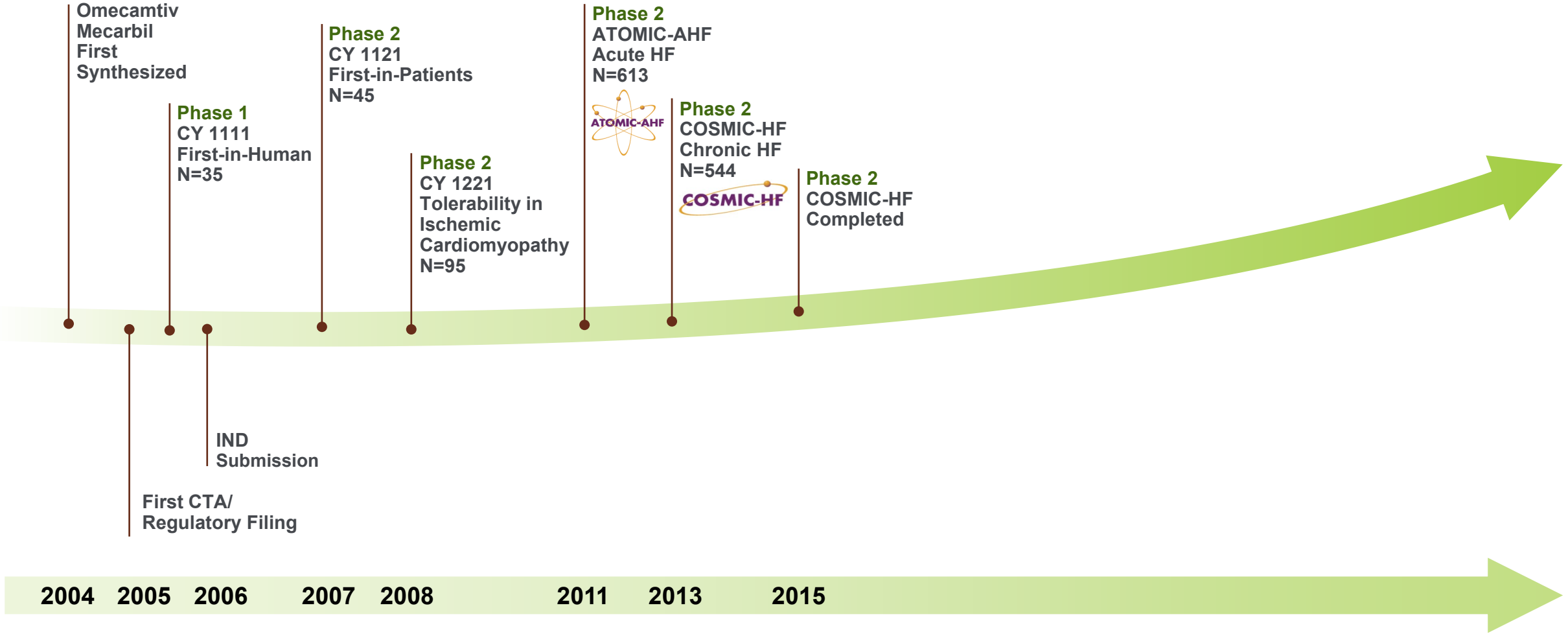

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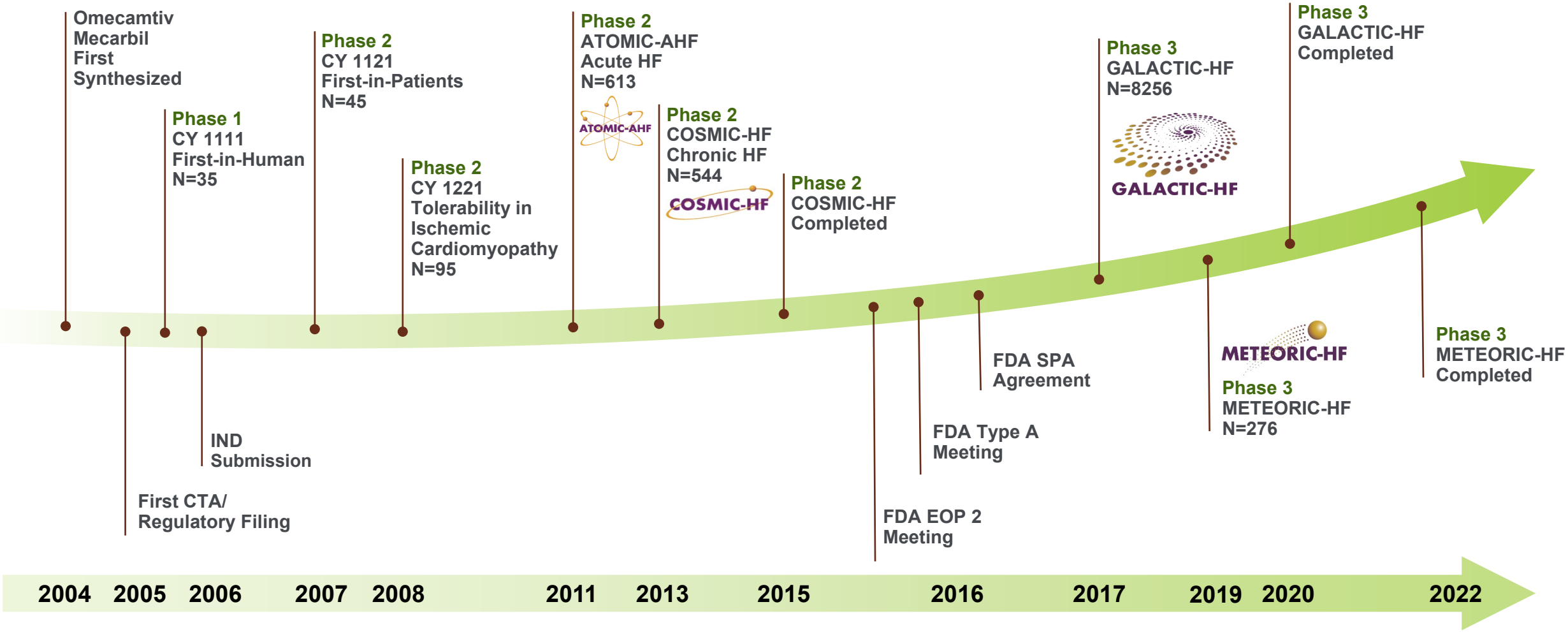

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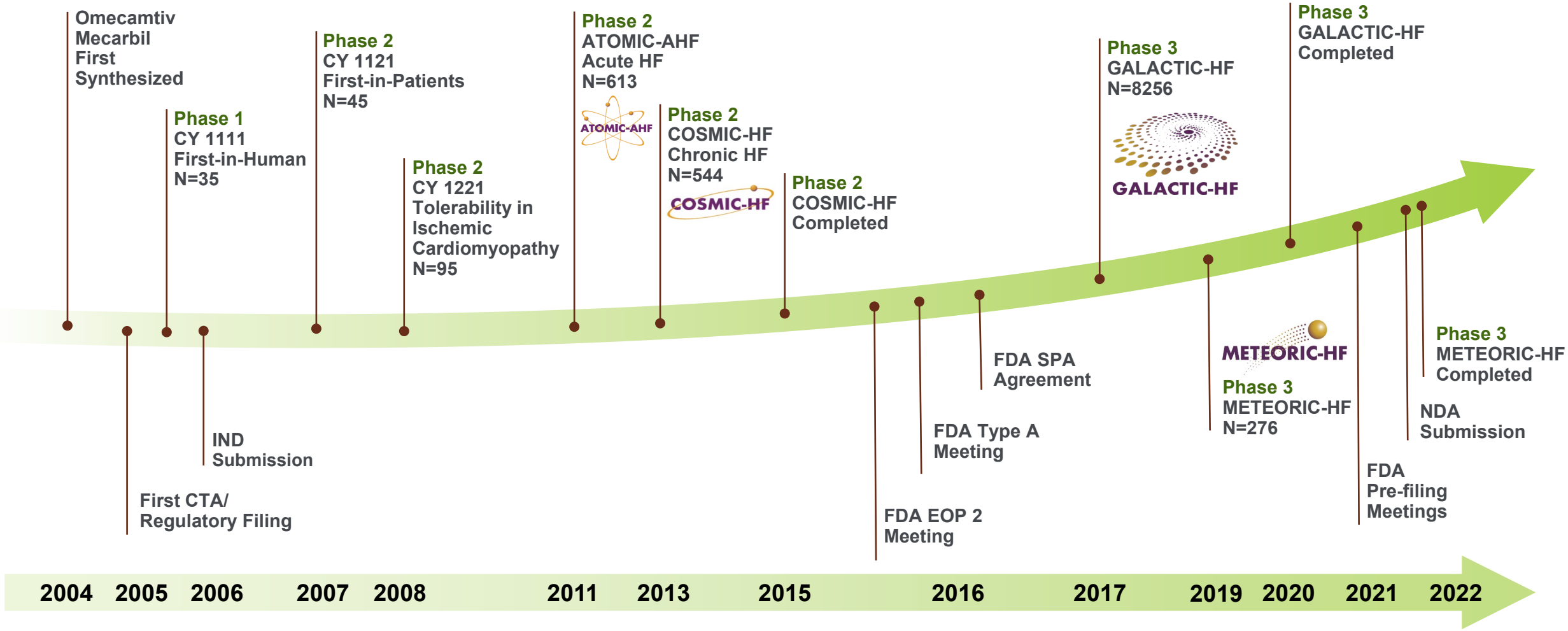

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Omecamtiv Mecarbil: First-in-Class Therapy for Patients with HFrEF

EFFICACY	• Positive effect of omecamtiv mecarbil on primary composite endpoint • Greater benefit observed in patients with increased risk
SAFETY	• No imbalances in adverse events • Safety profile is similar to that of the placebo group
BENEFIT/ RISK	• Evidence supports use of omecamtiv mecarbil in HFrEF patients with lower EF at increased risk for heart failure outcomes

Substantial Evidence of Effectiveness Based on One Clinical Trial and Confirmatory Evidence

1. One adequate and well-controlled clinical trial on a new indication for an approved drug, supported by existing adequate and well-controlled clinical investigation(s) that demonstrated the effectiveness of the drug for its other, closely related approved indication(s)
2. **One adequate and well-controlled clinical trial supported by data that provide strong mechanistic support**
3. One adequate and well-controlled clinical trial with compelling results, supported by additional data from the natural history of the disease
4. One adequate and well-controlled clinical trial of the new drug, supported by scientific knowledge about the effectiveness of other drugs in the same pharmacological class

FDA Guidance “Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products” (2019)

Substantial Evidence of Effectiveness Based on One Clinical Trial and Confirmatory Evidence

2. **One adequate and well-controlled clinical trial supported by data that provide strong mechanistic support**

FDA Guidance “Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products” (2019)

Substantial Evidence of Effectiveness Based on One Clinical Trial and Confirmatory Evidence

2. One adequate and well-controlled clinical trial supported by data that provide strong mechanistic support

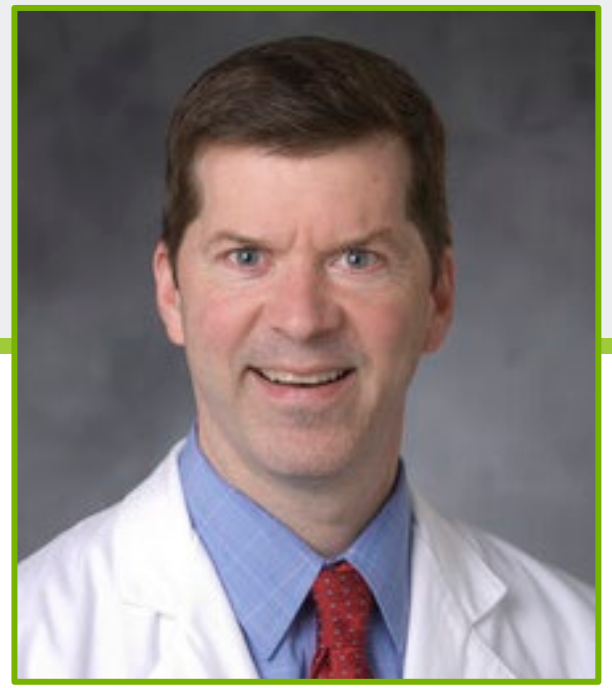
FDA Guidance “Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products” (2019)

Presentation Agenda

Introduction	**Rachel E. Melman, MBS, RAC** *Senior Director, Regulatory Affairs* *Cytokinetics*
Heart Failure with Reduced Ejection Fraction	**G. Michael Felker, MD, FACC, FAHA, FHFSA** *Professor of Medicine, Duke University* *Duke Clinical Research Institute*
Clinical Efficacy	**Fady Malik, MD, PhD, FACC, FHFA** *Executive Vice President, Research & Development* *Cytokinetics*
Clinical Safety	**Stuart Kupfer, MD** *Senior Vice President, Chief Medical Officer* *Cytokinetics*
Dosing	**Stuart Kupfer, MD**
Benefit/Risk	**Scott D. Solomon, MD** *Professor of Medicine, Harvard Medical School* *Brigham and Women's Hospital*
Conclusions	**Fady Malik, MD, PhD, FACC, FHFA**

Additional Experts

- **Brian Claggett, PhD**
  Assistant Professor, Harvard Medical School
  Brigham and Women's Hospital
- **Polina German, PharmD**
  Head of Clinical Pharmacology, Cytokinetics
- **Michael Pugsley, PhD, FBPhS, DSP**
  Senior Director, Toxicology and Safety Pharmacology, Cytokinetics



Unmet Needs in Heart Failure with Reduced Ejection Fraction (HFrEF)

G. Michael Felker, MD, MHS, FACC, FAHA, FHFSA

Vice-Chief of Cardiology
Director of Cardiovascular Research, DCRI
Professor of Medicine
Duke University School of Medicine

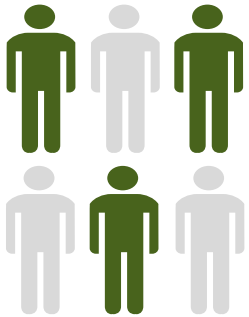
Overview

- HFrEF remains a major unsolved public health issue
- Despite improvements in guideline directed medical therapy (GDMT), the risk of adverse outcomes in HFrEF remains high, especially in high-risk patient groups
- Many higher risk patients with HFrEF cannot tolerate GDMT, further escalating their risk
- There is an unmet need for therapy that is effective and well-tolerated in higher risk patient groups

Heart Failure Is a Major Public Health Problem

46%

Increase in Americans living with HF through 2030 owing to aging population and decline in mortality[1]



50%

HF patients who will die within 5 years[1]

127%

Cost increase of HF through 2030 (increasing from $30.7 billion to $69.7 billion)[2]

An estimated 6.5 million Americans ≥20 years of age have HF, and 1 million new HF cases occur annually[1]

HF=heart failure.

1. Benjamin EJ, et al. *Circulation*. 2018;137:e67-e492; 2. Heidenreich PA, et al. *Circ Heart Fail*. 2013;6:606-619.

HF Hospitalizations are a Key Morbidity of Heart Failure

~ 1,000,000

Annual HF hospitalizations in the US[1]

21%

Patients readmitted to hospital within 30 days[2,a]

49%

Patients readmitted to hospital within 5 years[3,b]

Despite advances in treatment, nearly 50% of patients are readmitted to the hospital within 5 years[3,b]

a. In an investigational study of patients with an index hospitalization for HF from California, New York, and Florida from 2007–2011 (N=547,088).[2]
b. Among HFrEF patients (n=18,398), HFbEF patients (n=3285), and HFpEF patients (n=18,299) in the GWTG-HF registry, a study of patients on Medicare and Medicaid services (N=39,982)[3]
GWTG-HF=Get With the Guidelines®-Heart Failure; HFbEF=heart failure with borderline ejection fraction;
HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction.
1. Benjamin EJ, et al. *Circulation.* 2019;139:e56-e528; 2. Davis JD, et al. *Am J Med*. 2017;130:93.e9-93.e28; 3. Shah KS, et al. *J Am Coll Cardiol.* 2017;70:2476-2486.

Foundational GDMT for HFrEF

4 drug classes have been shown to improve outcomes and CV mortality in broad population of patients with HFrEF

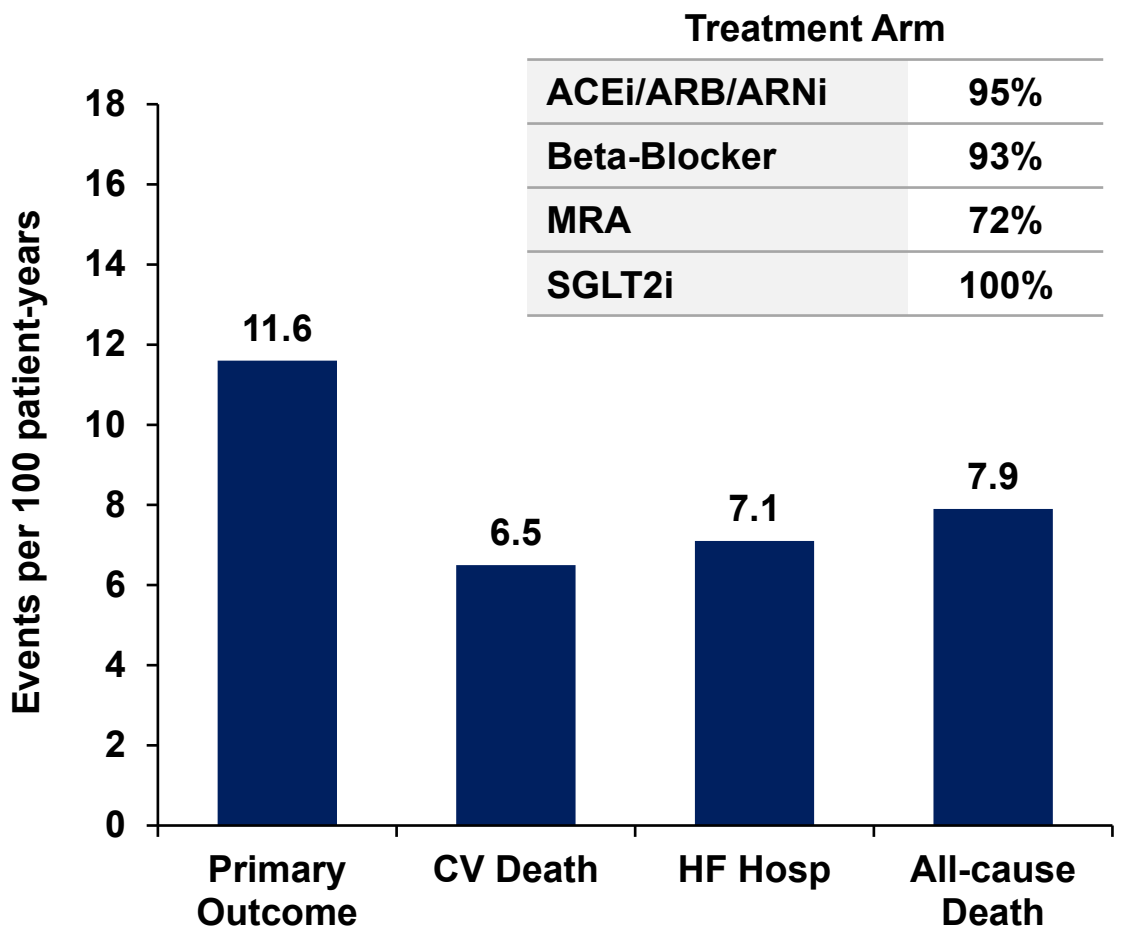
- **Beta-blocker**
- **ARNi**
- **MRA**
- **SGLT2-inhibitor**

Class I indication in Guidelines

ARNi=angiotensin receptor neprilysin inhibitor; MRA=Mineralocorticoid receptor antagonists; SGLT2=Sodium-glucose transport protein 2

Residual Risk in HFrEF Despite Quadruple Therapy

DAPA-HF



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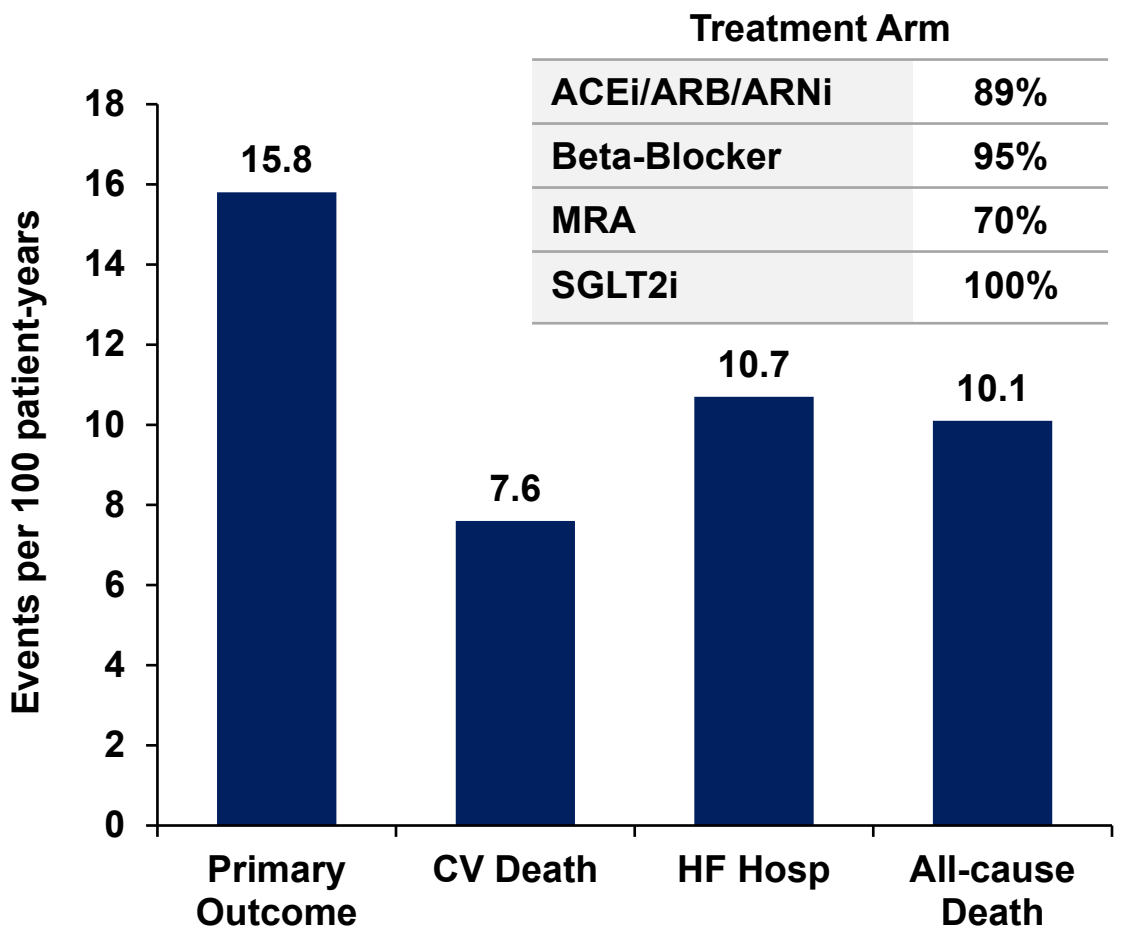
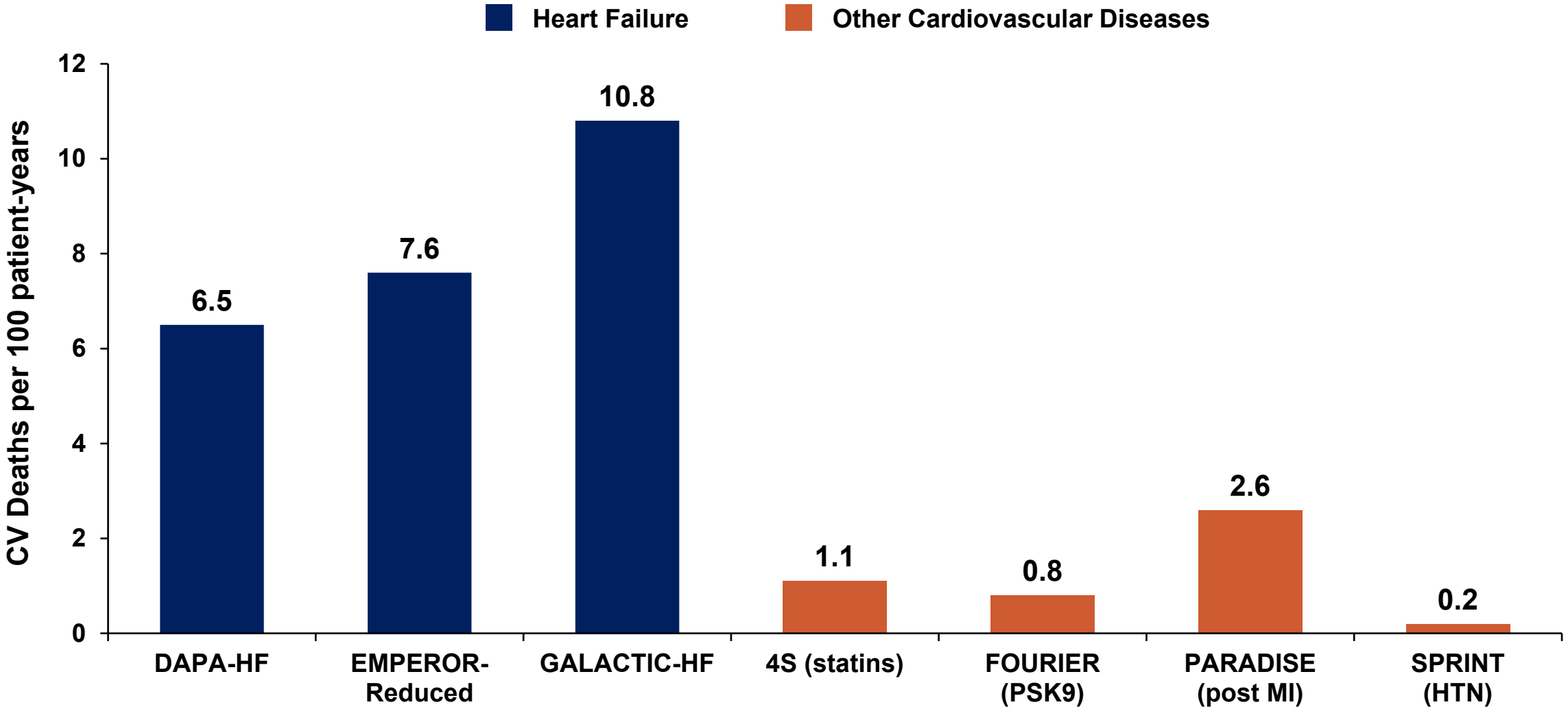


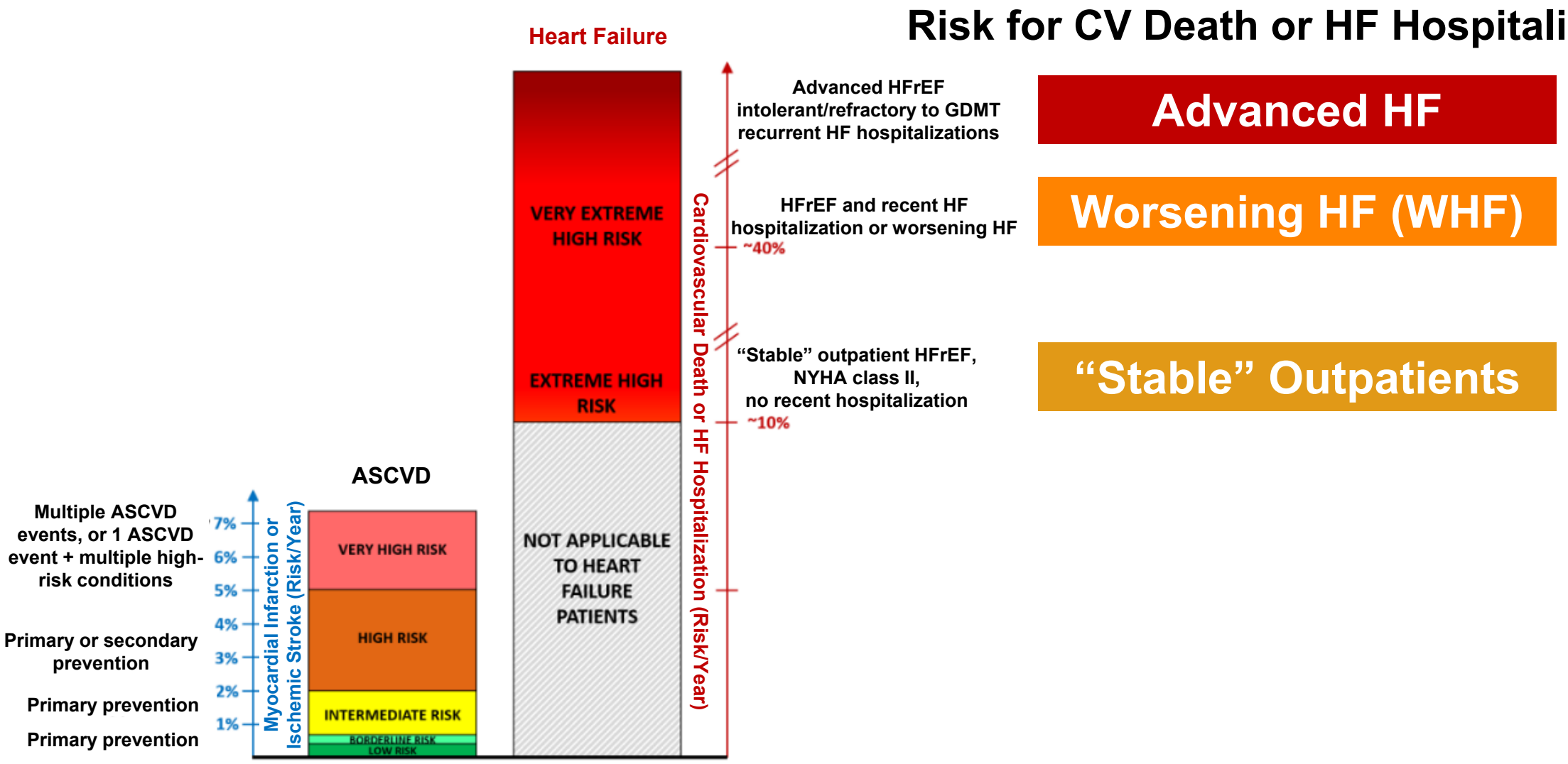
ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker

Residual Risk in Context

CV Death in HF vs. Other CV Diseases



Contextualizing Risk Among Patients with HF



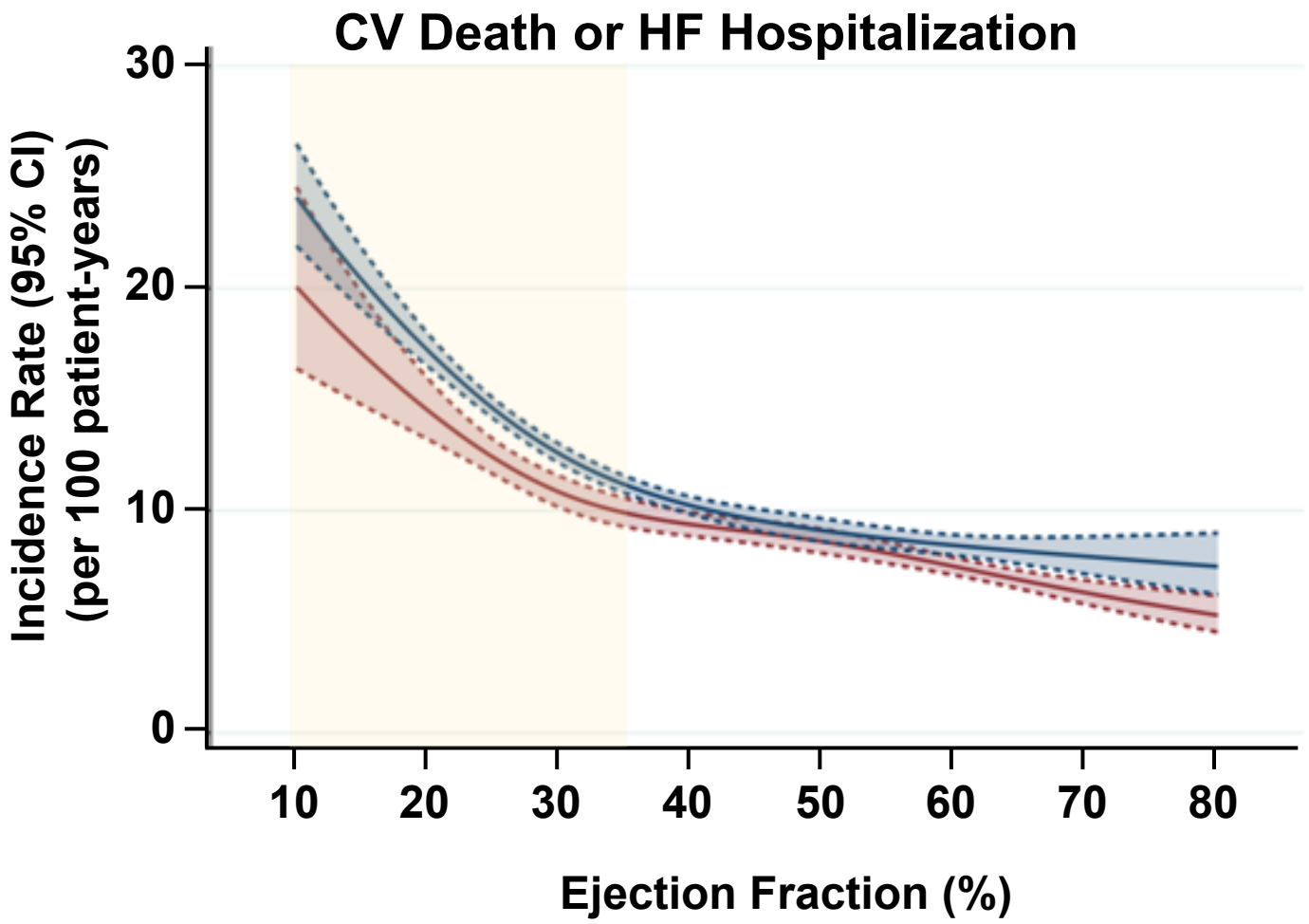
Greene SJ, *et al. JAMA.* 2021;326:2261-2262.

High Risk Features in HFrEF

- Lower ejection fraction
- Lower systolic blood pressure
- Higher NT-proBNP
- Recent HF hospitalization
- More severe symptoms (NYHA Class III-IV)

NT-proBNP=N-terminal pro-brain natriuretic peptide; NYHA=New York Heart Association

Heart Failure Risk Increases as Ejection Fraction Falls



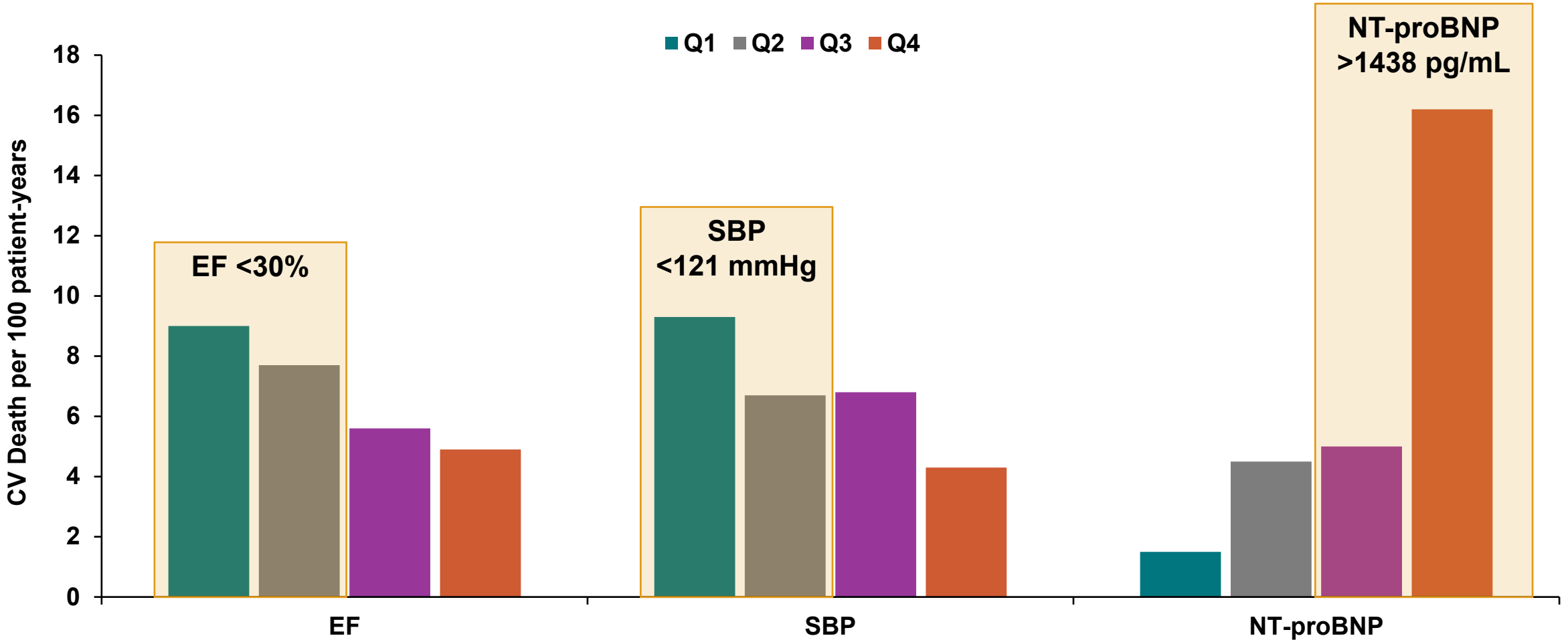
Combined Patient Level Analysis
6 Large Heart Failure Trials
N = 33,699 patients

Male
Female

Kondo T and McMurray JJV, *presented at ESC 2022*

Residual Risk in High-Risk Groups Despite Quadruple Therapy: CV Death

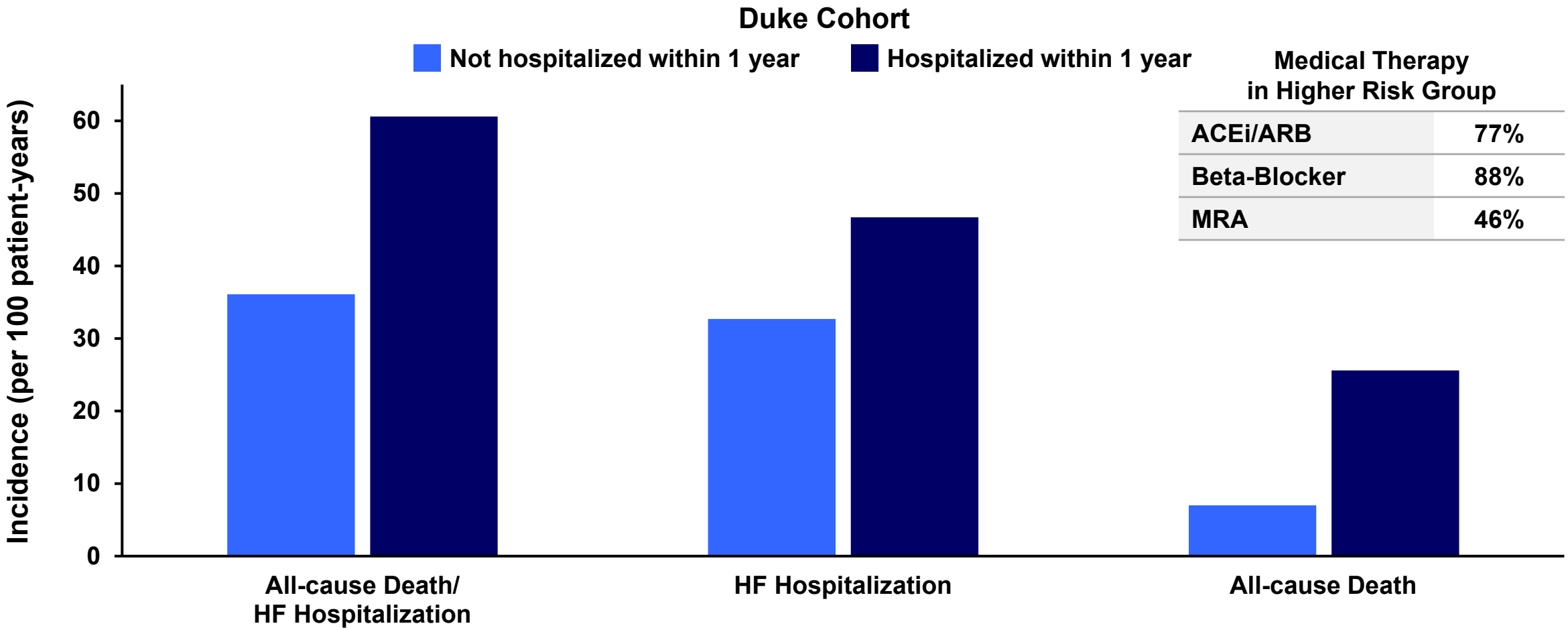
DAPA-HF Treatment Group



EF=Ejection Fraction; SBP=Systolic blood pressure

Real World Event Rates are Higher than Clinical Trials

Duke Heart Failure Cohort (LVEF <35%)

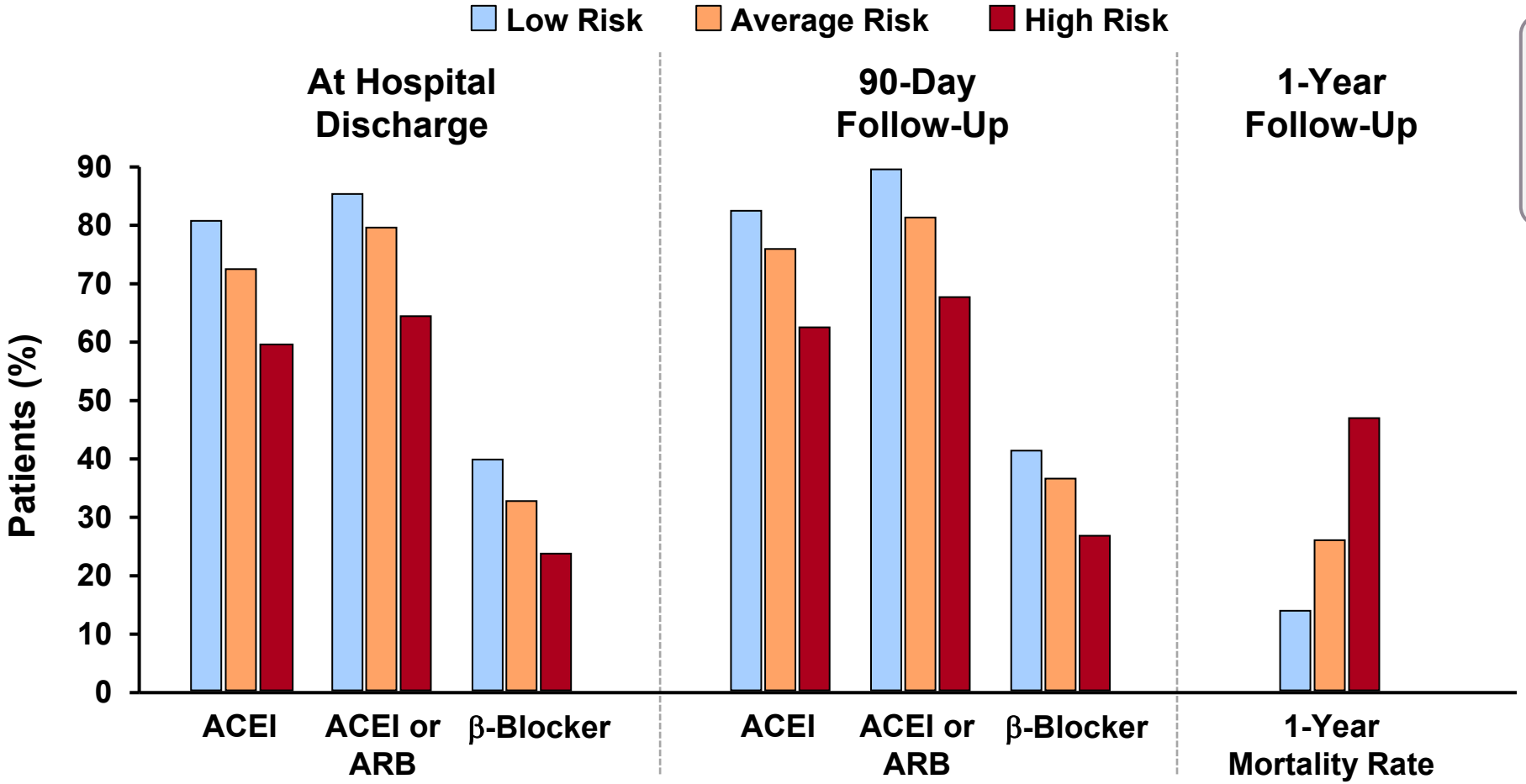


Medical Therapy in Higher Risk Group	
ACEi/ARB	77%
Beta-Blocker	88%
MRA	46%

Carnicelli et al. *J Am Heart Assoc.* 2021

Highest Risk Patients are Least Likely to be Treated

Risk-Treatment Mismatch in HF: Canadian EFFECT Study



The sickest patients are the most difficult to treat with existing therapies

GDMT LIMITATIONS

Renal Dysfunction
Azotemia
Hypotension
Hyperkalemia
Angioedema
Bradycardia
Fatigue

Lee D. *JAMA*. 2005;294:1240-1247

Challenges in Treating High Risk HFrEF Patients

- **Higher risk patients have the most to gain from effective therapies (greater absolute risk)**
- **Patients in higher risk groups are less likely to tolerate GDMT**
  - Older
  - More CKD and hyperkalemia
  - Lower blood pressure and less tolerance of orthostatic symptoms
  - Frailty/fatigue

Drug Intolerance to GDMT in HFrEF

Hypotension

- Diuretics
- ACE-inhibitors
- ARBs
- ARNIs
- Beta-blockers
- MRA
- Vericiguat

Azotemia/Renal/K^+

- Diuretics
- ACE-inhibitors
- ARBs
- ARNIs
- MRA

Bradycardia/Fatigue

- Beta-blockers

Angioedema

- ACE-inhibitors
- ARBs
- ARNIs

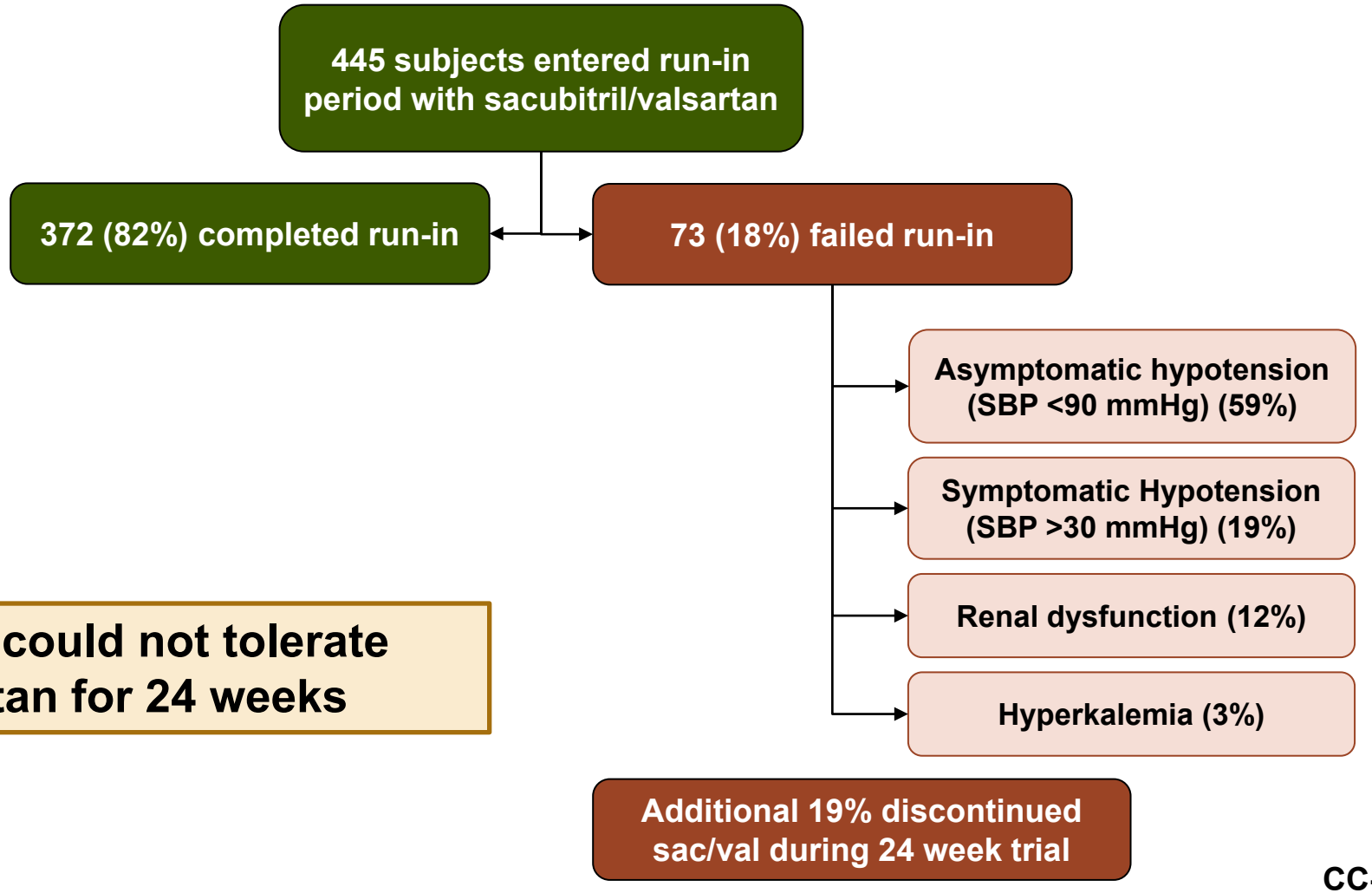
K^+=potassium

Higher Risk HFrEF Patients and GDMT Intolerance

LIFE Study Population

EF	20%
Ischemic (%)	78%
SBP (mmHg)	113
NT-proBNP (pg/mL)	1874
eGFR(mL/min/1.73m^2)	63

Noncompletion of Run-In with Sacubitril/Valsartan in the LIFE Trial[1]



Cumulatively 37% could not tolerate sacubitril/valsartan for 24 weeks

Vader JM, et al. *J Am Coll Cardiol HF*. 2022;10(7):449-458

Conclusions

- **Despite improvement in GDMT, there is substantial residual risk in patients with HFrEF**
- **High risk subgroups are at particularly high risk and less likely to tolerate GDMT**
- **There is an unmet need for therapies that improve outcomes in higher risk HFrEF subgroups and do not have overlapping intolerances with current therapies**

Efficacy of Omecamtiv Mecarbil in HFrEF

Fady Malik, MD, PhD, FACC, FHFA

Executive Vice President,
Research & Development Cytokinetics

Presentation Outline

1. Mechanism of Action
2. Overview Phase 1 and Phase 2 Clinical Development
3. GALACTIC-HF: Main Efficacy Results
4. GALACTIC-HF: EF and High-Risk HF Subgroup Analyses

Targeting the Cardiac Sarcomere

Rationale for Therapeutic Development

Current Inotropes

Increase myocyte calcium via

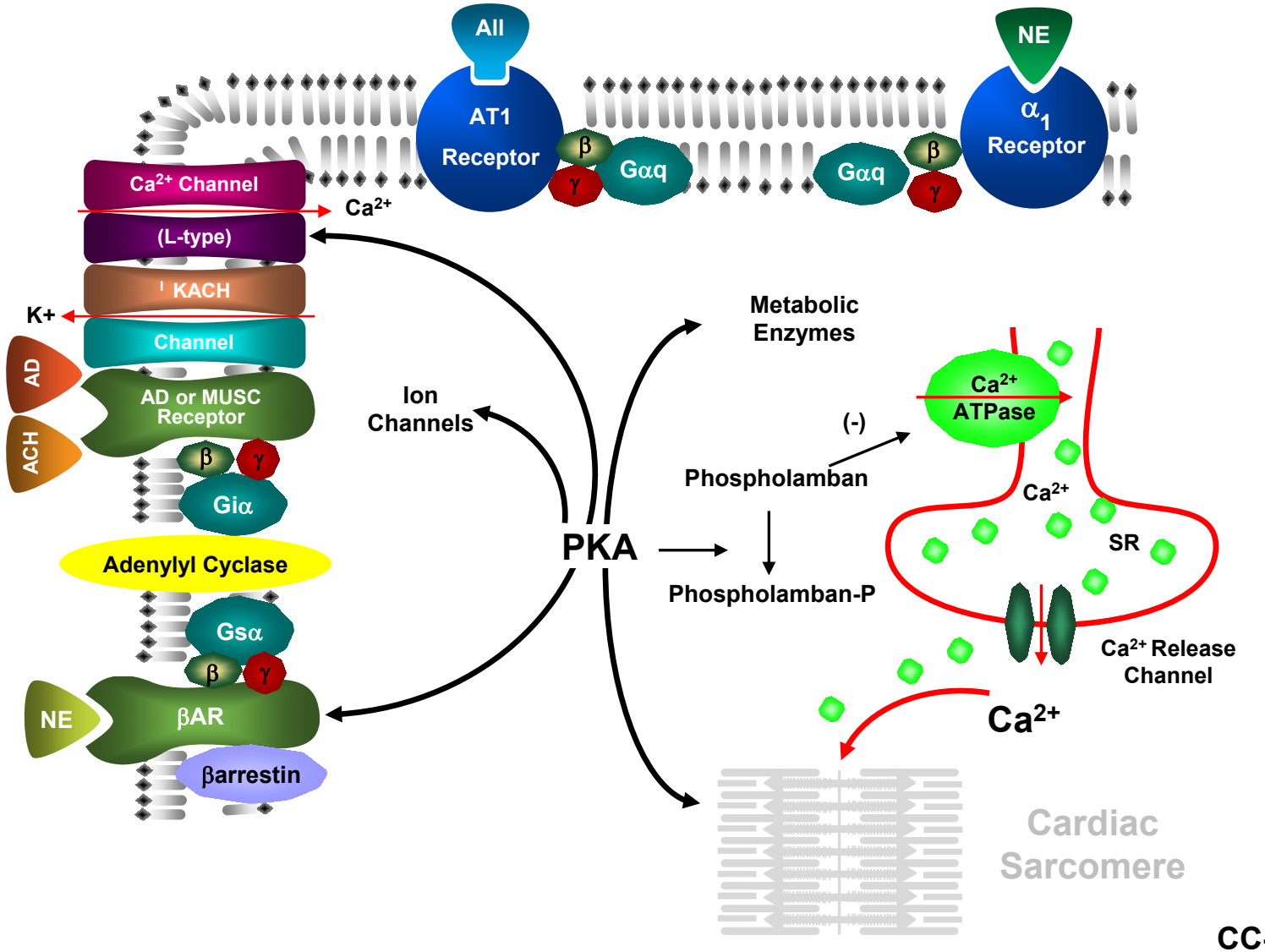
PKA activation

↓

Intracellular [Ca^{2+}] increased

↓

- ↑ **Contractility**
- ↑ **Heart rate**
- ↓ **Blood Pressure**
- ↑ **O_2 Demand**
- ↓ **Efficiency**
- ↑ **Arrhythmias**



PKA=Protein Kinase A

Targeting the Cardiac Sarcomere

Rationale for Therapeutic Development

Therapeutic Hypothesis

Directly target the sarcomere

Ø PKA activation

↓

Intracellular [Ca^{2+}] unchanged

↓

- ↑ **Contractility**
- ↔ **Heart rate**
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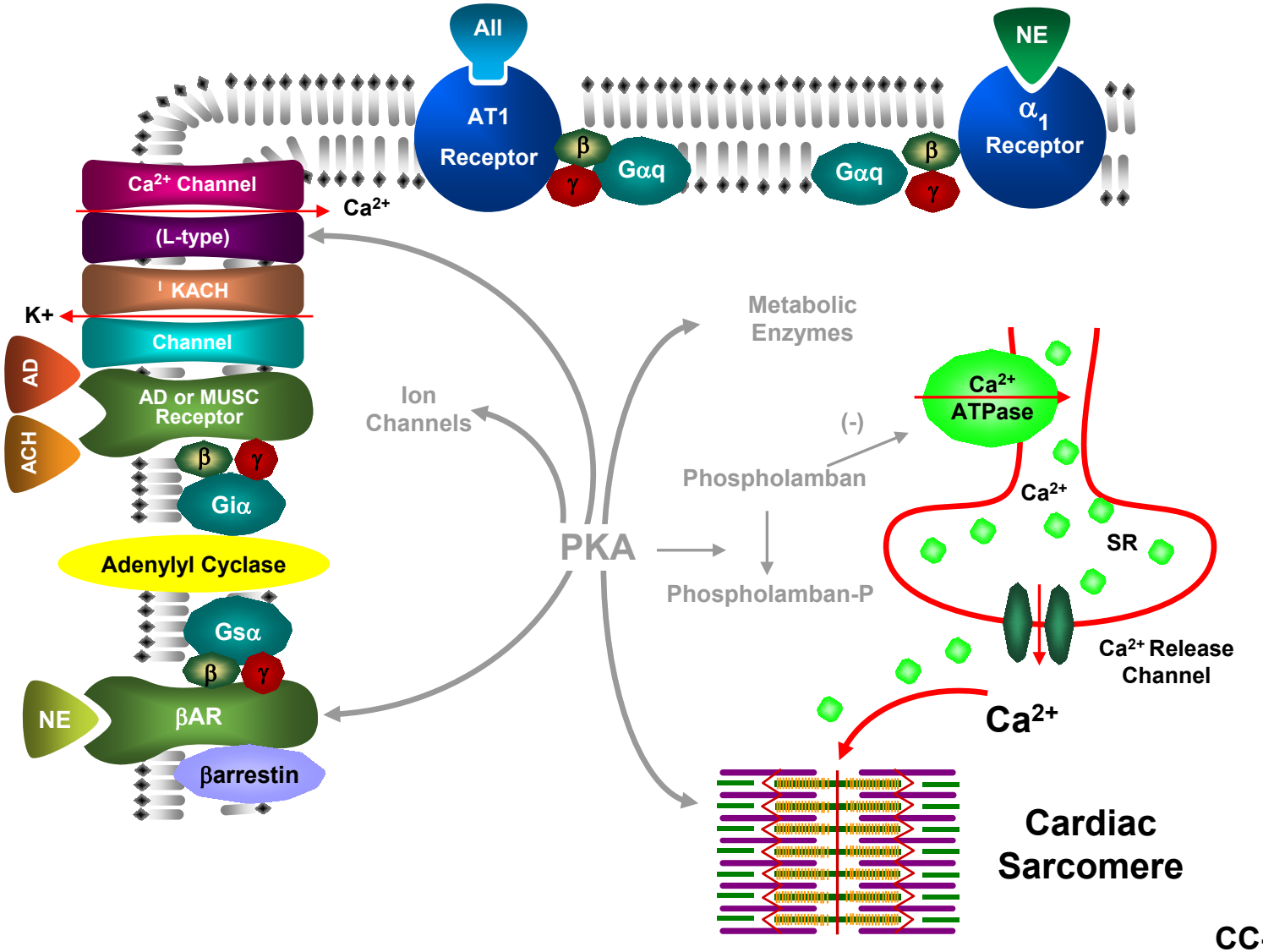
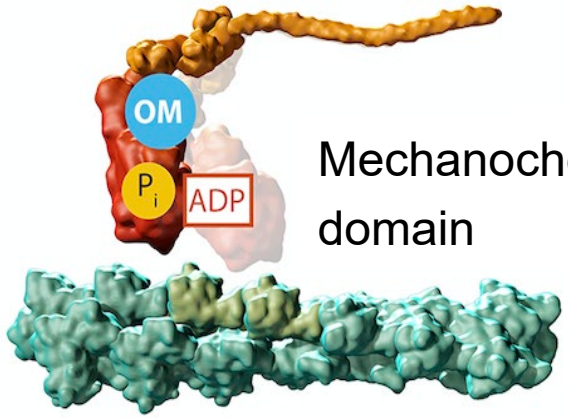


PKA=Protein Kinase A

Mechanism of Action

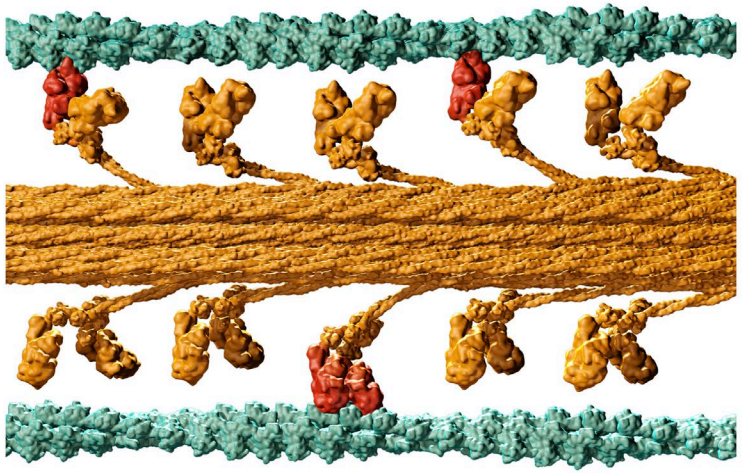
Omecamtiv mecarbil shifts equilibrium in favor of the pre-powerstroke state
"More hands pulling on the rope"



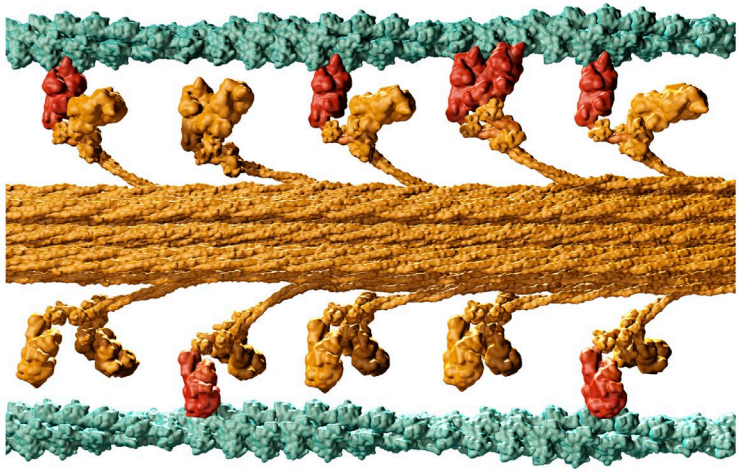
Mechanochemical domain

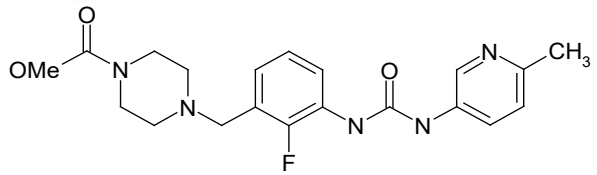
Pre-Powerstroke State

Before Omecamtiv Mecarbil



After Omecamtiv Mecarbil





Omecamtiv Mecarbil
(MW=401.43)

Malik, et al. *Science* 2011; 1439-1443
Planelles-Herrero, et al. *Nature Comm* 2017; 1-10
Shen et al, *Circ HF*, July 2010, 522-527
Teerlink, et al. *JACC-HF* 2020; 329-340

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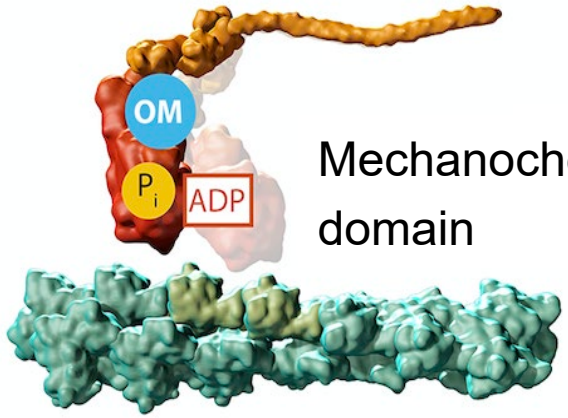
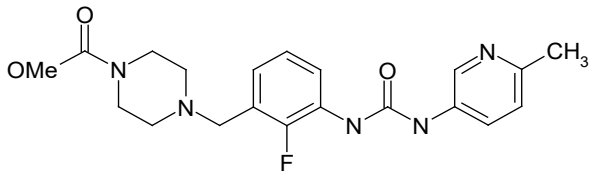


Pre-Powerstroke State

- **No increase in myocyte calcium**
- **Increases ejection fraction**
- **Increases duration of systole**
- **Increases stroke volume**
- **No change in blood pressure**
- **No increase in MVO_2**



Omecamtiv Mecarbil
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MVO_2=Myocardial Volume Oxygen

Malik, et al. *Science* 2011; 1439-1443
Planelles-Herrero, et al. *Nature Comm* 2017; 1-10
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Overview Phase 1 and Phase 2 Clinical Development

Key Phase 1 and Phase 2 Clinical Trials

Study #	N	Form	Trial Objectives	Results	
Healthy Participants (CY 1111)	34	IV	Safety and tolerability PK/ PD	PK:	Linear, Dose Proportional
				Echo:	Dose and concentration dependent increases in cardiac function
				Safety:	Well- tolerated up to MTD
Stable Heart Failure (CY 1121)	45	IV	Safety and tolerability PK/PD	PK:	Linear, Dose Proportional
				Echo:	Dose and concentration dependent increases in cardiac function
				Safety:	Well- tolerated up to MTD
Ischemic Cardiomyopathy (CY 1221)	94	IV Oral	Safety	Well-tolerated in the context of symptom-limited exercise	
ATOMIC-AHF	613	IV	Safety and tolerability, PK/PD, potential efficacy	Well-tolerated in inpatients with acute heart failure	
COSMIC-HF	544	Oral	Safety and tolerability, PK/PD	PK:	Consistent exposure over 20 weeks
				Echo:	Sustained improvements in cardiac function over 20 weeks of dosing
				Safety:	Well- tolerated in an outpatients with HFrEF

Supported design of a Phase 3 trial in a high-risk HF population inclusive of both inpatients and outpatients

MTD=maximum tolerated dose; PK=pharmacokinetics; PD=pharmacodynamics

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Study #	N	Form	Trial Objectives	Results
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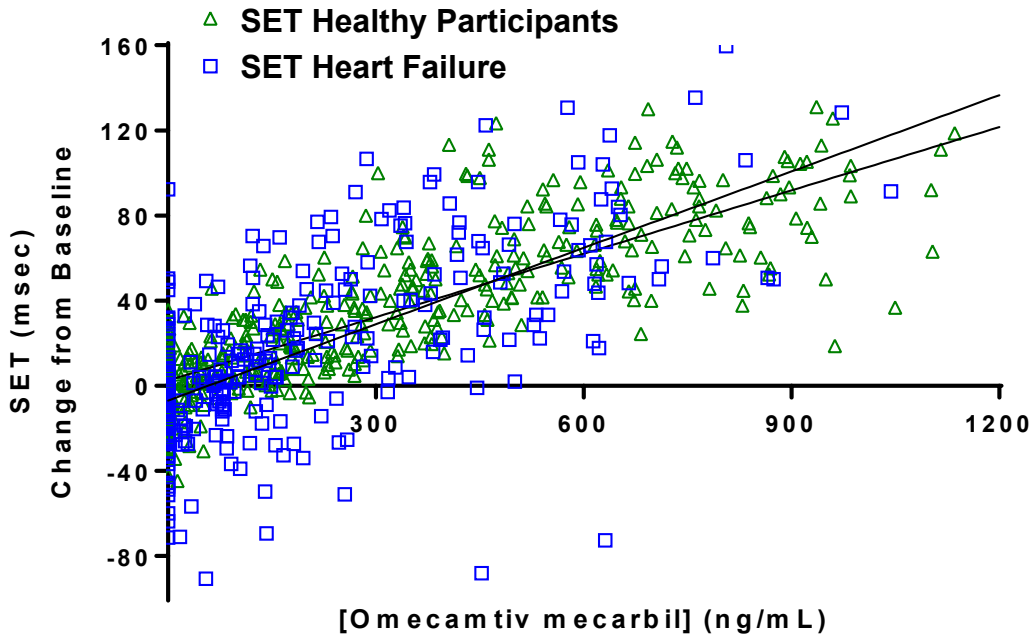
Omecamtiv Mecarbil Improves Cardiac Function

Systolic ejection time is a sensitive, exposure-dependent marker of drug effect

Healthy Participants vs. Stable HF Patients



Dose Ranging Finding Studies in Phase 1 (Healthy Participants) and Phase 2a (Stable HF Patients)

SET=Systolic Ejection Time
Teerlink JR, *et al. Lancet* 2011; 378: 667–75. Cleland JGF, *et al. Lancet* 2011; 378: 676–83.
Δ=placebo corrected change from baseline; Mean ± St Err of Mean

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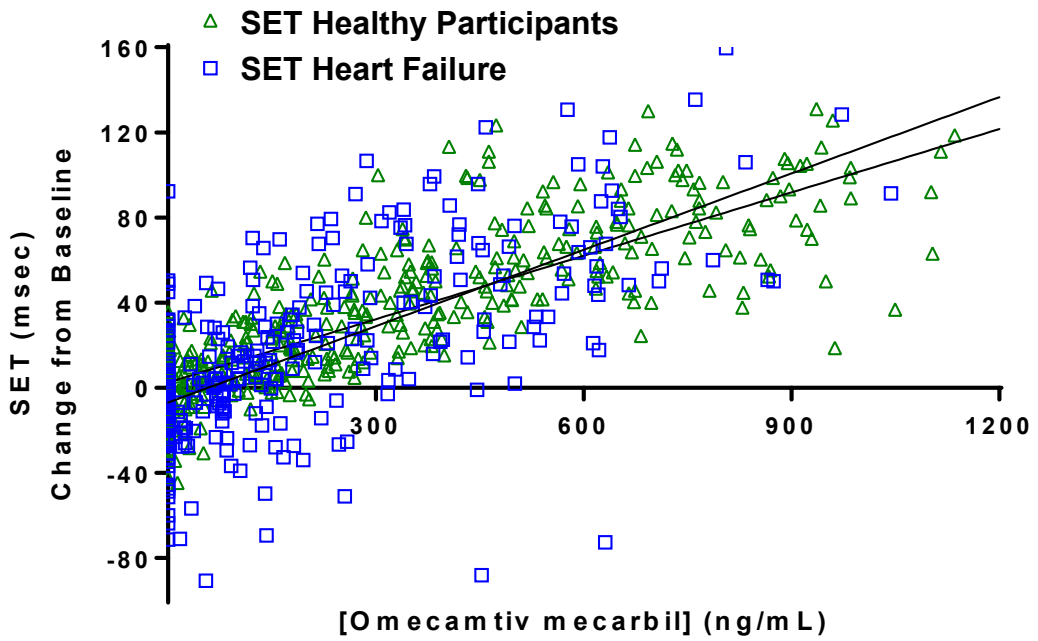
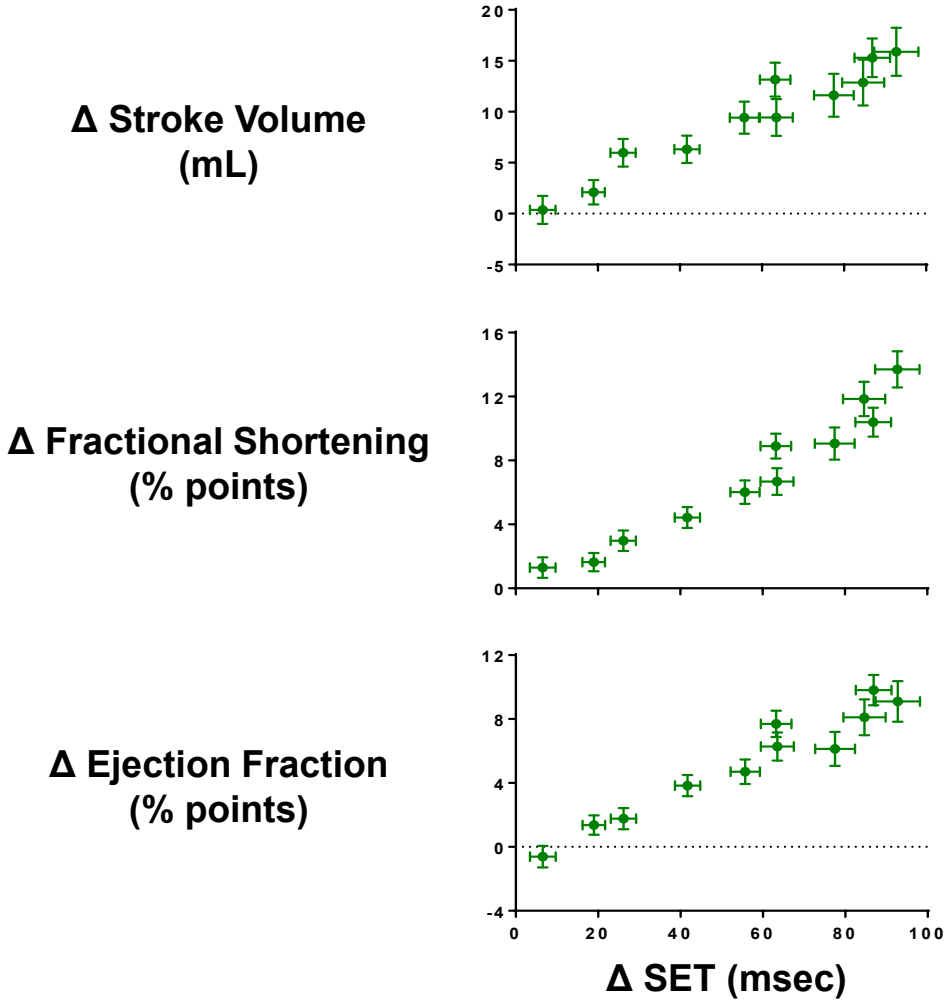
Healthy Participants vs. Stable HF Patients



Dose Ranging Finding Studies in Phase 1 (Healthy Participants) and Phase 2a (Stable HF Patients)

Healthy Participants



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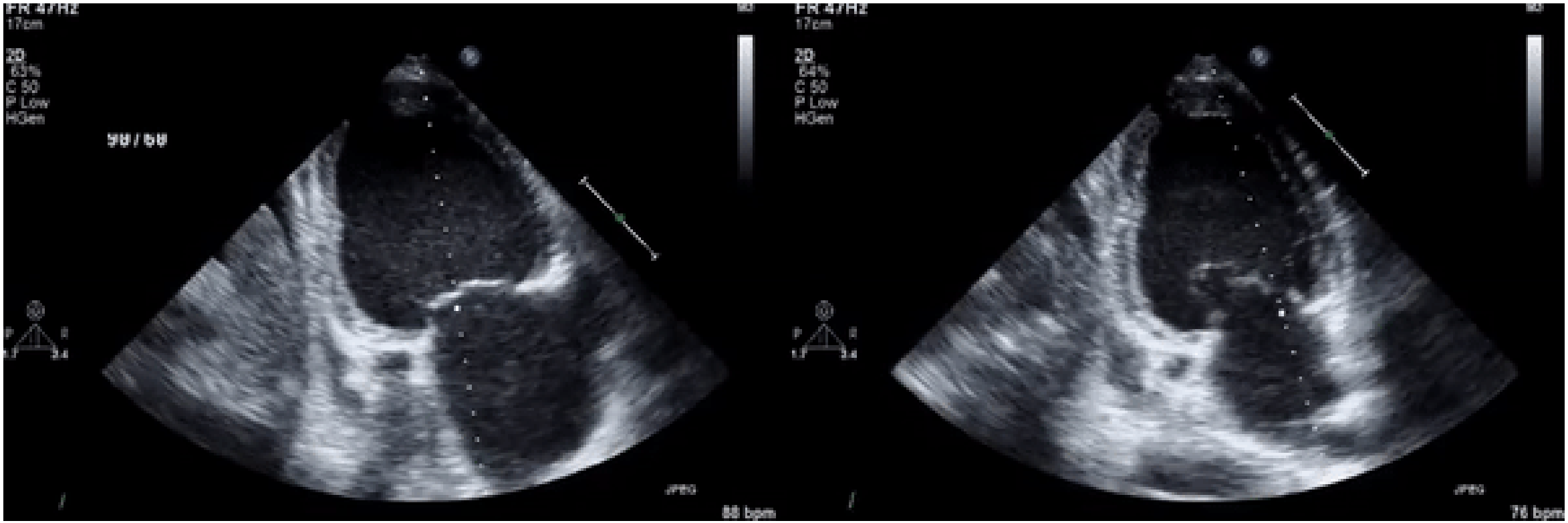
Effect of Omecamtiv Mecarbil on Cardiac Function

Illustrative Example

Before Treatment

After 24 hr Infusion

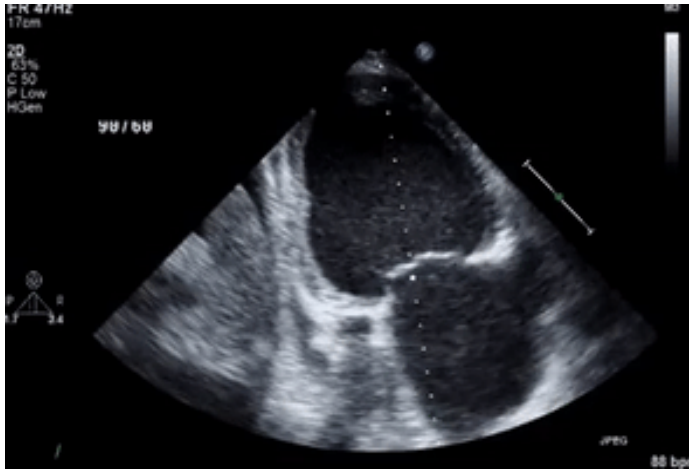


Cleland, et al. *Lancet* 2011; 667-675
Images and data from patient enrolled in CY 1121

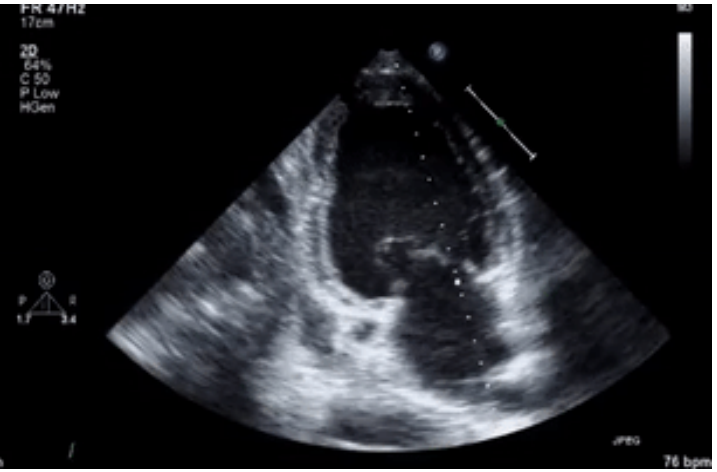
Effect of Omecamtiv Mecarbil on Cardiac Function

Illustrative Example

Before Treatment



After 24 hr Infusion



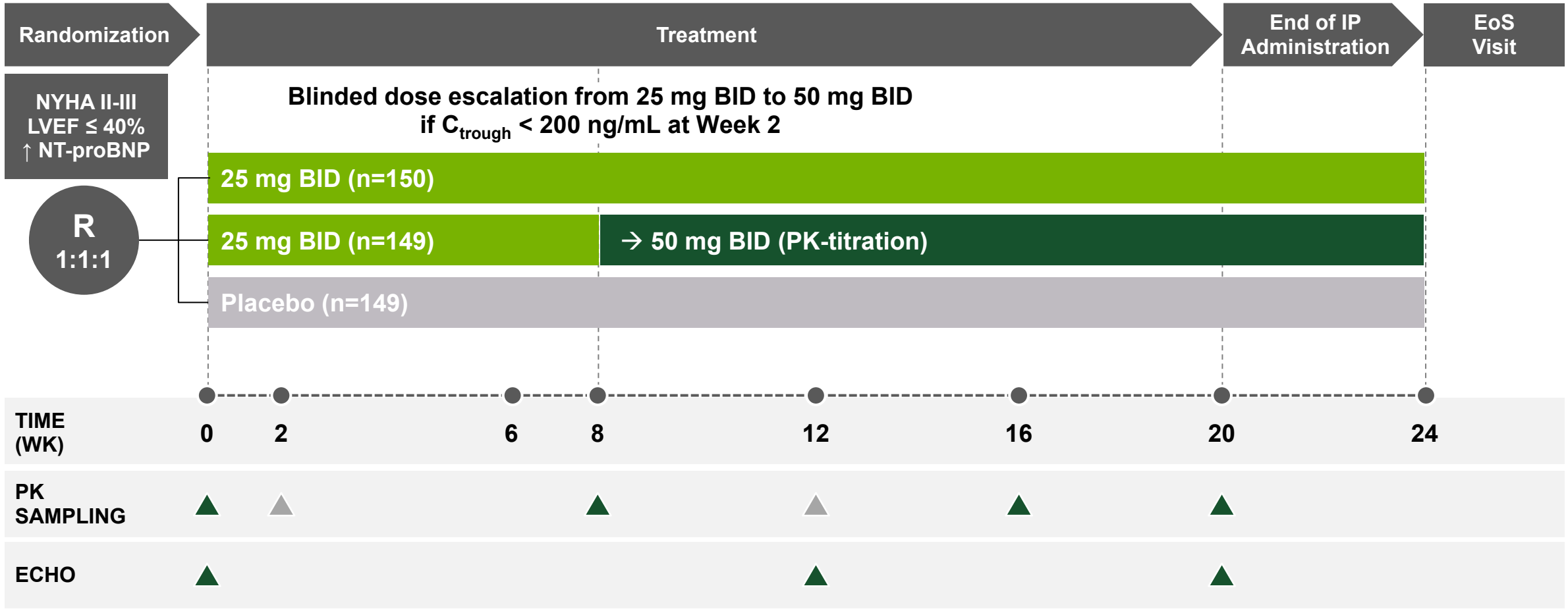
Characteristic	Omecamtiv Mecarbil	Placebo
LVOT SV (mL)		
Baseline	**23**	**26**
24 hrs	**54**	**24**
EF (%)		
Baseline	**18**	**18**
24 hrs	**23**	**18**
HR (bpm) – supine ECG		
Baseline	**88**	**85**
24 hrs	**57**	**86**
SET (msec)		
Baseline	**216**	**234**
24 hrs	**311**	**225**
Plasma Concentration (ng/mL)		
Baseline	**-**	**-**
24 hrs	**378**	**-**

LVOT=Left Ventricular Outflow Tract; SET=Systolic Ejection Time

Cleland, et al. *Lancet* 2011; 667-675

Images and data from patient enrolled in CY 1121

COSMIC-HF: Phase 2 Clinical Trial

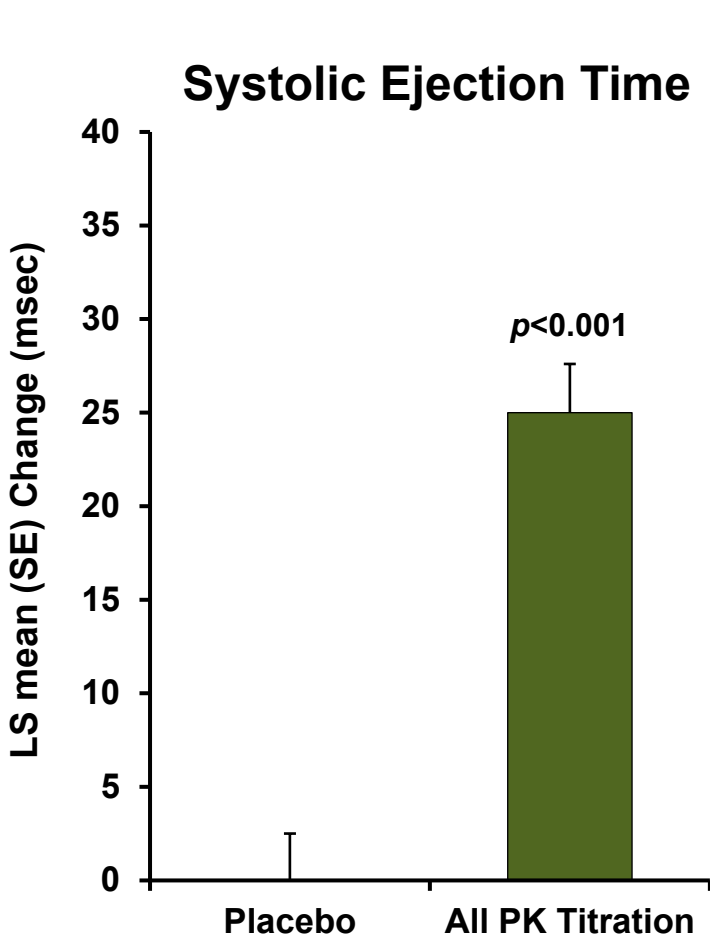


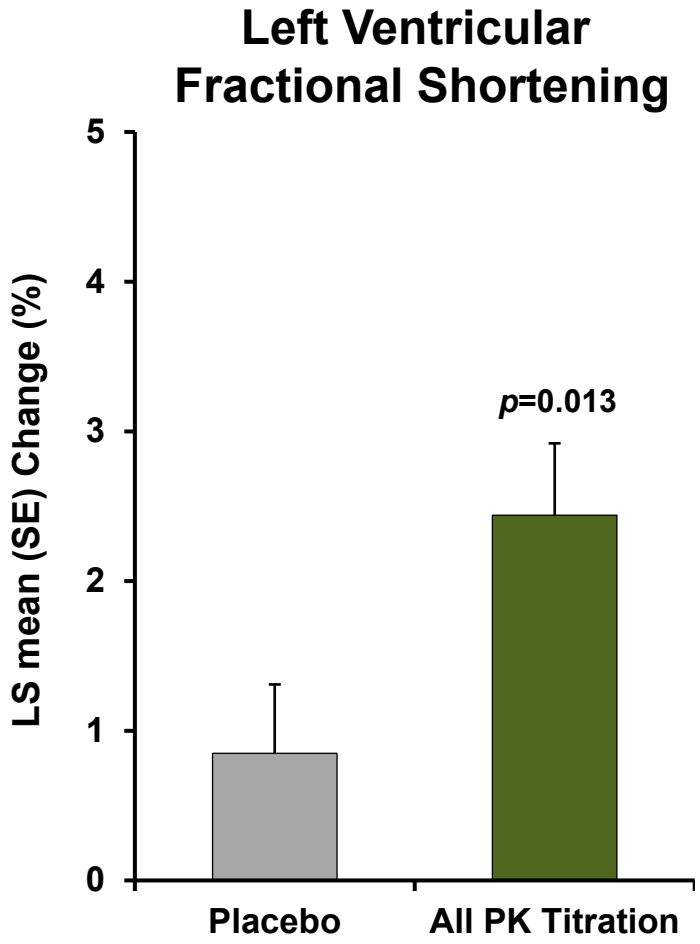
PK sampling: ▲ predose, ▲ intensive PK
Echo=echocardiographic parameters; IP=investigational product
Teerlink, et al. *Lancet* 2016; 2895-2903

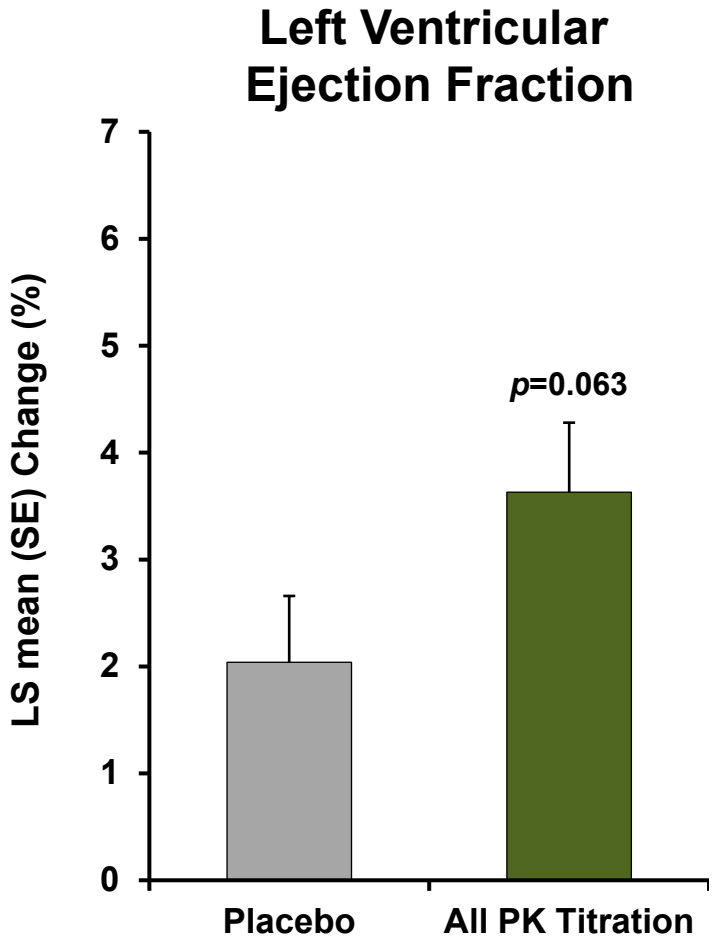
Durable Increases in Cardiac Function

Pharmacodynamic Results After 20 Weeks of Double-blind Treatment

COSMIC-HF



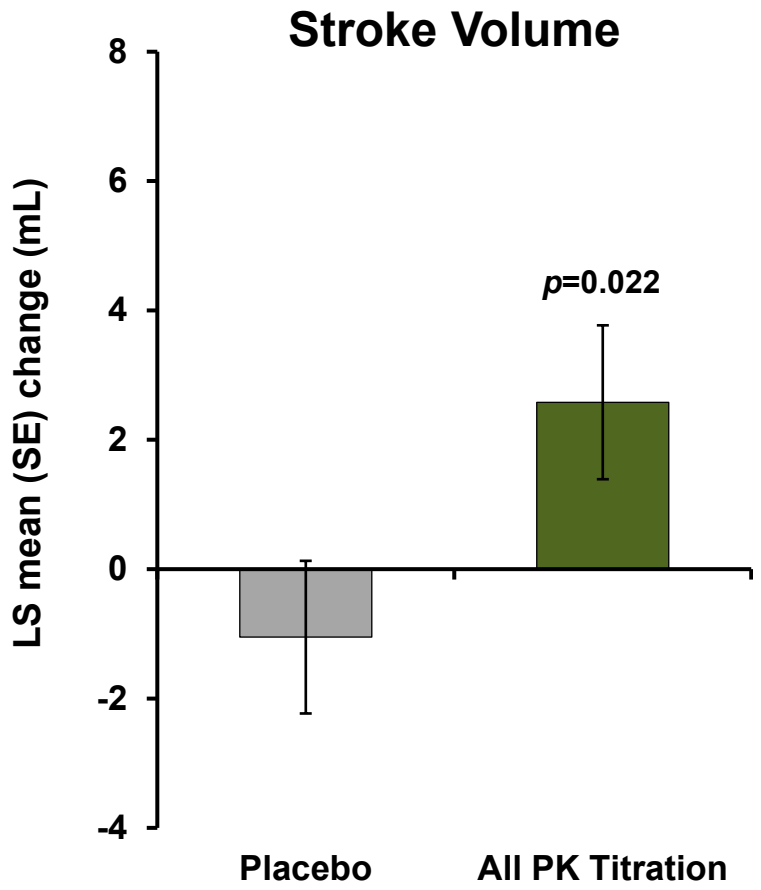


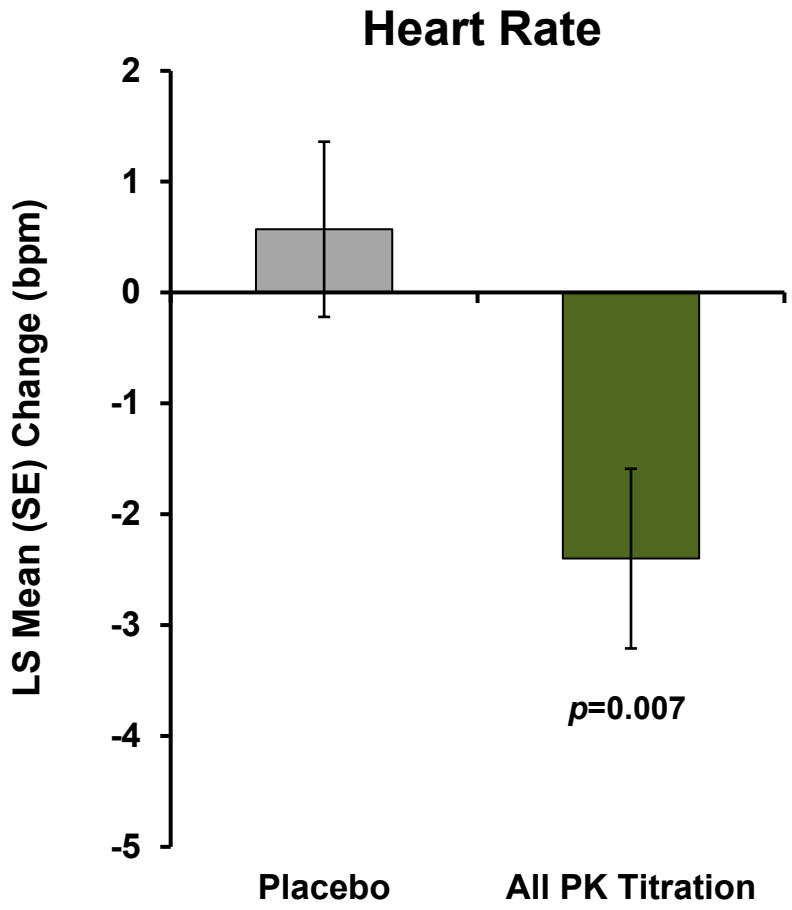


Teerlink et al. *Lancet* 2016
LS = least squares; SE=Standard Error

Stroke Volume Increased; Heart Rate Decreased

Pharmacodynamic Results After 20 Weeks of Double-blind Treatment

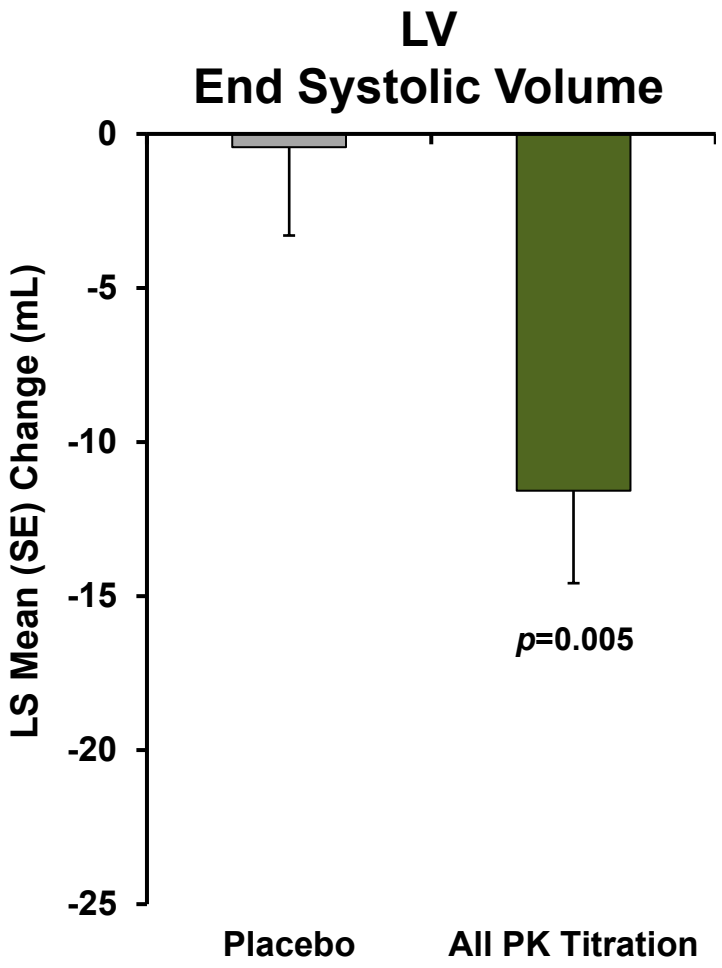


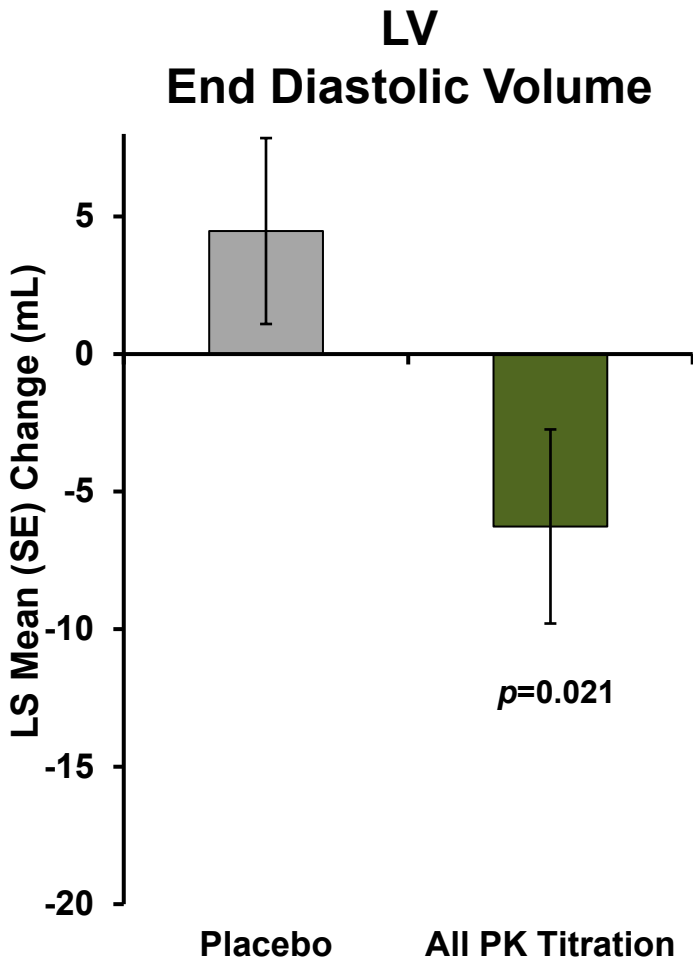


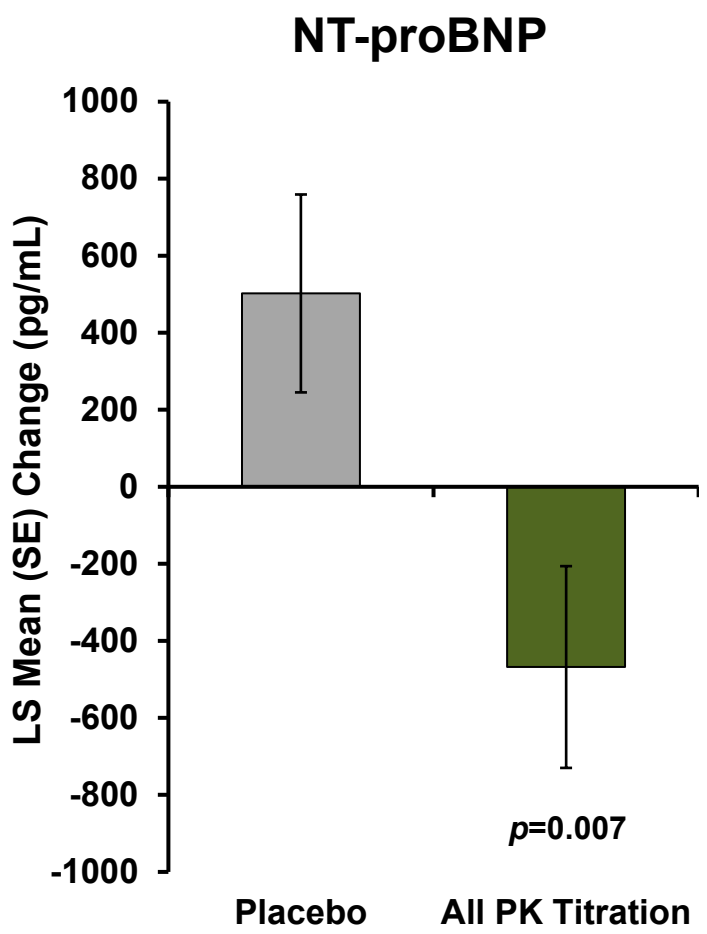
Teerlink et al. *Lancet* 2016

Decreases in Cardiac Volumes and NT-proBNP

Pharmacodynamic Results After 20 Weeks of Double-blind Treatment







Teerlink et al. *Lancet* 2016

LVESD=Left ventricular end systolic diameter; LVEDD=Left ventricular end diastolic diameter; LVESV=Left ventricular end systolic volume; LVEDV=Left ventricular end diastolic volume

GALACTIC-HF: Main Efficacy Results

GALACTIC-HF: Clinical Trial Overview

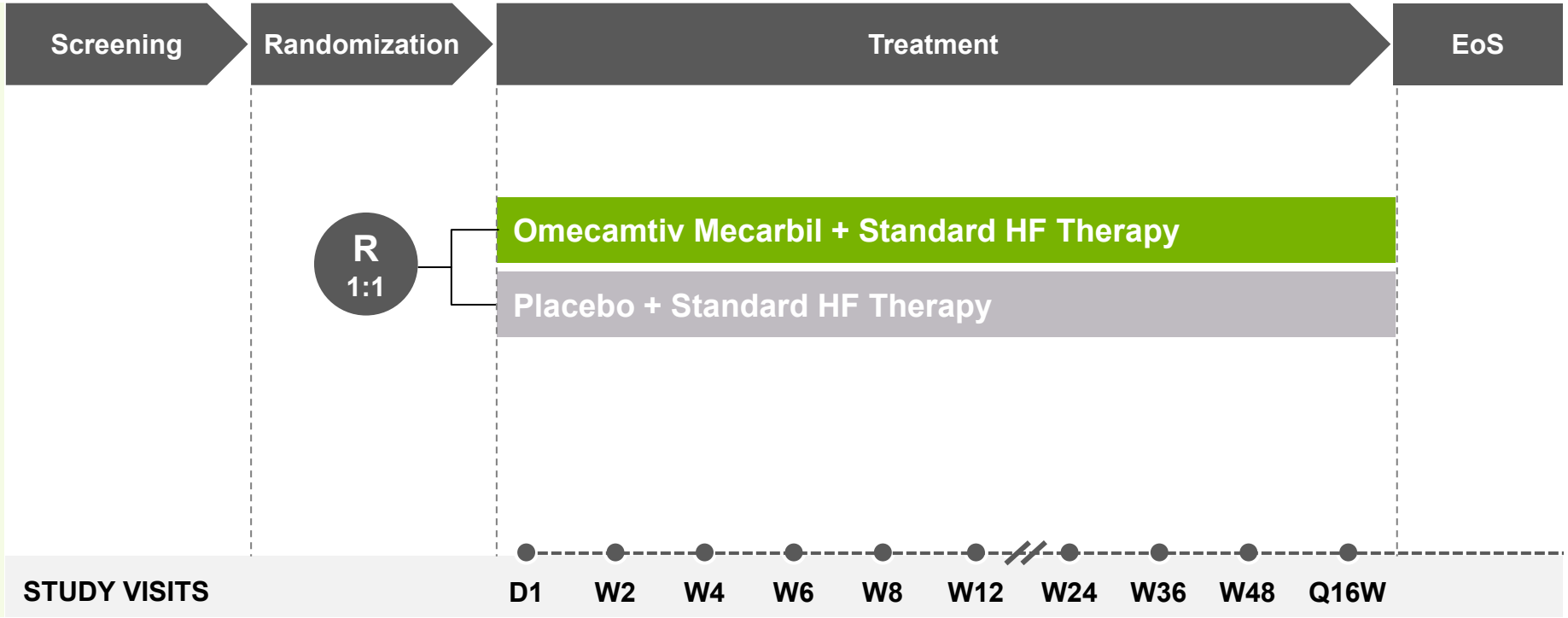
Multicenter, randomized, double-blind, placebo-controlled, event-driven Phase 3 study

8256 patients randomized in 35 countries at 944 clinical trial sites

HFrEF PATIENTS (LVEF ≤35%)

CURRENTLY hospitalized for primary reason of HF
(**INPATIENTS:** 25% of enrollment)

HISTORY of hospitalization or ER/ED admission for a primary reason of HF within 1 year
(**OUTPATIENTS:** 75% of enrollment)



Subject #1 enrolled	Subject #8256 enrolled	GALACTIC-HF results
JAN 2017	JUL 2019	NOV 2020

GALACTIC-HF: Clinical Trial Overview

Overview

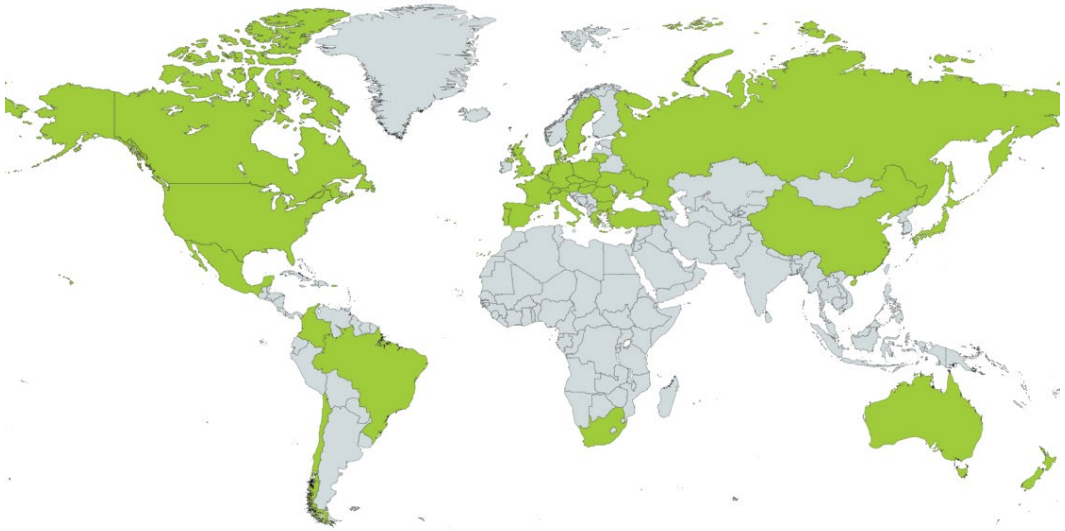
Enrolled 8,256 patients at ~1,000 sites in 35 countries

Primary Composite Endpoint

Composite of time to cardiovascular (CV) death or first HF event*, whichever occurs first

Secondary Endpoints

- Time to CV death
- Change in Kansas City Cardiomyopathy Questionnaire Total Symptoms Score (KCCQ TSS) from baseline to Week 24
- Time to first HF hospitalization
- Time to all-cause death



Second largest clinical trial ever conducted in heart failure
Most patients enrolled in North America (N=1386) in a contemporary heart failure trial

*An HF event defined as the presentation of the subject for an urgent, unscheduled clinic/office/ED visit, or hospital admission, with a primary diagnosis of HF, where the patient exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF (Hicks et al, 2015). Changes to oral diuretic therapy do not qualify as initiation or intensification of treatment.

Baseline Demographics and Medical History

GALACTIC-HF

Characteristic	Omecamtiv Mecarbil N=4120	Placebo N=4112
Demographics		
Age (years), median (Q1, Q3)	66 (58, 73)	66 (58, 73)
Sex, female, %	21	21
White/Asian/Black/other, %	78/9/7/7	78/9/7/7
Inpatient, n (%)	1044 (25.3)	1040 (25.3)
Heart Failure History and Medical Conditions		
Heart failure event prior to randomization (outpatients), median (months)	3.2	3.1
LVEF (%), mean (SD)	27 (6)	27 (6)
LVEF (%), median	28	28
NYHA class, II/III/IV, %	53/44/3	53/44/3
Ischemic etiology, %	53	54
Atrial fibrillation/flutter at screening, %	28	27
Type 2 diabetes, %	40	40

Teerlink JR, et al. *Eur J Heart Fail* 2020; 22:2160-71. Q=quartile

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Baseline Characteristics and Medical Therapy

GALACTIC-HF

Characteristic	Omecamtiv Mecarbil N=4120	Placebo N=4112
Vital signs and Laboratory Parameters		
SBP (mmHg), mean (SD)	116 (15)	117 (15)
Heart rate, mean (SD)	72 (12)	72 (12)
eGFR (mL/min/1.73m^2), median (Q1, Q3)	59 (44, 74)	59 (44, 74)
NT-proBNP (pg/mL), median (Q1, Q3)	1977 (980, 4061)	2025 (1000, 4105)
Cardiac TnI (ng/mL), median (Q3)	0.027 (0.052)	0.027 (0.052)
Medications and Cardiac Devices		
ACEI/ARB/ARNi , %	87	87
ARNi, %	20	19
BB, %	94	94
MRA, %	78	78
SGLT2i, %	2.5	2.8
CRT, %	14	14
ICD, %	32	31

Teerlink JR, et al. *Eur J Heart Fail* 2020; 22:2160-71.
BB=beta blocker; CRT=cardiac resynchronization therapy; eGFR=estimated glomerular filtration rate; fib=fibrillation; TnI=troponin I; ICD=implantable cardioverter-defibrillator

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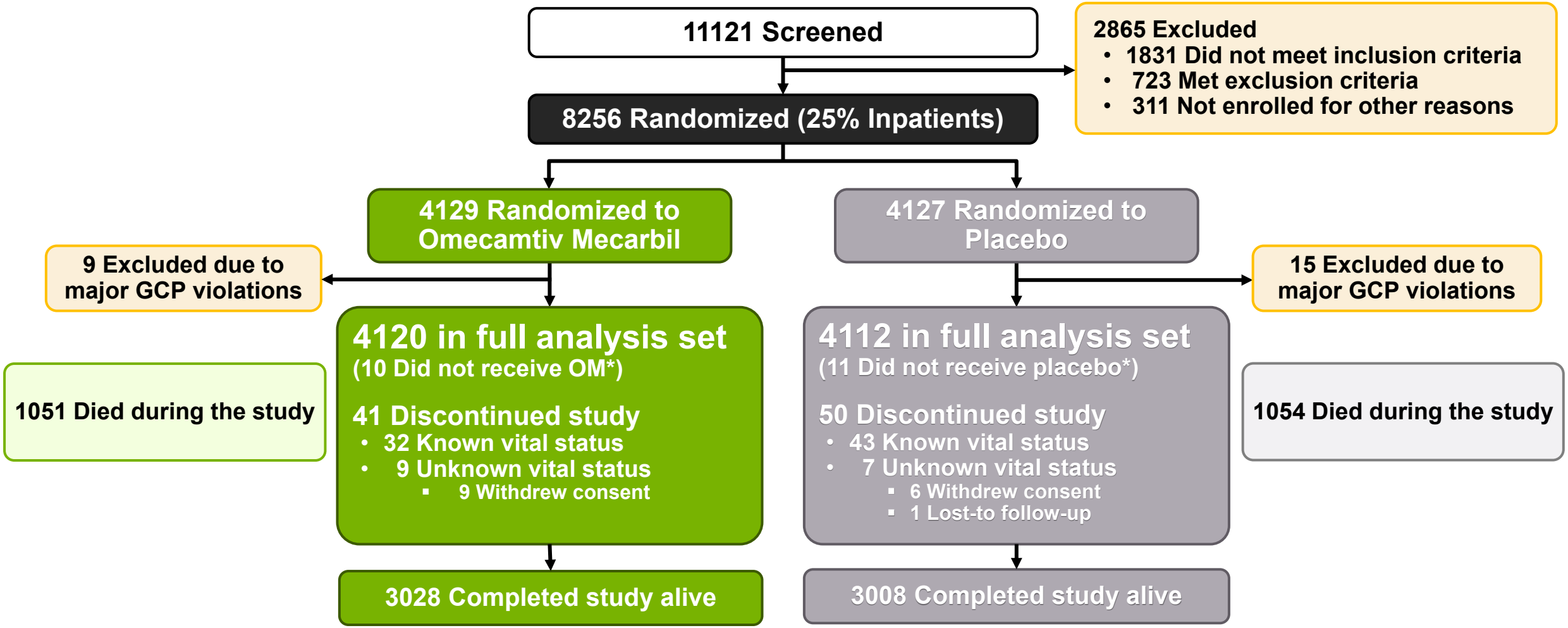
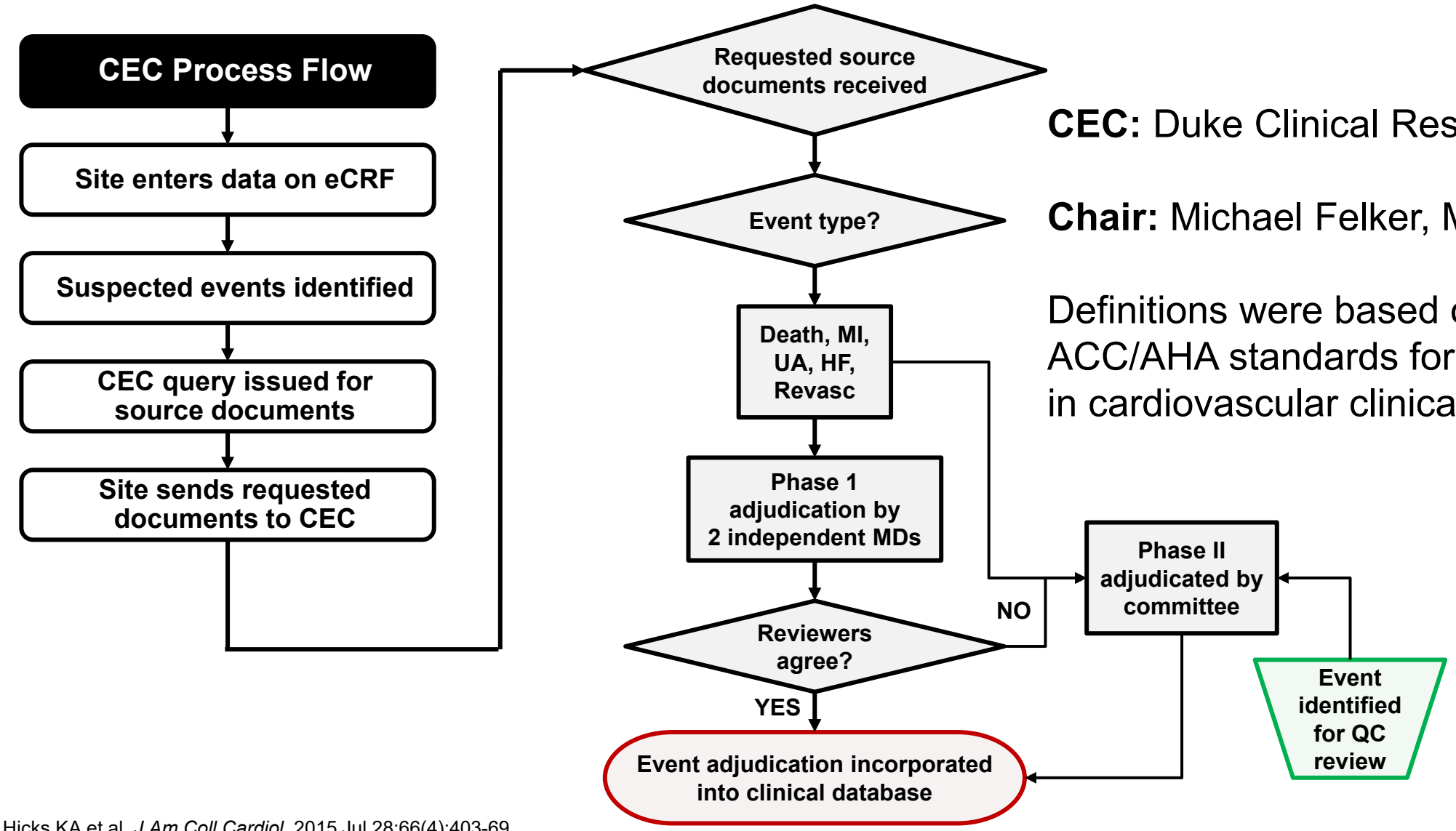
Patient Disposition



Overall median study exposure was 21.8 months

Teerlink JR, et al., *N Engl J Med* 2021; 384:Supplementary Appendix. GCP=good clinical practice; *Not included in safety analysis set.

Clinical Events Committee



CEC: Duke Clinical Research Institute

Chair: Michael Felker, MD

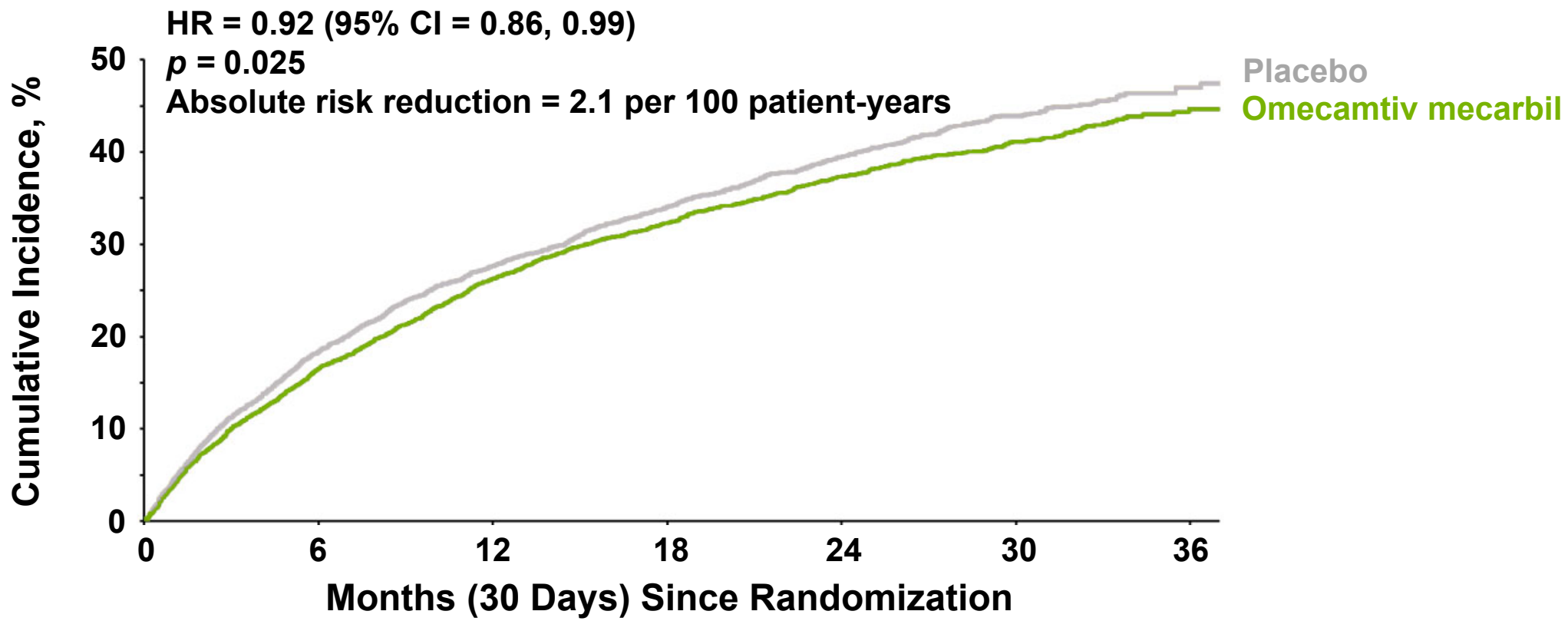
Definitions were based on the 2014 ACC/AHA standards for endpoint definitions in cardiovascular clinical trials*

* Hicks KA et al. *J Am Coll Cardiol*. 2015 Jul 28;66(4):403-69

Primary Composite Endpoint

Time to First Heart Failure Event or Cardiovascular Death

GALACTIC-HF



Patients at risk, n

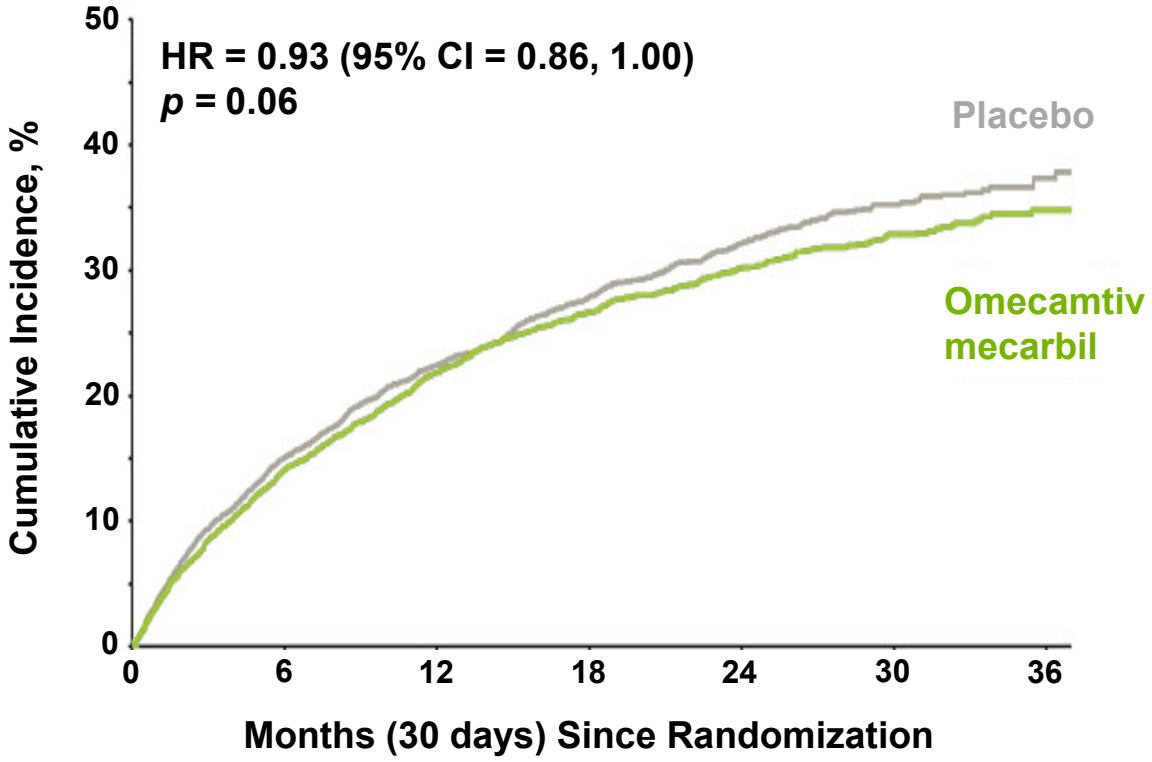
Placebo	4112	3310	2889	2102	1349	647	141
Omecamtiv mecarbil	4120	3391	2953	2158	1430	700	164

CI=confidence interval; HR=hazard ratio

Individual Components of Primary Endpoint

GALACTIC-HF

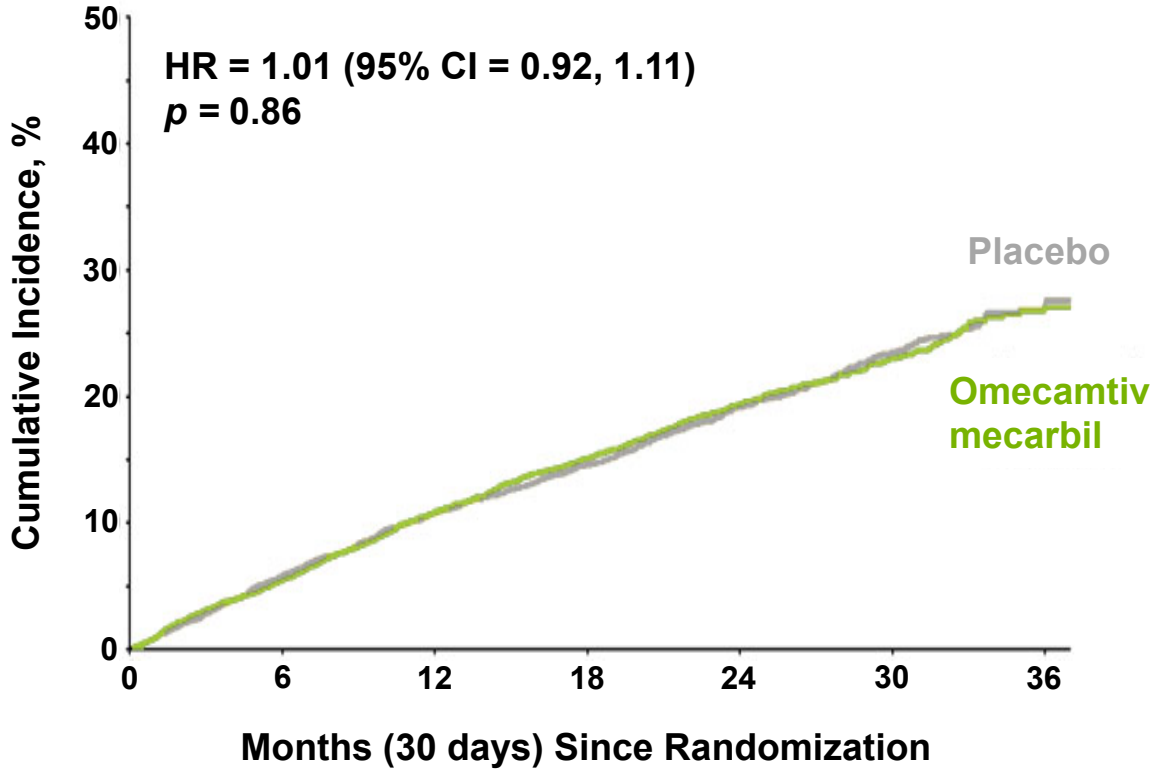
First Heart Failure Event



Patients at risk, n

Placebo	4112	3309	2889	2102	1348	647	141
OM	4120	3391	2953	2156	1430	699	164

Cardiovascular Death

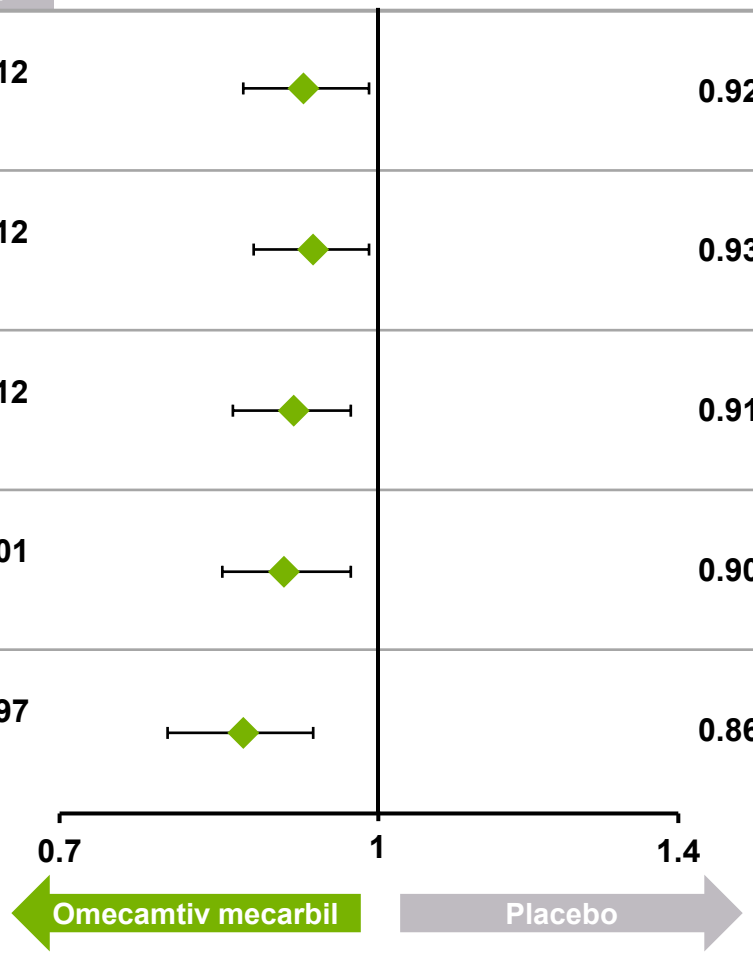


4112	3821	3560	2722	1788	885	201
4120	3838	3556	2710	1838	903	224

Sensitivity Analyses

GALACTIC-HF

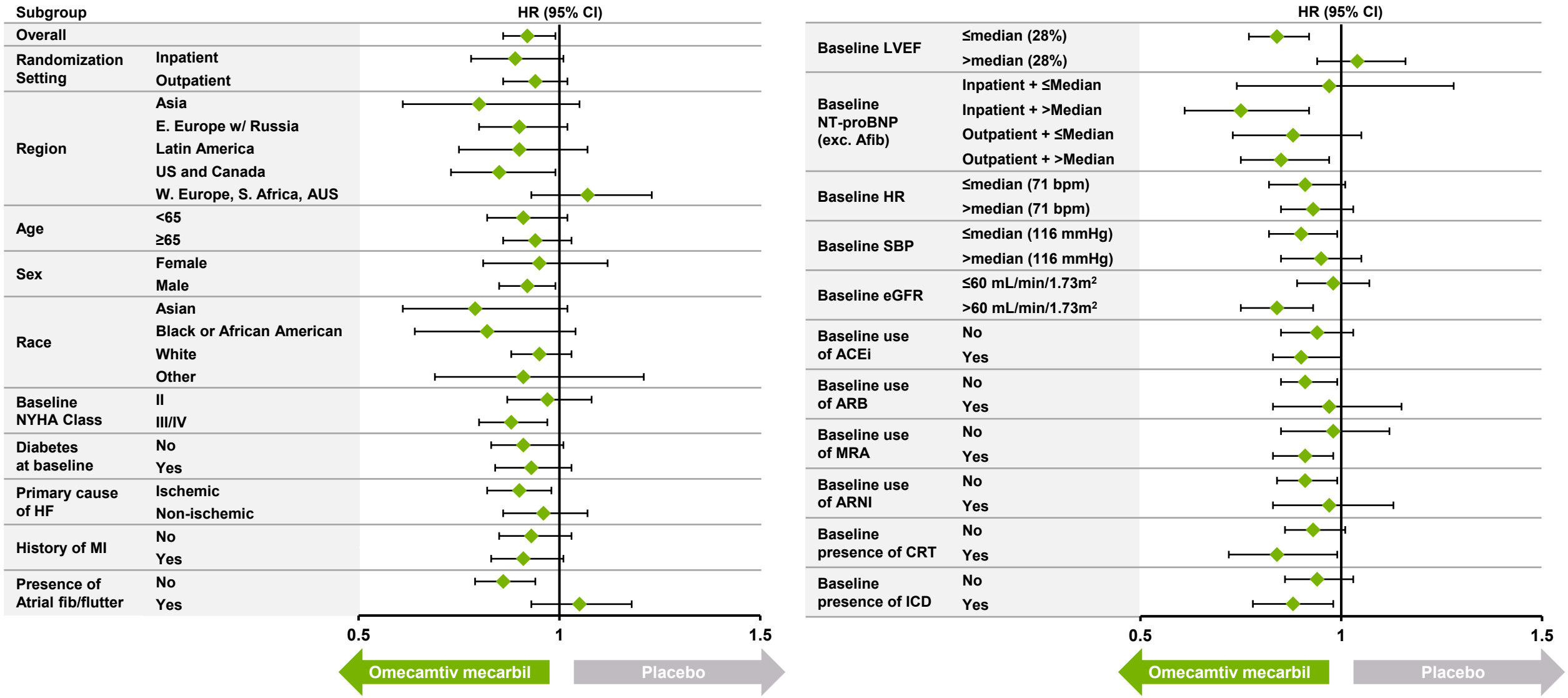
	OM n/N (%)	Placebo n/N (%)	HR (95% CI)	*p*-value	ARR (per 100 pt yrs)
Primary Analysis*	1523/4120 (37.0)	1607/4112 (39.1)	0.92 (0.86, 0.99)	0.025	2.1
Primary Analysis using Investigator Reported Events	1787/4120 (43.4)	1868/4112 (45.4)	0.93 (0.87, 0.99)	0.03	2.6
Adjusting for Significant Pre-Specified Baseline Covariates	1523/4120 (37.0)	1607/4112 (39.1)	0.91 (0.85, 0.97)	0.008	2.1
On Treatment, Primary Analysis	1361/4110 (33.1)	1454/4101 (35.5)	0.90 (0.84, 0.97)	0.007	2.6
Patients in the Therapeutic Range (200 - <750 ng/mL), Adjusting for Significant Pre-Specified Baseline Covariates	942/2663 (35.4)	1477/3897 (37.9)	0.86 (0.79, 0.93)	<0.001	2.1



*Cox model stratified by randomization setting (inpatient or outpatient) and region and including terms for baseline eGFR and treatment group using centrally adjudicated outcomes.
ARR=Absolute risk reduction

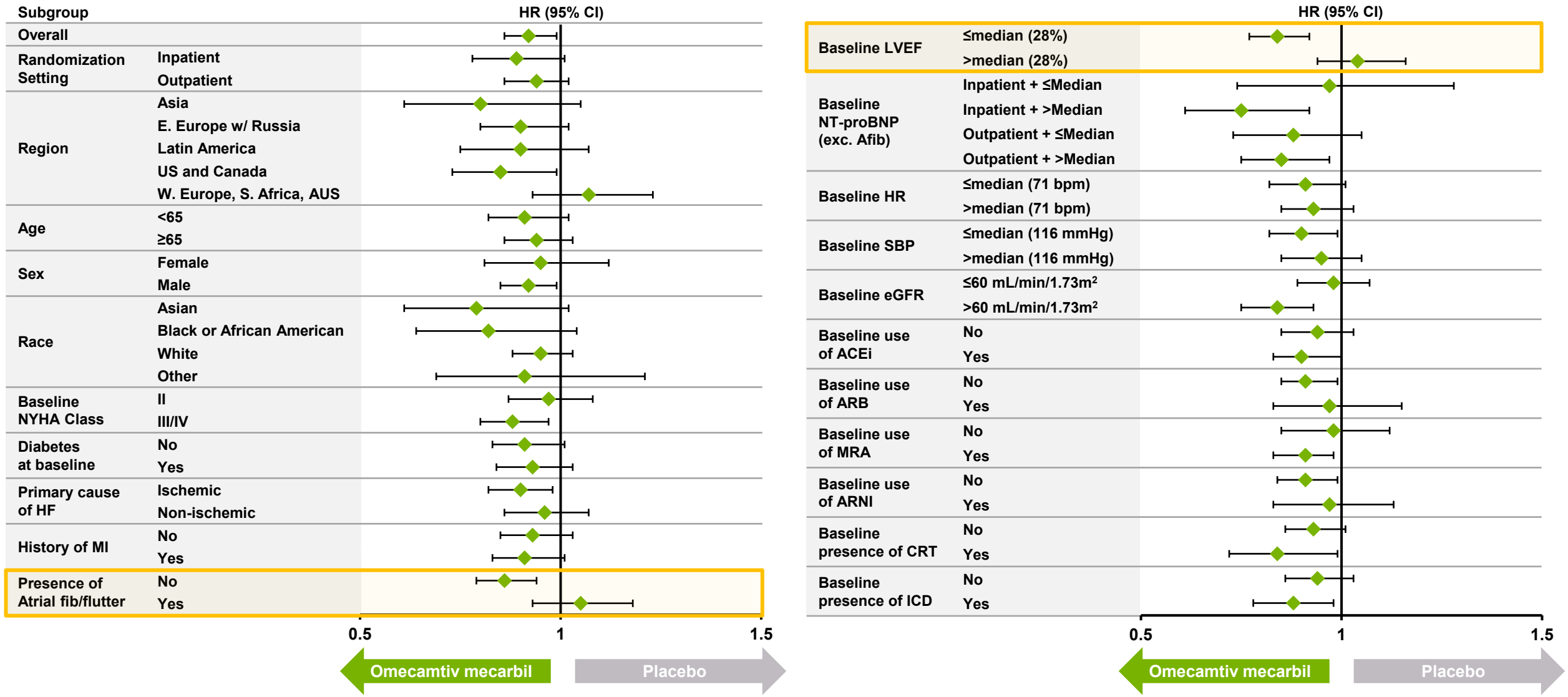
Primary Outcome: Prespecified Subgroups

GALACTIC-HF



Primary Outcome: Prespecified Subgroups

GALACTIC-HF



CC-69

Significant Subgroups for the Treatment Effect

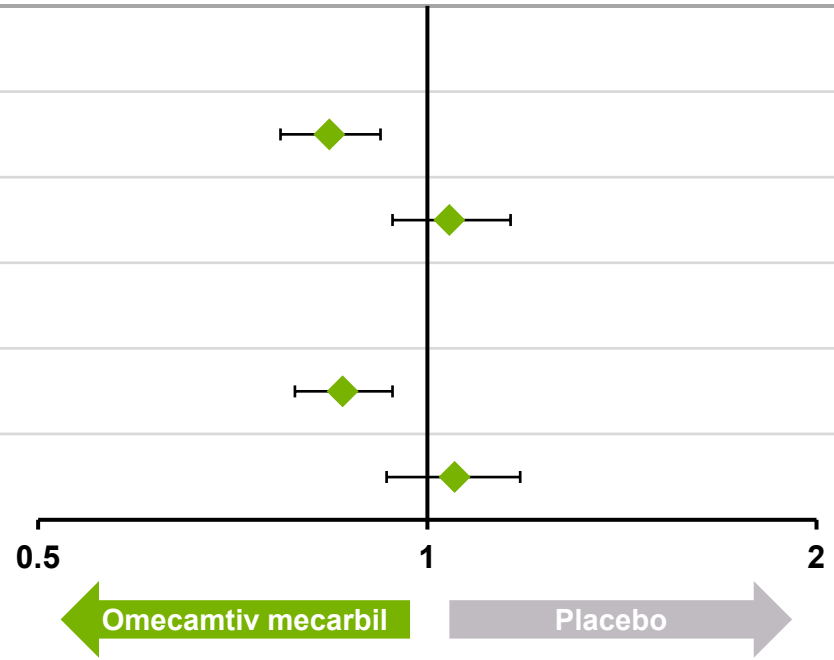
Primary Composite Endpoint

GALACTIC-HF

Bonferroni Threshold

p-value = 0.0009

Subgroup	No. of Events/Patients	Hazard Ratio (95% CI)	Nominal *p*-value
LVEF			
≤28%	1821 / 4456	0.84 (0.77, 0.92)	0.0003
>28%	1309 / 3776	1.04 (0.94, 1.16)	0.45
AFF at screening			
No	2084 / 5987	0.86 (0.79, 0.94)	0.0009
Yes	1046 / 2245	1.05 (0.93, 1.18)	0.47



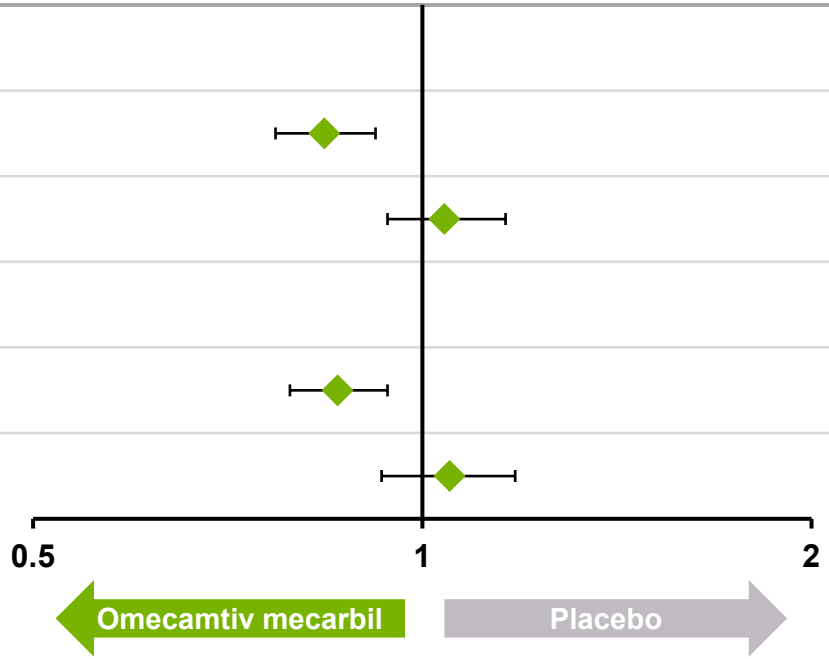
Teerlink JR, Diaz R, Felker GM, et al. *JACC*. 2021
Solomon SD, Claggett BL, Miao ZM, et al. *EHJ* 2022

Significant Subgroups for the Treatment Effect

Primary Composite Endpoint

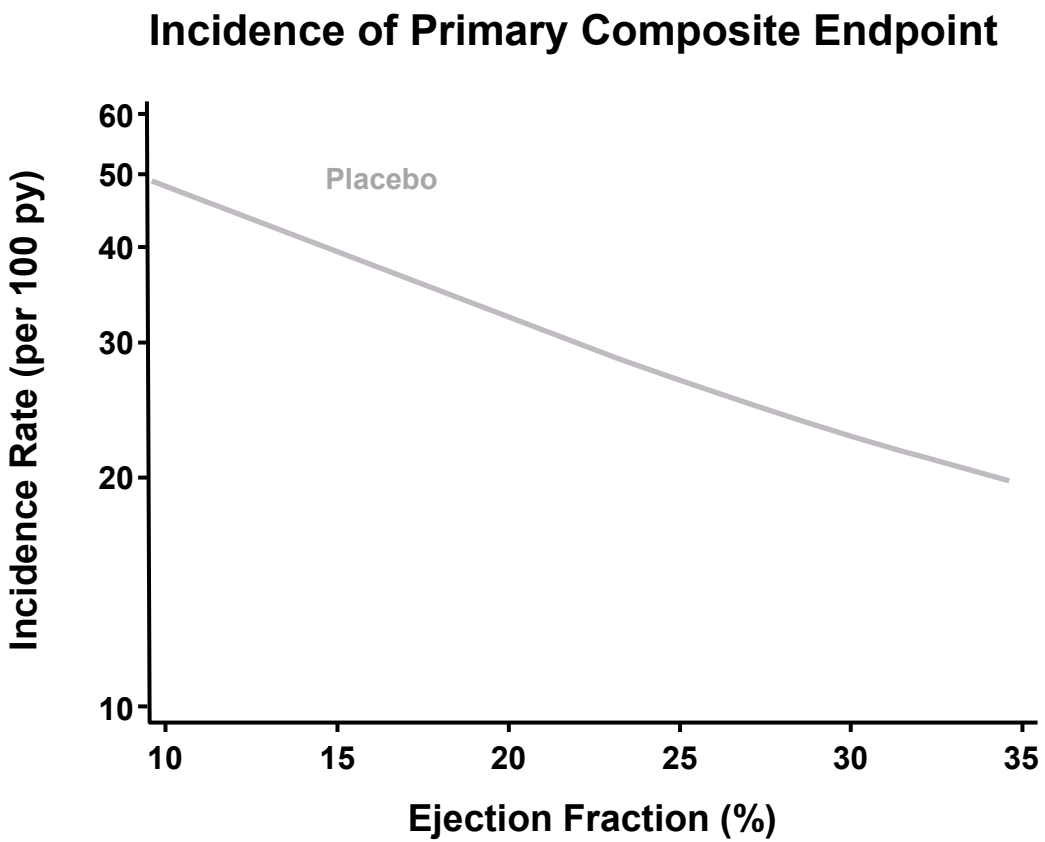
GALACTIC-HF

			Bonferroni Threshold	Global Test for Heterogeneity
			p-value = 0.0009	*p*-value = 0.008
Subgroup	**No. of Events/Patients**	**Hazard Ratio (95% CI)**	**Nominal *p*-value**	**Multivariable Interaction *p*-value**
LVEF				
≤28%	**1821 / 4456**	**0.84 (0.77, 0.92)**	**0.0003**	**0.005**
>28%	**1309 / 3776**	**1.04 (0.94, 1.16)**	**0.45**	
AFF at screening				
No	**2084 / 5987**	**0.86 (0.79, 0.94)**	**0.0009**	**0.006**
Yes	**1046 / 2245**	**1.05 (0.93, 1.18)**	**0.47**	



Teerlink JR, Diaz R, Felker GM, et al. *JACC*. 2021
Solomon SD, Claggett BL, Miao ZM, et al. *EHJ* 2022

Benefit Increases as Baseline LVEF Decreases



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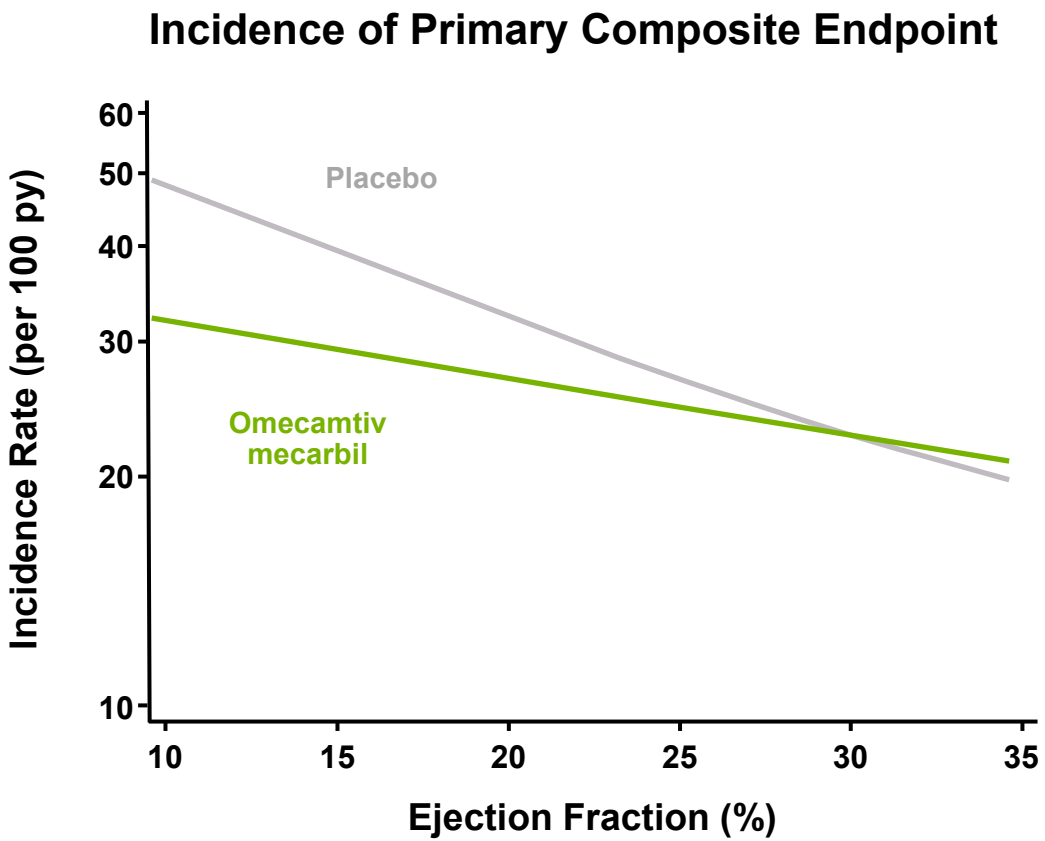
Benefit Increases as Baseline LVEF Decreases

GALACTIC-HF



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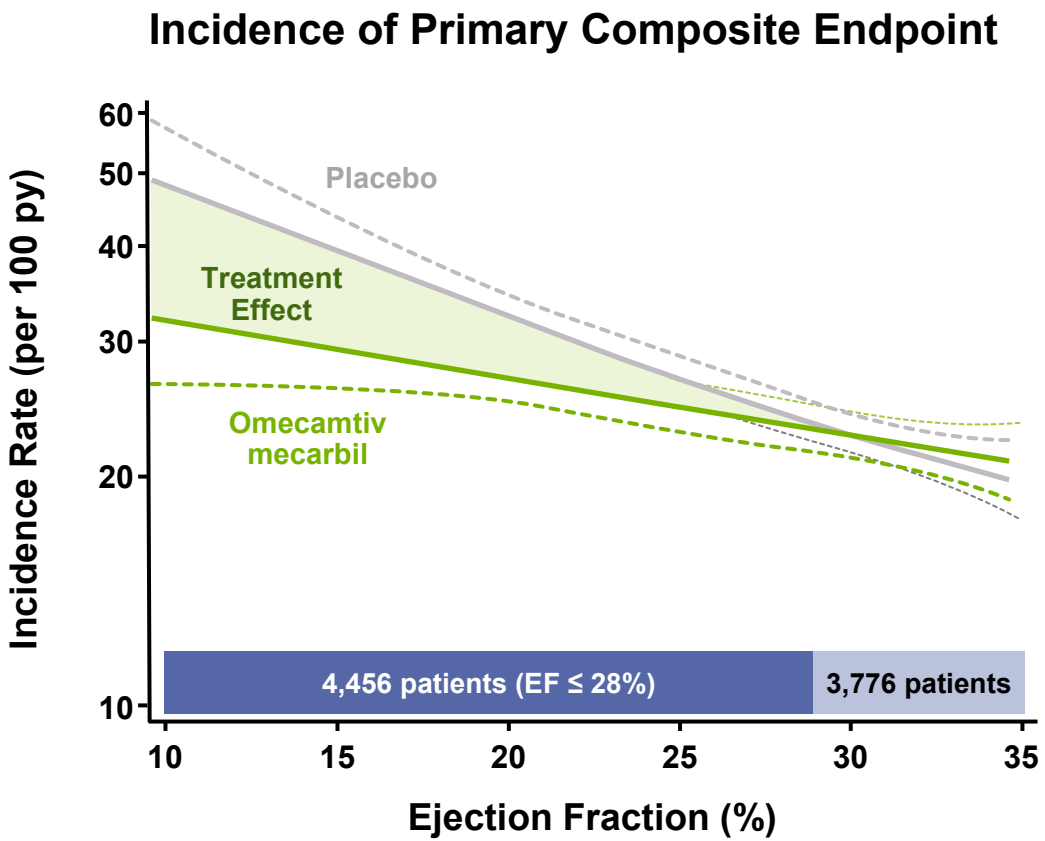

Dashed lines are 95% confidence intervals
Teerlink JR., Diaz R., Felker GM., et al. *JACC*. 2021

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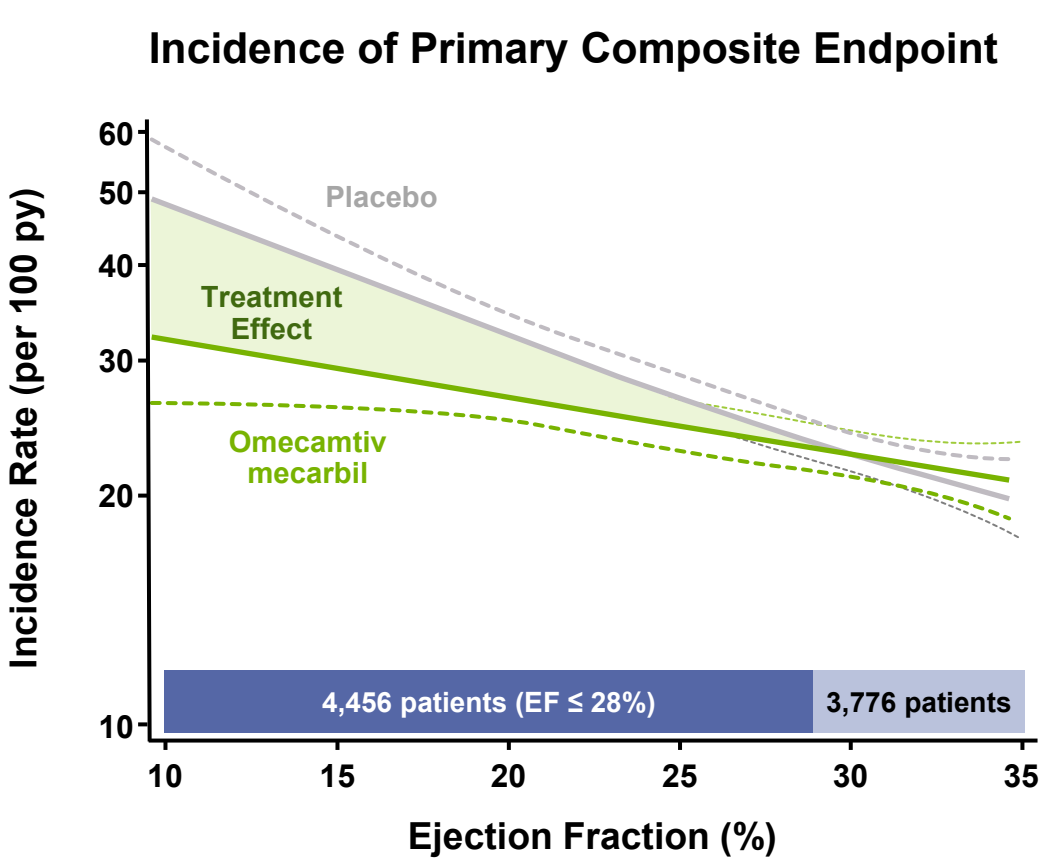
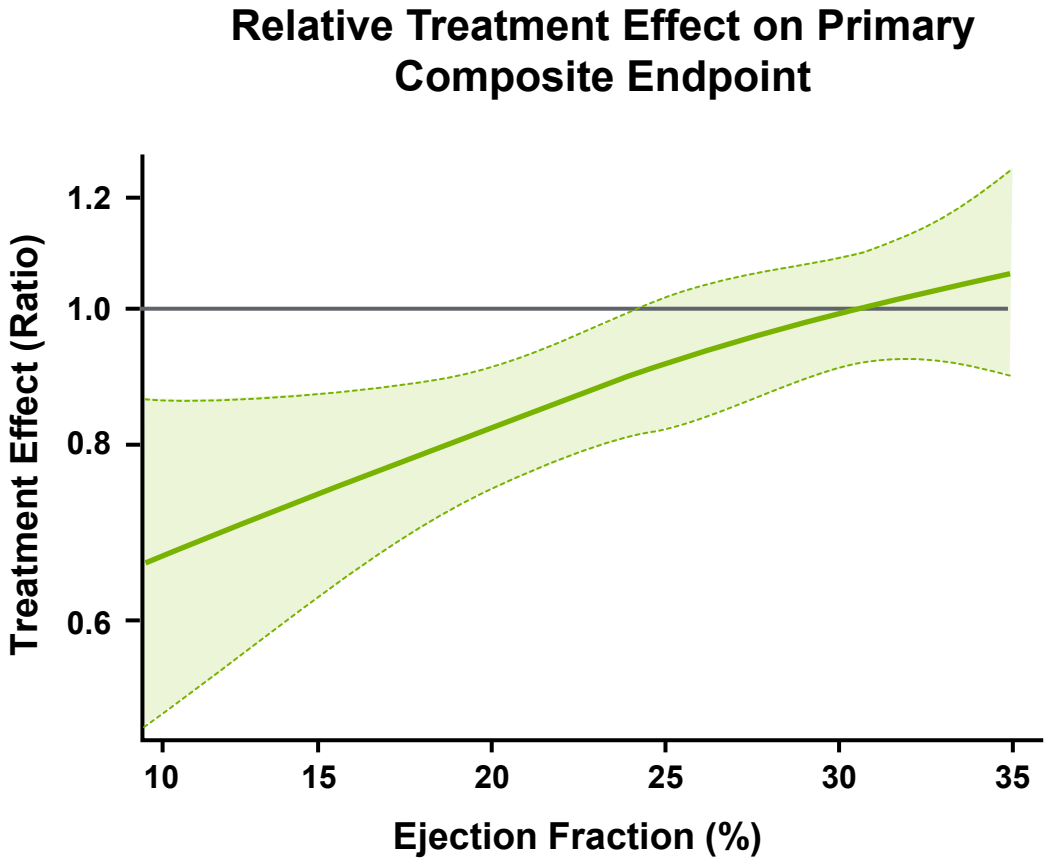




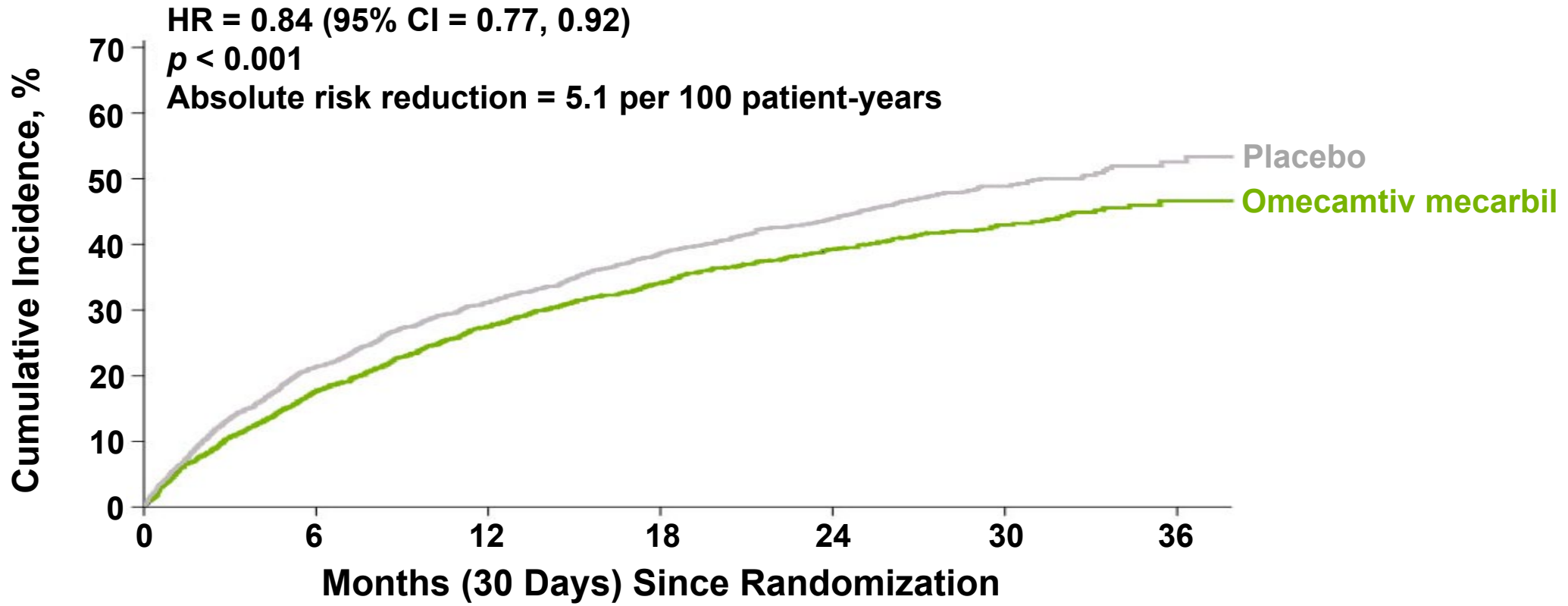
Dashed lines are 95% confidence intervals

Teerlink JR., Diaz R., Felker GM., et al. *JACC*. 2021

Primary Composite Endpoint

Time to First Heart Failure Event or Cardiovascular Death: LVEF ≤28%

GALACTIC-HF



Patients at risk, n

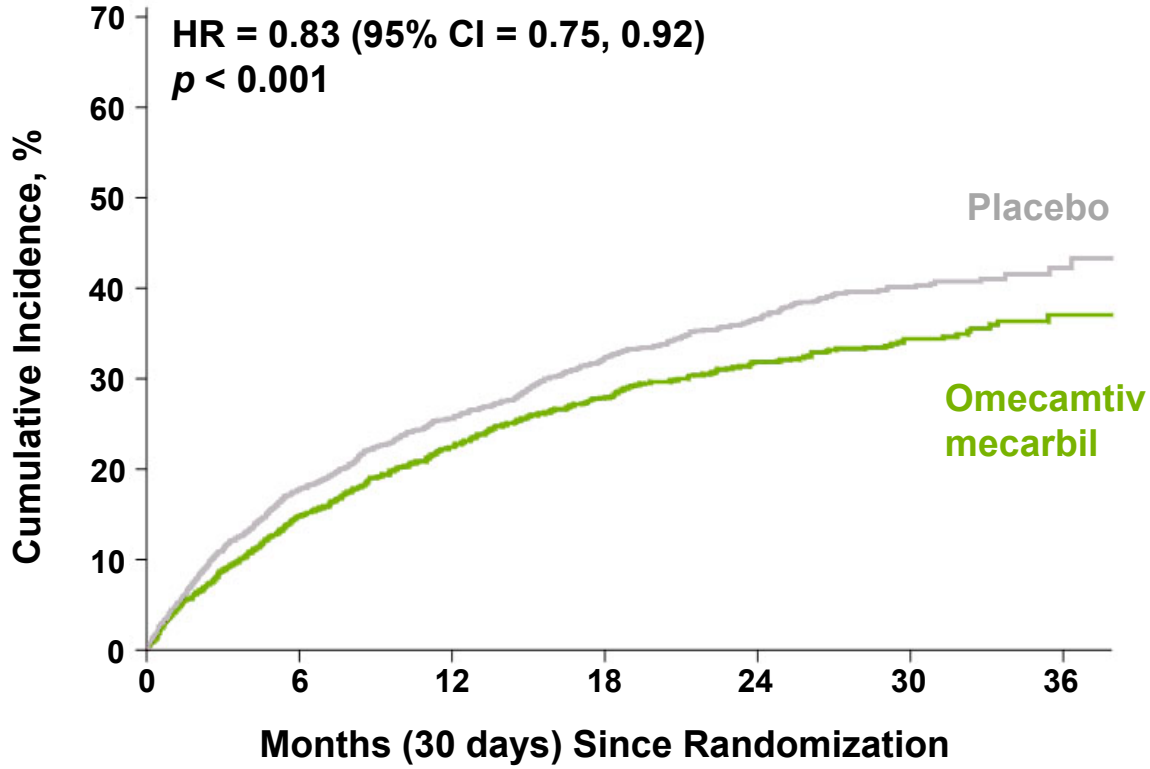
Placebo	2243	1735	1492	1035	649	295	64
Omecamtiv mecarbil	2213	1799	1557	1100	711	314	76

Individual Components of Primary Endpoint

LVEF ≤28%

GALACTIC-HF

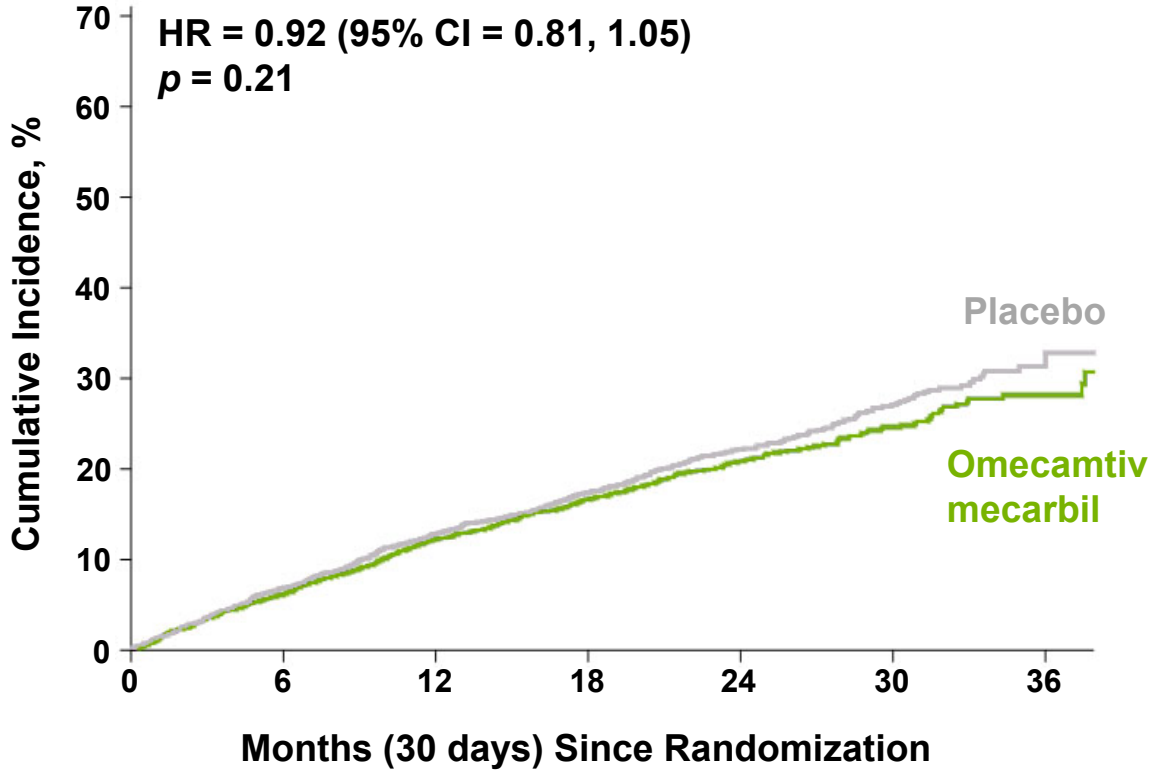
First Heart Failure Event



Patients at risk, n

Placebo	2243	1734	1492	1035	649	295	64
OM	2213	1799	1557	1099	711	314	76

Cardiovascular Death

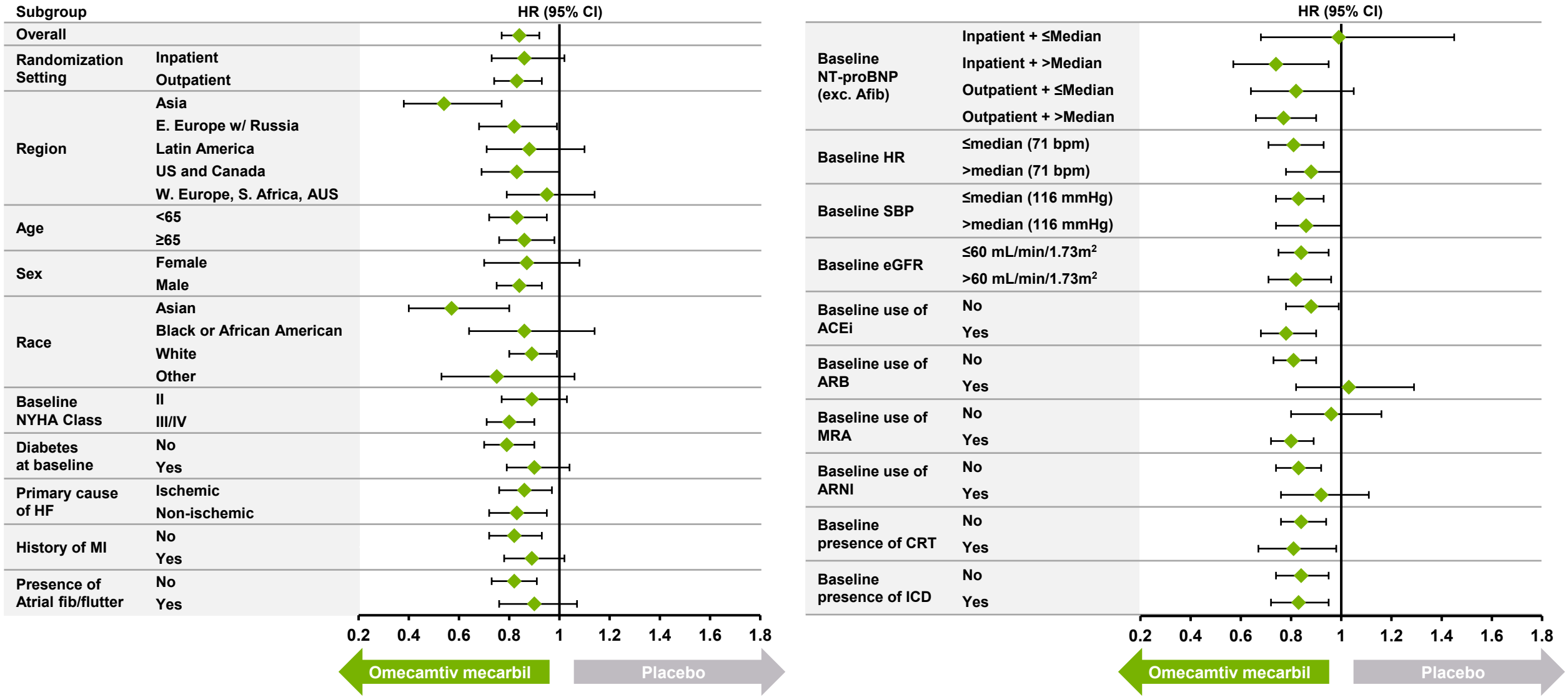


2243	2055	1888	1390	894	431	98
2213	1799	1557	1099	711	314	76

Primary Outcome: Prespecified Subgroups

LVEF ≤28%

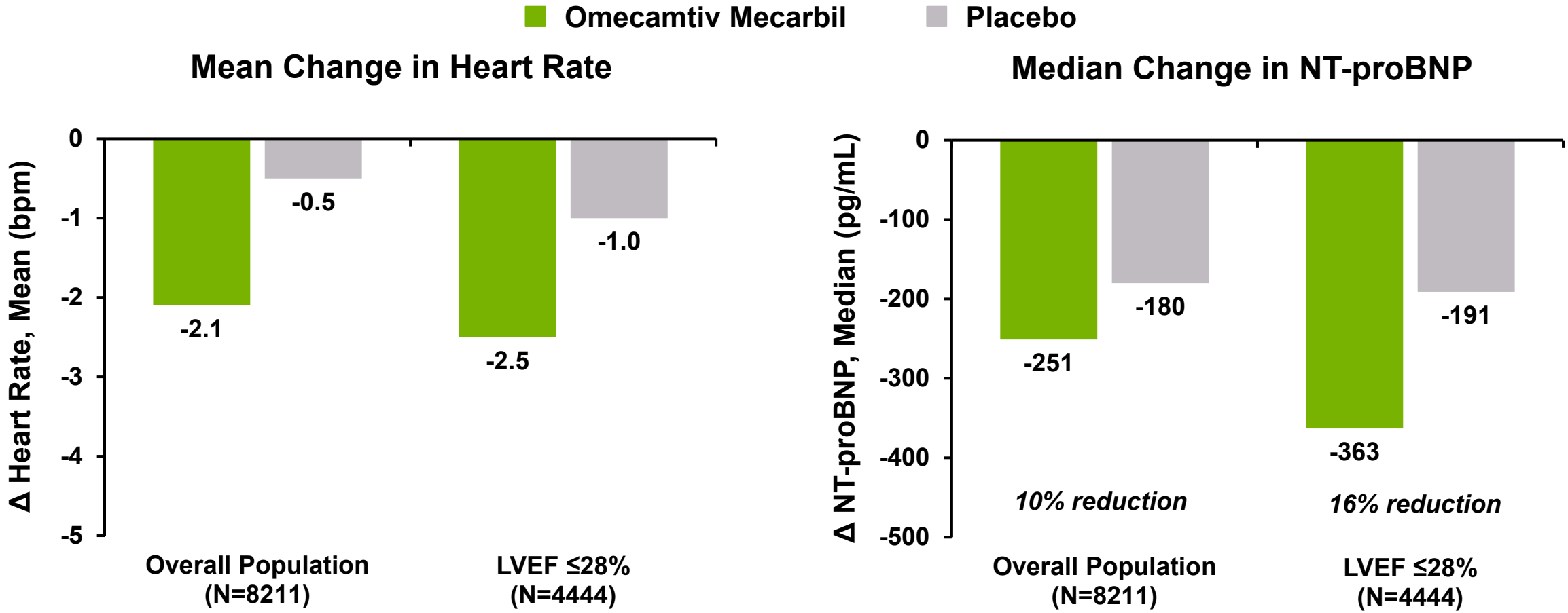
GALACTIC-HF



Decreases in Heart Rate and NT-proBNP

Pharmacodynamic Results After 24 Weeks of Double-blind Treatment

GALACTIC-HF

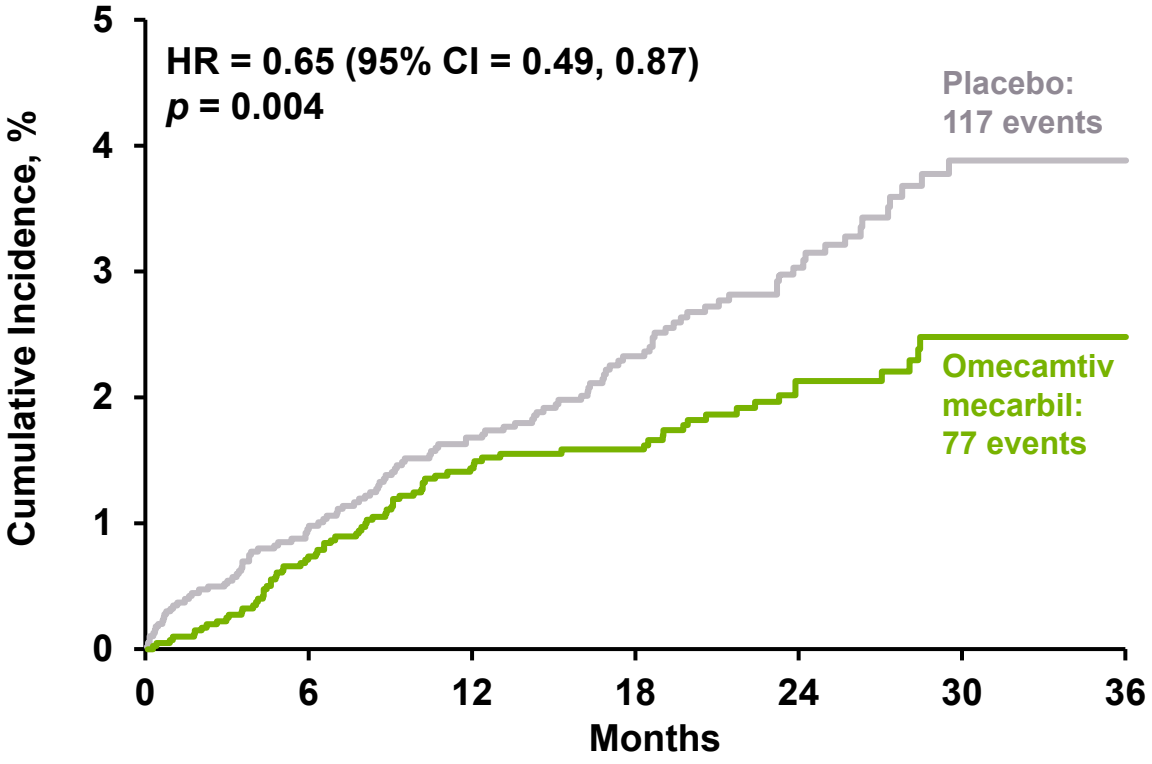


Changes observed in GALACTIC-HF generally consistent with those observed in COSMIC-HF

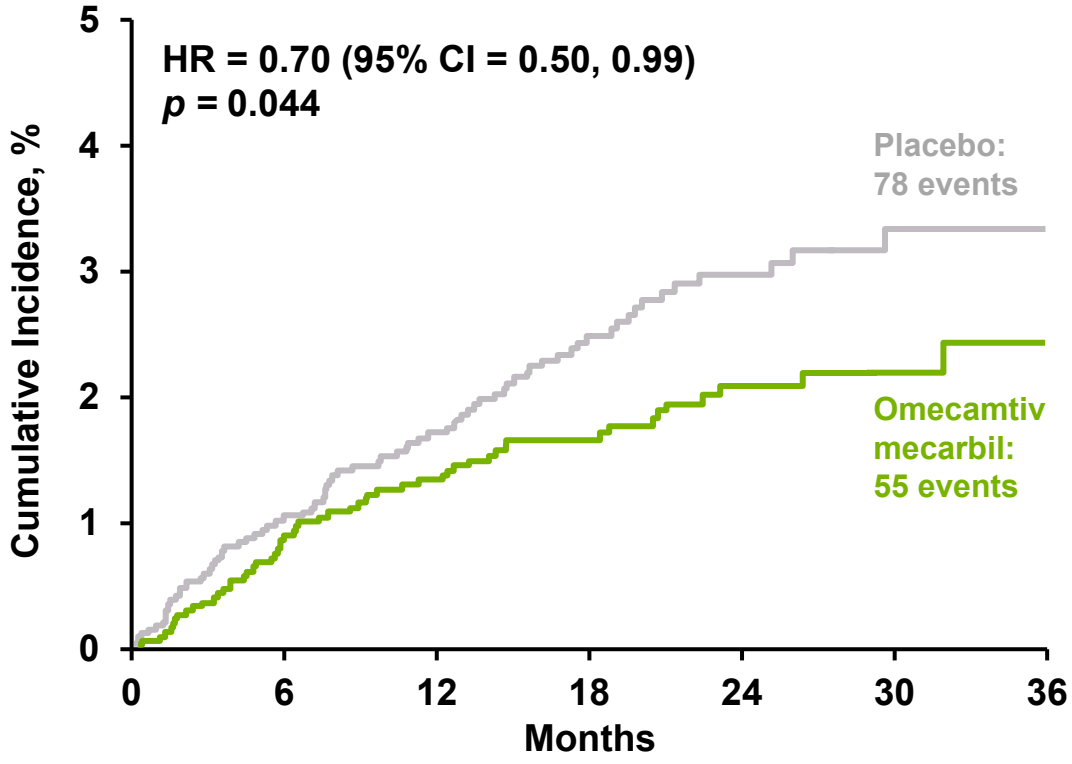
Adjudicated Stroke and New Atrial Fibrillation

GALACTIC-HF

Adjudicated Stroke (n=8232)

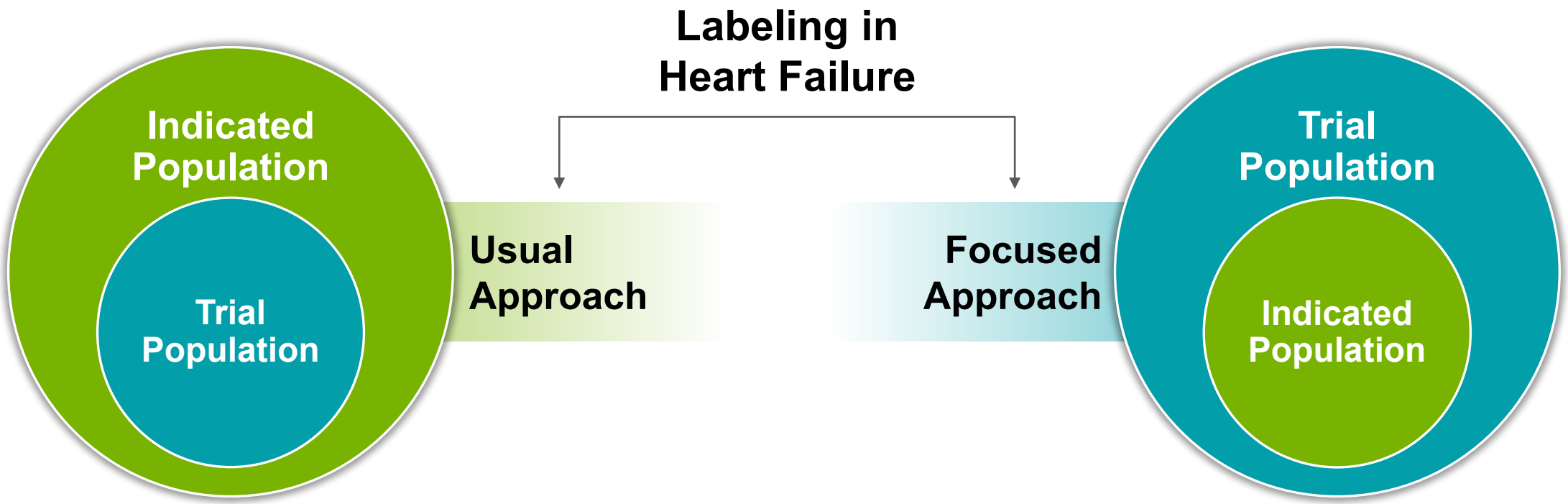


New Atrial Fibrillation (SAE) (n=5987)



Clinical outcomes observed in GALACTIC-HF are generally consistent with the mechanistic data observed in COSMIC-HF

Focusing on Patients Where Benefit is Greatest



Summary – Evidence of Effectiveness

- **Innovative mechanism developed to test therapeutic hypothesis that improving cardiac function would improve clinical outcomes**
- **Omecamtiv mecarbil improved cardiac function with positive effects on cardiac structure and biomarkers predictive of a therapeutic benefit**

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- Omecamtiv mecarbil improved cardiac function with positive effects on cardiac structure and biomarkers predictive of a therapeutic benefit
- GALACTIC-HF achieved a statistically significant effect on the pre-specified primary outcome robust to several sensitivity analyses
- In the prespecified subgroup of lower LVEF, the absolute treatment effect was more than double the effect in the overall study
- Driver of greater clinical benefit (LVEF) is biologically plausible given the mechanism of action of omecamtiv mecarbil

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- Innovative mechanism developed to test therapeutic hypothesis that improving cardiac function would improve clinical outcomes
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- In the prespecified subgroup of lower LVEF, the absolute treatment effect was more than double the effect in the overall study
- Driver of greater clinical benefit (LVEF) is biologically plausible given the mechanism of action of omecamtiv mecarbil
- GALACTIC-HF and the confirmatory evidence from COSMIC-HF provide persuasive substantial evidence of effectiveness

Safety of Omecamtiv Mecarbil in HFrEF

Stuart Kupfer, MD

Senior Vice President, Chief Medical Officer
Cytokinetics

Presentation Outline

1. Adverse Events
2. Vital Signs and Labs
3. Atrial Fibrillation

Treatment-emergent Adverse Events

	Overall Population		LVEF ≤28%	
	Omecamtiv Mecarbil N=4110 %	Placebo N=4101 %	Omecamtiv Mecarbil N=2208 %	Placebo N=2236 %
All treatment-emergent adverse events	87.4	88.3	87.1	88.7
Grade ≥2	79.5	81.1	79.4	82.9
Grade ≥3	62.1	63.6	62.9	66.2
Grade ≥4	31.6	32.5	32.0	35.1
Serious adverse events	57.7	59.4	58.8	61.9
Leading to discontinuation of investigational product	10.5	10.9	10.5	12.6
Serious	8.1	8.2	8.4	9.9
Non-Serious	2.7	2.7	2.3	2.8
Fatal adverse events	20.4	20.1	21.3	22.4

Overall incidences of adverse events and serious adverse events were similar between omecamtiv mecarbil and placebo

Events of Special Interest

	Overall Population		LVEF ≤28%	
	Omecamtiv Mecarbil N=4110 %	Placebo N=4101 %	Omecamtiv Mecarbil N=2208 %	Placebo N=2236 %
Serious adverse events	57.7	59.4	58.8	61.9
Adverse events				
Ventricular tachyarrhythmia (narrow SMQ)	7.1	7.4	8.0	8.2
Torsade de pointes/QT prolongation (SMQ)	4.3	4.8	5.2	5.8
Serious adverse ventricular arrhythmia requiring treatment	2.9	3.1	3.4	3.6
Adjudicated major cardiac ischemic event	4.9	4.6	4.6	4.2
Myocardial infarction	3.0	2.9	3.0	2.9
Hospitalized for unstable angina	0.6	0.3	0.4	0.2
Coronary revascularization	2.8	2.9	2.6	2.5
Adjudicated stroke	1.6	2.8	2.1	2.6

Incidence of ventricular arrythmias was similar between omecamtiv mecarbil and placebo

SMQ=Standardized Medical Dictionary for Regulatory Activities Queries.

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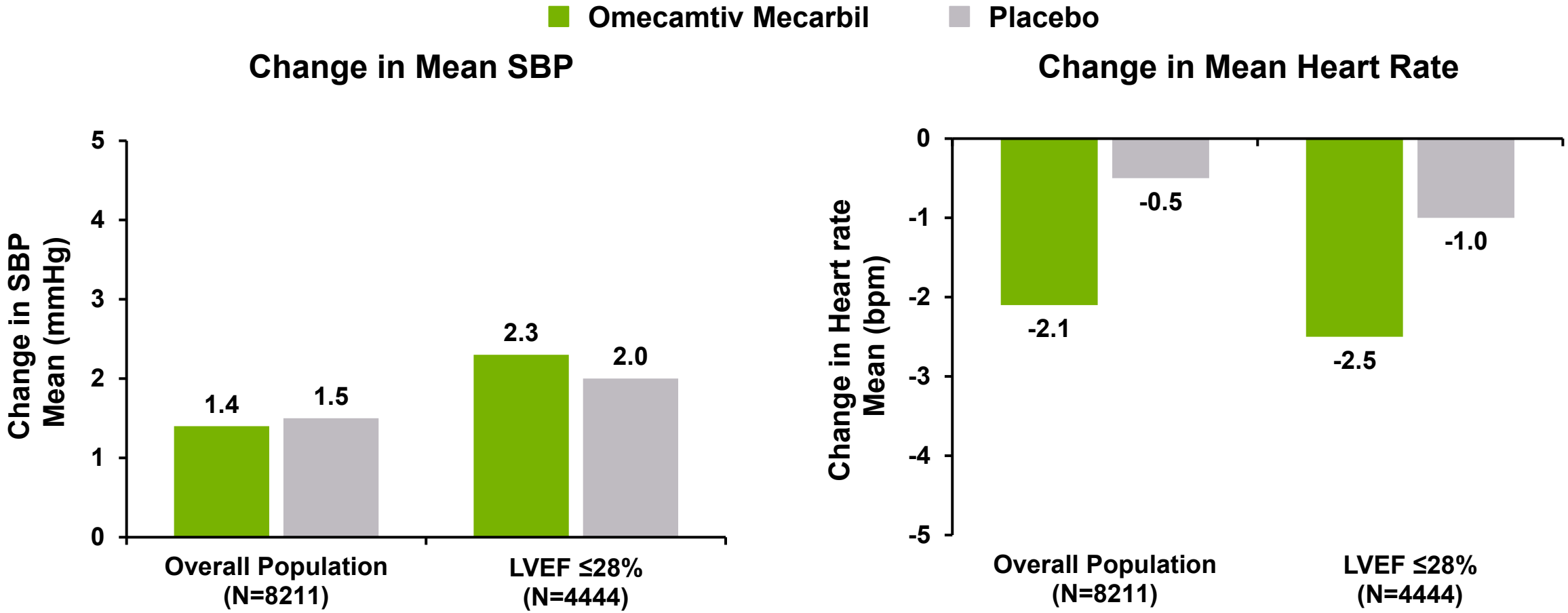
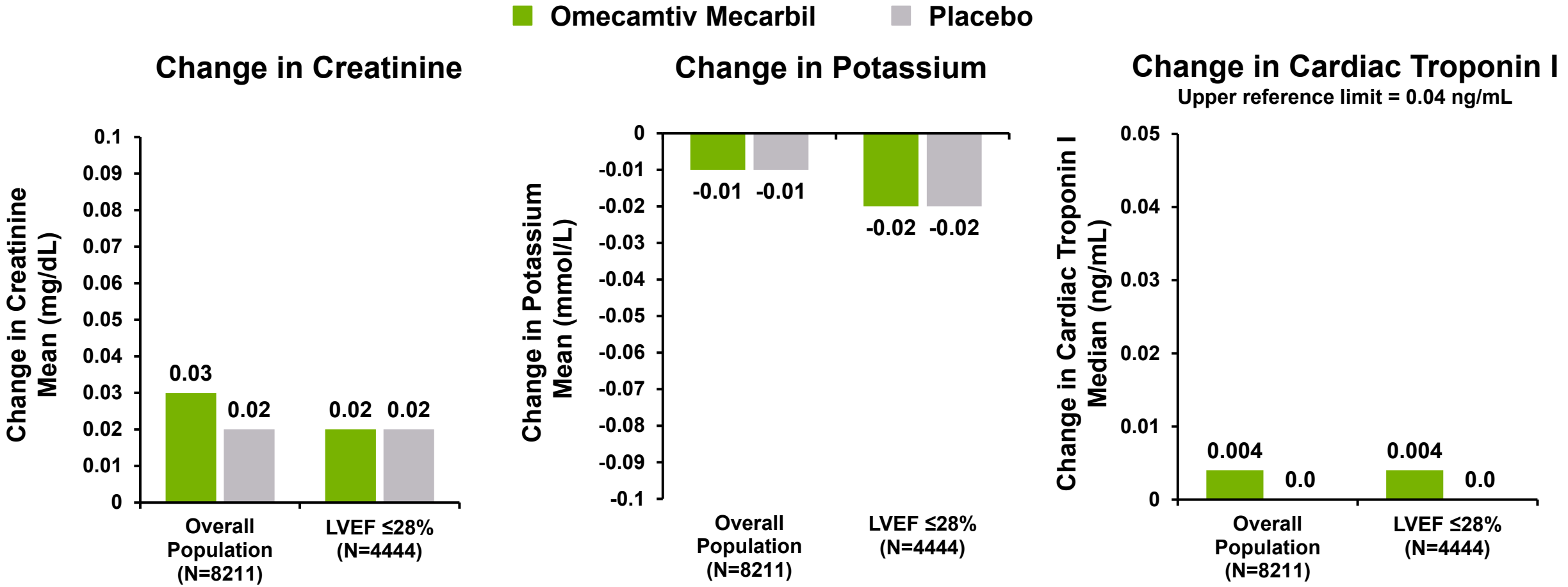
Vital Signs
Change from Baseline to Week 24



No meaningful difference in blood pressure
Small decrease in resting heart rate

RR=relative risk

Laboratory Parameters
Change from Baseline to Week 24

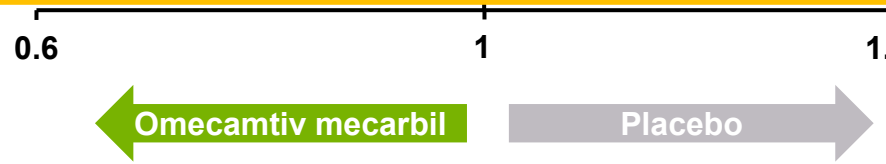


No clinically meaningful changes in creatinine, potassium or troponin

*The change from baseline on NT-proBNP analysis included all patients who underwent randomization.
IQR=interquartile range

Atrial Fibrillation/Flutter
Primary Composite Endpoint

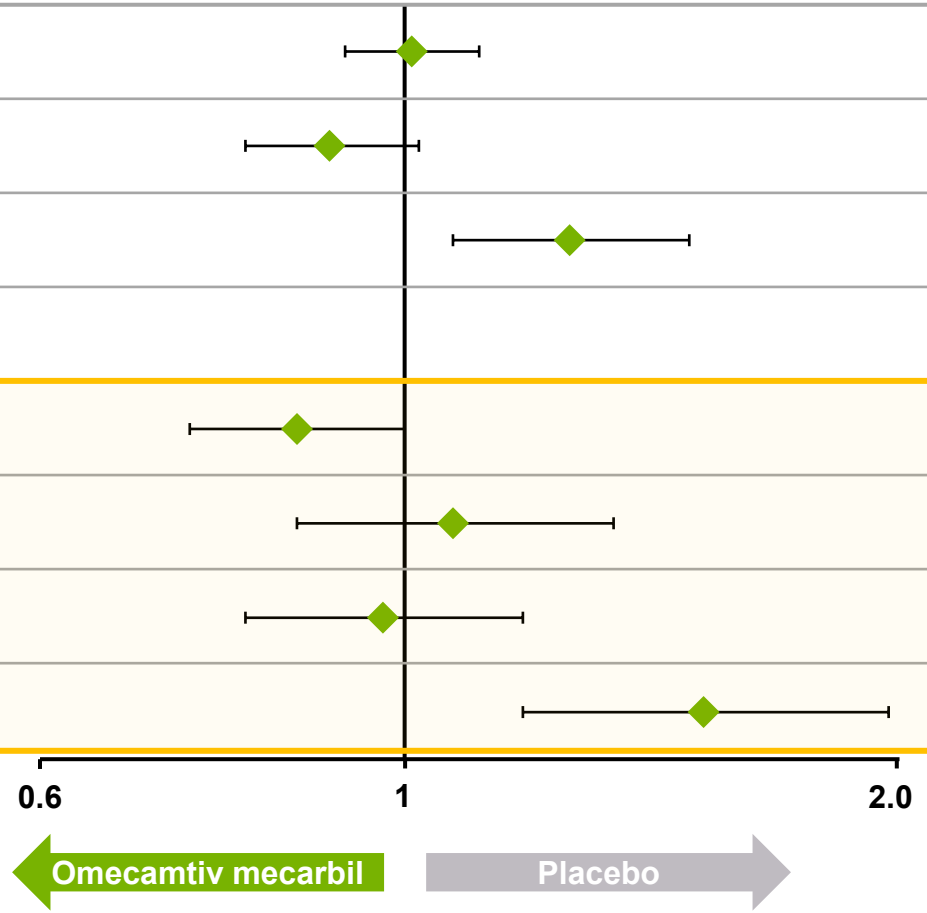
		Omecamtiv Mecarbil N	Placebo N	HR (95% CI)	p-value
Overall study population		4120	4112		0.025
No AFF		2974	3013		0.0009
AFF		1146	1099		0.47
LVEF ≤28%	No AFF	1663	1685		<0.001
	AFF	550	558		0.24
LVEF >28%	No AFF	1311	1328		0.39
	AFF	596	541		0.04



AFF=atrial fibrillation/flutter

Atrial Fibrillation/Flutter
CV Death

		Omecamtiv Mecarbil N	Placebo N	HR (95% CI)	p-value
Overall study population		4120	4112		0.86
No AFF		2974	3013		0.09
AFF		1146	1099		0.007
LVEF ≤28%	No AFF	1663	1685		0.05
	AFF	550	558		0.53
LVEF >28%	No AFF	1311	1328		0.77
	AFF	596	541		0.001

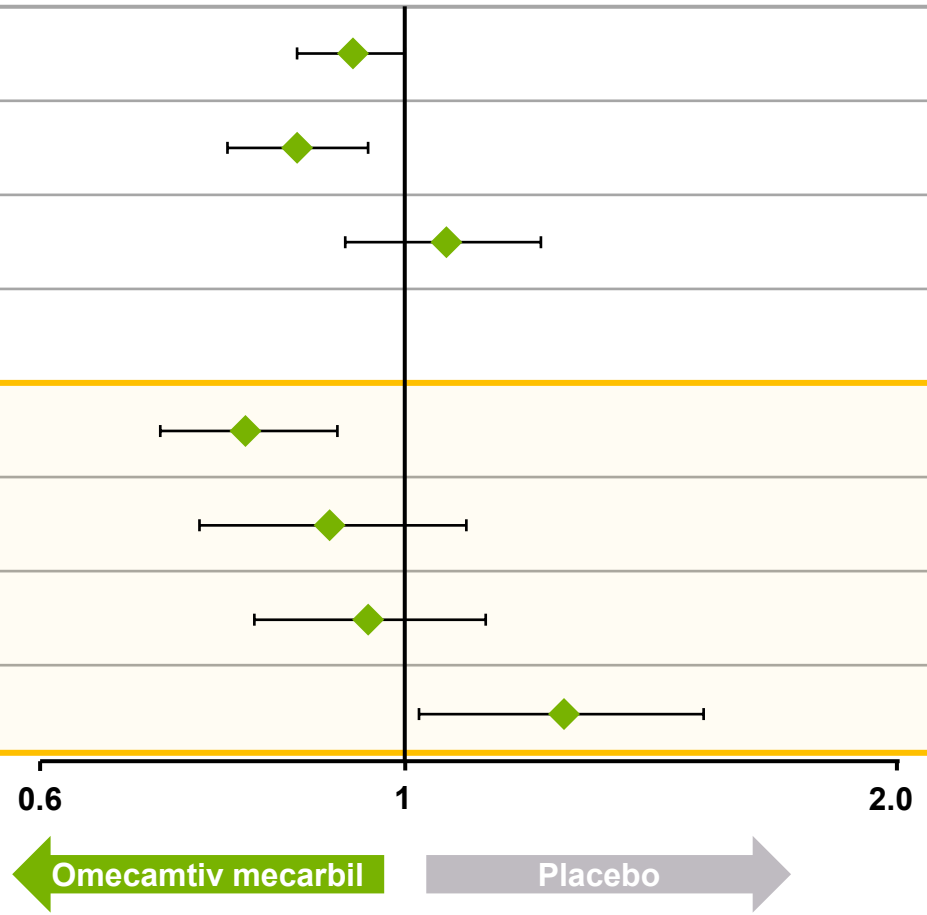


AFF=atrial fibrillation/flutter

Atrial Fibrillation/Flutter

First Heart Failure Event

		Omecamtiv Mecarbil N	Placebo N	HR (95% CI)	p-value
Overall study population		4120	4112		0.06
No AFF		2974	3013		0.003
AFF		1146	1099		0.41
LVEF ≤28%	No AFF	1663	1685		<0.001
	AFF	550	558		0.27
LVEF >28%	No AFF	1311	1328		0.55
	AFF	596	541		0.03



AFF=atrial fibrillation/flutter

Evaluation of Outcomes in Patients with Atrial Fibrillation

- **Adverse events**
  - ↔ Serious adverse events
  - ↔ Cardiac ischemia
  - ↔ Ventricular arrythmias
- **Adjudicated causes of death**
  - ↑ Heart failure
  - ↔ Sudden death
  - ↔ Myocardial infarction
- **Atrial fibrillation status**
  - ↔ History of atrial fibrillation
  - ↔ New onset atrial fibrillation
- **Concomitant medications**
  - ↔ Anticoagulants
  - ↔ Antiarrhythmics
  - ↑ Digoxin

Increased risk with atrial fibrillation at baseline concentrated in patients receiving digoxin

Summary: Safety Profile of Omecamtiv Mecarbil

- Incidence of adverse events of interest is similar in omecamtiv mecarbil and placebo groups
- Safety profile is similar in higher risk patients with LVEF ≤28%
- No adverse effect on blood pressure, heart rate, renal function, or potassium homeostasis
- Increased heart failure outcomes in patients with atrial fibrillation and higher LVEF, possibly related to digoxin use

Dosing Strategy

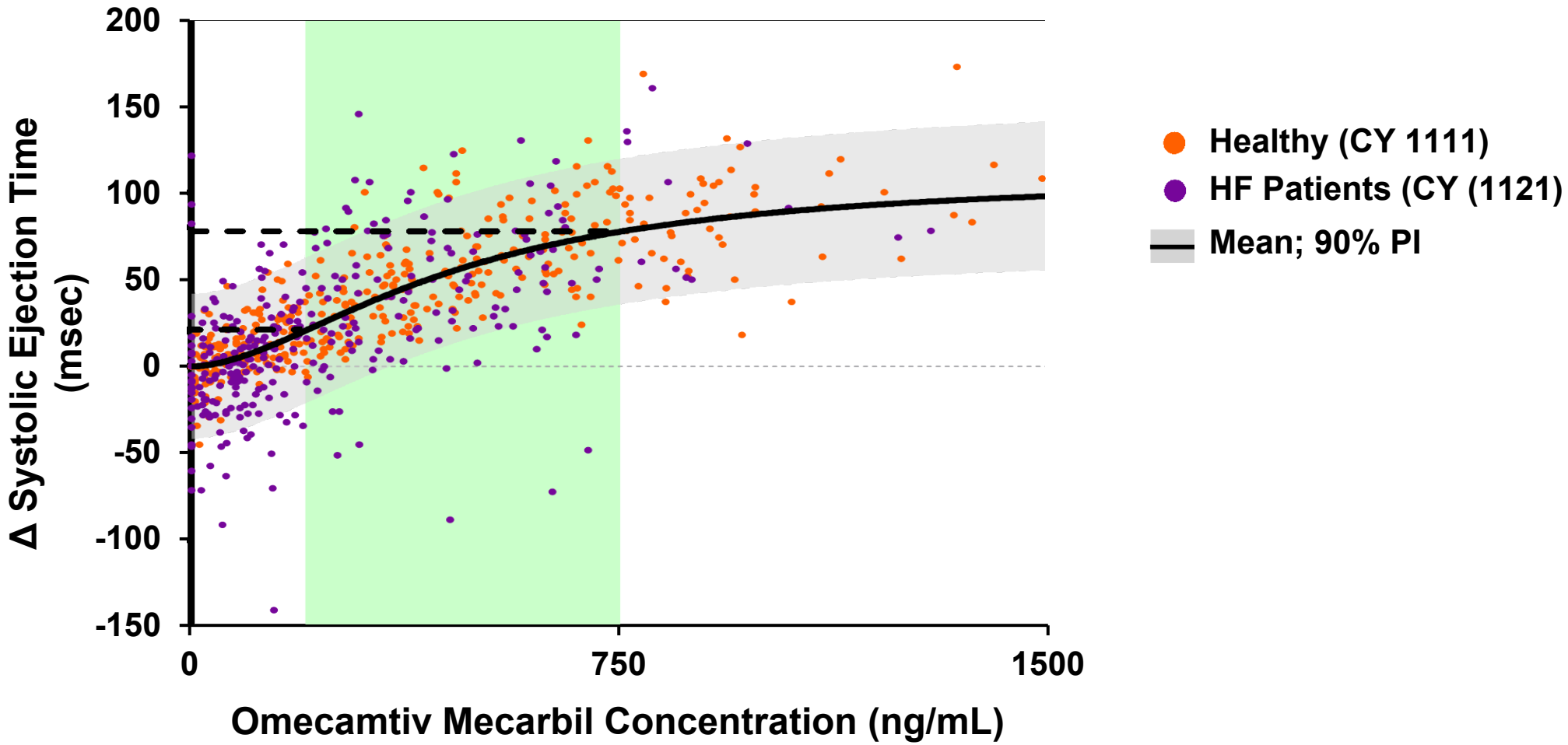
Stuart Kupfer, MD

Senior Vice President, Chief Medical Officer
Cytokinetics

Presentation Outline

1. Therapeutic Concentration Range
2. PK-Guided Dose Titration
3. Therapeutic Drug Monitoring Assay

Therapeutic Concentration Range of Omecamtiv Mecarbil

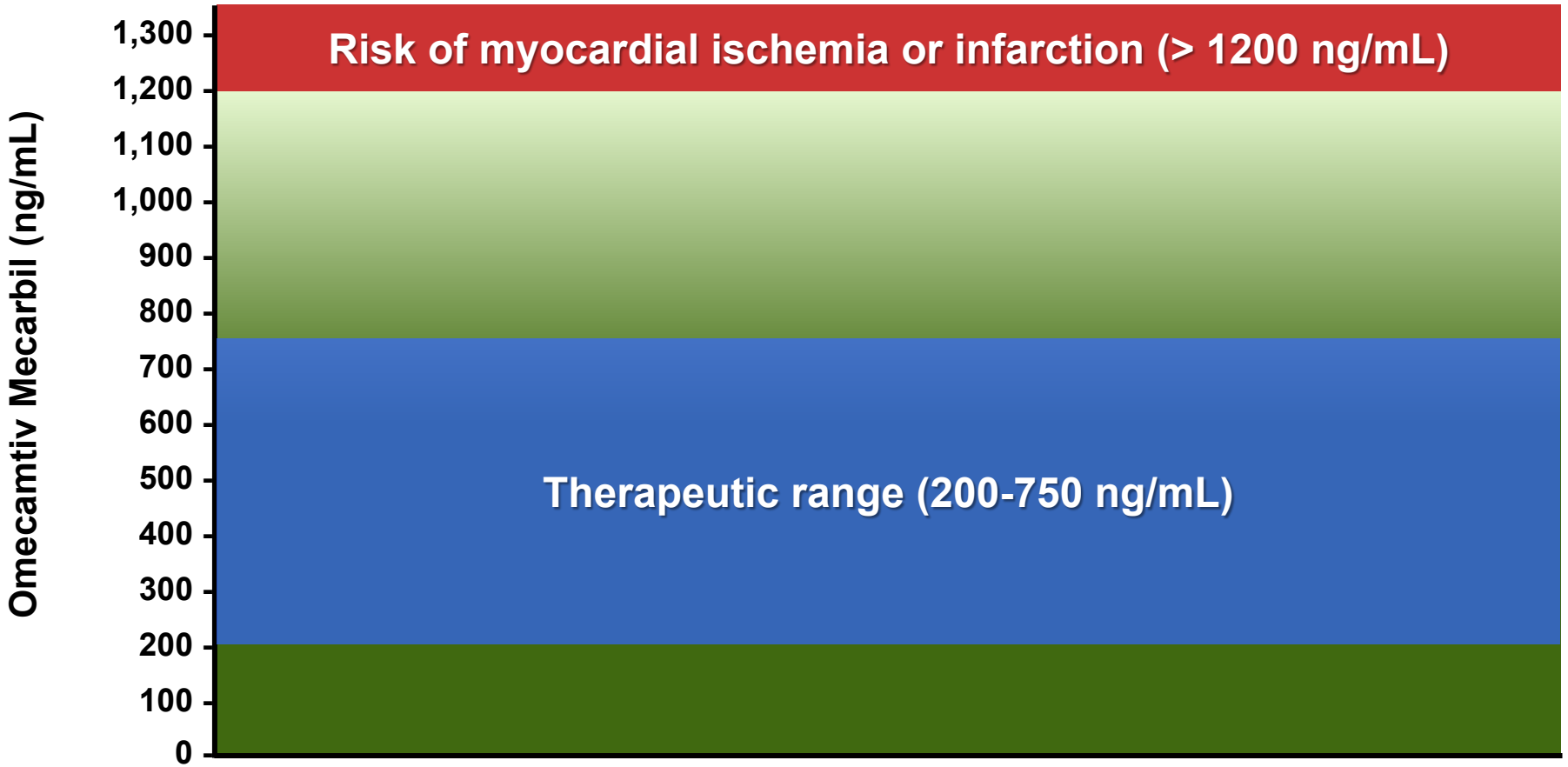


PI=predicted interval

Dose-limiting Effects of Omecamtiv Mecarbil are Related to Excessive Pharmacology

- **During the dose-finding phase of development, omecamtiv mecarbil concentration exceeded 1200 ng/mL in 16 participants**
- **6 participants developed signs of cardiac ischemia**
  - Prolonged systolic ejection time
  - Anginal symptoms
  - Tachycardia
  - ECG changes consistent with cardiac ischemia
  - Small increases in troponin
- **Resolution of symptoms with discontinuation of dosing**
- **No evidence of irreversible effect on cardiac function**

Therapeutic Concentration Range of Omecamtiv Mecarbil



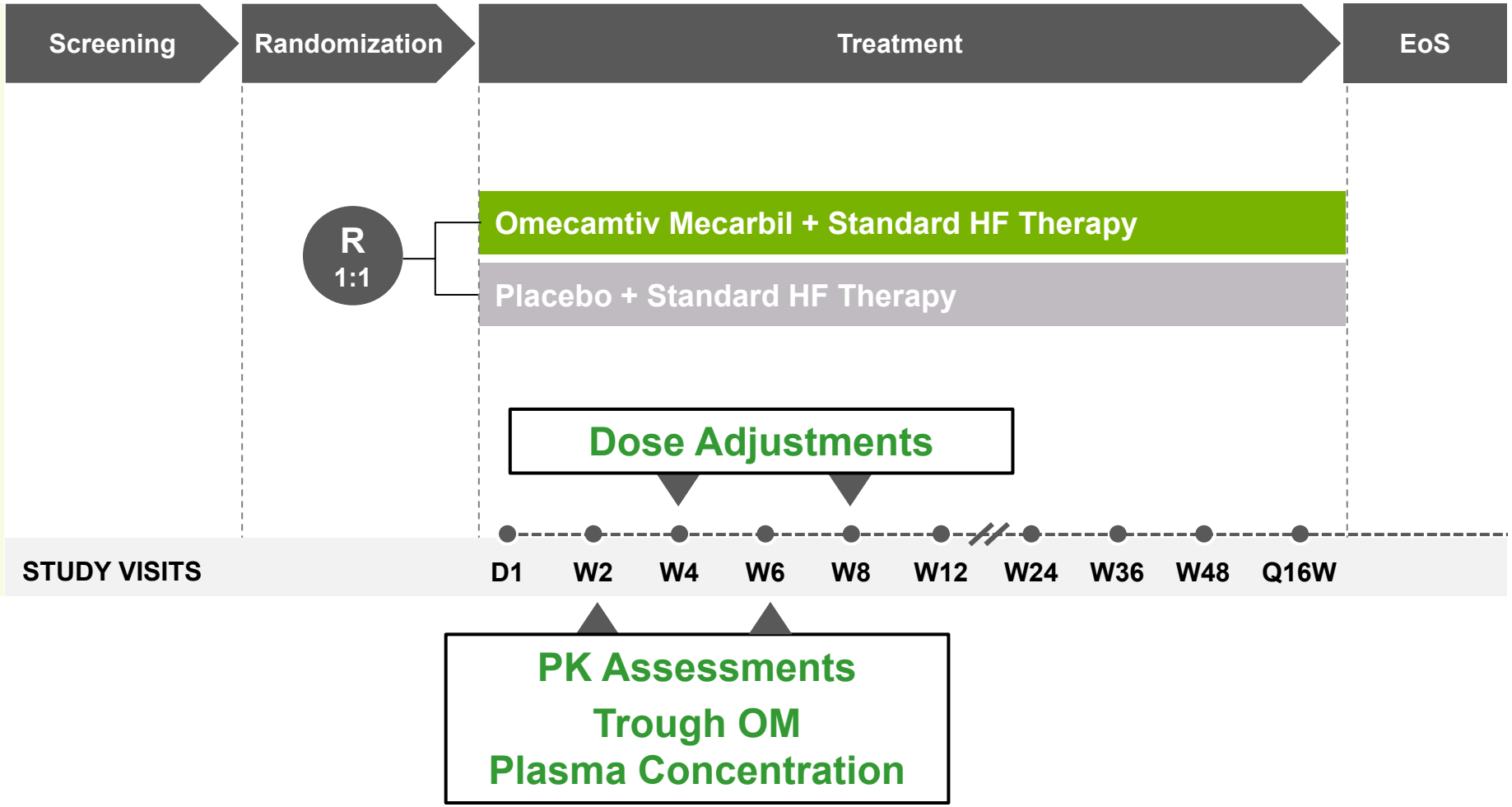
GALACTIC-HF: PK-guided Dose Titration

Starting Dose

25 mg BID

Titrated Doses

37.5 mg BID
50 mg BID

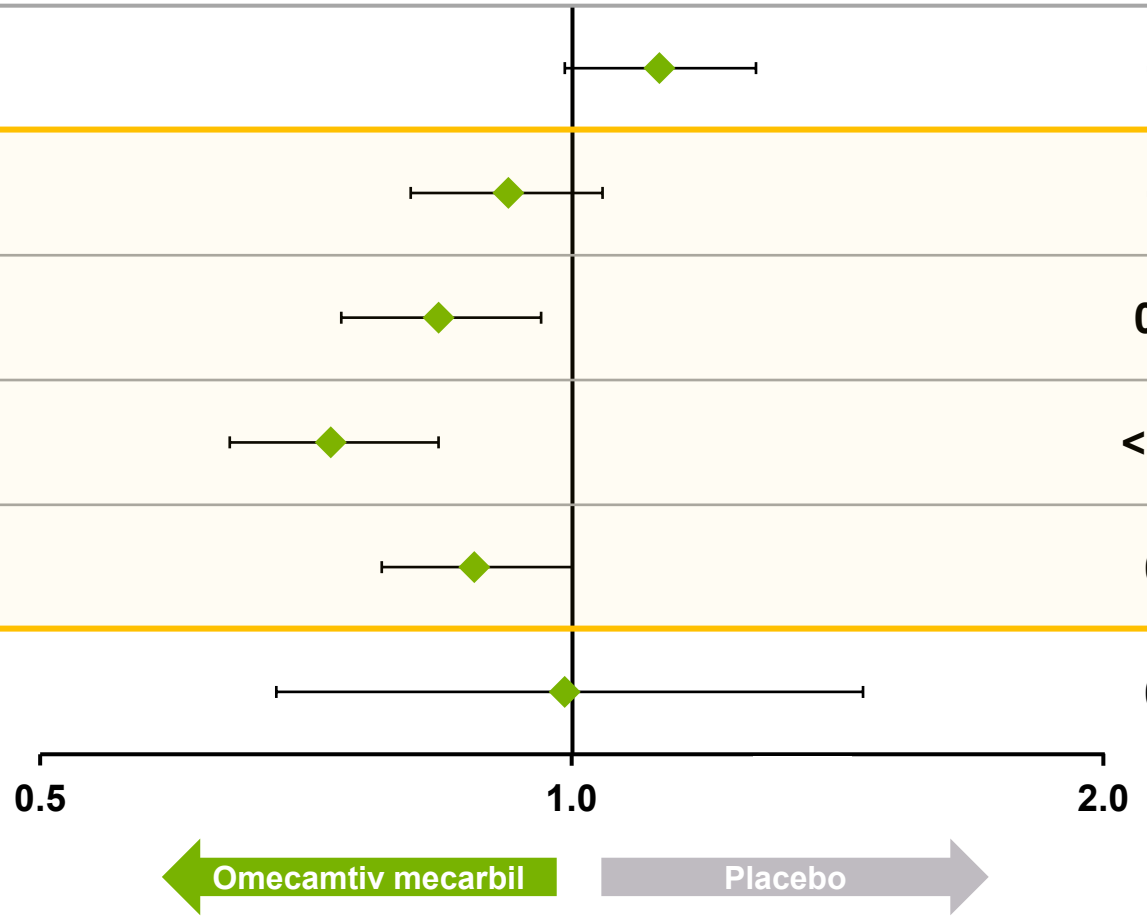


BID=twice daily; OM=omecamtiv mecarbil; PK=pharmacokinetic.
Teerlink JR, et al. *JACC Heart Fail*. 2020;8:329-340.

Treatment Benefit in the Therapeutic Concentration Range

Primary Composite Endpoint

OM Concentration* ng/mL	Omecamtiv Mecarbil N	Placebo N	Hazard Ratio (95% CI)	P-value
Q1: ≤199	803	4112		0.06
Q2: >199 – ≤291	794	4112		0.18
Q3: >291 – ≤366	794	4112		0.008
Q4: >366 – ≤454	798	4112		<0.001
Q5: >454 – ≤750	792	4112		0.04
>750	61	4112		0.97



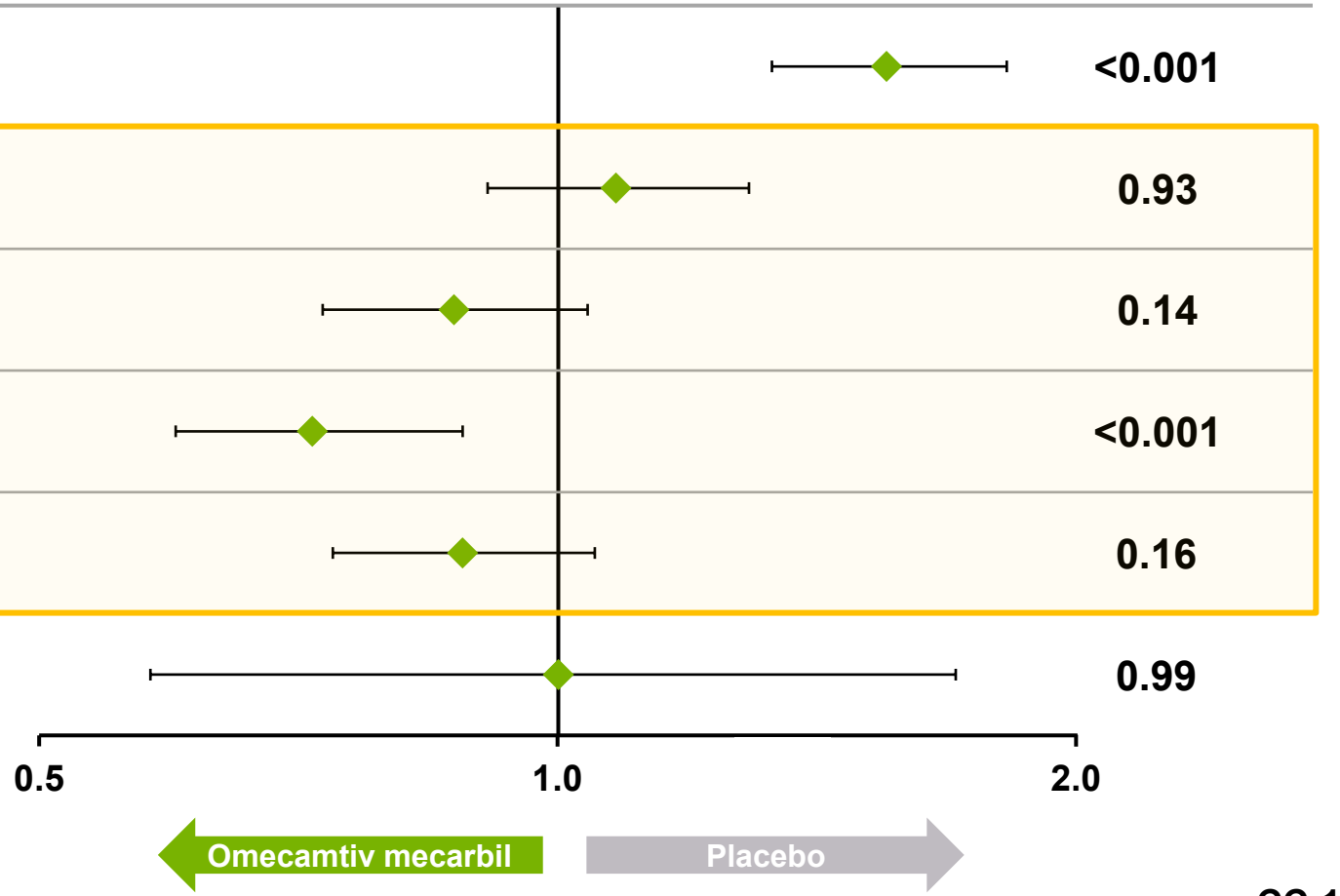
*Maximum achieved plasma concentration

CC-104

Treatment Benefit in the Therapeutic Concentration Range

CV Death

OM Concentration* ng/mL	Omecamtiv Mecarbil N	Placebo N	P-value
Q1: ≤199	803	4112	<0.001
Q2: >199 – ≤291	794	4112	0.93
Q3: >291 – ≤366	794	4112	0.14
Q4: >366 – ≤454	798	4112	<0.001
Q5: >454 – ≤750	792	4112	0.16
>750	61	4112	0.99



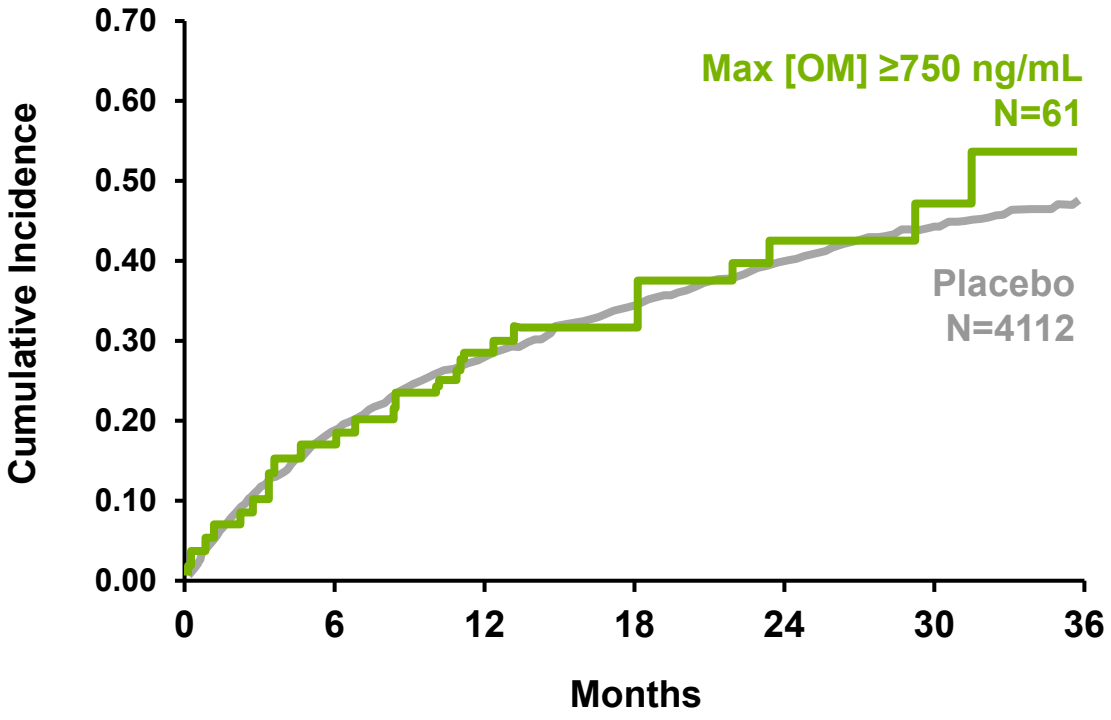
*Maximum achieved plasma concentration

CC-105

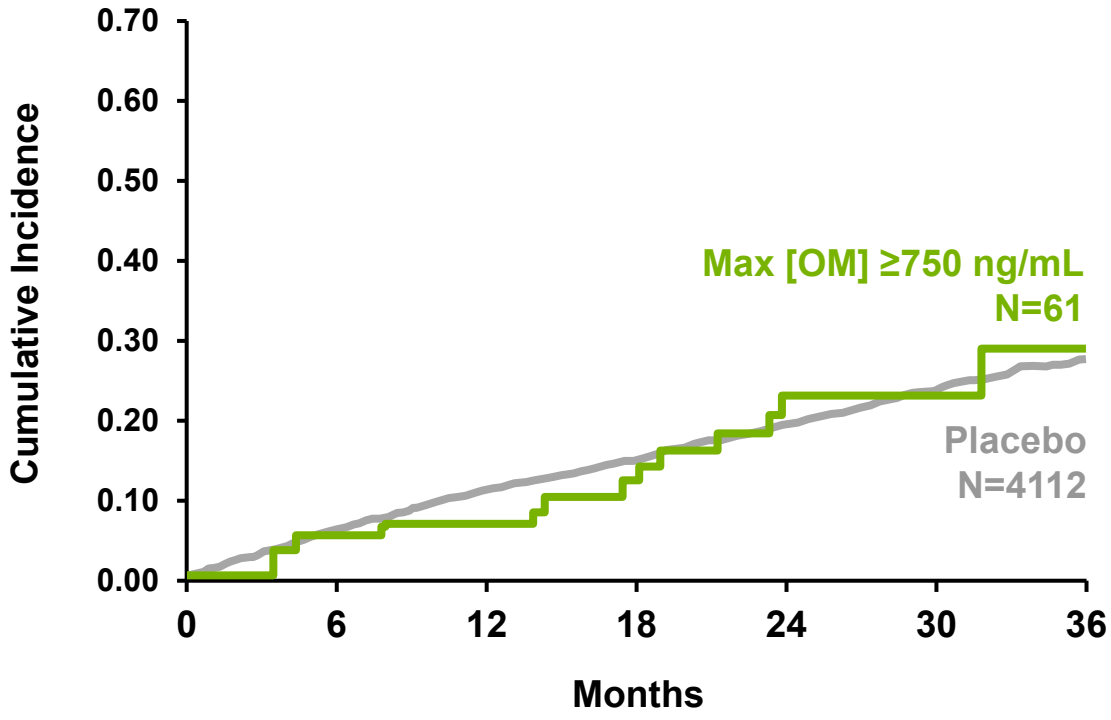
Maximum Observed Plasma Concentration ≥750 ng/mL

Efficacy Outcomes

Primary Composite Endpoint



Cardiovascular Death

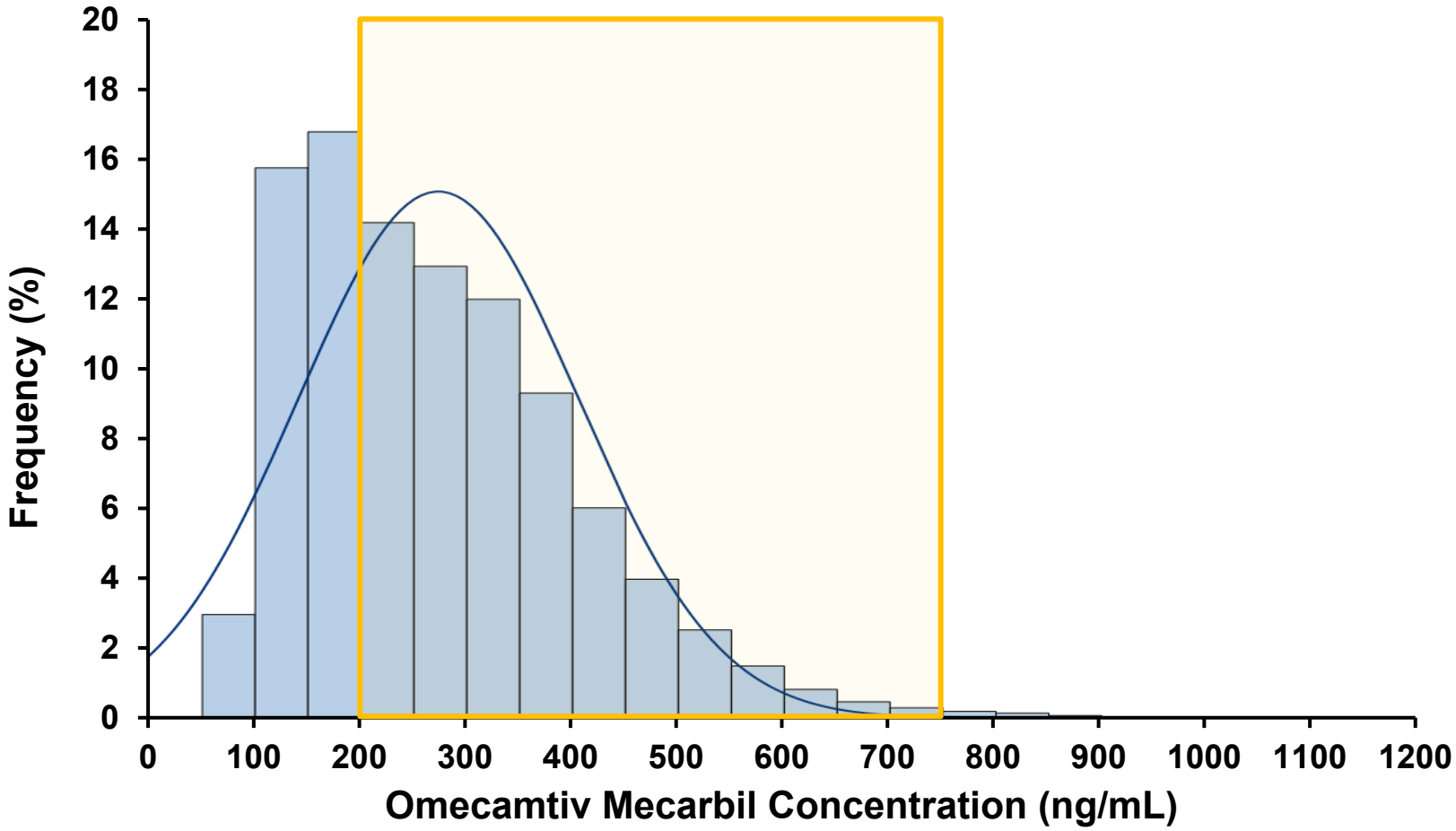


No increased risk above the therapeutic concentration range in GALACTIC-HF

[OM] indicates omecamtiv mecarbil plasma concentration

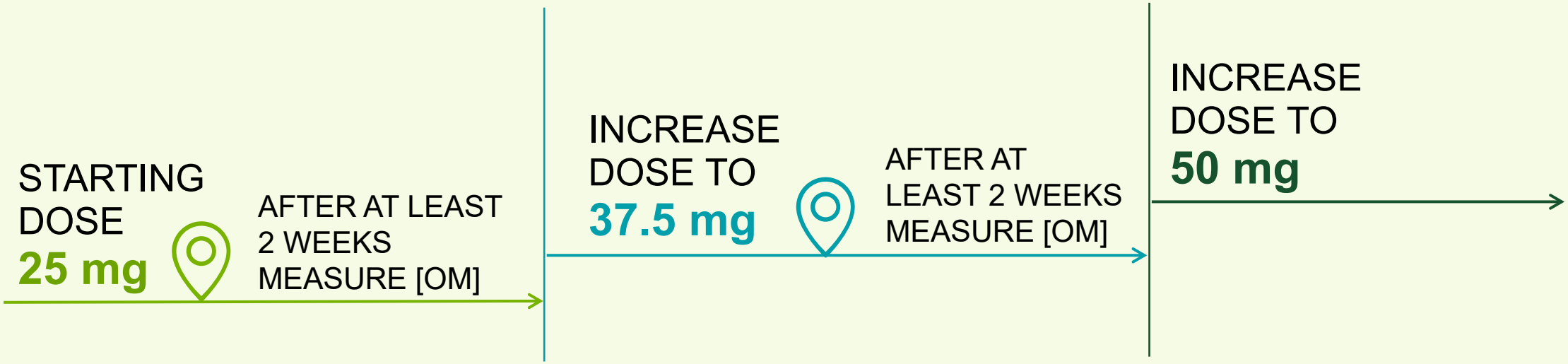
Histogram of Omecamtiv Mecarbil Concentrations

GALACTIC-HF – PK-guided Dosing



Majority in therapeutic range --- Avoidance of excessive concentrations

Proposed Simplified PK-guided Dose Titration



If plasma concentration is:	Adjust to:
<300 ng/mL	Increase to next higher dose
300 – 750 ng/mL	No change in dose
>750 ng/mL	Decrease to next lower dose

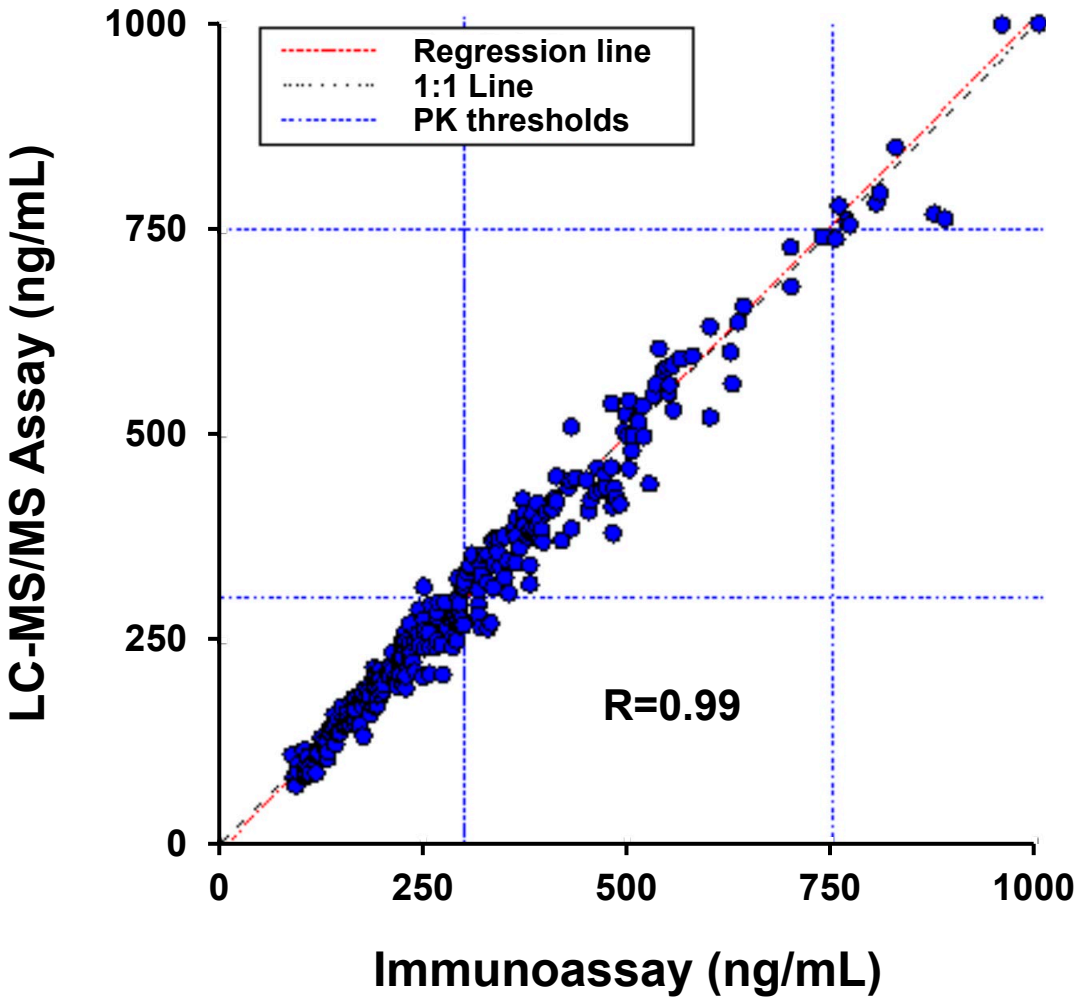
Modeling of GALACTIC-HF and proposed dosing shows same concentration profile

[OM] indicates omecamtiv mecarbil plasma concentration

Implementation of a Therapeutic Drug Monitoring Assay

- **PK-guided dose titration in GALACTIC-HF supported by immunoassay validated with reference LC-MS/MS assay used in Phase 2 studies**
- **LC-MS/MS technology is widely used for therapeutic drug monitoring due to its high reproducibility, accuracy, specificity, and selectivity**
- **Validated LC-MS/MS assay will support PK-guided dose titration at approval**
  - Compliant with the latest CLSI and FDA guidances for analysis of therapeutic drugs
  - Developed on the instrumentation platform intended for commercial implementation
  - Assay run in a single central commercial lab to maximize quality control
  - Validation report provided to FDA indicating that LC-MS/MS assay is fit-for-purpose

High Degree of Correlation Between LC-MS/MS and Immunoassay



Identical plasma samples from GALACTIC-HF were used for measurement of omecamtiv mecarbil:

- Immunoassay (2017 – 2020)
- LC-MS/MS assay (2022)

PK thresholds for dose titration in GALACTIC-HF

Companion Diagnostic Devices

- *An IVD companion diagnostic device is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.* - FDA Guidance, 2014
- **Therapeutic drug monitoring assays are rarely categorized as companion diagnostics**
- **Nearly all companion diagnostics are associated with oncology products**
- **Companion diagnostics are generally used prior to treatment to identify patients most likely to benefit from the therapeutic product**
  - Genetic variants, mutations, deletions, rearrangements
  - Gene amplification
  - Gene overexpression

In Vitro Companion Diagnostic Devices: Guidance for Industry, FDA 2014

LC-MS/MS Technology is Widely Used for Therapeutic Drug Monitoring

- **Prescription drugs* that have currently available LC-MS/MS based assay at each of LabCorp, the Mayo Clinic, and NMS Labs**
- **None classified as companion diagnostics**
- **If a companion diagnostic is required, availability of omecamtiv mecarbil would be delayed by at least one year**

Alprazolam	Gabapentin	Perphenazine
Amphetamine	Glipizide	Posaconazole
Apixaban	Glyburide	Pregabalin
Aripiprazole	Haloperidol	Repaglinide
Baclofen	Hydromorphone Hydrochloride	Rifampin
Buprenorphine	Ibuprofen	Risperidone
Caffeine Citrate	Itraconazole	Rivaroxaban
Carbamazepine	Ketoconazole	Rufinamide
Clobazam	Lamotrigine	Sirolimus
Clomipramine Hydrochloride	Levetiracetam	Tacrolimus
Clonazepam	Lidocaine	Temazepam
Clozapine	Methotrexate	Teriflunomide
Cyclosporine	Methylphenidate	Testosterone
Dabigatran Etexilate Mesylate	Midazolam	Theophylline
Diazepam	Mirtazapine	Thiothixene
Digoxin	Mycophenolic Acid	Topiramate
Ethosuximide	Niacin	Triazolam
Everolimus	Olanzapine	Valproic Acid
Felbamate	Oxcarbazepine	Vigabatrin
Fentanyl	Oxycodone	Voriconazole
Fluconazole	Paliperidone	Zonisamide

*Sourced from the FDA Orange Book with updated labels or approvals (2015 to present)

Conclusions

- **With PK-guided dose titration in GALACTIC-HF:**
  - Large proportion of patients achieved the therapeutic concentration range associated with treatment benefit
  - No patients exceeded 1200 ng/mL, which is associated with risk of cardiac ischemia
- **Simplified PK-guided dose titration is proposed to optimize benefit-risk profile of omecamtiv mecarbil**
- **LC-MS/MS assay validated and run in a single central commercial lab can effectively support PK-guided dose titration**

Benefit/Risk

Scott D. Solomon, MD

Professor of Medicine, Harvard Medical School
Brigham and Women's Hospital

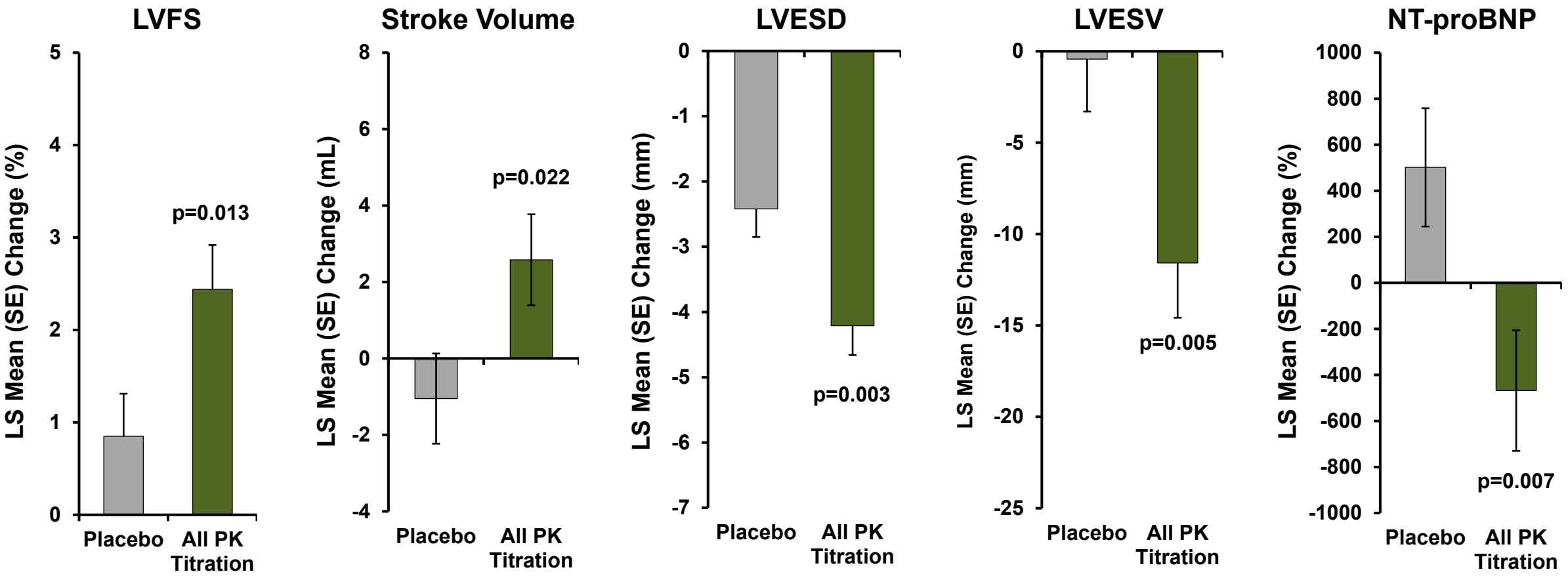
Summary

- Omecamtiv mecarbil is the first heart failure drug specifically designed to target the primary pathophysiologic abnormality in heart failure with reduced ejection fraction – contractile dysfunction
- Strong Phase 2 data to support mechanism of action
- GALACTIC-HF met its primary endpoint with modest overall treatment effect, but greater benefit in those with greater contractile dysfunction and with greatest need
- Omecamtiv mecarbil was safe

Omecamtiv Mecarbil Improves Cardiac Structure and Function

COSMIC-HF

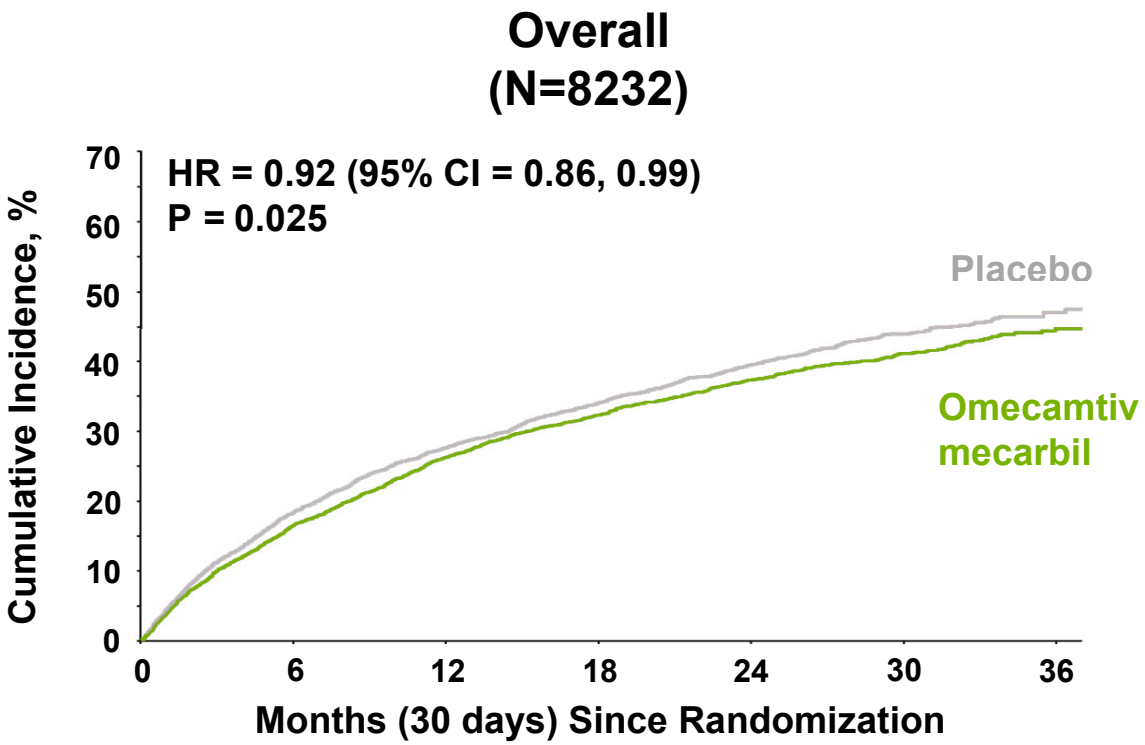
Function: Improved Contraction → **Structure: Reverse Remodeling** → **Hemodynamic Benefit**



LVFS = left ventricular fractional shortening

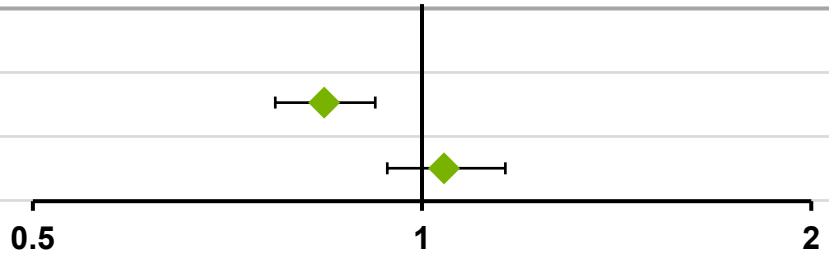
CC-116

GALACTIC-HF: Overall

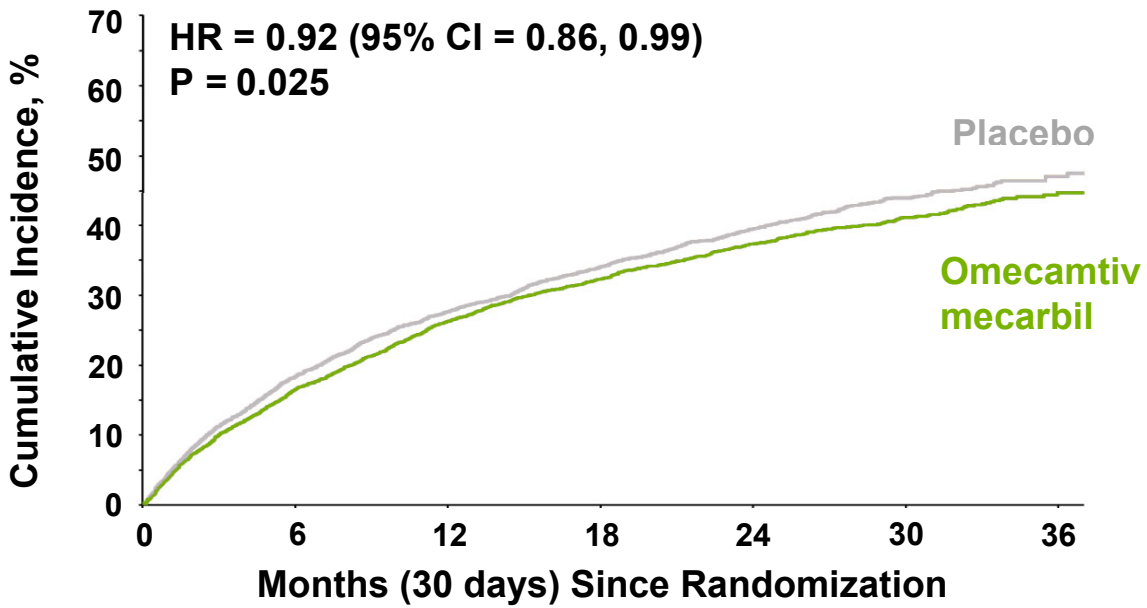


GALACTIC-HF: Overall and in Patients with EF at or Below the Median (28%)

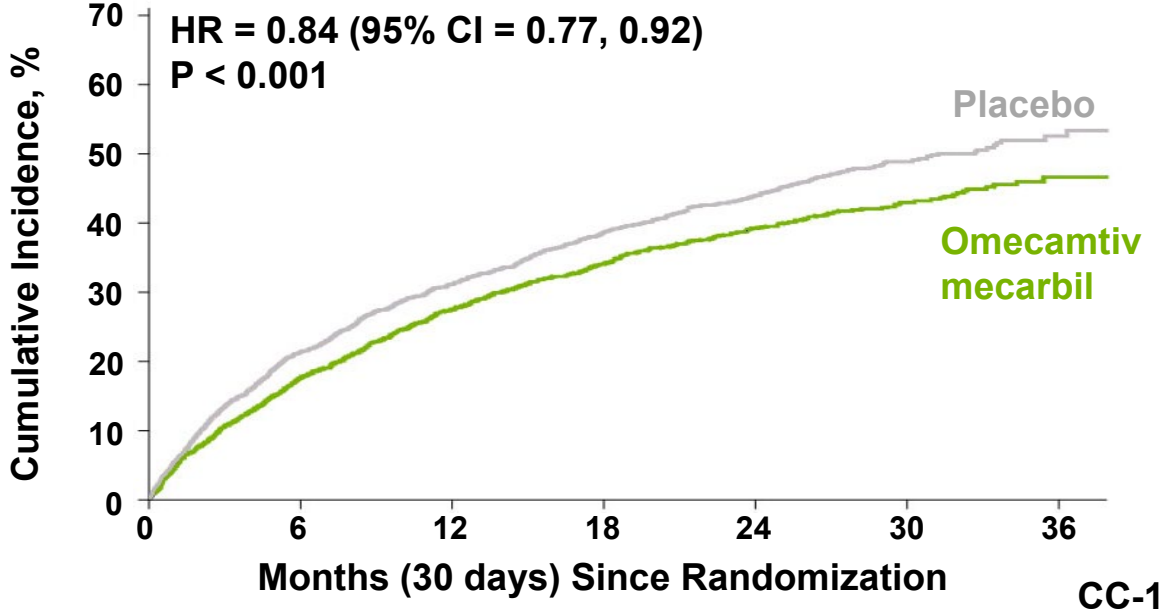
Subgroup	No. of Events/Patients	Rate Ratio (95% CI)	Multivariable Interaction p-value
LVEF			
≤28%	1821/4456	0.84 (0.77, 0.92)	0.005
>28%	1309/3776	1.04 (0.94, 1.16)	



Overall (N=8232)



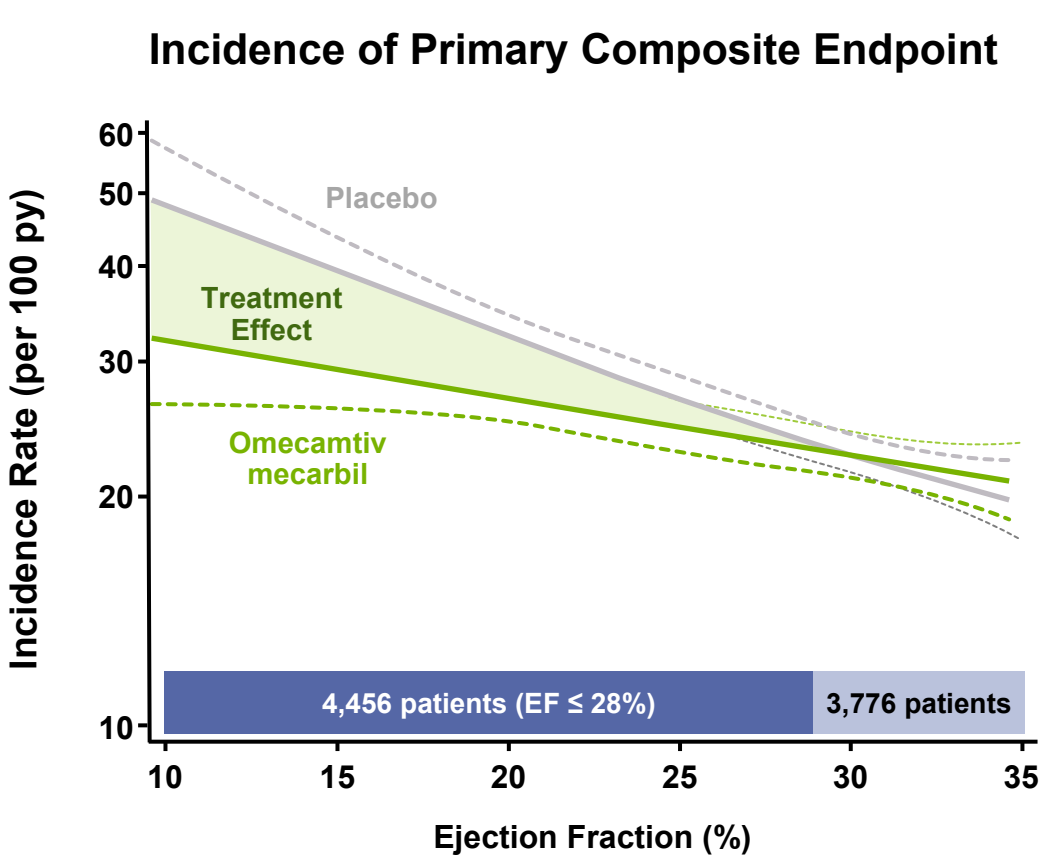
LVEF ≤28% (Median) (N=4456)

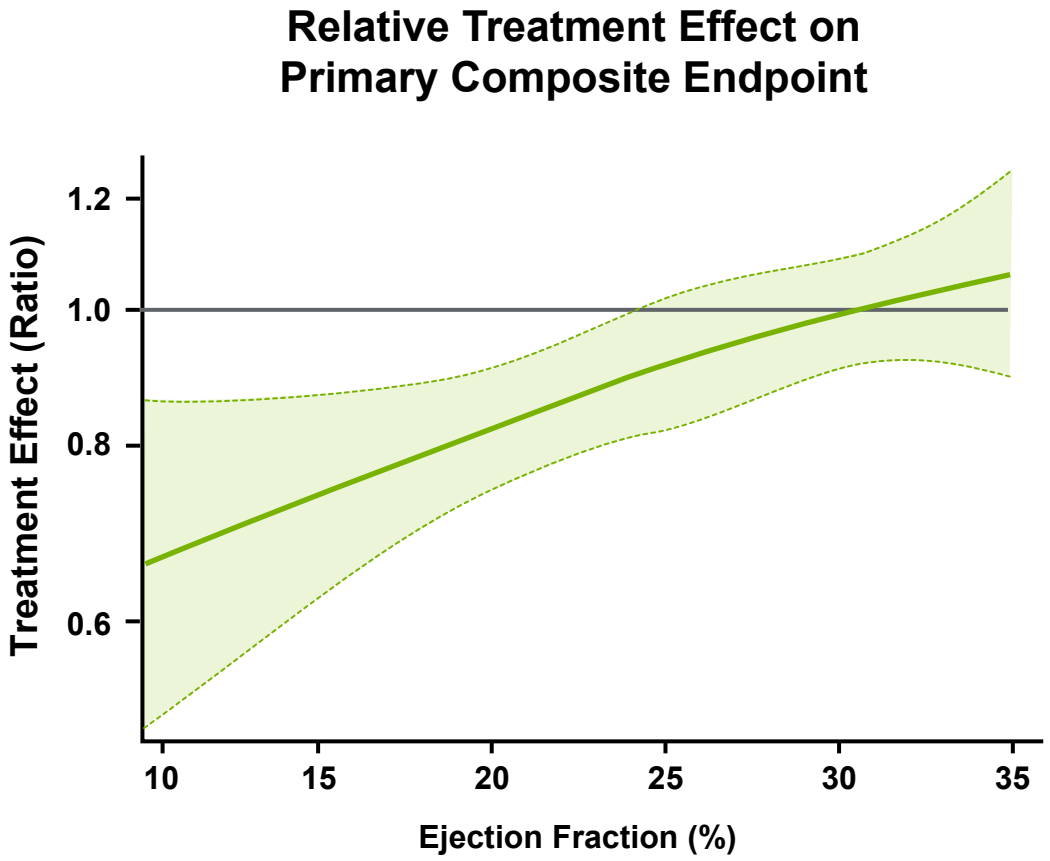


CC-118

Benefit Increases as Baseline LVEF Decreases

Pre-specified Subgroup			
	Baseline LVEF	≤ Median (28%)	0.84 (0.77, 0.92)
		> Median (28%)	1.04 (0.94, 1.16)
Multivariable interaction *p*-value = 0.005			





Dashed lines are 95% confidence intervals

Teerlink JR., Diaz R., Felker GM., et al. *JACC*. 2021

CC-119

Is the benefit truly greatest in lowest LVEF patients?

- **Subgroups need to be pre-specified**
  - ✓ EF (median) was pre-specified
  - ✓ Continuous analysis of EF demonstrates continuously-increasing benefit as EF decreases
- **Subgroups should be large, patients-wise and event-wise**
  - ✓ > 4400 patients were included in the LVEF ≤ 28% subgroup
  - ✓ Hundreds (n=1821) of events occurred in the LVEF ≤ 28% subgroup
- **An interaction test should be applied and adjusted for multiplicity in a multivariate analysis**
  - ✓ Ejection fraction was the most significant univariate interaction effect identified
  - ✓ The interaction was robust to a global test for heterogeneity and a multivariate analysis of the prespecified subgroups
- **Internal consistency of effect**
  - ✓ The treatment effect continuously grows larger as ejection fraction falls
- **Biological plausibility of the interaction proposed**
  - ✓ The mechanism of action is intended to increase cardiac function; EF is the most common measure of cardiac function

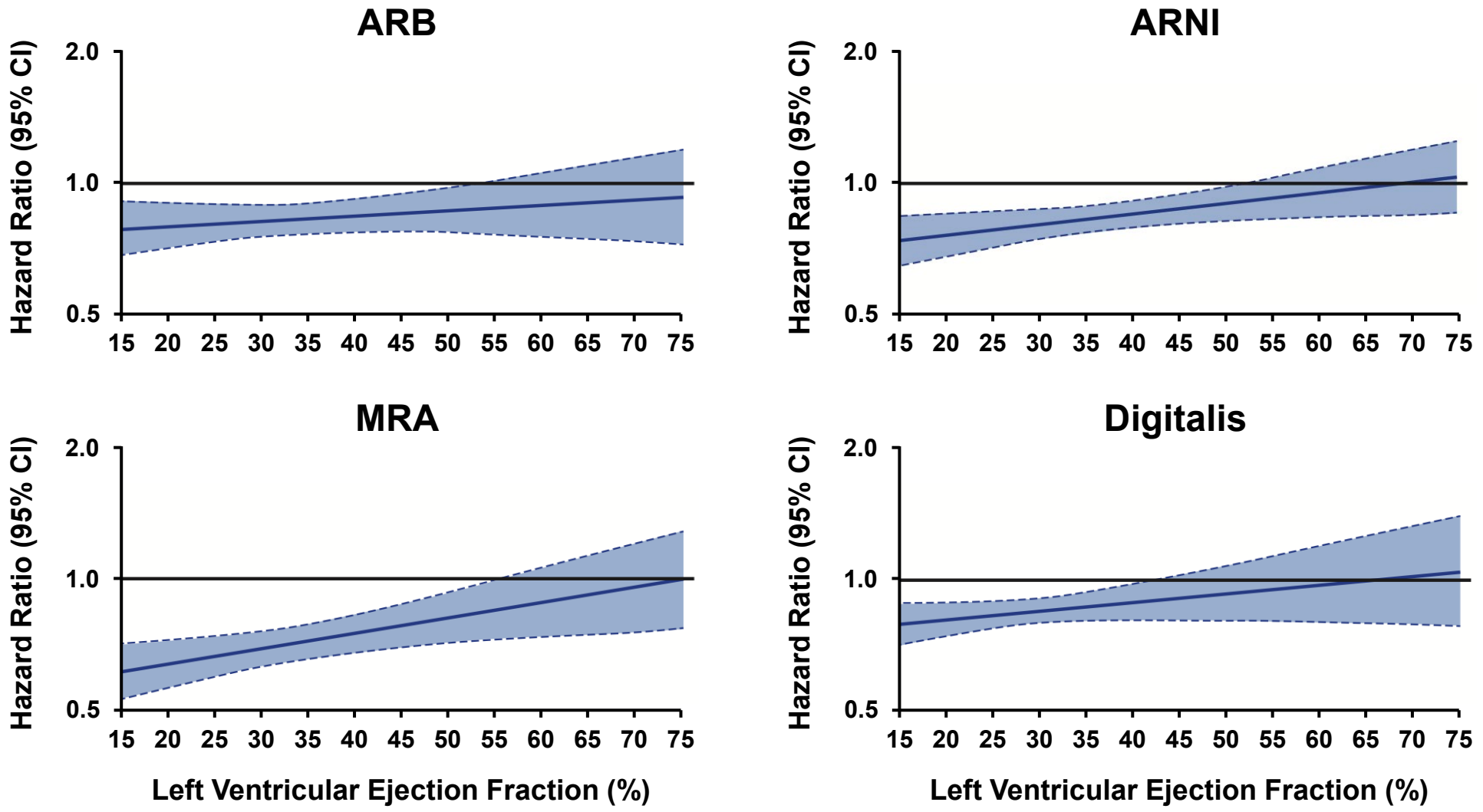
The analyses of the LVEF subgroup check all the boxes

Importantly, the intent is to direct therapy to patients where it is most effective

Wittes J. et al. *Circulation* 2009

Ejection Fraction is a Treatment Effect Modifier

CV Death or Heart Failure Hospitalization



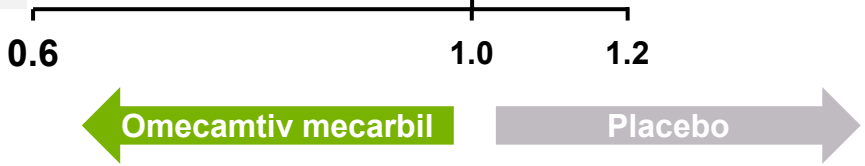
ARB, MRA and Digitalis compared with placebo; ARNI compared with enalapril or valsartan

Kondo T and McMurray JJV. *Eur. Heart J.* (2022) 43, 427–429

Greater Benefit in Higher-Risk Patients

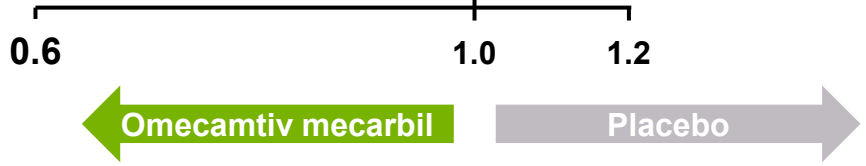
Primary Composite Endpoint

	N	HR (95% CI)	P-value	ARR
All Patients	8232		0.025	2.1
LVEF ≤28%	4456		<0.001	5.1
+ Hosp <3 mos	2692		0.002	6.0
+ SBP <110	1820		0.002	8.0
+ Class III/IV	2132		<0.001	9.1
+ NT-proBNP >2000	2431		<0.001	11.3



CV Death

HR (95% CI)	P-value	ARR
	0.86	-0.1
	0.21	1.0
	0.26	1.2
	0.34	1.3
	0.07	2.3
	0.05	2.5



Treatment benefit is consistently larger amongst meaningful clinical subgroups of increased risk

Greater Benefit in Higher-Risk Patients

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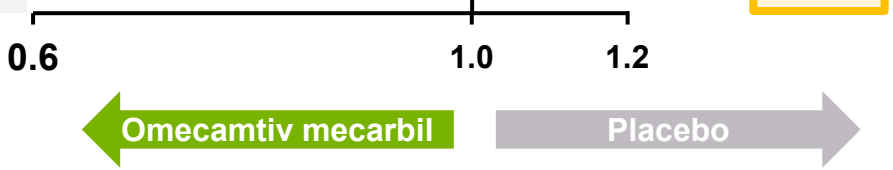

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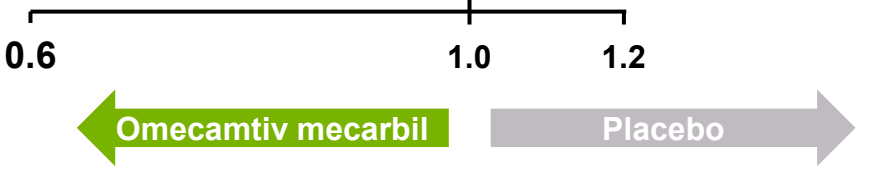
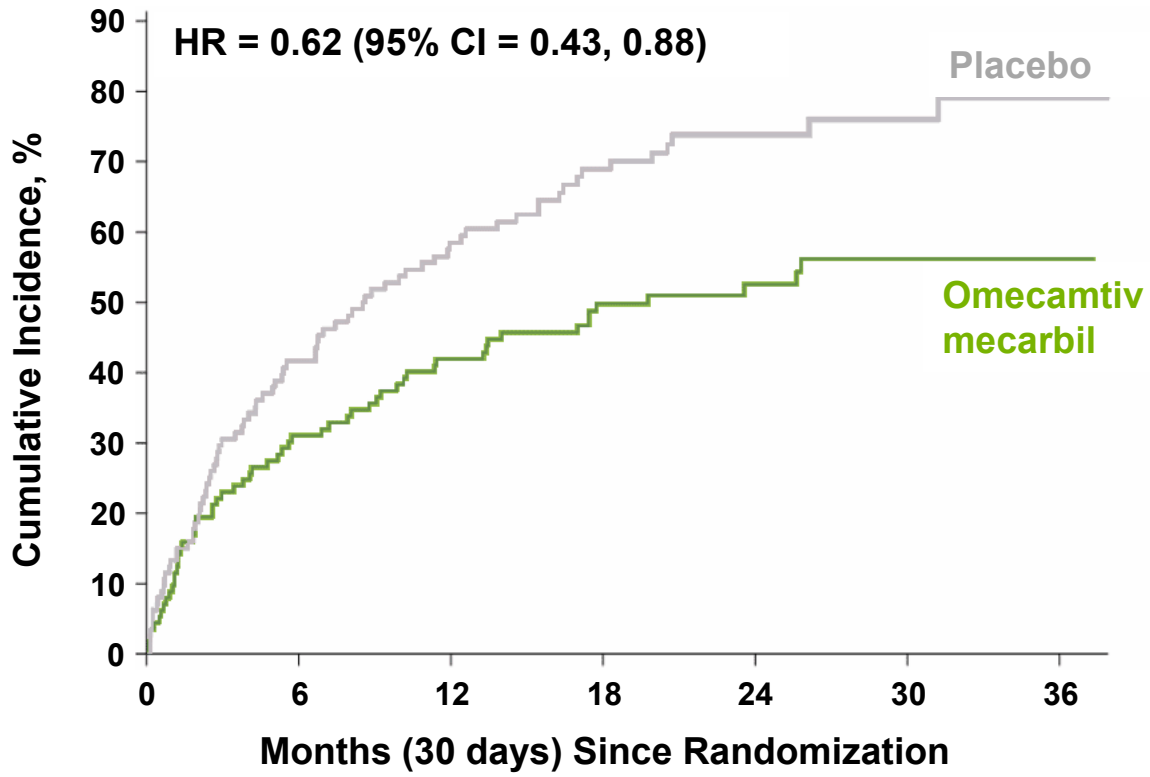


Treatment benefit is consistently larger amongst meaningful clinical subgroups of increased risk

Outcomes Improved in Patients Intolerant to ACE/ARB/ARNI

LVEF ≤28%

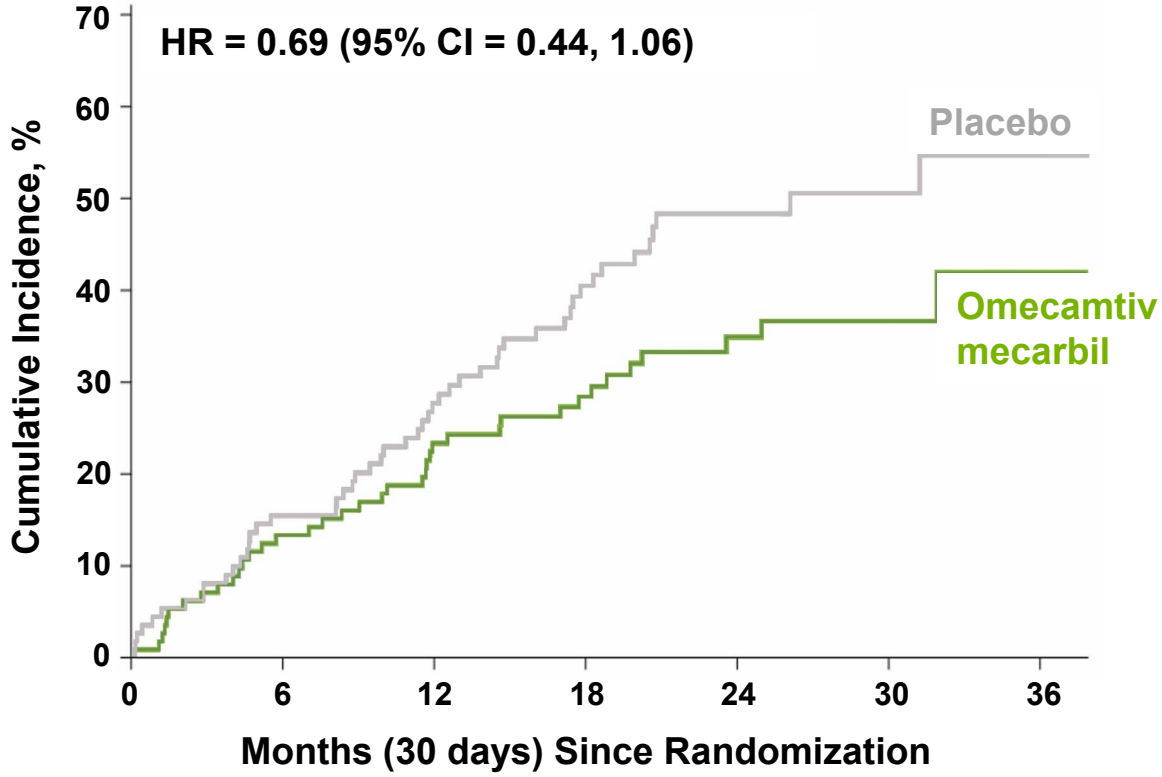
Primary Endpoint



Patients at risk, n

Placebo	113	63	43	28	15	9	3
OM	113	76	64	46	30	9	3

CV Death



	113	91	75	51	30	15	5
	113	96	83	62	40	15	5

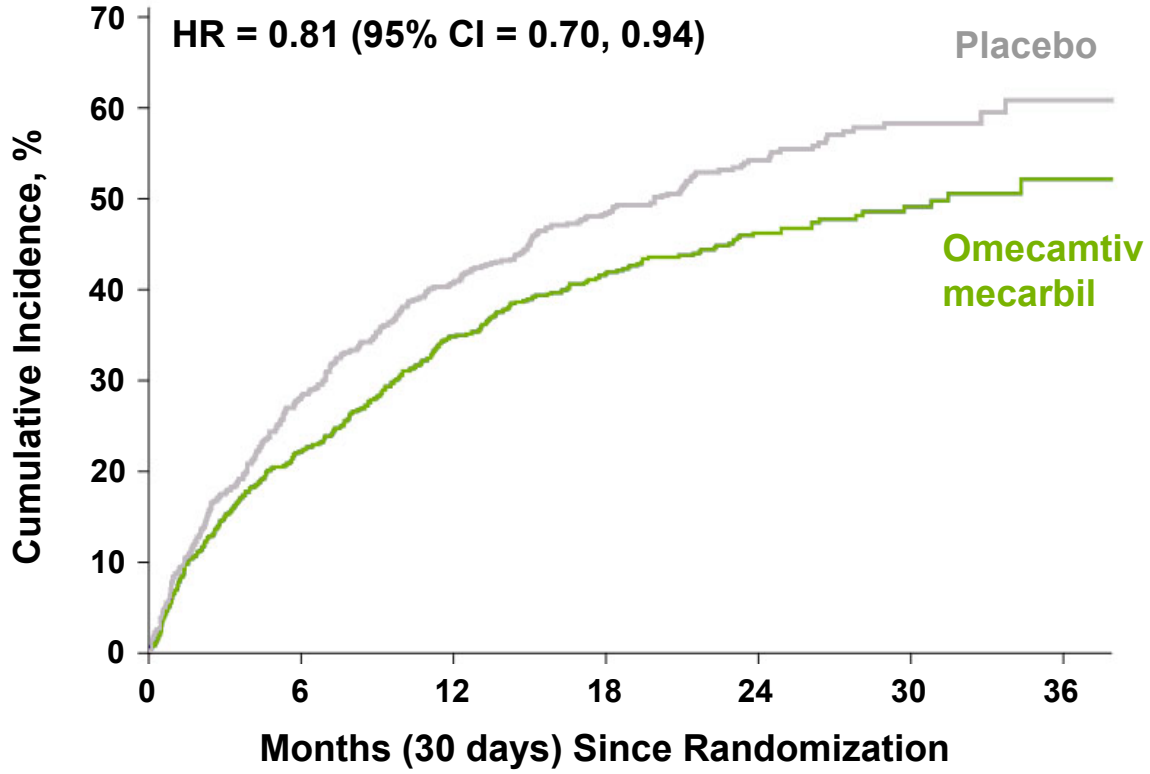
CI, confidence interval; HR, hazard ratio.

CC-124

Effect of Omecamtiv Mecarbil with Low Blood Pressure

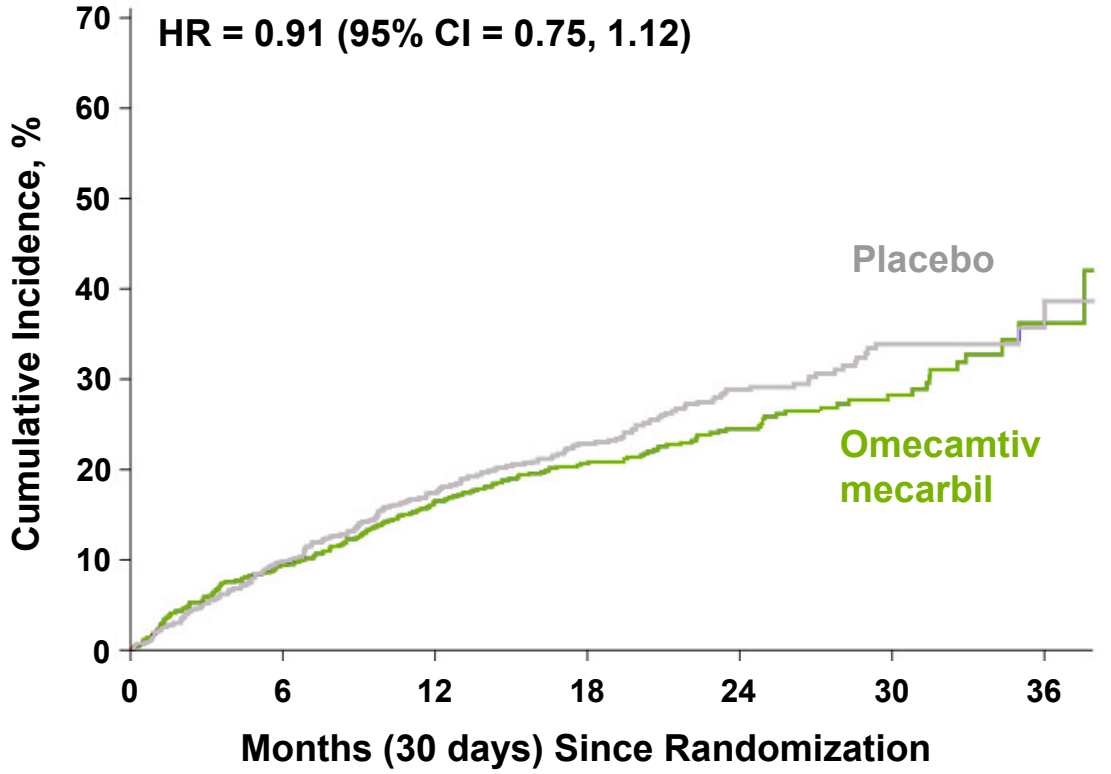
SBP ≤100 mmHg

Primary Composite Endpoint



Patients at risk, n							
Placebo	692	488	397	276	160	62	13
OM	781	599	493	339	227	89	18

CV Death



692	613	551	407	247	109	22
781	696	628	465	316	127	25

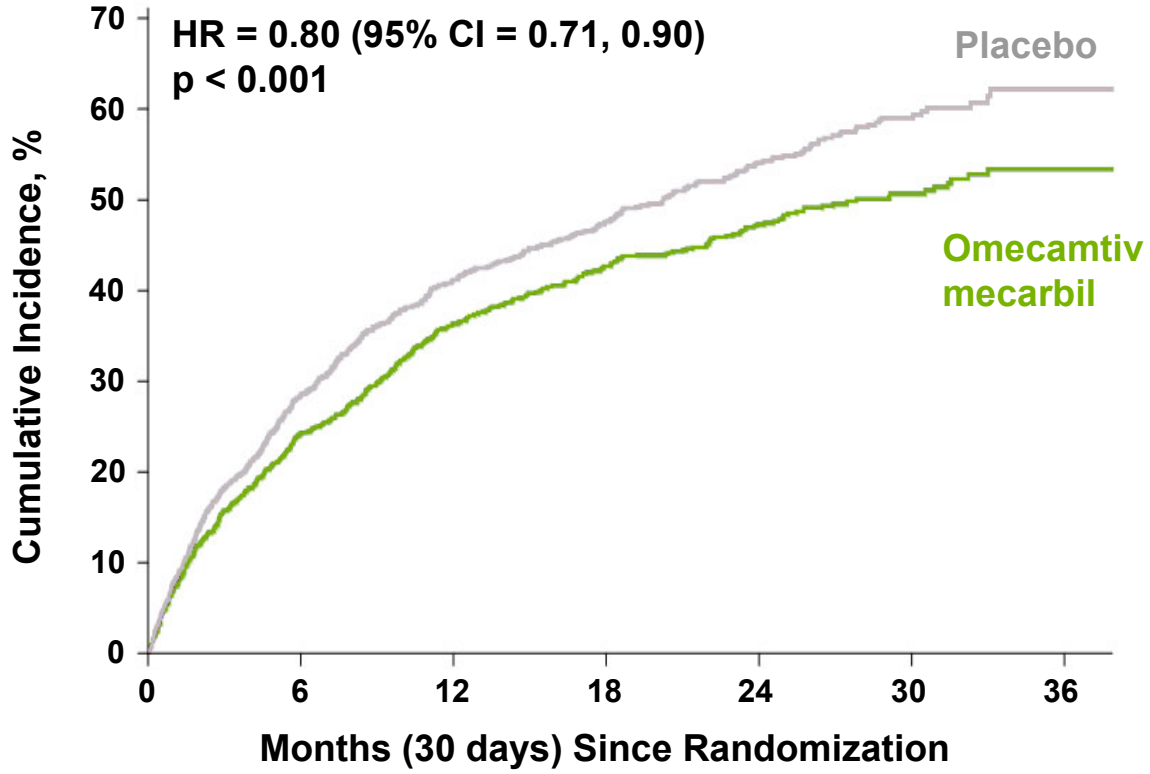
Metra et al. *Eur Heart J* 2022

CC-125

Effect of Omecamtiv Mecarbil in Severe HF

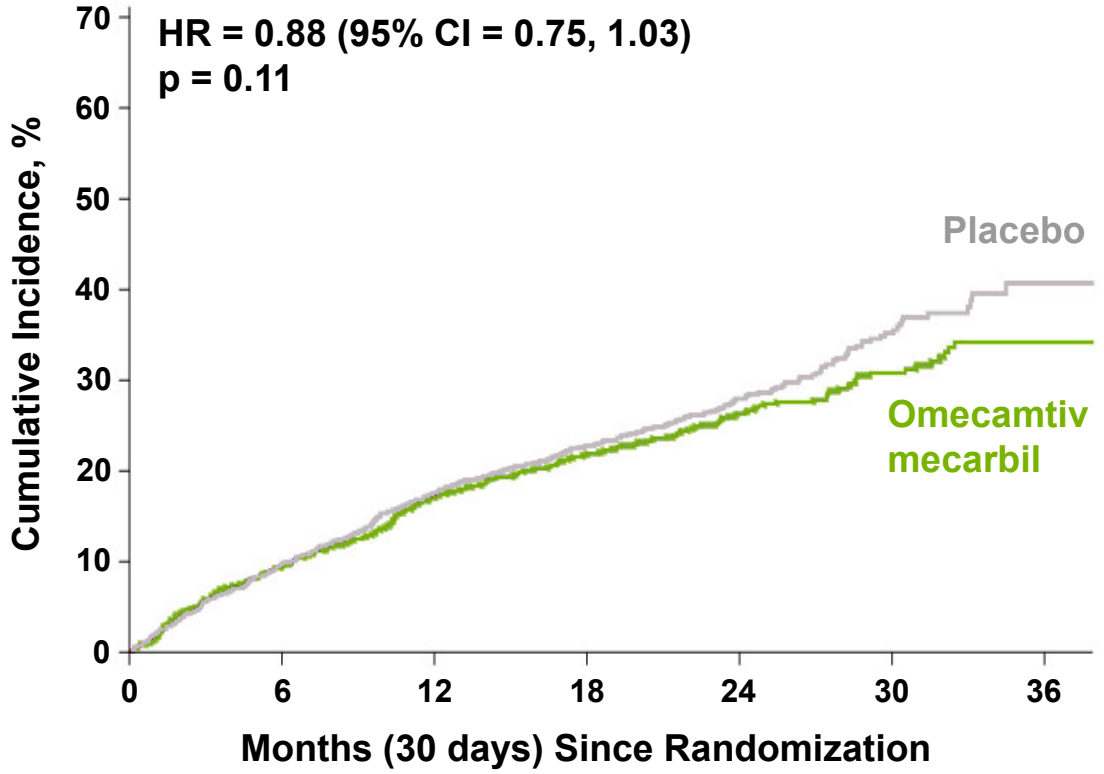
LVEF ≤30%, NYHA Class III/IV, Hospitalized ≤6 months

Primary Composite Endpoint



Patients at risk, n							
Placebo	1152	808	650	464	290	119	13
OM	1106	814	671	480	320	137	31

CV Death



1152	1022	911	687	450	192	26
1106	976	874	656	438	186	40

Felker et al. *JAMA Cardiol* 2022

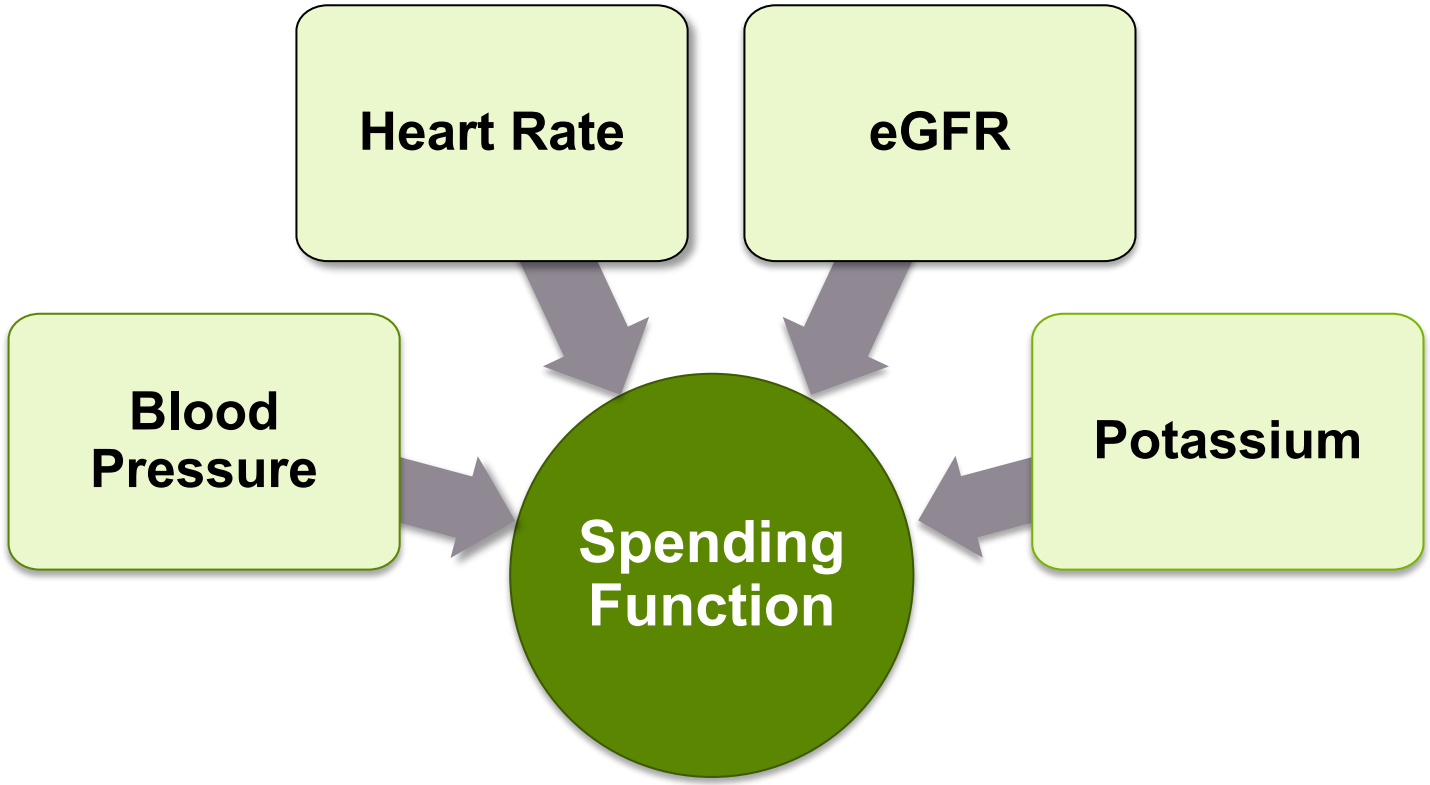
CC-126

In LVEF ≤28% Subgroup, Absolute Risk Reduction is Comparable Across Contemporary Trials in HFrEF

	GALACTIC-HF Overall	GALACTIC-HF LVEF ≤28%	PARADIGM-HF	DAPA-HF	EMPEROR-REDUCED	VICTORIA
N	8232	4456	8442	4744	3730	5050
Comparator	Placebo	Placebo	Enalapril	Placebo	Placebo	Placebo
Comparator Events/100 pt-yr	26.3	31.2	13.2	15.6	21.0	37.8
Absolute Risk Reduction	2.1	5.1	2.7	4.0	5.2	4.2
HR (95% CI)	0.92 (0.86, 0.99)	0.84 (0.77, 0.92)	0.80 (0.73, 0.87)	0.74 (0.65, 0.85)	0.75 (0.65, 0.86)	0.90 (0.82, 0.98)
p-value	0.025	<0.001	<0.001	<0.001	<0.001	0.02
Follow-up (mo)	21.8	21.8	27	18.2	16	10.8

Butler, et al. *Circulation*. 2020;142:717–719.
Packer, et al. *N Engl J Med*. 2020 Oct 8;383(15):1413-1424.

“Spending Function” in Patients With HFrEF



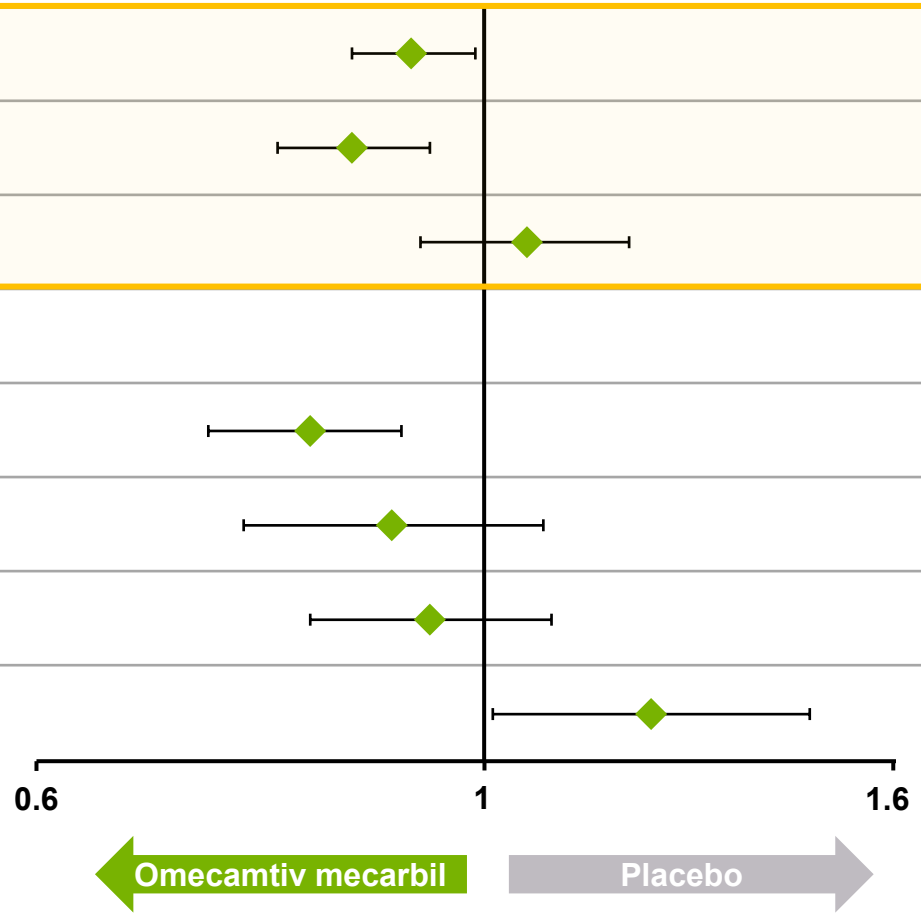
Drug therapy for HFrEF affects each clinical parameter

Patients have a limited amount of each to “spend” on their HFrEF therapies

Atrial Fibrillation/Flutter

Primary Composite Endpoint

		Omecamtiv Mecarbil N	Placebo N	HR (95% CI)	p-value
Overall study population		4120	4112		0.025
No AFF		2974	3013		0.0009
AFF		1146	1099		0.47
LVEF ≤28%	No AFF	1663	1685		<0.001
	AFF	550	558		0.24
LVEF >28%	No AFF	1311	1328		0.39
	AFF	596	541		0.04



AFF=atrial fibrillation/flutter
n/N = number of events/number of patients without atrial fibrillation at baseline

CC-129

Conclusions

- GALACTIC-HF was a positive outcomes trial of a drug with a unique mechanism of action central to the pathophysiology of HFrEF
- Greatest benefit on patient outcomes was in those with worse heart failure and the highest event rates
- Characteristics of omecamtiv mecarbil allow for its use where current standard of care can be challenging
- Benefits of omecamtiv mecarbil outweigh its risks and make it a compelling addition to therapies we have available to treat our neediest patients with HFrEF

Conclusion

Fady Malik, MD, PhD, FACC, FHFA

Executive Vice President, Research & Development Cytokinetics

Substantial Evidence of Effectiveness

COSMIC-HF

- An adequate and well-controlled clinical trial
- Statistically significant improvements indicative of improved LV cardiac function and structure
- Increase in stroke volume, decrease in heart rate
- Improvements in left atrial size and function
- Decrease in NT-proBNP similar in extent to that observed in GALACTIC-HF
- Persuasive strong mechanistic data that provide confirmatory evidence

GALACTIC-HF

- An adequate and well-controlled clinical trial
- Met its prospectively-defined primary efficacy endpoint
- Effect on the primary endpoint was statistically robust to a variety of sensitivity analyses
- Treatment effect is larger in those with lower EF
- Decreases in NT-proBNP consistent with pharmacodynamic effects in COSMIC-HF
- Strongly positive benefit-risk in lower EF patients

An adequate and well-controlled clinical trial (GALACTIC-HF) supported by confirmatory evidence that provide strong mechanistic support (COSMIC-HF)

Indication Proposed in the NDA

Omecamtiv mecarbil is a cardiac myosin activator indicated to reduce the risk of cardiovascular death and heart failure events in patients with symptomatic chronic heart failure with reduced ejection fraction. Benefits are increasingly evident the lower the left ventricular ejection fraction (LVEF).

Cytokinetics Recommendation:
Focus labeling on patients who derive the greatest benefit

Implementation of PK-guided Dosing

- **LC-MS/MS**
  - Validated assay
  - Performed at a central lab
  - Gold standard methodology
  - Deploy at time of approval
  - Approach consistent with many drugs requiring therapeutic drug monitoring

- **Immunoassay**
  - Same validated assay employed in GALACTIC-HF
  - Can be performed centrally as well as more locally
  - Submission under preparation for clearance by FDA

Cytokinetics Recommendation:
Use of LC-MS/MS assay at time of approval

Cytokinetics

Omecamtiv Mecarbil

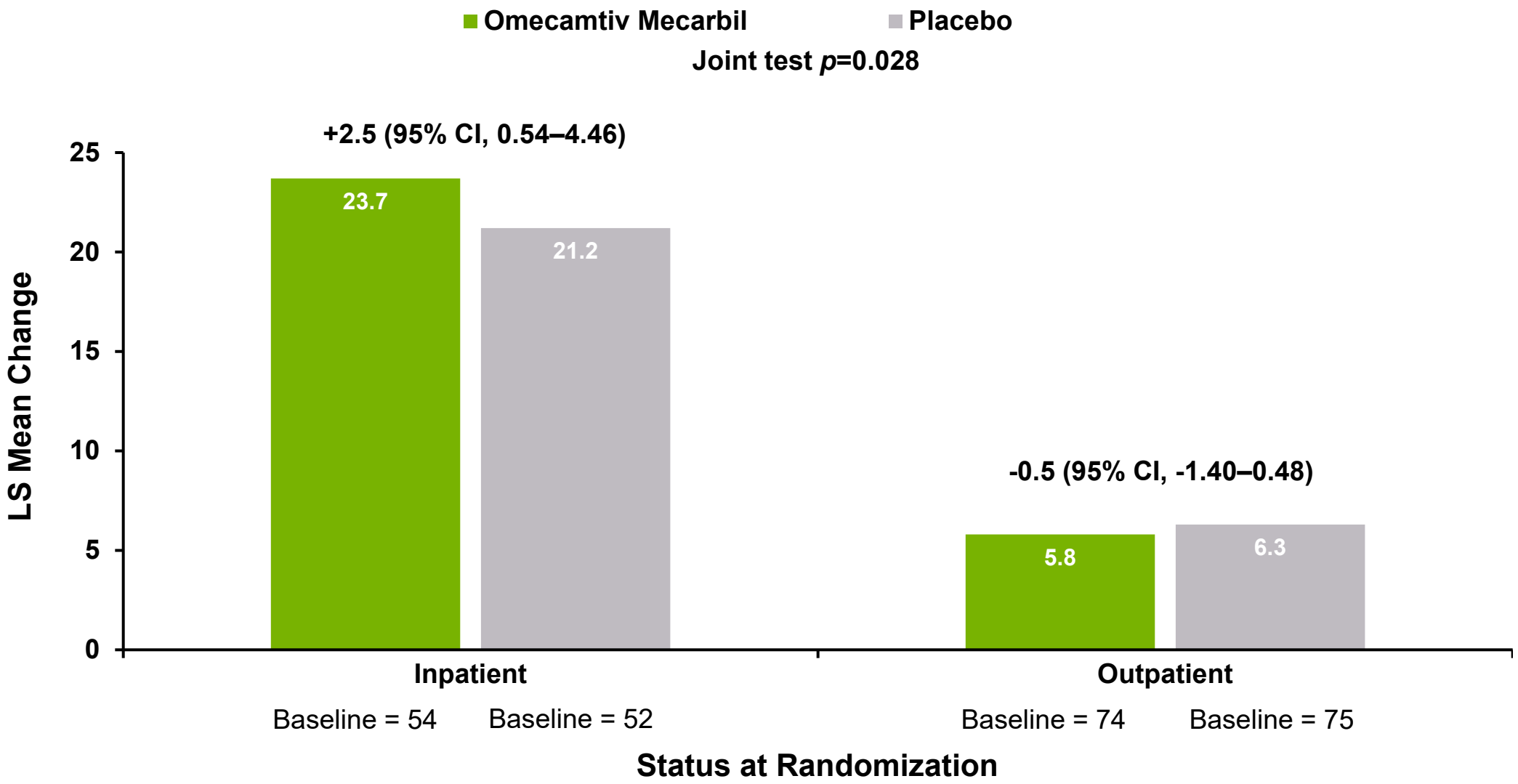
Cardiovascular and Renal Drugs Advisory Committee

NDA 216401
13 December 2022

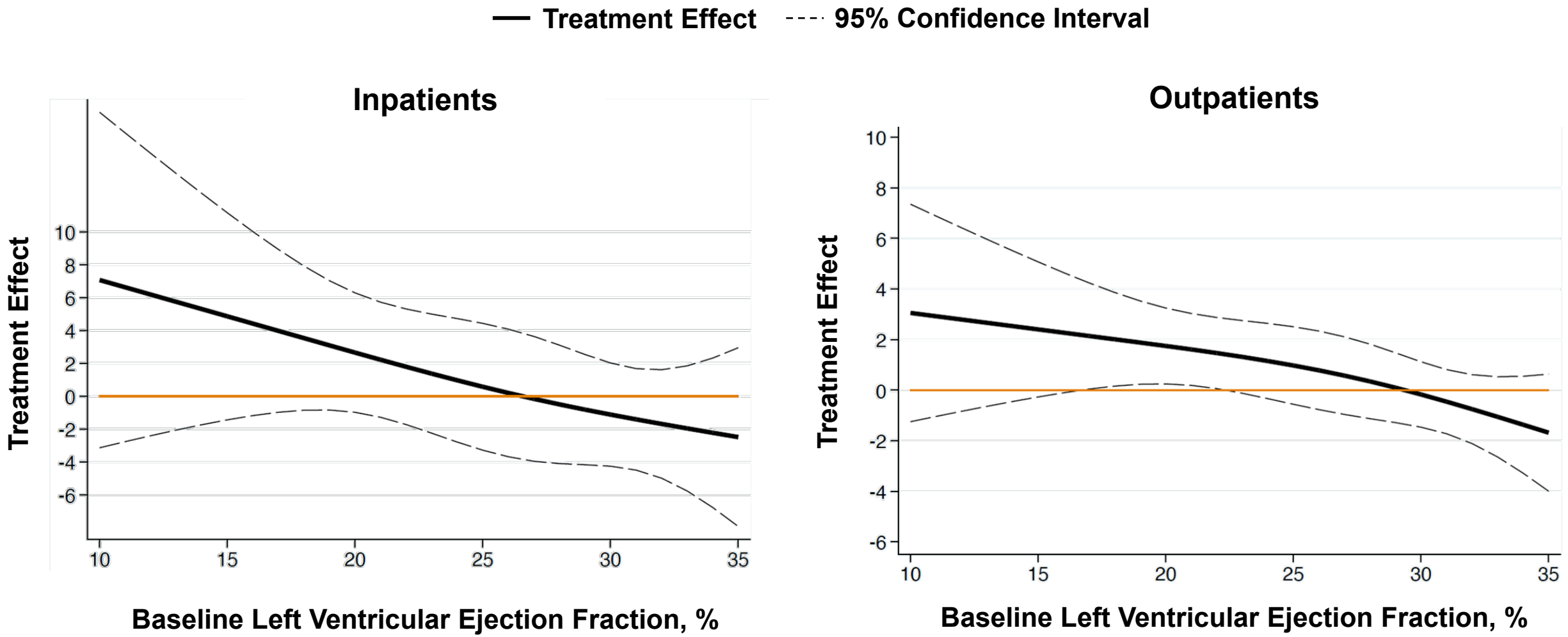
Backup Slides Shown

Change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score from Baseline to Week 24

GALACTIC-HF



KCCQ: Inpatient and Outpatient Week 12 TSS Change



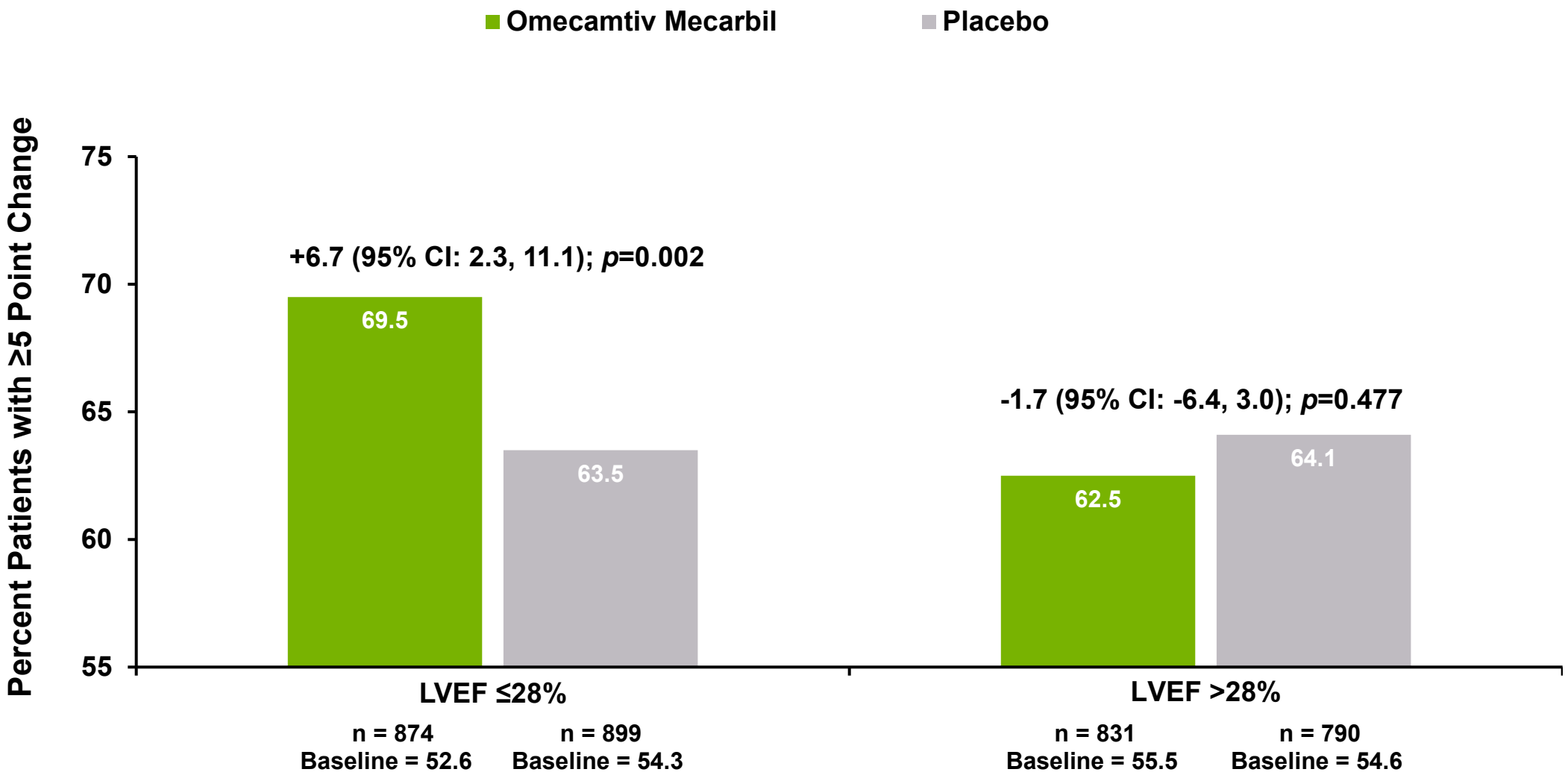
KCCQ= Cardiomyopathy Questionnaire (Kansas City)

BU-655

Change in KCCQ in Patients with Moderate or Greater PGR-S

Change ≥5 Points

GALACTIC-HF

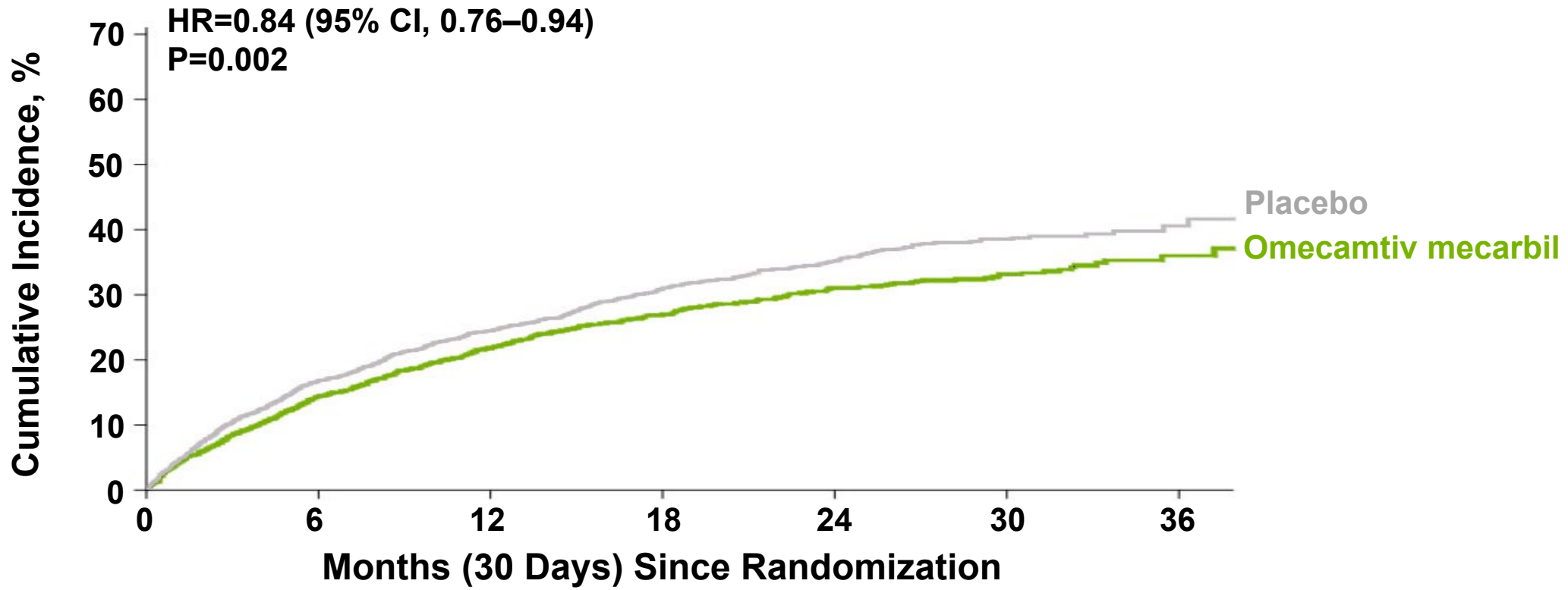


BU-706

Heart Failure Hospitalization

LVEF ≤28%

GALACTIC-HF



Patients at risk, n

Placebo	2243	1755	1516	1055	658	300	64
Omecamtiv mecarbil	2213	1808	1568	1113	718	322	79

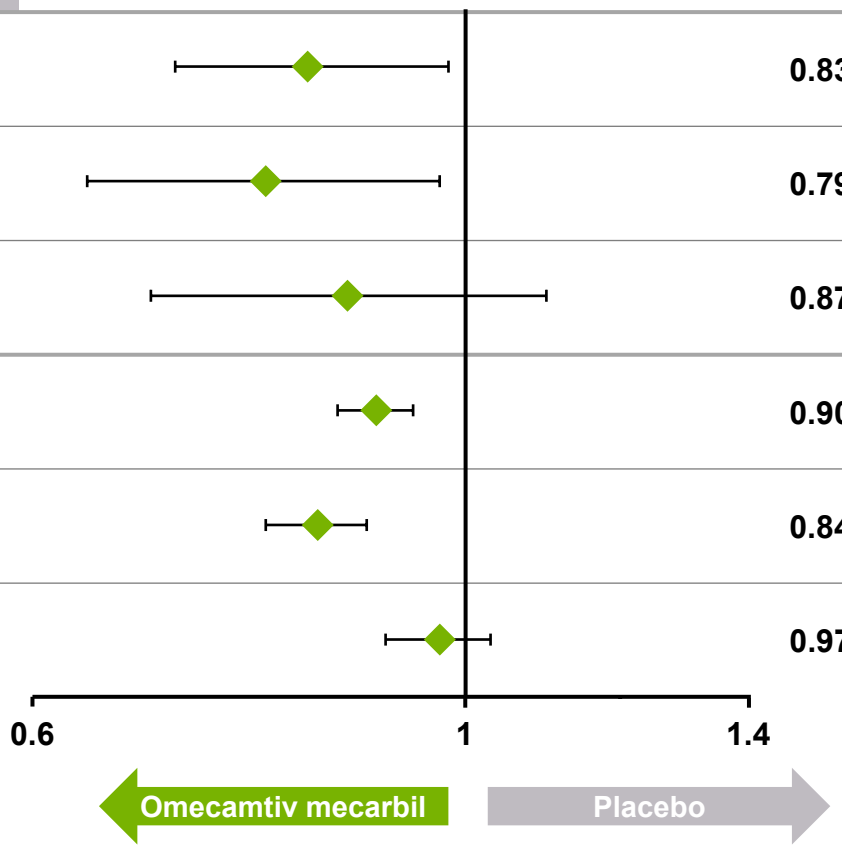
BU-495

Frequency Count of CV Death by Maximum Increase Post-baseline Troponin I Category

Maximum Troponin I Increase (ng/mL)	Placebo CV Death Studies n/N (%)	Omecamtiv Mecarbil CV Death Studies n/N (%)
<0	156/745 (20.9)	76/359 (21.2)
0 - <0.04	381/2387 (16.0)	306/2285 (13.4)
≥0.04	212/847 (25.0)	391/1355 (28.9)
≥2	14/31 (45.2)	12/36 (33.3)
≥10	2/6 (33.3)	2/7 (28.6)

Change in NT-pro BNP by LVEF
COSMIC-HF and GALACTIC-HF

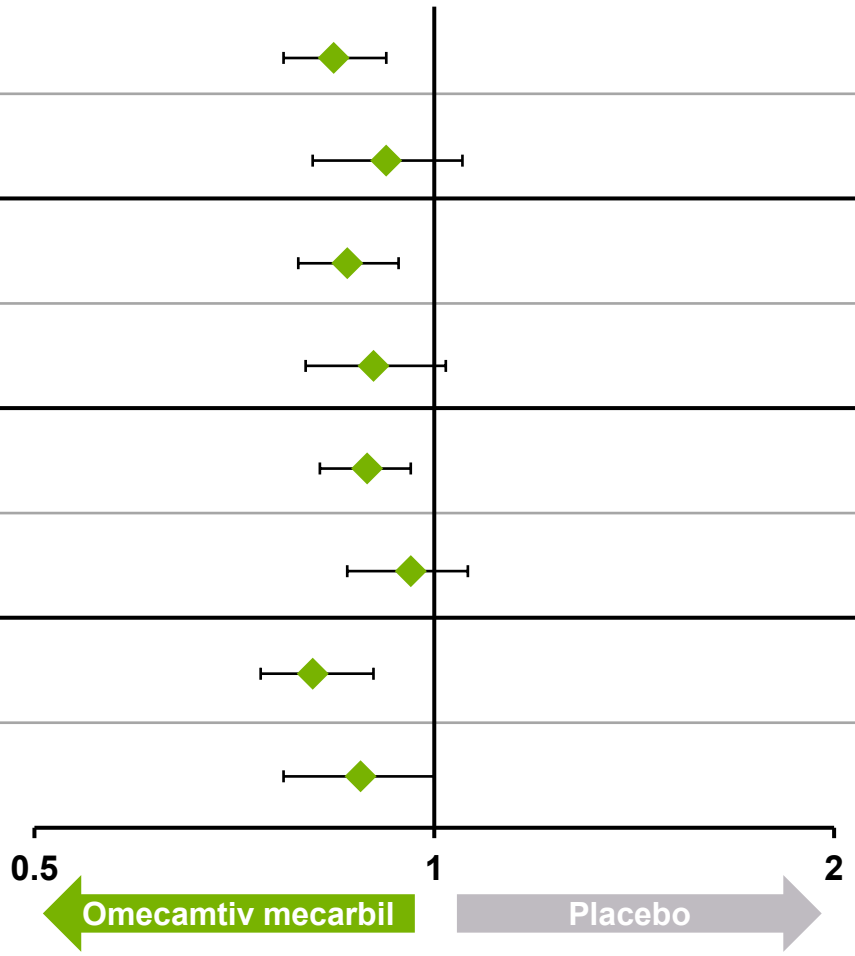
		Omecamtiv Mecarbil N	Placebo N		P-value
COSMIC-HF (Week 20)	FAS	306	149	0.83 (0.71 to 0.98)	0.0283
	Baseline LVEF ≤28%	125	64	0.79 (0.64 to 0.97)	0.0251
	Baseline LVEF >28%	171	85	0.87 (0.69 to 1.10)	0.2344
GALACTIC-HF (Week 24)	FAS	4120	4112	0.90 (0.86 to 0.94)	<0.0001
	Baseline LVEF ≤28%	2213	2243	0.84 (0.79 to 0.89)	<0.0001
	Baseline LVEF >28%	1907	1869	0.97 (0.91 to 1.03)	0.3224



BU-605

Potential Labelled Populations

		Omecamtiv Mecarbil N	Placebo N	HR (95% CI)	p-value
LVEF ≤28%	Primary Composite Endpoint	2213	2243	0.84 (0.77, 0.92)	<0.001
	CV Death	2213	2243	0.92 (0.81, 1.05)	0.21
No AFF	Primary Composite Endpoint	2974	3013	0.86 (0.79, 0.94)	<0.001
	CV Death	2974	3013	0.90 (0.80, 1.02)	0.09
No (AFF + Digoxin)	Primary Composite Endpoint	3779	3761	0.89 (0.82, 0.96)	0.002
	CV Death	3779	3761	0.96 (0.86, 1.06)	0.39
LVEF ≤28% No (AFF + Digoxin)	Primary Composite Endpoint	2043	2058	0.81 (0.74, 0.90)	<0.001
	CV Death	2043	2058	0.88 (0.77, 1.00)	0.06

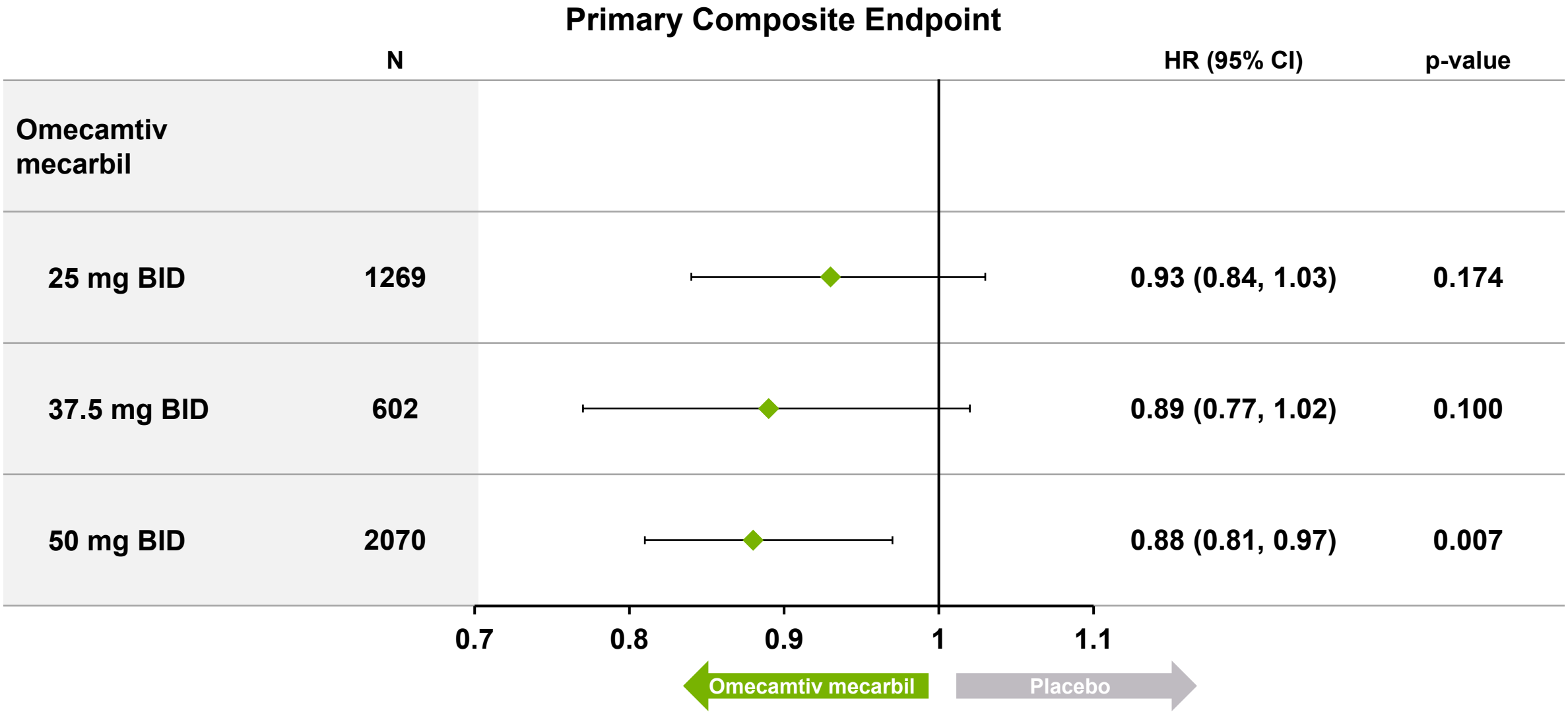


AFF = atrial fibrillation/flutter; LVEF = left ventricular ejection fraction.

BU-703

Omecamtiv Mecarbil: GALACTIC-HF

Dose-Response Profile



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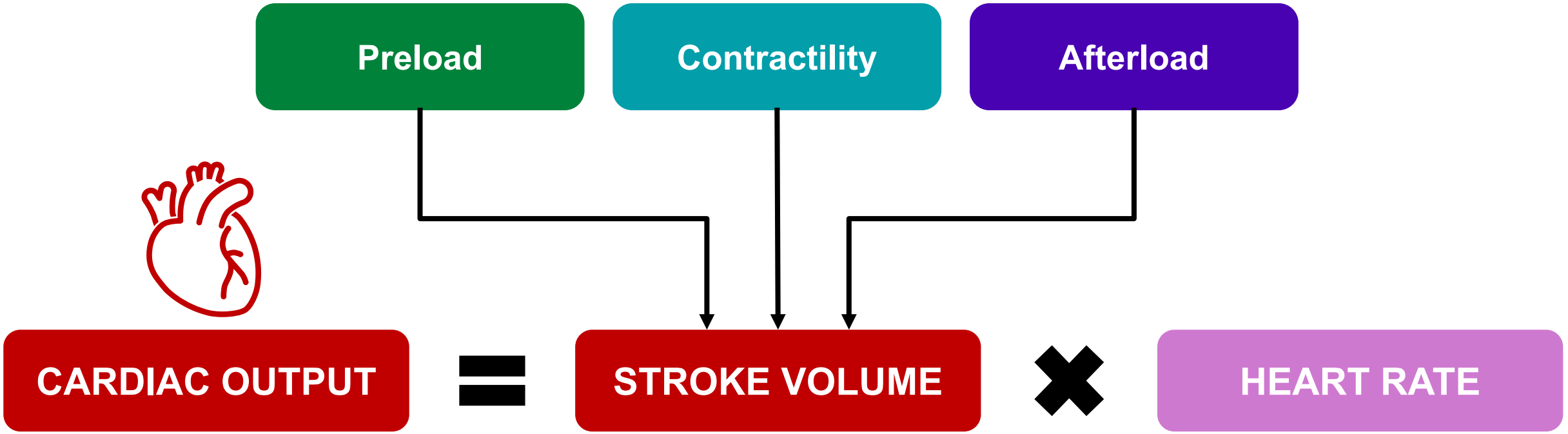
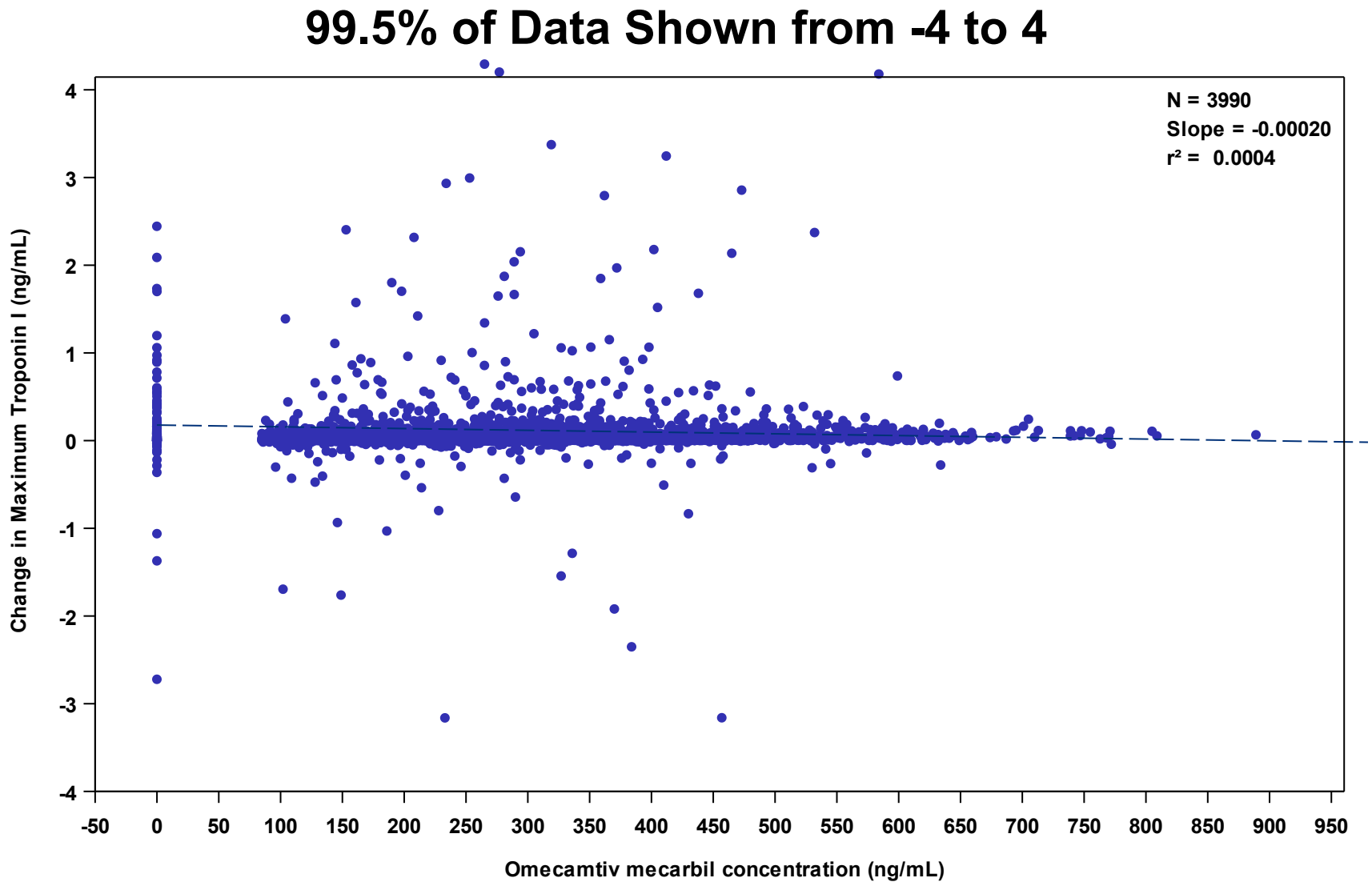
Determinants of Cardiac Output



Regression Line of Maximum Change in Post-Baseline Troponin (ng/mL) as a Function of Last Omecamtiv Mecarbil Concentration Up to Week 12 (Placebo Excluded) Overall Population



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Categorical Covariate-Interaction p-values for Original Pre-specified Subgroups in Multivariate Analysis for MCIE

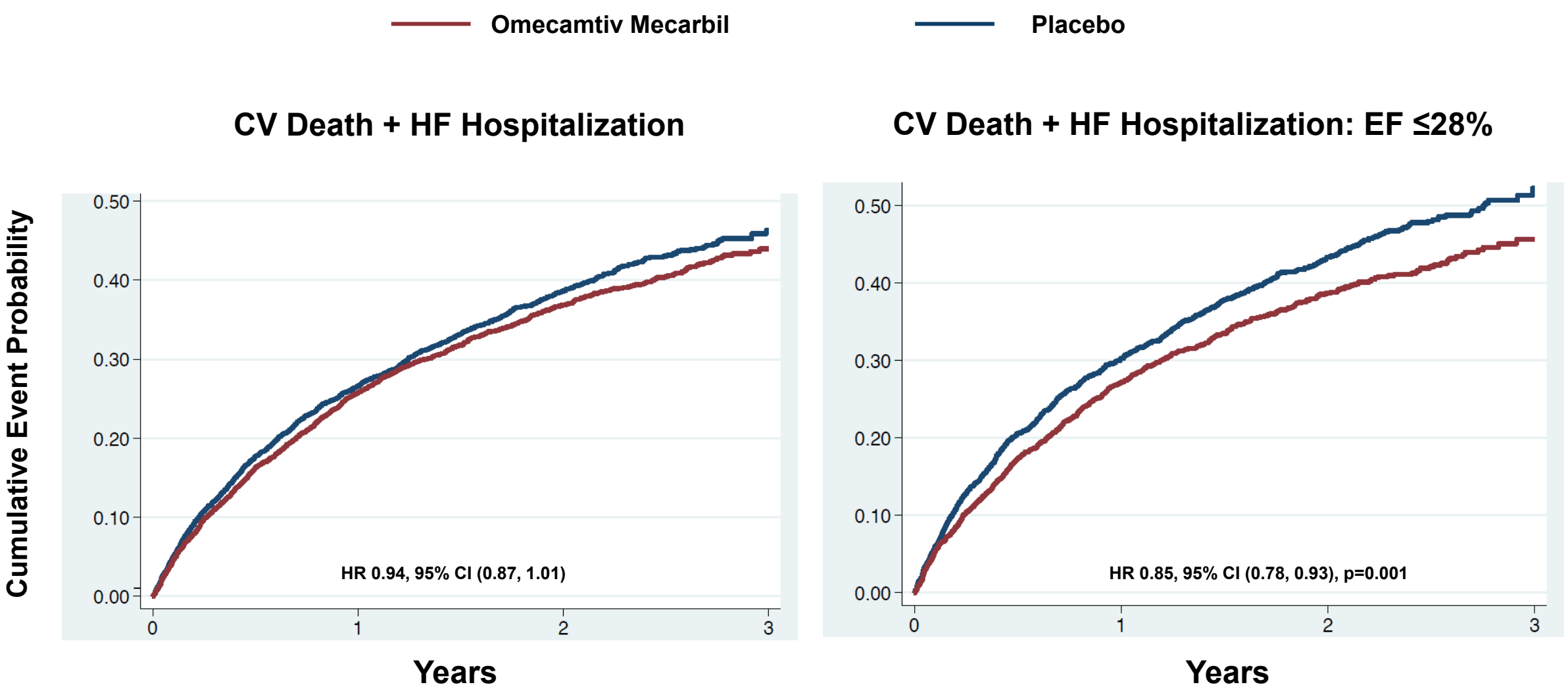
Treatment-Covariate Interaction	p-value
Global (n = 8202, 31 covariates)	0.21
Region (ref = E. Europe)	0.010
Inpatient status	0.044
ICD	0.12
Troponin (below median)	0.12
ARB use	0.14
ARNi use	0.18
SBP (below median)	0.20

Clinical Outcomes in New Onset Atrial Fibrillation
GALACTIC-HF

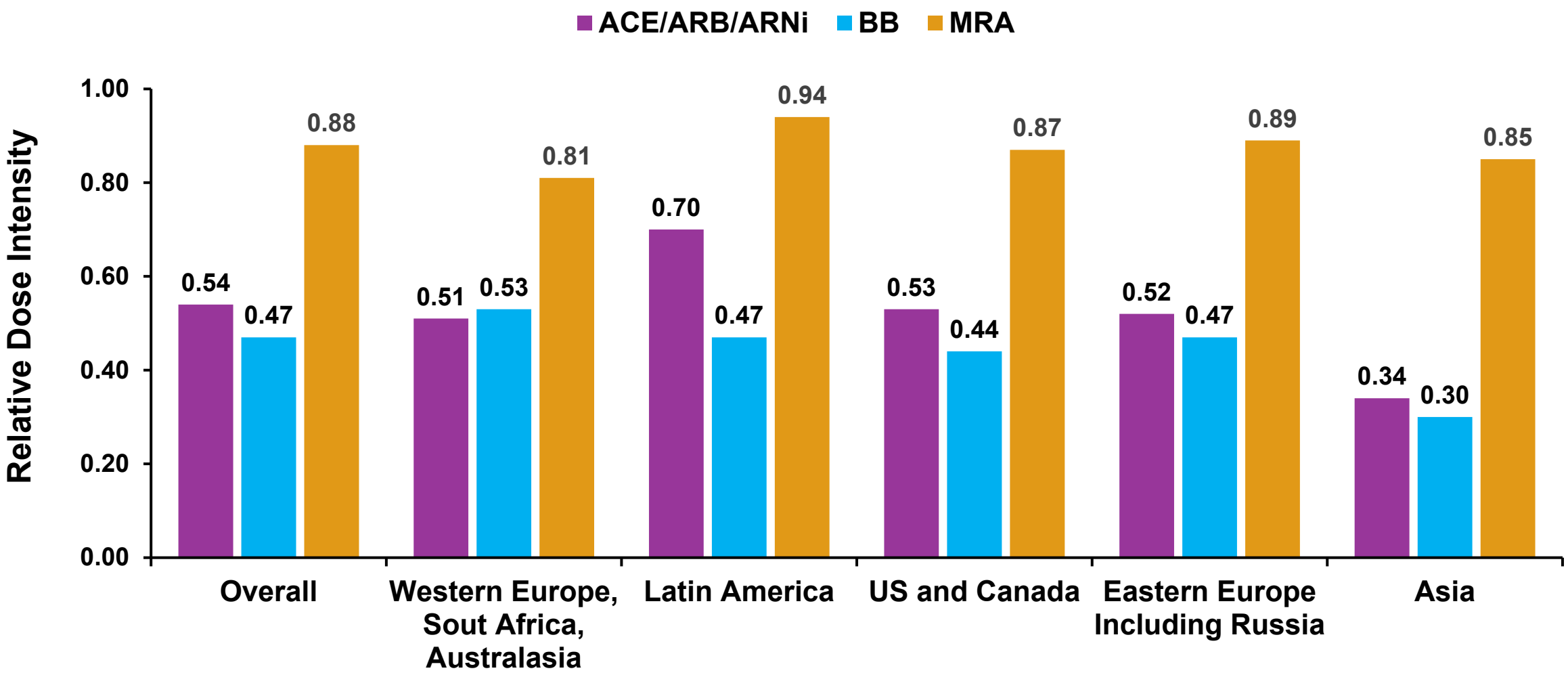
Patients without atrial fibrillation at Screening	Omecamtiv Mecarbil N=2974	Placebo N=3013	RR (95% CI)
Patients with new atrial fibrillation (n, %)	187 (6.3%)	222 (7.4%)	
Outcomes after randomization and prior to new atrial fibrillation			
Primary Endpoint	31 (16.6%)	41 (18.5%)	0.90 (0.59, 1.37)
Recurrent HF events (per 100 pt-yrs)	0.4	0.5	0.8 (0.5, 1.3)
Adjudicated stroke	2 (1.1%)	0	NA
Outcomes after new atrial fibrillation (n, %)			
First HF event or CV death	85 (45.5%)	112 (50.5%)	0.90 (0.73, 1.10)
HF event	72 (38.5%)	93 (41.9%)	0.92 (0.72, 1.17)
CV death	39 (20.9%)	54 (24.3%)	0.86 (0.60, 1.23)
Recurrent HF events and CV death (per 100 pt-yrs)	2.0	1.9	1.0 (0.7, 1.6)
Adjudicated stroke	4 (2.1%)	8 (3.6%)	0.59 (0.18, 1.94)

CV Death or Heart Failure Hospitalization

GALACTIC-HF



Relative Dose Intensity by Region in Patients on SoC Formulation



Detailed Reasons for Demonstrated or Feared Intolerance (% of Total Patients Not on Max Dose)

ACEi/ARB/ARNI

- Hypotension, presyncope, or orthostatism (n= 4154, 81%)
- Renal dysfunction (n=510, 10%)
- Hyperkalemia (n=107, 2%)
- Cough (n=54, 1%)

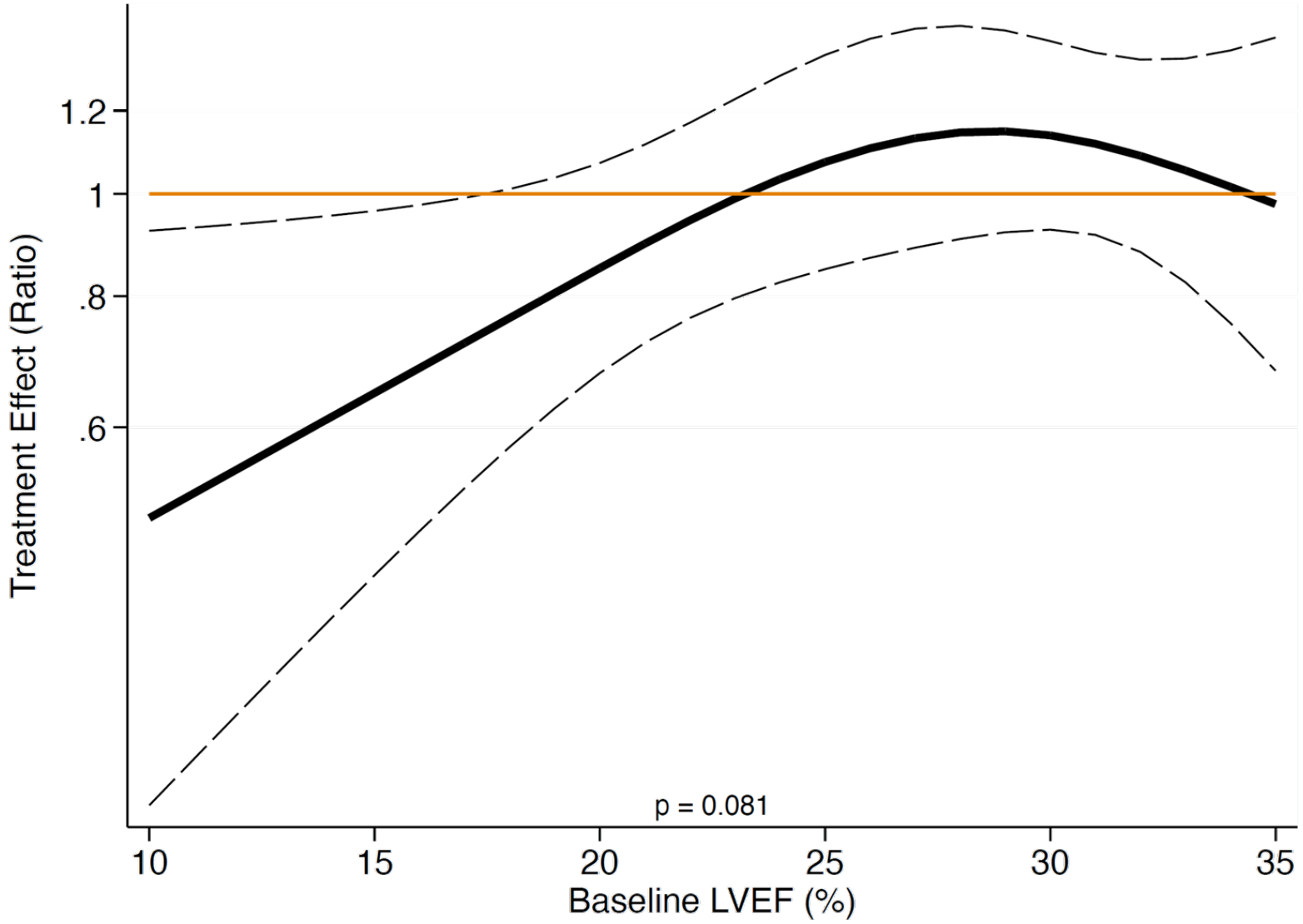
Beta Blocker

- Hypotension, presyncope, or orthostatism (n=3261, 60%)
- Bradycardia (n=1536, 28%)
- Renal Dysfunction (n=115, 2%)
- Airway reactivity (n=81, 2%)

MRA

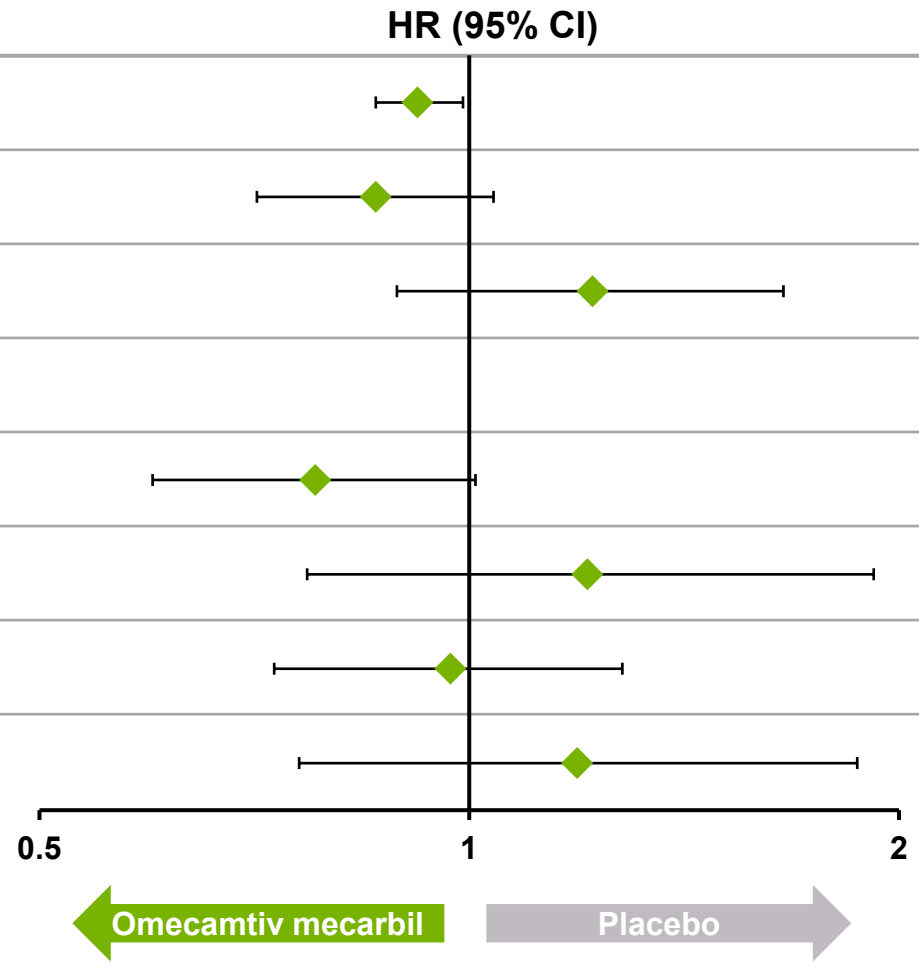
- Hypotension, presyncope, or orthostatism (n=1147, 43%)
- Hyperkalemia (n=661, 25%)
- Renal dysfunction (n=630, 24%)
- Gynecomastia (n=52, 2%)

Treatment Effect Ratio of Primary Composite Endpoint as a Function of Baseline LVEF in Women



Primary Composite Endpoint in Females by Atrial Fibrillation/Flutter and LVEF

		Omecamtiv Mecarbil n/N	Placebo N	p-value
Overall study population		1523/4120	1607/4112	0.025
No AFF		212/663	230/677	0.11
AFF		94/212	77/197	0.21
LVEF ≤28%	No AFF	108/331	132/364	0.06
	AFF	44/89	40/89	0.41
LVEF >28%	No AFF	104/332	98/313	0.83
	AFF	50/123	37/108	0.45



AFF=atrial fibrillation/flutter