FDA Briefing Document

NDA# 216401

Drug name: Omecamtiv Mecarbil

Applicant: Cytokinetics, Inc.

Cardiovascular and Renal Drugs Advisory Committee

December 13, 2022

Division of Cardiology and Nephrology, Office of Cardiology, Hematology, Endocrinology and Nephrology

Division of Biometrics II, Office of Biostatistics

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Glossary

AC	Advisory Committee
AE	adverse event
AFF	atrial fibrillation or atrial flutter
ARB	angiotensin II receptor blocker
BID	twice a day
BP	blood pressure
CDRH	Center for Devices and Radiological Health
CDx	Companion Diagnostics
CI	confidence interval
CK-MB	creatine kinase-MB
CV	cardiovascular
C_{max}	maximum plasma concentration
C_{trough}	trough plasma concentration
ECG	electrocardiogram
E-R	exposure-response
FDA	Food and Drug Administration
HF	heart failure
HR	hazard ratio
HFrEF	heart failure with reduced ejection fraction
IND	investigational new drug
IV	intravenous
LDT	laboratory-developed test
LVEF	left ventricular ejection fraction
NDA	New Drug Application
MI	myocardial infarction
MR	modified-release
MRA	mineralocorticoid receptor antagonists
MRHD	maximum recommended human dose
OM	omecamtiv mecarbil
PK	pharmacokinetic
PY	patient-years
SAE	serious adverse event
SGLT2	sodium-glucose cotrasporter-2

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The Food and Drug Administration (FDA) is convening this Advisory Committee (AC) meeting to discuss:

1. Whether the results of the GALACTIC-HF Phase 3 trial provide substantial evidence of effectiveness for omecamtiv mecarbil (OM) to reduce the risk of cardiovascular death and heart failure (HF) events in adults with symptomatic chronic heart failure with reduced ejection fraction (HFrEF), and
2. Whether the proposed pharmacokinetic (PK)-guided posology is critical for the safe and effective use of OM to ensure that the benefits of OM outweigh its risks.

1.2 Context for Issues to be Discussed at the AC

HF is a chronic, progressive condition associated with premature mortality and significant morbidity, with high rates of hospitalization. The 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) Class I recommendations[1] for first-line pharmacologic therapies for patients with HFrEF comprise a variety of drug classes including the recently approved sodium-glucose cotransporter-2 (SGLT2) inhibitors. Despite available treatment options, there is a continued need to reduce morbidity and mortality in patients with HFrEF.

There are three acceptable approaches for establishing substantial evidence of effectiveness of a drug[2]:

- Generally, FDA requires at least two adequate and well-controlled trials. This reflects the need for substantiation of experimental results and minimizes the possibility of bias or chance findings with a single trial that would lead to a false conclusion that a drug is effective when in fact it is not.
- Under specific circumstances, FDA has considered a large multicenter trial to satisfy the legal requirement for substantial evidence of effectiveness. Using a single, large multicenter trial should generally be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality, severe or irreversible morbidity, or prevention of a disease with a potentially serious outcome, whereby confirmation of the result in a second trial would be impracticable or unethical. Other characteristics that support the persuasiveness of a single trial include no single trial site being the main contributor of the observed effect and finding consistent and clinically meaningful effects on distinct prospectively specified endpoints within the trial.
- The last approach to establishing substantial evidence of effectiveness is one adequate and well-controlled trial plus confirmatory evidence (e.g., adequate and well-controlled clinical investigations in a related disease area; compelling mechanistic evidence in the setting of well-understood disease pathophysiology). FDA considers several factors when determining whether this approach is appropriate, including the persuasiveness of the single trial, the robustness of the confirmatory evidence, the seriousness of the disease (particularly if there is unmet medical need), the size of the

[1] Class I recommendations are strong and indicate that the treatment, procedure, or intervention is useful and effective and should be performed or administered for most patients under most circumstances.
[2] Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. FDA draft guidance for industry, December 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

patient population, and whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation.

In the HF treatment space, a single, large multicenter, adequate, and well-controlled cardiovascular (CV) outcome trial with persuasive results over standard of care therapy is considered acceptable as the basis of substantial evidence of effectiveness. Additionally, the drug must demonstrate safety for the intended use, thus producing a favorable benefit/risk profile as a prerequisite for approval. For drugs with known dose-limiting toxicity and a narrow therapeutic range, safe dosing by carefully monitoring relevant PK and/or pharmacodynamic (PD) markers may be required for therapeutic use.

1.3 Brief Description of Issues for Discussion at the AC

Cytokinetics, Inc. (Applicant) submitted this New Drug Application (NDA) to obtain the approval of OM, a cardiac myosin activator, to reduce the risk of CV death and HF events in patients with symptomatic, chronic HFrEF. The NDA includes one Phase 3 trial (GALACTIC-HF): a double-blind, randomized, placebo-controlled, multicenter, event-driven CV outcomes study. The trial implemented a PK-guided posology to optimize dosing and ensure safety by minimizing the risk due to excessive exposure of OM. The trial enrolled subjects globally from both inpatient and outpatient settings during December 2016 through 2019. A total of 8256 subjects were randomized (1:1 ratio) to the OM or placebo group. A majority of the subjects were on at least one or more HF standard of care therapies but only approximately 3% of the subjects were on SGLT2 inhibitors.

The primary efficacy endpoint was the time to a first HF event (i.e., hospitalization, emergency department treatment, urgent clinic visit) or CV death. Key secondary endpoints were time to CV death, Kansas City Cardiomyopathy Questionnaire-total symptom score (KCCQ-TSS[3]), time to first HF hospitalization, and time to all-cause death. This trial was also sufficiently powered for the key secondary endpoint of CV death. The FDA has previously stated, in principle, a single Phase 3 trial using the proposed primary composite endpoint could provide adequate support for an effectiveness claim if the primary endpoint was significant at a p-value <0.01 or if CV mortality was significant at a p-value <0.05 (see Section 3.1.3.1 for more details).

The results of the GALACTIC-HF trial showed a statistically significant but small treatment effect for the primary efficacy endpoint (hazard ratio [HR] of 0.92; 95% confidence interval [CI]: 0.86, 0.99; two-sided p=0.025). The estimated difference in incidence rate of the primary composite endpoint comparing OM with placebo was 2 per 100 patients-years (PY) (95% CI: 0.3, 3.8 per 100 PY). Although the results were driven by HF events, the treatment effect on HF events did not show statistically significant improvement for subjects on OM compared to placebo (HR 0.93; 95% CI: 0.86, 1.00; two-sided p=0.06). There were no differences between the arms of the trial for CV death or for all key secondary endpoints that otherwise may have supported the persuasiveness of a single trial. Phase 2 trials focused only on echocardiographic parameters.

Heterogeneity of the efficacy findings were observed in the GALACTIC-HF trial. In a prespecified subgroup analysis, subjects with left ventricular ejection fraction (LVEF) less than or equal to the median LVEF of 28% appeared to show differential benefit (HR: 0.84; 95% CI: 0.77, 0.92) while subjects with

[3] The KCCQ, a disease-specific measure for HF, is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QOL) within a 2-week recall period. The TSS covers the symptom frequency domain and the symptom burden domain.

LVEF above 28% did not show differential benefit (HR: 1.04; 95% CI: 0.94, 1.16). Subjects with atrial fibrillation or atrial flutter (AFF) at baseline had no apparent improvement with OM on the primary efficacy endpoint and were at increased risk of CV death compared to placebo. Except for this subgroup of subjects with AFF, the safety profile of OM was generally acceptable in the GALACTIC-HF trial under the PK-guided posology used in the trial.

Following discussion with the Applicant on issues regarding substantial evidence and benefit /risk, the Applicant noted the results of a prespecified subgroup analysis (that was no controlled for multiplicity) suggesting a greater benefit in a subgroup of patients whose LVEF at baseline was lower than 28%. The Applicant proposed that OM be approved in this subgroup population. The Division has concerns about the reliance on the subgroup finding for an efficacy claim, especially in the setting where the trial may not have met the statutory requirements for substantial evidence of effectiveness.

The Applicant initially proposed a post-approval dosing strategy based on scheduled, forced dose titration (i.e., all patients will titrate up to the maximum dose of 50 mg 4 weeks after the start of treatment), rather than the PK-guided dosing algorithm used in the GALACTIC-HF trial. PK simulations predicted a higher exposure with this post-approval approach than that observed in the GALACTIC-HF trial, with further exposure increases in certain patient populations (e.g., poor metabolizer of CYP2D6). More patients with this post-approval approach are predicted to have excessive exposure (e.g., concentration >1000 ng/mL).

There are limited data to assess the clinical risk of OM with the excessive exposure because the PK-guided dosing strategy used in the clinical trials controlled the PK exposures. A drug concentration threshold beyond which a definitive safety risk is in effect has not been established. However, there were findings from the GALACTIC-HF trial as well as from Phase 2 trials showing correlations between increased concentrations of OM with increased values of troponin-I and/or NT-proBNP in association with cardiac adverse events such as myocardial ischemia and HF (see Appendix 6.5.10). Given the cardiac toxicology profile of OM (see Section 6.3), the FDA has a concern that the proposed scheduled, forced titration could increase the potential risk of OM-associated cardiotoxicity. The Applicant subsequently agreed to implement a PK-guided dosing strategy that resembles a simplified version of the PK-dosing strategy that was used in GALACTIC-HF.

The Applicant is now proposing to use PK-guided dosing to inform the use of OM. It is important to determine whether PK testing is essential for safe and effective use of OM. Generally, if diagnostic testing, such as PK-guided dosing, is essential for safe and effective use of a therapeutic, the test meets the definition of an in vitro companion diagnostic device (CDx) and use of the CDx with the therapeutic should be stipulated in the instructions for use in the approved labeling of both the therapeutic and the CDx. Ideally, the therapeutic and its corresponding CDx should be developed contemporaneously, with the clinical performance of the test established using data from the therapeutic's clinical development program. FDA reviews data about the performance of the test to confirm that the test is analytically and clinical valid for the intended use. In addition to therapeutics that require a CDx, there may also be situations in which diagnostic testing is informative, but not essential, for safe and effective use of a therapeutic. These tests do not meet the definition of a CDx.

In most circumstances, a CDx used to make treatment decisions in the clinical trial for the therapeutic product should be cleared or approved by FDA's Center for Devices and Radiological Health (CDRH) contemporaneously with the therapeutic to ensure that health care providers are able to appropriately

prescribe the therapeutic. However, as discussed in FDA's guidance document, *Guidance for Industry: In Vitro Companion Diagnostic Devices*, there are certain scenarios in which it may be appropriate to approve a therapeutic product without contemporaneous clearance or approval of a CDx, even though use of a CDx is essential. Specifically, the guidance states: *"FDA may decide to approve a therapeutic product even if an IVD[4] companion diagnostic device is not yet approved or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device."*

The Applicant is proposing to implement PK-guided dosing using a liquid chromatography-tandem mass spectrometry assay developed in a single central laboratory, referred to as a laboratory-developed test (LDT), that is not FDA approved or cleared. An LDT is a type of in vitro diagnostic test that is designed, manufactured, and used within a single site CLIA[5]-certified laboratory that meets the requirements for high complexity testing. The FDA has generally exercised enforcement discretion with respect to LDTs, including those developed by hospitals or academic laboratories, meaning that, except in certain circumstances, the FDA generally does not exercise its authority to enforce the regulatory requirements for these devices, although it maintains that authority.

When an LDT is not reviewed or authorized by FDA for the intended use, FDA does not have information regarding the performance of the test. Further, the FDA does not have information regarding the design, development, and ongoing maintenance of the test, including any modifications to the test and whether there are any performance issues or adverse events that occur with real world use. LDTs that are not properly validated and/or are unable to inform the safe and effective use of the corresponding therapeutic pose safety risks to patients. If PK guided dosing is deemed essential for the safe and effective use of OM, a CDx should be cleared or approved contemporaneously with OM, unless it meets the criteria for non-contemporaneous approval specified in guidance.

In summary, GALACTIC-HF met the primary objective as pre-specified. The primary efficacy results were driven by HF events with no trends of improvement on CV mortality. The small treatment effect, with a p-value that is not very persuasive for a single trial, without established effects on any of the secondary efficacy endpoints, calls into question whether the statutory requirement for substantial evidence of effectiveness has been met (see Section 3.1.3.1). If the obstacles to establishing effectiveness can be overcome, then we need to consider whether PK-guided dosing is critical for the safe and effective use of OM. The Applicant is proposing a central laboratory whose OM assay will not be FDA approved or cleared. Use of this approach may not ensure that OM concentrations are measured appropriately for the purpose of dose adjustment for every patient in the real-world setting. The question here is whether the currently proposed PK-dosing strategy is sufficient, thus potentially accepting an unapproved central lab result as the basis of dose titration, or critical, thus requiring a CDx, to maximize risk mitigation.

1.4 Draft Points for Consideration

We ask the AC to opine on the main issues raised during the review of the GALACTIC-HF trial, stated here:

[4] in vitro diagnostics

[5] Clinical Laboratory Improvement Amendments

- Whether the results of the GALACTIC-HF Phase 3 trial satisfy the statutory requirement for substantial evidence of effectiveness for OM in reducing the risk of CV death and HF events in adults with symptomatic chronic HFrEF.
    - Also discuss the benefits of OM by baseline LVEF and the Applicant's proposal to state in the indication that benefits are increasingly evident the lower the LVEF.
- In the GALACTIC-HF Phase 3 trial, subjects with AFF at baseline had no apparent improvement with OM on the primary efficacy endpoint and were at increased risk of CV death compared to placebo. Discuss the benefits and risks of OM in subjects with AFF.
- Whether the PK-guided posology is critical for the safe and effective use of OM to ensure that the benefits of OM outweigh its risks.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Heart failure (HF) is a chronic, progressive condition and a major global health concern, affecting 60 million people worldwide (Collaborators 2017). The annual incidence of HF in the United States is >650,000 cases and it increases with age (Yancy et al. 2013). The estimated prevalence of HF in adults ≥20 years of age is 6.2 million in the United States and the prevalence is predicted to increase 46% by 2030. About half of these cases are HF with reduced ejection fraction (HFrEF), which is associated with considerable morbidity and mortality. The 5-year mortality and HF readmission in HFrEF patients aged ≥65 years are approximately 75% and 48%, respectively (Shah et al. 2017). The clinical course for HFrEF patients is variable, but acute episodes of clinical decompensation requiring hospitalization and/or intravenous (IV) diuretic use are common, and decompensation is associated with a poor long-term prognosis.

Treatment of patients with HFrEF is targeted towards reduction of morbidity/mortality, symptom relief, and adequate management of comorbidities such as hypertension and atrial fibrillation. The latest 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA)[6] Class I recommendations for initial treatments to address congestion in patients with chronic HFrEF include beta-blockers, renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitor [ACEi], angiotensin II receptor blocker [ARB] or angiotensin receptor neprilysin inhibitor [ARNi]), mineralocorticoid receptor antagonists (MRAs), sodium-glucose cotransporter-2 (SGLT2) inhibitors, and diuretics as needed. According to the patient's clinical symptoms and status, additional Class I recommendations for pharmacological therapy include hydralazine/isosorbide dinitrate in African Americans; and for device therapy include implantable cardioverter-defibrillator and cardiac resynchronization therapy with defibrillation (CRT-D) (Heidenreich et al. 2022). Other HF therapies approved to reduce morbidity and/or mortality in patients with HFrEF include digoxin, ivabradine, and vericiguat. Despite the use of these therapies, notwithstanding issues with medication adherence, the rate of cardiovascular (CV) Death and HF hospitalization remains high in patients with HFrEF.

[6] The American Heart Association/American College of Cardiology/Heart Failure Society of America

2.2 Pertinent Drug Development and Regulatory History

Omecamtiv mecarbil (OM) is a small molecule that activates cardiac myosin and increases contraction of cardiac myocytes. OM exhibited high selectivity for activating ATPase of cardiac myosin with EC_{50} of 0.62µM, ≥30-fold relative to fast skeletal and smooth muscle myosin. OM activates the enzymatic domain of cardiac myosin by stabilizing its lever arm in a primed position, resulting in an increase in cardiac myosin heads in the pre-power-stroke state. OM increases cardiac myocyte contraction without increasing cardiac myocyte intracellular calcium. Nonclinical studies demonstrated a dosing-limiting toxicity of OM including mortality and myocardial degeneration/necrosis/fibrosis. In animals, OM appears to have a narrow therapeutic window and no or minimal safety margin relative to the maximum recommended human dose (MRHD) of 50 mg twice a day (BID) based on maximum plasma concentration (C_{max}). The dose-limiting toxicity of OM in animals was thought to be related to exaggerated pharmacological action that resulted in prolongation of systolic ejection time (SET) to an extent that would impact cardiac filling and reduce cardiac output.

FDA has expressed concerns about CV safety in association with safe dosing of OM throughout the development program. Antecedent nonclinical studies demonstrated a steep dose-response for lethality, a narrow safety margin for myocardial injury, and measurable amounts of cardiac troponin-I. The original investigational new drug (IND) application was placed on partial clinical hold because of a CV safety signal observed in a Phase 1 trial in the context of a very narrow safety margin observed in animals. The Phase 1 healthy volunteer study showed that some participants experienced clinical symptoms and electrocardiogram (ECG) changes consistent with myocardial ischemia. There were also dose-related echocardiographic findings consistent with drug effect, predominately at higher doses. The partial clinical hold was subsequently removed after the Applicant made significant revisions to the protocol to optimize the therapeutic index, including reducing the proposed doses of OM to be studied and increasing the vital sign and ECG monitoring. During the course of development, myocardial ischemia including myocardial infarction (MI) related to excessive exposure of OM occurred in both healthy adults and patients with HFrEF. A small increase in troponin-I of unclear clinical significance was also observed in Phase 2 studies.

To reduce the rate of absorption and minimize excessive plasma concentrations and peak-trough fluctuation, the Applicant developed a modified-release (MR) formulation of the OM tablet after early studies of the IV formulation and immediate-release formulation.

To ensure safety, a pharmacokinetics (PK)-guided titration was explored in the Phase 2 study (COSMIC-HF); and a refined PK-dosing strategy was implemented in the Phase 3 trial (GALACTIC-HF). This strategy used PK measurements (plasma levels of OM) at set timepoints during the trial to adjust the OM dose and thus achieve target plasma concentrations within a predetermined range, while minimizing the frequency of excessive exposure. Prior to the New Drug Application (NDA) submission, the FDA had stated that the PK assay should be appropriately developed as a companion diagnostic. A companion diagnostic device is defined as "an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product." For example, a PK assay may provide information that is essential for the safe and effective use of a drug if monitoring drug concentrations for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) is critical to achieve improved safety or effectiveness of the therapeutic product. If the use of an in vitro diagnostic companion diagnostic device is essential for the safe and effective use of a therapeutic product, an approved or cleared in vitro diagnostic companion diagnostic device should be available for use once the

therapeutic product is approved. FDA expects that the therapeutic product sponsor will address the need for an approved or cleared in vitro diagnostic companion diagnostic device in its therapeutic product development plan. The Applicant claimed that obtaining plasma concentrations of OM in clinical practice was not necessary to ensure safe and effective use of OM, and therefore submitted the NDA with a proposed stepwise, scheduled dose titration without the need for PK guidance. During the review of the NDA, the Applicant subsequently agreed to implement a PK-guided dosing strategy that resembles a simplified version of the PK-guided dosing strategy that was used in GALACTIC-HF. Consequently, an FDA-authorized companion diagnostic would not be available to guide OM dosing.

3 Summary of Issues for the AC

3.1 Efficacy Issues

To support the proposed indication, the Applicant conducted a randomized, multicenter, placebo-controlled, double-blind, parallel-group, event-driven trial 20110203 (GALACTIC-HF) to determine the efficacy and safety of oral OM compared to placebo in subjects with chronic HFrEF receiving standard of care therapy. The primary efficacy endpoint was the composite of CV death or first HF event, whichever occurred first. The trial met the primary objective as pre-specified, driven only by the HF event component. The trial did not meet any of the prespecified secondary endpoints. The treatment effect for the primary endpoint was small (hazard ratio [HR] of 0.92); The upper limit of the 95% confidence interval approached the null line for the primary endpoint (i.e., 0.99). Of note, HF as a first event analysis was not nominally statistically significant (HR: 0.93; 95% CI: 0.88, 1.00; two-sided p=0.06). There was evidence of effect modification of left ventricular ejection fraction (LVEF) with the primary endpoint and appeared to favor those with a LVEF <28%, but there is no scientific basis for this differential effect.

This single trial, as the basis of the NDA, was not accompanied by additional confirmatory evidence. In general, an antecedent Phase 2 trial may serve as confirmatory evidence, but in this case, the relationship between the hemodynamic evidence derived from the Phase 2 trial (i.e., systolic ejection time, left ventricular ejection fraction, and left ventricular end systolic and diastolic diameters), and clinical outcome remains unclear, thereby attenuating their reliability to serve as confirmatory evidence. The review issue here is the small treatment effect from the single pivotal trial that may not meet statutory requirements, with little to serve as confirmatory evidence.

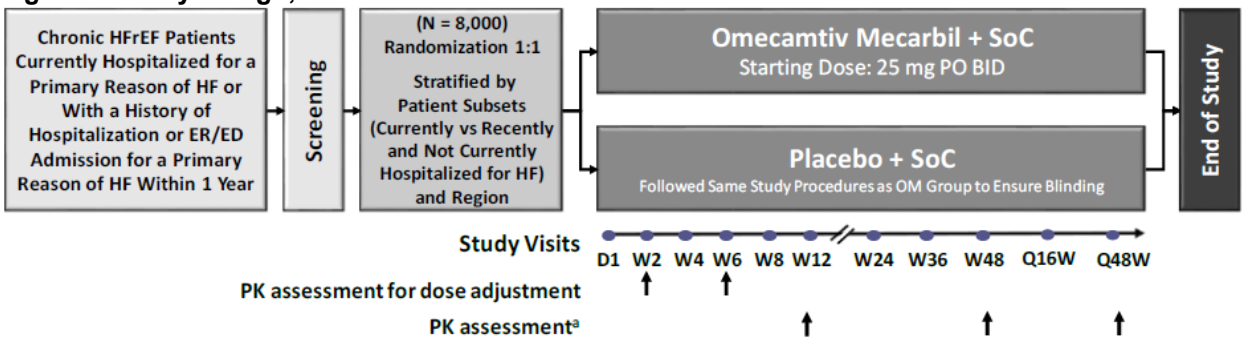
3.1.1 Sources of Data for Efficacy

In addition to the GALACTIC-HF trial, two Phase 2b studies in subjects with chronic HFrEF (Appendix 6.2) provided data for mechanism-based pharmacodynamic (PD) effects (e.g., concentration-dependent increase in systolic ejection time). Important details of the study design for GALACTIC-HF are included below.

GALACTIC-HF (Study 20110203) evaluated subjects with HFrEF, including subjects with ongoing or history of HF hospitalization (Figure 1). The study randomized a total of 8256 HF subjects in a 1:1 ratio to receive either OM or placebo. Randomization was stratified by hospitalization (i.e., currently hospitalized for HF, or recently and not currently hospitalized for HF) and region (Five groupings: United States and Canada, Latin America, Western Europe, South Africa, and Australasia - Eastern Europe including Russia - Asia).

GALACTIC-HF implemented a PK-based dose selection strategy to determine escalation from the initial starting dose of 25 mg BID to higher doses (i.e., 37.5 or 50 mg BID) to achieve target plasma concentrations of OM and reduce the risks associated with excessive exposure to OM (Table 30).

Figure 1. Study Design, GALACTIC-HF



Source: Figure 8-1 of the clinical study report
PK assessment was performed at Week 24 rather than Week 12 for subjects who enrolled before protocol amendment 1.
Abbreviations: BID, twice a day; D, day; ED, emergency department; ER, emergency room; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; N, number of subjects; OM, omecamtiv mecarbil; PK, pharmacokinetics; PO, by mouth; Q16W, every 16 weeks; Q48W, every 48 weeks; SoC, standard of care; W, week

The primary endpoint was adjudicated CV death, or first HF event, whichever happened first.

- A death is defined as a CV death endpoint if the death is positively adjudicated as a CV death, presumed CV death, or presumed sudden death.
- A HF event is defined as an urgent, unscheduled clinic/office/emergency department (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.

An independent external Clinical Event Committee adjudicated the prespecified endpoints, centrally and in a blinded fashion, in accordance with the Clinical Event Committee charter.

The overall Type 1 error for the study is 0.05 for two-sided testing. The Applicant specified a multiplicity plan (Figure 11) for the following list of key secondary endpoints. The key secondary endpoints were (a) time to CV death, (b) change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score from baseline to Week 24, (c) time to first HF hospitalization, and (d) time to all cause death.

Of note, the Applicant had prespecified two planned interim analyses when approximately one-third and two-third of the planned total cardiovascular death endpoints were observed. To enable stopping early due to superiority, both primary composite and time to cardiovascular death endpoints will be assessed using the Haybittle-Peto approach with an overall one-sided alpha of 0.0005 (two-sided 0.001). To stop for early superiority, both endpoints must achieve statistical significance at an overall one-sided alpha of 0.0005. The study was monitored by an independent Data Monitoring Committee, an independent biostatistical group conducted the interim analysis, and appropriate firewalls were in place to maintain study integrity. After both interim analyses, the Data Monitoring Committee recommended the study to continue unchanged.

All efficacy analyses are performed on the full analysis set unless otherwise specified. This included all randomized subjects except for 24 subjects from study center 29002 who were excluded due to Good Clinical Practice violations. The full analysis set consisted of 8232 randomized subjects.

All safety analyses are performed on the safety analysis set, herein referred to as safety population, which included all randomized subjects who had at least one dose of investigational product during the study excluding 24 subjects from study center 29002 due to GCP violations.

3.1.2 Efficacy Summary: GALACTIC-HF

Demographic and baseline characteristics were generally balanced across the study arms (Table 1). A total of 79% of the randomized subjects were male, 78% were white, and 78% were Non-Hispanic. Only 15% of the randomized subjects were from the United States. A total of 26% of the randomized subjects were currently hospitalized for HF at baseline. HF-related history was balanced across the treatment groups. Ninety-seven percent (97%) of the subjects had NYHA Class II-III HF; only 3% had NYHA class IV.

Table 1. Baseline Demographic and Clinical Characteristics, FAS, GALACTIC-HF

Characteristic	OM (N=4120)	Placebo (N=4112)
Sex, n (%)		
Male	3245 (79%)	3238 (79%)
Female	875 (21%)	874 (21%)
Age, years		
Mean (SD)	65 (11)	65 (11)
Median (min, max)	66 (18, 89)	66 (20, 85)
Age group (years), n (%)		
≥18 to <65	1874 (45%)	1873 (46%)
≥65 to <75	1443 (35%)	1438 (35%)
≥75	803 (19%)	801 (19%)
Race, n (%)		
White	3196 (78%)	3201 (78%)
Black/African American	285 (7%)	277 (7%)
Asian	355 (9%)	355 (9%)
Other	143 (3%)	139 (3%)
American Indian or Alaska Native	35 (<1%)	38 (<1%)
Native Hawaiian or Other Pacific Islander	7 (<1%)	6 (<1%)
Multiple	99 (2%)	96 (2%)
Ethnicity, n (%)		
Hispanic	886 (22%)	885 (22%)
Non-Hispanic	3234 (78%)	3227 (78%)
Country of participation, n (%)		
United States and Canada	693 (17%)	693 (17%)
United States only	613 (15%)	607 (15%)
Latin America	961 (23%)	960 (23%)
Western EU, South America, and Australia	1344 (33%)	1337 (33%)
Eastern Europe and Russia	787 (19%)	787 (19%)
Asia	335 (8%)	335 (8%)
Randomization HF status, n (%)		
Currently HF hospitalized	1051 (26%)	1050 (26%)
Not currently HF hospitalized	3069 (74%)	3062 (74%)

Characteristic	OM (N=4120)	Placebo (N=4112)
Actual HF status, n (%)		
Currently HF hospitalized	1044 (25%)	1040 (25%)
Not currently HF hospitalized	3076 (75%)	3072 (75%)
Atrial fibrillation at screening, n (%)	1146 (28%)	1099 (27%)
Primary cause of heart failure, n (%)		
Nonischemic	1927 (47%)	1890 (46%)
Ischemic	2193 (53%)	2222 (54%)
HF NYHA Class, n (%)		
Class II	2195 (53%)	2173 (53%)
Class III	1801 (44%)	1815 (44%)
Class IV	124 (3%)	124 (3%)
Baseline LVEF (%)		
Mean (SD)	27 (6)	27 (6)
Median (min, max)	28 (5, 42)	27 (4, 40)
Baseline NT-proBNP (pg/mL)		
Mean (SD)	3645 (5630)	3610 (5220)
Median (min, max)	1977 (13, 136735)	2025 (13, 74950)
Baseline creatine kinase-MB (ng/mL)		
Mean (SD)	2 (2)	2 (2)
Median (min, max)	2 (0, 84)	2 (0, 61)
Baseline eGFR[1] (mL/min/1.73 m^2)		
Mean (SD)	60 (22)	60 (22)
Median (min, max)	59 (8, 205)	59 (14, 244)
≤60 mL/min/1.73 m^2	2156 (52%)	2165 (53%)
>60 mL/min/1.73 m^2	1964 (48%)	1947 (47%)
Baseline troponin-I (ng/mL)		
Mean (SD)	0.06 (0.2)	0.06 (0.3)
Median (min, max)	0.03 (0.01, 9)	0.03 (0.01, 10)

Source: Statistical Reviewer
[1] Derived from the Modification of Diet in Renal Disease Study equation.
Abbreviations: eGFR, estimated glomerular filtration rate; EU, Europe; FAS, full analysis set; HF heart failure; LVEF, left ventricular ejection fraction; max, maximum; min, minimum; N, number of randomized subjects excluding the site with GCP violation; n, number of randomized subjects with available data; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association; OM, omecamtiv mecarbil; SD, standard deviation

Baseline target HF medication use was similar in both treatment groups (Table 2). Nearly all subjects (8228 of 8232) reported the use of at least one of the following HF medications: beta-blocker, angiotensin-converting enzyme inhibitor (ACEi), ARB, or angiotensin receptor neprilysin inhibitor (ARNi), MRAs, and diuretics other than MRAs. Concomitant use of other antihypertensives, lipid-lowering drugs, or antithrombotic drugs at baseline and during the planned treatment period were balanced across the treatment groups.

Table 2. Baseline SoC HF Treatments, FAS, GALACTIC-HF

Characteristic	OM (N=4120)	Placebo (N=4112)
Medication use, n (%)		
ACEi	2006 (49)	2038 (50)
ARB	801 (19)	788 (19)
ARNi	819 (20)	782 (19)
ACEi, ARB or ARNI	3588 (87)	3577 (87)
MRA	3199 (78)	3198 (78)
SGLT2 inhibitor	104 (3)	114 (3)
Beta blocker	3881 (94)	3883 (94)
(ACEi, ARB, or ARNI) + MRA	2827 (69)	2852 (69)
(ACEi, ARB, or ARNI) + beta blocker	3407 (83)	3405 (83)
Beta Blocker + MRA	3039 (74)	3019 (73)
(ACEi, ARB, or ARNI) + beta blocker + MRA	2711 (66)	2716 (66)
Diuretics other than MRA	3692 (90)	3686 (90)
Device use history, n (%)		
Cardiac devices	1609 (39)	1548 (38)
Any cardiac resynchronization therapy	592 (14)	566 (14)
ICD only (no CRT)	843 (20)	826 (20)

Source: Statistical Reviewer
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; FAS, full analysis set; HF, heart failure; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor agonist; N, number of randomized subjects excluding the site with GCP violation; OM, omecamtiv mecarbil; SGLT, sodium glucose transport protein 2; SoC, standard of care

The study disposition is reported in Table 3. In general, <2% of the randomized subjects did not have complete follow-up. Of note, the Applicant considered subjects who died during the study to not have completed the study.

Table 3. Patient Disposition, FAS, GALACTIC-HF

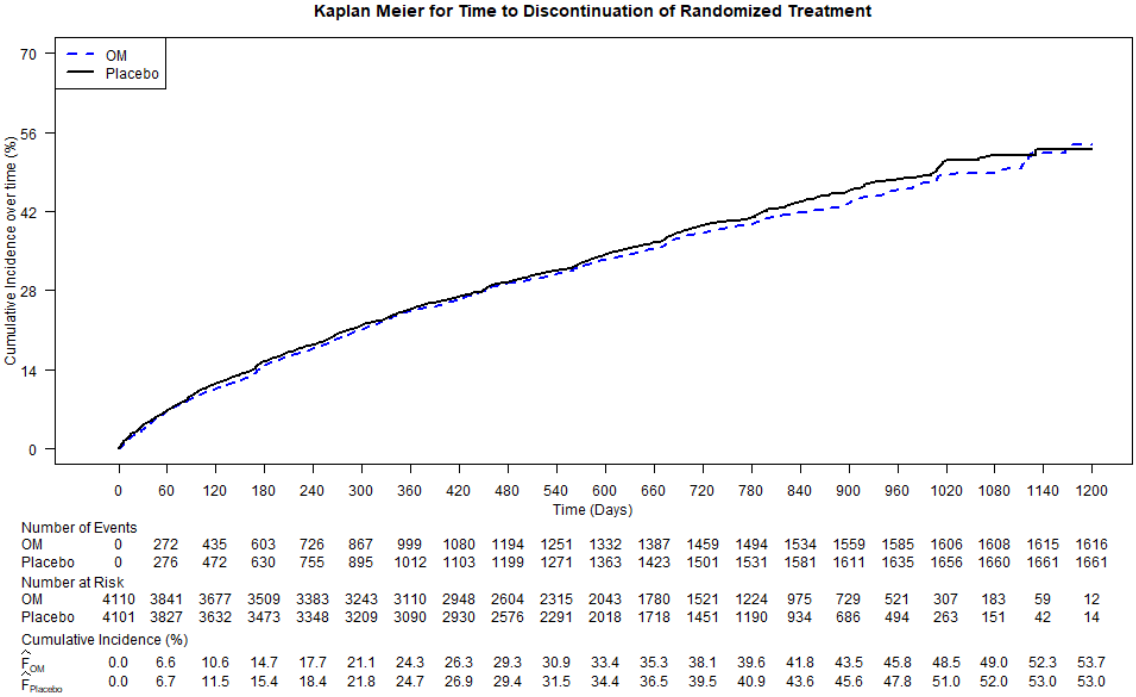
Disposition	OM N=4120	Placebo N=4112
Subjects randomized, n (%)[1]	4129	4127
Excluded for GCP violation, n (%)[1]	9 (<1%)	15 (<1%)
Included in analysis, n (%)[1]	4120 (>99%)	4112 (>99%)
Safety population, n (%)[1]	4110 (>99%)	4101 (>99%)
Completed the study, n (%)[2]	3028 (73%)	3008 (73%)
Did not complete the study, n (%)[2]	1092 (27%)	1104 (27%)
Died	1051 (26%)	1054 (26%)
Lost to follow-up	20 (<1%)	26 (<1%)
Withdrawal of consent	21 (<1%)	24 (<1%)

Source: Statistical Reviewer
[1] Counts and percentages in parentheses were relative to the total number subjects randomized.
[2] Counts and percentages in parentheses were relative to N, i.e., the number of randomized subjects excluding the site with GCP violation.
Definition follows from Applicant's EOSFL in the adsl dataset.
Abbreviations: FAS, full analysis set; GCP, Good Clinical Practices; HF, heart failure; N, number of randomized subjects excluding the site with GCP violation; n, number of subjects with available data after excluding the site with GCP violation; OM, omecamtiv mecarbil

A total of 21 randomized subjects did not initiate randomized treatment. The proportion of randomized subjects who initiated randomized treatment and discontinued randomized treatment was similar between the arms during the study. A total of 1617 (39%) and 1661 (40%) subjects from the OM and placebo arms, respectively, discontinued randomized treatment. Most reasons for treatment discontinuation were death (n=1537, 18.7%), subject request (n=980, 11.9%), and adverse events

(n=753, 9.1%).[7] Figure 2 shows the Kaplan-Meier curves for the time to discontinuation of randomized treatment.

Figure 2. Treatment Discontinuation Over the Course of the Study, Safety Set, GALACTIC-HF



Source: Statistical Reviewer
Abbreviations: F, cumulative incidence; HF, heart failure; OM, omecamtiv mercabil

Primary Efficacy Endpoint

The primary efficacy endpoint was the composite of time to adjudicated CV death or adjudicated first HF event, whichever occurred first (Table 4). In GALACTIC-HF, a total of 1508 (incidence rate of 24 per 100 patients-years [PY]) subjects in the OM arm and 1607 (26 per 100 PY) subjects in the placebo arm experienced a primary composite endpoint, with an estimated adjusted HR of 0.92 (95% CI: 0.86, 0.99; two-sided p=0.025). The estimated difference in incidence rate of the primary composite endpoint comparing placebo with OM is 2 per 100 PY (95% CI: 0.3, 3.8 per 100 PY).

The observed treatment effect in the primary composite endpoint is mainly driven by HF events. A majority of the HF events was contributed by hospitalization for heart failure (Table 4). The analysis of the time to first HF event showed a numerical trend towards lower risk for the OM arm compared to the placebo arm (HR 0.93; 95% CI: 0.86, 1.00). For CV death, the number of events was similar between the OM and the placebo arms (HR 1.01; 95% CI: 0.92, 1.11).

[7] Percentages for treatment discontinuation were calculated based on the total number of subjects who received at least one dose of investigational product (n=8211).

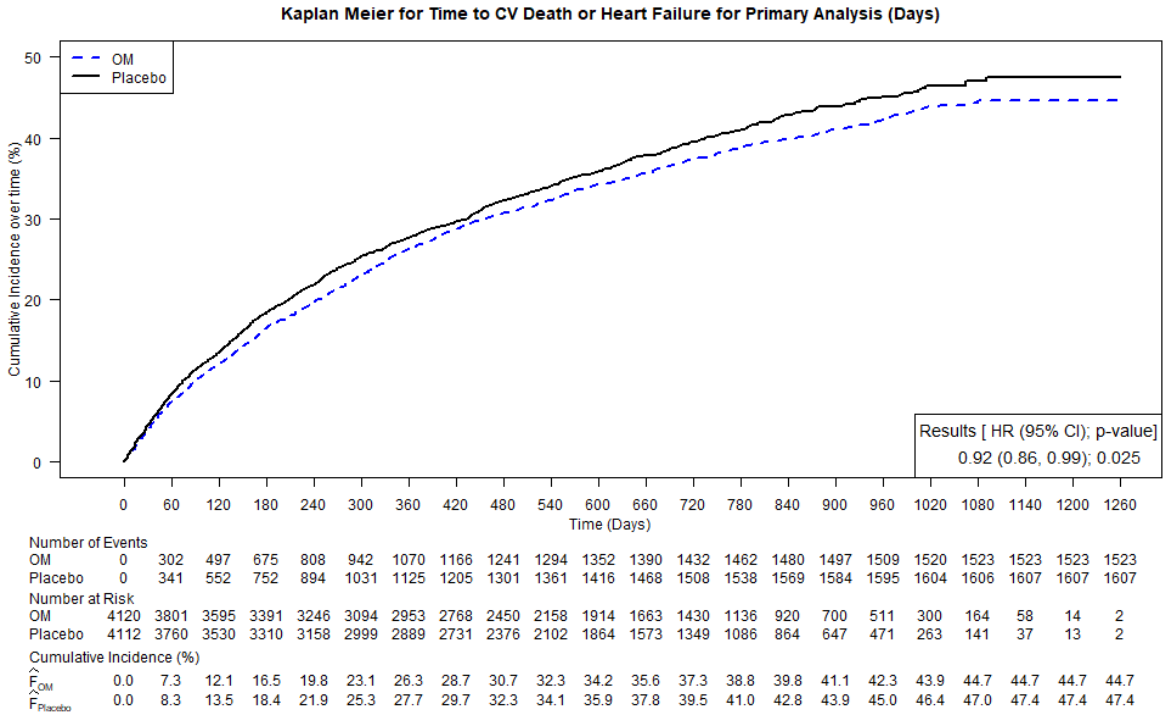
Table 4. Results for the Primary Composite Endpoint, FAS, GALACTIC-HF

Endpoint	OM N=4120	Placebo N=4112	HR (95% CI)	P-Value[1]
Primary composite endpoint, n (IR)[2]	1523 (24.2)	1607 (26.3)	0.92 (0.86, 0.99)	0.025
CV death as first event, n (%)[3]	346 (8%)	371 (9%)		
HF as first events, n (%)[3]	1177 (29%)	1236 (30%)		
Hospitalization, n (%)[3]	1107 (27%)	1133 (28%)		
Urgent ER/ED visit, n (%)[3]	45 (1%)	74 (2%)		
Urgent office/practice visit, n (%)[3]	25 (<1%)	29 (<1%)		
Time to first individual component, n (IR)[2]				
CV death	808 (10.9)	798 (10.8)	1.01 (0.92, 1.11)	0.9
HF event	1177 (18.7)	1236 (20.3)	0.93 (0.86, 1.00)	0.06

Source: Statistical Reviewer
A Cox proportional hazards regression adjusting for baseline eGFR and treatment group. The model was stratified by combination of randomization setting and region. The hazard ratio comparing OM with placebo, along with respective 95% CI, and Wald-based p-value were reported from the regression model.
[1] Two-sided p-values included for the individual components of the primary efficacy endpoint are not controlled for type I error.
[2] The number of subjects with an event and the incidence rate per 100 PY in parenthesis are reported for each arm. Incidence rate is defined by the number of subjects with the first event divided by patient-years at risk of experiencing the outcome.
[3] Total number of subjects with first event and percentages with respect to N in parenthesis are reported for each arm.
Abbreviations: CI, confidence interval; CV, cardiovascular; ER/ED, emergency room/emergency department; FAS, full analysis set; HF, heart failure; HR, hazard ratio; IR, incidence rate; N, number of randomized participants excluding study site 29002; n, sample size of randomized participants excluding study side 29002; OM, omecamtiv mecarbil; PY, patient-years; eGFR, estimated glomerular filtration rate.

The observed cumulative incidence of the primary composite endpoint for the OM arm was slightly lower than that for the placebo arm over the follow-up period (Figure 3), consistent with the above results of the Cox proportional hazards regression.

Figure 3. Kaplan-Meier Curve for Primary Composite Endpoint, FAS, GALACTIC-HF

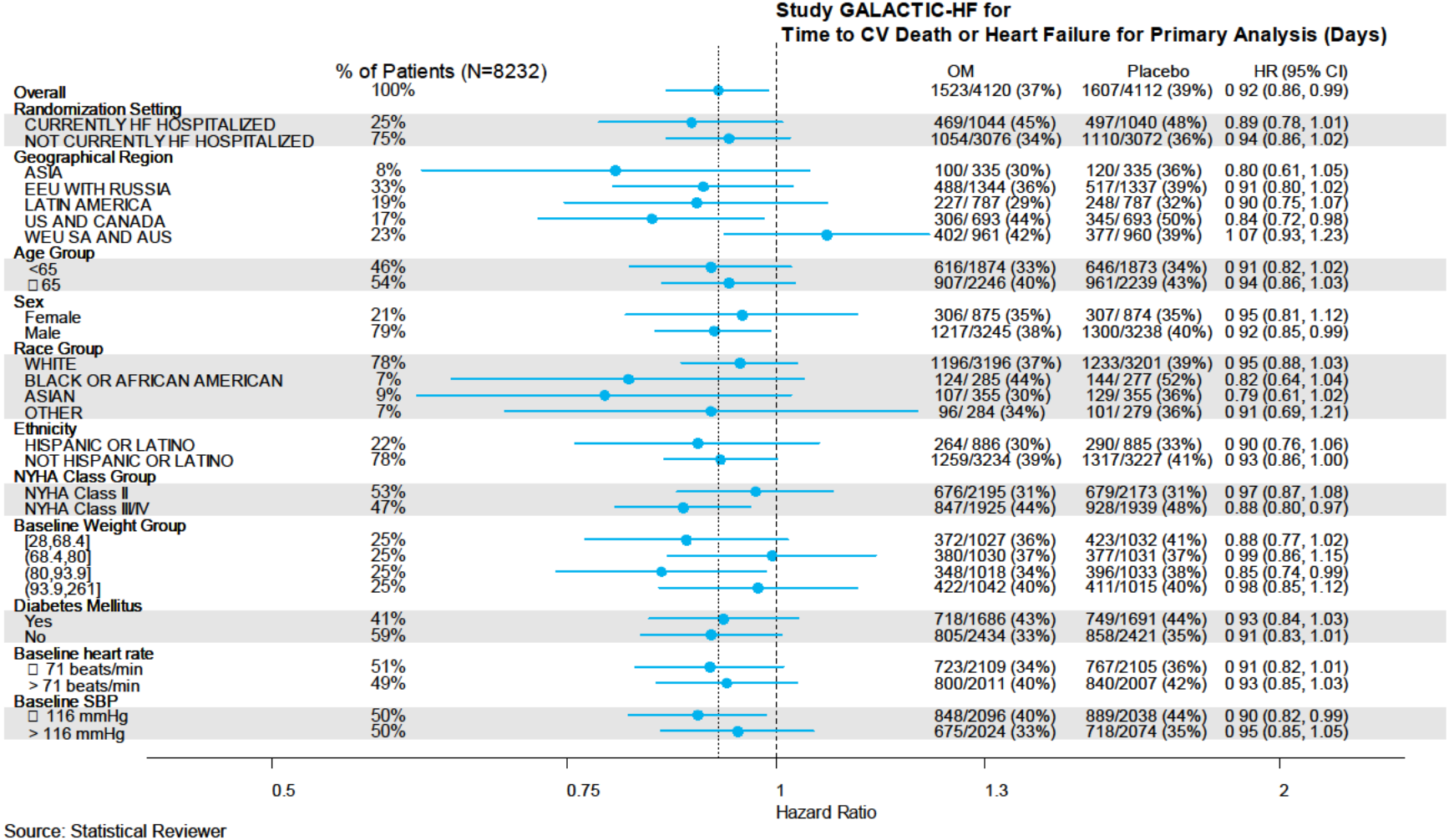


Source: Statistical Reviewer
Abbreviations: CI, confidence interval; CV, cardiovascular; F, cumulative incidence; FAS, full analysis set; HF, heart failure; HR, hazard ratio; OM, omecamtiv mecarbil

Several sensitivity analyses were conducted for the primary efficacy endpoint. Specifically, we conducted additional analyses of the primary endpoint that were based on investigator-reported events (included non-positive events that were reported by the investigator and adjudicated by the Clinical Event Committee), inclusion of unknown deaths to the primary endpoint, as well as individual components of the primary efficacy endpoint that included investigator-reported events (Table 14 and Table 15). To address concerns on missing follow-up of the primary endpoint (see Section 6.4), a retrieved dropout analysis (He et al. 2022) and a simple worst-case analysis were conducted. In summary, these sensitivity analysis results were generally consistent with the primary efficacy endpoint showing a small treatment effect with the upper 95% CI touching the null line.

Forest plots for the primary results by prespecified baseline subgroups are shown below (Figure 4 and Figure 5). In summary, the subgroup findings by key demographic, geographic, and clinical subgroups of interest were generally consistent with the findings of the primary composite endpoint favoring OM relative to placebo, with the exception of LVEF and AFF subgroups (see Sections 3.1.3.2 and 3.2.3.2). The Applicant noted nominally significant interaction effects for baseline LVEF (defined by >median LVEF of 28%, or ≤median LVEF of 28%) (p=0.003), presence of AFF at screening (p=0.01), and baseline eGFR (≤60 mL/min/1.73 m^2 or >60 mL/min/1.73 m^2) (p=0.04) for the primary composite efficacy endpoint.

Figure 4. Prespecified Subgroup Analyses for Time to Composite of CV Death or Heart Failure, FAS, GALACTIC-HF (Part 1/2)

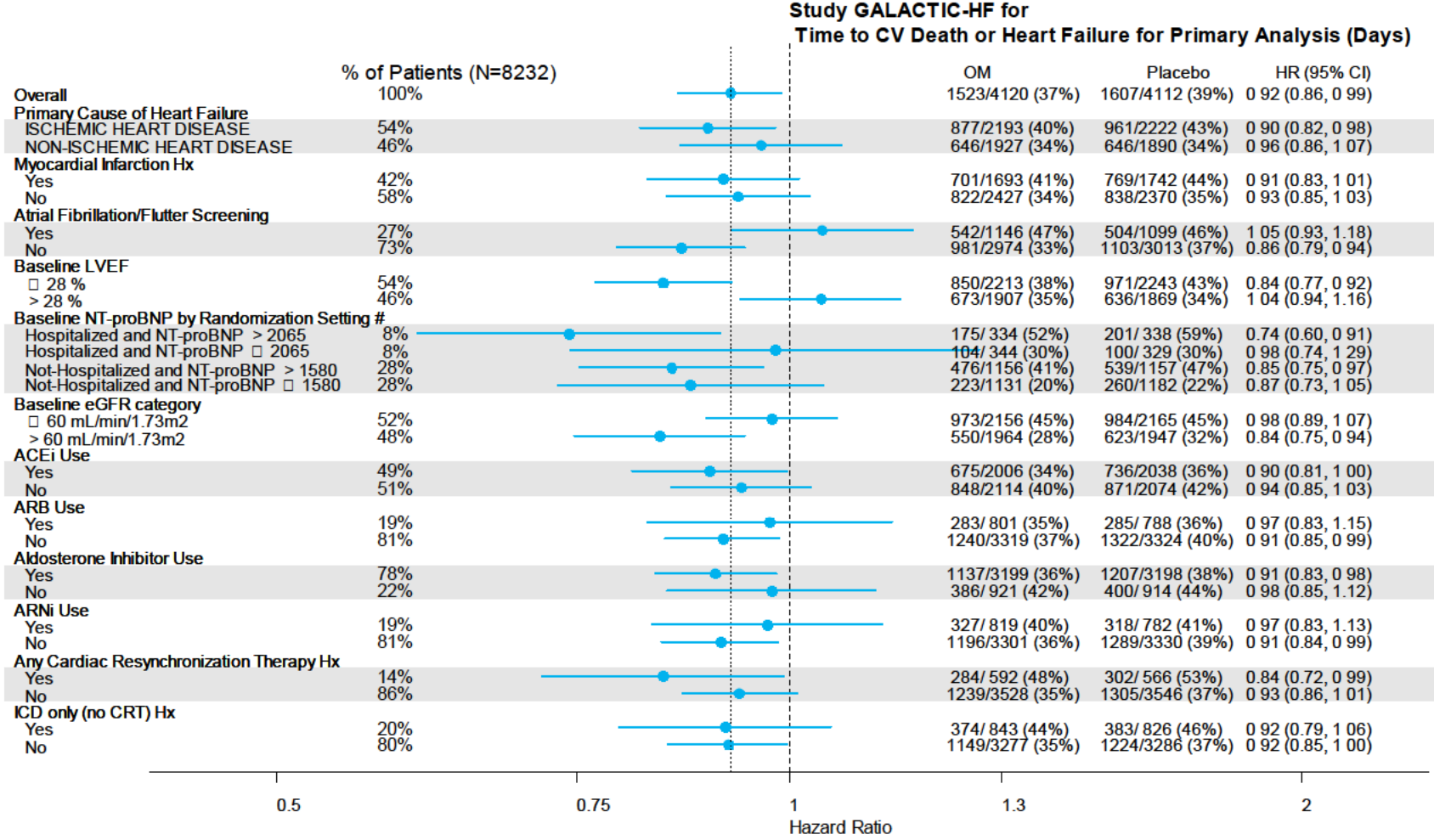


Source: Statistical Reviewer

For each arm (OM or placebo), the number of subjects with a first event/ total number of subjects within each subgroup category and percentages in parenthesis are presented.

Abbreviations: AUS, Australia; BL, baseline; CI, confidence interval/credible interval (shrinkage); CV, cardiovascular; EEU, Eastern Europe; FAS, full analysis set; HF, heart failure; HR, hazard ratio; N, number of randomized participants excluding study site 29002; NYHA, New York Heart Association; OM, omecamtiv mecarbil; SA, South America; SBP, systolic blood pressure; WEU, Western Europe

Figure 5. Prespecified Subgroup Analyses for Time to Composite of CV Death or Heart Failure, FAS, GALACTIC-HF (Part 2/2)



Source: Statistical Reviewer

Based only on subjects without atrial f brillation/flutter. Median NT-proBNP was obtained within each randomization setting.

For each arm (OM or placebo), the number of subjects with a first event/ total number of subjects within each subgroup category and percentages in parenthesis are presented.

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; BL, baseline; CI, confidence interval/cred ble interval (shrinkage); CRT, cardiac resynchronization therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HF, heart failure; HR, hazard ratio; Hx, history; ICD, implantable cardioverter-defibrillator; LVEF, baseline left ventricle ejection fraction; N, number of randomized participants excluding study site 29002; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; OM, omecamtiv mecarbil

Key Secondary Endpoints

The following key secondary endpoints were included in the multiplicity testing based on a graphical approach. Because the primary endpoint was statistically significant, the alpha was subsequently split to test the time to CV death endpoint using a two-sided alpha of 0.048 and the Kansas City Cardiomyopathy Questionnaire-total symptom score endpoint using a two-sided alpha of 0.002, neither of which were statistically significant. Therefore, no further testing was conducted on the remaining key secondary endpoints. The results are reported in Table 5.

Table 5. Results for Key Secondary Endpoints, FAS, GALACTIC-HF

Key Secondary Endpoint	OM N=4120	Placebo N=4112	HR (95% CI)[1]/ Diff (95% CI)[2]	Nominal P-Value
Time to CV death, n (IR)[1]	808 (10.9)	798 (10.8)	1.01 (0.92, 1.11)	0.9
Change from baseline in KCCQ TSS				0.03
Not currently hospitalized[2]	5.8 (0.3)	6.3 (0.3)	-0.5 (-1.4, 0.5)	
Currently hospitalized[2]	23.7 (0.7)	21.2 (0.7)	2.5 (0.5, 4.5)	
Time to first HF hospitalization, n (IR)[1]	1142 (18.0)	1179 (19.1)	0.95 (0.87, 1.03)	0.2
Time to all-cause death, n (IR)[1]	1067 (14.4)	1065 (14.4)	1.00 (0.92, 1.09)	>0.9

Source: Statistical Reviewer reproduced the results based on the Applicant's prespecified analysis.
[1] A Cox proportional hazards regression adjusting for baseline eGFR and treatment group. The model was stratified by combination of randomization setting and region. The hazard ratio comparing OM with placebo, along with respective 95% CI, and Wald-based p-value were reported from the regression model. The number of subjects with an event and the incidence rate per 100 PY in parenthesis are reported for each arm. Incidence rate is defined by the number of subjects with the first event divided by patient-years at risk of experiencing the outcome.
[2] For KCCQ, within each randomization setting subgroup, LS mean is from the mixed model repeated measures, which includes baseline TSS value, region, baseline estimated glomerular filtration rate, scheduled visit, treatment group, and interaction of treatment with scheduled visit as covariates. The LS mean treatment difference is using placebo as the reference. The p-value was obtained based on an omnibus F-test with 2 numerator degrees of freedom to test the OM vs. the placebo. LS mean difference and standard error estimated are presented in parenthesis for each arm.
All p-values reported in the table are nominal.
Abbreviations: CI, confidence interval; CV, cardiovascular; FAS, full analysis set; HF, heart failure; HR, hazard ratio; IR, incidence rate; KCCQ TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; N, number of randomized participants excluding study site 29002; OM, omecamtiv mecarbil

Totals of 808 (11 per 100 PY) and 798 (11 per 100 PY) subjects in the OM and placebo arms, respectively, died from a CV event, with an estimated adjusted HR of 1.01 (95% CI: 0.9, 1.1; two-sided p=0.9). Subgroup analysis for this endpoint is presented in Figure 13 and Figure 14. Consistent findings were seen for on-treatment CV deaths (HR: 1.0; 95% CI: 0.9, 1.1; two-sided p=0.96). A summary of the causes of adjudicated deaths are reported in Table 6. A sensitivity analysis for the CV death endpoint that included unknown death showed similar findings (HR: 1.03, 95% CI: 0.94, 1.13).

Table 6. Summary of the Causes of Death, FAS, GALACTIC-HF

Cause of Death	OM N=4120 n (%)	Placebo N=4112 n (%)
Total deaths	1067 (26%)	1065 (26%)
Cardiovascular deaths	808 (20%)	798 (19%)
Due to heart failure	414 (10%)	390 (9%)
Sudden cardiac	172 (4%)	190 (5%)
Due to an acute MI	19 (<1%)	15 (<1%)
Due to stroke	18 (<1%)	32 (<1%)
Due to other cardiovascular causes	9 (<1%)	11 (<1%)
Due to cardiovascular procedure	6 (<1%)	7 (<1%)
Due to cardiovascular hemorrhage	5 (<1%)	2 (<1%)
Presumed cardiovascular[1]	110 (3%)	97 (2%)
Presumed sudden death[1]	55 (1%)	54 (1%)
Non-cardiovascular deaths	259 (6%)	267 (6%)
Unknown death[2]	99 (2%)	77 (2%)
Infection; includes sepsis	82 (2%)	97 (2%)
Malignancy	29 (<1%)	38 (<1%)
Trauma	13 (<1%)	13 (<1%)
Gastrointestinal	6 (<1%)	10 (<1%)
Hepatobiliary	4 (<1%)	3 (<1%)
Non-cardiovascular hemorrhage	4 (<1%)	7 (<1%)
Pulmonary	4 (<1%)	7 (<1%)
Renal	4 (<1%)	5 (<1%)
Neurological	3 (<1%)	1 (<1%)
Other non-cardiovascular	3 (<1%)	-
Suicide	3 (<1%)	5 (<1%)
Non-cardiovascular procedure or surgery	2 (<1%)	2 (<1%)
Intracranial hemorrhage	1 (<1%)	1 (<1%)
Nonprescription drug reaction or overdose	1 (<1%)	-
Pancreatic	1 (<1%)	1 (<1%)

Source: Statistical Reviewer

[1] Presumed cardiovascular death and presumed sudden deaths were classified as "Undetermined" per the Applicant's database and included as cardiovascular deaths per the definition of the primary endpoint.

[2] Unknown deaths were included as non-cardiovascular deaths (i.e., not a primary event) for the primary efficacy endpoint but were classified as "Undetermined" per the Applicant's database.

Abbreviations: FAS, full analysis set; HF, heart failure; MI, myocardial infarction; N, number of randomized subjects excluding study site 29002; n, sample size of subjects excluding study site 29002; OM, omecamtiv mecarbil

3.1.3 Efficacy Issue in Detail

3.1.3.1 Issue 1: Adequacy of the Study to Demonstrate Substantial Evidence

During development, the FDA stated, in principle, a single Phase 3 trial using the proposed primary composite endpoint could provide adequate support for an effectiveness claim, "if the primary endpoint were significant at a p-value <0.01 (and there was no adverse effect on mortality) or if CV mortality were significant at a p-value <0.05." The FDA also stated a single trial with a p-value of 0.05 would probably not be sufficient for approval if the p-value for the primary endpoint were driven by "urgent heart failure visits" (i.e., ED/office visit) in the absence of at least strong trends for the other components of the composite endpoint.

The Applicant has conducted a single pivotal, multicenter, event-driven study (GALACTIC-HF) to provide evidence of OM as a treatment for reduction in risk of CV death or first HF event. The trial was powered based on CV death with the plan to randomize approximately 8000 subjects to obtain 1590 CV death

events. The planned sample size should yield at least 99% power for the primary composite endpoint and 90% power for the CV death endpoint with the predetermined trial assumptions.

The GALACTIC-HF study population included stable HFrEF subjects from both inpatient and outpatient settings, which was reasonably representative of a HFrEF population. The background HF therapy was generally appropriate with 66% of subjects treated with all three standard of care therapies for HF (beta-blocker, renin-angiotensin system inhibitor, or MRA). SGLT2 inhibitors became available during the conduct of GALACTIC-HF, therefore the use of SGLT2 inhibitors was limited to only 2.6% of subjects in the trial. The conduct of the study was acceptable. No single site was observed to drive the primary efficacy findings.

The analysis of the primary endpoint showed a statistically significant effect (HR: 0.92; 95% CI: 0.86, 0.99; two-sided p=0.025). The treatment effect was an 8% reduction in risk on the relative scale with the 95% upper CI barely precluding null difference. On the absolute scale, the difference in incidence rate was 2 per 100 PY (95% CI: 0.3, 3.8 per 100 PY) comparing placebo with OM. Analysis of the individual components of the composite endpoint showed a numerical trend favoring OM for the HF events, which included HF hospitalization and urgent HF office/emergency room/emergency department visits. Although the study was powered for CV death, a key secondary endpoint, CV death was numerically similar between arms and did not trend in the direction favoring OM (HR 1.01; p=0.9). Because the CV death endpoint did not meet statistical significance, the remaining secondary endpoints were not evaluated.

The KCCQ TSS quantifies the symptom frequency and severity, with higher scores representing better health status. The KCCQ TSS endpoint was not statistically significant according to the pre-specified multiplicity hierarchy (at 2-sided alpha of 0.002). The nominally significant findings for KCCQ TSS were not supported by consistent improvements from baseline between arms favoring OM. Among those who were not hospitalized at randomization, there was no difference between arms (-0.5 point difference comparing OM with placebo). Among subjects who were hospitalized for HF at randomization, the change from baseline to Week 24 was 2.5 points, with numerical improvement towards the OM arm compared to the placebo arm. This small improvement in KCCQ TSS observed among those hospitalized for HF at randomization was not considered clinically meaningful in patients with HFrEF.

In summary, the FDA review team agrees that the GALACTIC-HF met its prespecified primary endpoint. However, the small observed treatment effect, whether on the relative or absolute scale, was not considered clinically and statistically persuasive, in the absence of a favorable trend for CV death, significant key secondary endpoints, nor clinically meaningful improvement in patient symptoms. Thus, it is unclear GALACTIC-HF, as a standalone, adequate and well-controlled study would provide substantial evidence of effectiveness as a potential treatment for patients with HFrEF.

The FDA review team also considered whether the results of the Phase 2b trial can serve as confirmatory evidence of effectiveness. The Phase 2b trial (COSMIC-HF) evaluated hemodynamic parameters that, although characterized as hypothesis-generating putative surrogates, have an ambiguous relationship with clinical outcome. Despite the improvement seen in several hemodynamic parameters (e.g., systolic ejection time, stroke volume, left ventricular end systolic, and diastolic diameter), OM was associated with a modest increase in LVEF and had no effect on increasing left ventricular cardiac output. The inotropic effects of OM are plausibly related to outcomes in HFrEF; however, the degree of clinical

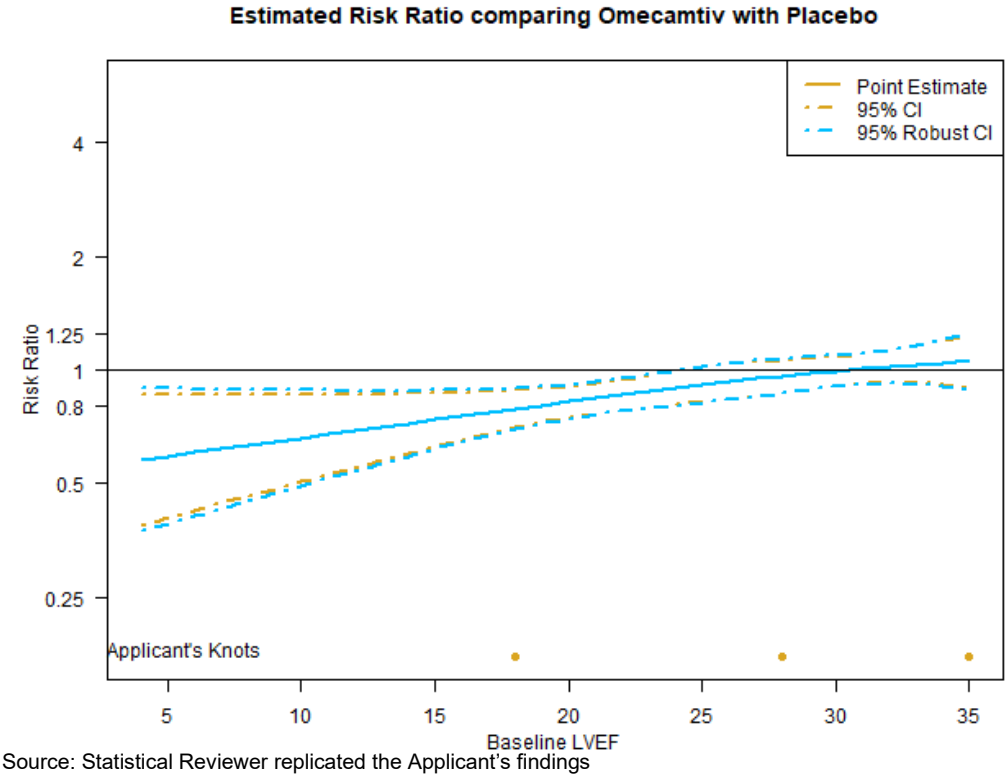
benefits associated with this mechanism and these hemodynamic changes are uncertain. Thus, it is not clear whether hemodynamic data in this case provide robust confirmatory evidence.

3.1.3.2 Issue 2: Heterogeneity of Efficacy Findings in the GALACTIC-HF Trial

After the FDA review team communicated the concern regarding the observed overall small benefit in the GALACTIC-HF trial, the Applicant proposed several approaches to narrow the intended population to high-risk HFrEF patients based on baseline LVEF cutoff points. Currently, the Applicant proposes to include the following language as part of the indication: "Benefits are increasingly evident the lower the left ventricular ejection fraction (LVEF)."

To support their current proposal, the Applicant relied mainly on exploratory analysis based on a Poisson regression model fit to the composite primary endpoint including the treatment variable, restricted cubic spline function[8] for baseline LVEF, and interaction of treatment variable and restricted cubic spline function for baseline LVEF. The Applicant's results are shown in Figure 6. The reference horizontal line indicates the null effect based on risk ratio. In general, we note that the estimated risk ratio increases in a linear trend on the log scale as the baseline value of LVEF increases.

Figure 6. Applicant's Analysis of Baseline LVEF With Primary Composite Endpoint, FAS, GALACTIC-HF



Source: Statistical Reviewer replicated the Applicant's findings
The blue 95% CI were obtained based on a Poisson regression model similar to the Applicant but Huber-White sandwich errors were used to relax the model assumptions. The difference in the point estimates were negligible while the 95% robust CI were slightly wider for lower quantiles of the baseline LVEF. Baseline LVEF values of ≥35 were not reported due to sparsity of data (See Table 16).
Abbreviations: CI, confidence interval; FAS, full analysis set; HF, heart failure; LVEF, left ventricular ejection fraction

[8] Per the Applicant, knots were placed at 18, 28, and 35 for the cubic spline function.

The FDA review team conducted additional analysis for the primary composite endpoint considering similar restricted cubic spline function[9] treating LVEF as a continuous variable based on different statistical models. The FDA note that differences in choice of knots or model specification can produce differences in the trend of the LVEF relationship with the outcome of interest, i.e., whether linear, quadratic, or cubic and provide different interpretation of the relationships. For example, if a different choice of knots were selected, the relationship between LVEF with the outcome of interest would no longer be linear on the log relative risk scale. Nevertheless, in both the Applicant's and the FDA analyses, there was no considerable gain in efficacy for LVEF values ranging between 25% and 30% (whether the trend was linear on the log relative risk scale or was nonlinear on the log-relative risk scale). Both models were consistent to conclude that there were trends of benefit for LVEF less than 24%, with the 95% confidence bands excluding 1 (Figure 6 and Figure 12).

With respect to the Applicant's proposal to state in the indication that "Benefits are increasingly evident the lower the left ventricular ejection fraction (LVEF)," the concerns are as follows:

Reliance on LVEF: Given the small treatment effect in the overall population, the Applicant relies on baseline LVEF to determine the subpopulation who would benefit most from OM. From Figure 6, it is unclear scientifically why OM showed benefit for HFrEF patients with much lower EF while subjects with higher EF in the study but still with reduced ejection fraction did not benefit from the treatment.

In addition, relying on LVEF to determine the treatment benefit also ignores the known measurement error associated with LVEF, a continuous measurement.

Relationship between baseline LVEF with outcome of interest: The review team noted that different choices of knots, or model assumptions, as well as different choices of the functional form for LVEF can produce different relationships between baseline LVEF and the outcome of interest (Figure 12). These different relationships can give different conclusions across the different models, i.e., whether we believe the trend is linear, nonlinear, or cubic on the log relative risk/hazard ratio scale. Determination of these model choices was conducted post hoc, thus lending difficulty for interpretation.

3.2 Safety Issues

The potential risk of OM in patients with HFrEF is dose-limiting cardiotoxicity due to its exaggerated pharmacological action. In the GALACTIC-HF trial, under a PK-guided dosing strategy and monitoring, the risks of OM, including major myocardial ischemic events, appear to be contained.

The Applicant required PK measurements of OM during GALACTIC-HF and titrated OM based on these results. In contrast, the Applicant is proposing to not require PK monitoring when OM is used in the real-world setting. Therefore, the major safety issue with real-world use is the potential risk of cardiotoxicity associated with the proposed posology of the scheduled, forced titration without a mandatory requirement of measuring plasma OM concentrations for the purpose of dose adjustment. There are various intrinsic and extrinsic factors that could impact concentrations of OM. With the proposed scheduled, forced titration, higher exposure is expected in the general population compared to what was seen in GALACTIC-HF with exacerbation in certain populations such as patients who are poor

[9] Interior knots were determined based on the rms function in R. The function selected values at LVEF values of 23, 28, and 31 (corresponding to 25th, 50th, and 75th percentiles, respectively, of the baseline distribution of LVEF), and boundary knots[9] at values of 15 and 35 (corresponding to the 5th and 95th percentiles, respectively, of the distribution).

metabolizers of CYP2D6 who would have increased exposure by 47% compared to those with a normal metabolizing rate (see Section 3.2.3.1 for more details). This could increase the potential risk of OM-associated cardiotoxicity. Because GALACTIC-HF used PK to guide OM dosing, there are very limited data to evaluate the clinical risk associated with long-term, excessive exposure of OM. With the available data, the FDA review team has a concern that excessive exposure to OM increases the risk of myocardial ischemia and HF. Hence, the intended use of OM with the scheduled, forced titration without required PK guidance cannot ensure safe use of the drug. Of note, the Applicant subsequently agreed to implement a PK-guided dosing strategy in response to the FDA's concern regarding the initial proposed posology of scheduled, forced titration.

Another safety issue raised from the GALACTIC-HF trial is the finding of an increased risk of CV death in subjects with AFF at screening. Patients with AFF could be more susceptible to the potential cardiotoxicity related to OM. The FDA is convening this Advisory Committee Meeting to discuss these issues further.

3.2.1 Sources of Data for Safety

The safety evaluation primarily focused on the GALACTIC-HF Phase 3 trial in 8,211 subjects with HFrEF. The Applicant also provided safety data from Phase 1 and 2 studies, which were used as supportive data in FDA's safety evaluation. In particular, an oral MR formulation of OM with a PK-guided titration was evaluated in two Phase 2b studies in subjects with chronic HFrEF. An overview of these two studies is summarized below.

Study 20110151 (COSMIC-HF)

COSMIC-HF was a Phase 2b, double-blind, randomized, placebo-controlled, multicenter study in subjects with chronic HFrEF. The study consisted of two study periods: 1) the Dose Escalation Period of the study (N=94) designed to select 1 of 3 oral MR formulations after 7 days of treatment (Cohort 1: 25 mg BID, Cohort 2L 50 mg BID); and 2) the Expansion Period of the study (N=445) that evaluated the safety and tolerability of the selected oral MR formulation of OM at 2 target dose levels (25 mg BID or PK-guided titration from 25 to 50 mg BID) compared with placebo for a 20-week treatment period.

Study 20120227

Study 20120227 was a Phase 2b, double-blind, randomized, placebo-controlled, multicenter study in Japanese subjects with chronic HFrEF. The study evaluated 16 weeks of administration of OM at 3 dose levels (25 mg BID, 25 to 37.5 mg BID PK-based titration, and 25 to 50 mg BID PK-based titration), compared with placebo (N=81).

3.2.2 Safety Summary

In the GALACTIC-HF Phase 3 trial, 8,211 subjects received at least one dose of OM (n=4,110) or placebo (n=4101) with a median duration of exposure of 20 months. The incidence and severity of adverse events (AEs) were generally similar between treatment groups (Table 7). There were no concerning imbalances in the incidence and type of AEs leading to drug discontinuation, and the patterns of serious AEs (SAEs) and deaths during treatment (Table 18, Table 19, and Table 20).

Table 7. Overview of Adverse Events[1] GALACTIC-HF Trial, Safety Population, On-Treatment

Event	OM N=4110 n (%)	Placebo N=4101 n (%)	Absolute Risk Difference (95.0% CI)[2]
SAE	2373 (57.7%)	2435 (59.4%)	-1.6 (-3.8, 0.5)
Fatal outcome	837 (20.4%)	823 (20.1%)	0.3 (-1.4, 2.0)
AE leading to permanent discontinuation	432 (10.5%)	447 (10.9%)	-0.4 (-1.7, 0.9)
AE leading to dose modification of study drug	1192 (29.0%)	1248 (30.4%)	-1.4 (-3.4, 0.5)
AE leading to interruption of study drug	901 (21.9%)	929 (22.7%)	-0.7 (-2.5, 1.1)
Any AE	3594 (87.4%)	3622 (88.3%)	-0.9 (-2.3, 0.5)
Mild	1983 (48.2%)	1997 (48.7%)	-0.4 (-2.6, 1.7)
Moderate	2269 (55.2%)	2350 (57.3%)	-2.1 (-4.2, 0.0)
Severe	2055 (50.0%)	2150 (52.4%)	-2.4 (-4.6, -0.3)
Life threatening	754 (18.3%)	785 (19.1%)	-0.8 (-2.5, 0.9)
Death	837 (20.4%)	823 (20.1%)	0.3 (-1.4, 2.0)

Source: Reviewer's table; adsl, adae; software: R
[1] Treatment-emergent AEs defined as occurring within 30 days after last treatment.
[2] Difference in proportions comparing OM and Placebo is presented. The 95% CI is based on normal approximation to binomial proportions.
Abbreviations: AE, adverse event; CI, confidence interval; HF, heart failure; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil; SAE, serious adverse event

Safety Endpoint—Major Cardiac Ischemic Events

In the GALACTIC-HF trial, adjudicated major cardiac ischemic events were a prespecified safety endpoint that included fatal and nonfatal MI, hospitalization for unstable angina, and coronary revascularization (coronary artery bypass graft surgery [CABG] or percutaneous coronary intervention). Table 8 shows the incidence, event rate, and the hazard ratio of the time to first major cardiac ischemic event and MI in the GALACTIC-HF trial. Overall, the risk of experiencing major cardiac ischemic events was similar between treatment groups in the GALACTIC-HF trial under the PK-guided posology. Subgroup analyses of major cardiac ischemic events by baseline characteristics of interest were explored. Overall, the results were consistent across most of the subgroups with a hazard ratio around one (see Appendix 6.5.5.1 and Figure 19 for additional details).

Table 8. Analysis of Adjudicated Safety Endpoints, Safety Population, GALACTIC-HF

	OM (N=4110)		Placebo (N=4101)		
Adjudicated Safety Endpoint	n (%)	ER (%PY)	n (%)	ER (%PY)	HR (95% CI) OM vs. Placebo
Major cardiac ischemic event	207(5.0)	2.9	191 (4.7)	2.7	1.08 (0.89, 1.32)
Myocardial infarction	118 (2.9)		101 (2.5)		
Hospitalization for unstable angina	23 (0.6)		9 (0.2)		
Coronary revascularization	66 (1.6)		81 (2.0)		
Myocardial infarction	130 (3.2)	1.8	122 (3.0)	1.7	1.06 (0.83, 1.36)

Source: Reviewer's table; adsl adtte2; software: SAS
Abbreviations: CI, confidence interval; ER, event rate; HF, heart failure; HR, hazard ratio; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil; PY, patient-years

Safety Endpoint—Ventricular Arrhythmias Requiring Treatment

The incidence of SAEs of ventricular arrhythmias requiring any therapeutic intervention was ~4% in both treatment groups. There were no differences between treatment groups regarding the nature or the severity of the event (Table 21).

Adverse Events of Interest

An evaluation of AEs of interest including myocardial ischemic and arrhythmia related events in the GALACTIC-HF trial is summarized in Table 22. A numerically higher incidence of myocardial ischemia related events was observed in the OM group compared to placebo (7.4% versus 6.6%), which was primarily driven by a higher frequency of angina pectoris and unstable angina. There was no difference between treatment groups for myocardial ischemia related SAEs (5% in both groups) (Table 23) (See Appendix 6.5.6 for additional details). Myocardial ischemia-related AEs include events with mild and moderate severity that did not meet the definition of major cardiac ischemic events listed in Table 8.

Cardiac Biomarkers

OM caused a small increase in cardiac biomarkers including cardiac troponin-I and creatine kinase-MB (CK-MB) (see Appendix 6.5.8 for more details). The peak increase for both biomarkers occurred at Week 6 (Figure 20 and Figure 21). It should be noted that the Week 6 measurement was the last measure before subjects could potentially be down titrated at Week 8 in the GALACTIC-HF trial (~13% of treated subjects at Week 4 down-titrated at Week 8). In the OM group, the median changes from baseline at Week 6 for troponin-I and CK-MB were 0.008 ng/mL and 0.8 ng/mL, respectively. More subjects in the OM group met abnormality criteria for troponin-I compared to the placebo group (Table 27). For example, 62% of subjects in the OM group compared to 50% of subjects on placebo had at least one troponin level >0.04 ng/mL during the study. The corresponding percentages for troponin level >0.10 ng/mL were 27.4% for OM and 20.5% for placebo. There was a low incidence of subjects meeting the abnormality criteria for CK-MB in both groups, with minor imbalances such as 1.4% of subjects in the OM arm and 0.8% of subjects on placebo having CK-MB above 3× the upper limit of normal. The clinical significance of these findings is unclear.

CV Death Subgroup Finding

Subgroup analyses of time to CV death in the GALACTIC-HF trial revealed nominally statistically significant interaction effects ($p<0.05$ with no adjustment for multiplicity) between OM and placebo for the following subgroups: presence of AFF at screening ($p=0.001$), baseline use of ARB ($p=0.009$), and median LVEF at baseline ($p=0.03$) (Figure 13). In a post hoc multivariate model of CV death,[10] AFF ($p<0.001$) remained a highly significant covariate that modified the treatment effect. Hence, several post hoc analyses were provided by the Applicant to further characterize the risk (see safety issue in Section 3.2.3.2).

3.2.3 Safety Issues in Detail

3.2.3.1 Issue 1: Proposed Dosing Strategy

The GALACTIC-HF trial implemented a PK-guided dose selection strategy to ensure that subjects randomized to the OM group achieved trough OM concentrations (C_{trough}) in the target range of 300 to 750 ng/mL and avoided an excessive exposure of >1000 ng/mL. The Applicant determined that the OM concentration safety threshold was 1000 ng/mL. This determination was primarily based on empirical data from early clinical studies with an IV formulation where myocardial ischemia and MI occurred with

[10] A Cox regression model, fit to time to CV death, included 28 baseline subgroup, treatment variable, and interaction of each subgroup with treatment variable. The p-value was reported for each treatment and subgroup interaction.

excessive exposure of OM (>1000 ng/mL). To ensure safety, the Phase 2b studies employed the PK-guided titration which was largely successful to achieve pharmacodynamically active OM concentrations (>200 ng/mL) while maintaining mean C_{trough} in the range 200 to 350 ng/mL and preventing excessive OM concentrations (>1000 ng/mL). Hence, the FDA team considered the proposed PK-guided posology for the Phase 3 trial reasonable to mitigate the risk even though the optimal therapeutic range had not been established in the OM clinical program. Under the PK-guided posology, the risk profile of OM was similar to that of placebo in the GALACTIC-HF trial with the exception among subjects with AFF (Section 3.2.3.2).

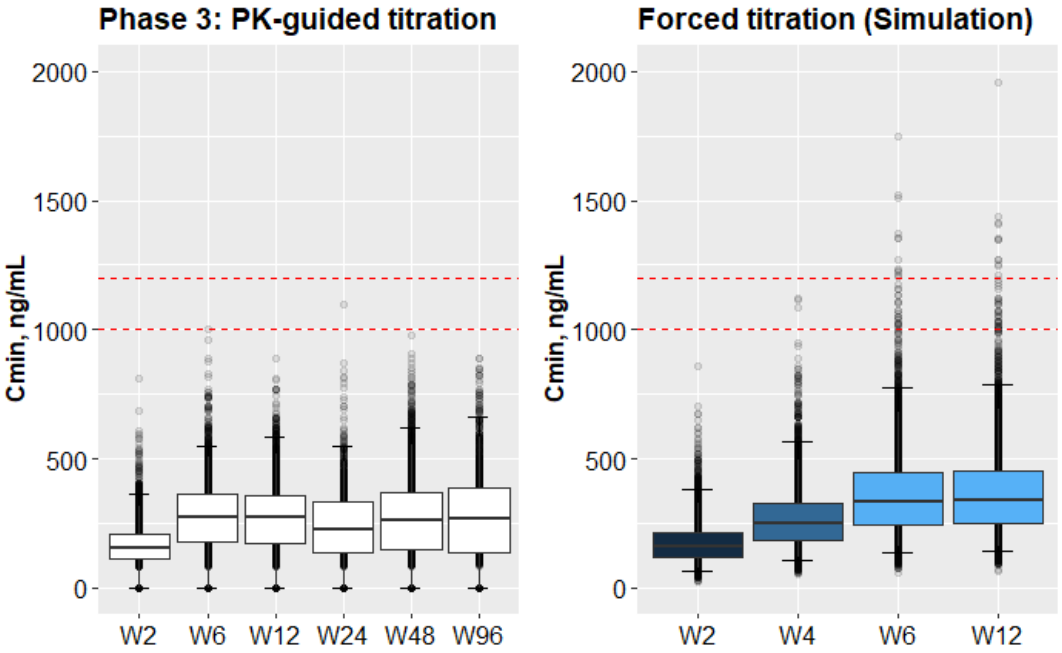
However, the NDA was submitted with an untested posology for real-world use based on a stepwise and scheduled dose titration without the need for PK guidance. This proposal has all patients receive an initial dose of 25 mg BID, increase to 37.5 mg BID after 2 weeks, and increase to the maximum dose of 50 mg BID after another 2 weeks. The Applicant however stated that measurements of plasma concentrations of OM may be a useful adjunct to its dosing and proposed to make available liquid chromatography-tandem mass spectrometry assay that could voluntarily be used to support dose titration of OM in clinical practice post approval. FDA's assessment on whether this untested dosing strategy could ensure safe use of OM is summarized below.

3.2.3.1.1 Predicted Exposure With Scheduled, Forced Titration (Versus Phase 3 PK Experience)

In GALACTIC-HF, all subjects in the OM group were started on an initial dose of 25 mg BID. At Week 2, OM concentrations were assessed to determine the target dose for each subject (25, 37.5, or 50 mg BID), then these target doses were initiated from Week 4. At Week 6, OM concentrations were measured again to determine whether the selected doses were adequate, then the dose was further adjusted at Week 8, if needed. Following these PK-guided dose adjustments, 29%, 14% and 48% of subjects were receiving 25 mg, 37.5 mg, and 50 mg BID, respectively, as their final doses by Week 12. However, with the scheduled dosing scheme initially proposed for real-world use, all patients (100%) are to receive 50 mg BID from Week 4 with the exception that some may choose to perform the voluntary PK-guided dosing adjustment.

The observed predose concentrations following the PK-guided titration in GALACTIC-HF and the predicted PK exposures following the proposed scheduled, forced titration are graphically summarized in Figure 7. Following the scheduled, forced titration, the predicted PK exposures when all patients receive 50 mg BID from Week 4 are projected to be higher than those observed in GALACTIC-HF. Particularly, a notable proportion of patients are estimated to have excessive PK exposures (i.e., plasma concentrations >1000 ng/mL or >1200 ng/mL) when all patients are receiving 50 mg BID from Week 4 per the scheduled, forced titration. See Section 3.2.3.1.2 for further discussion regarding the safety concern of excessive PK exposures.

Figure 7. Comparison of Observed Predose Concentrations In GALACTIC-HF and Predicted PK Exposures Following the Scheduled, Forced Titration



Source: FDA analysis. Left panel was generated using adpc.xpt. Right panel was generated based on FDA's population simulations.
Abbreviations: C, concentration; HF, heart failure; PK, pharmacokinetics; W, week

In the GALACTIC-HF trial, the PK-guided dosing reasonably prevented excessive PK exposures: less than 1% of subjects had a predose concentration of OM above 750 ng/mL, only 0.1% (n=3) of subjects were reported to have predose concentrations of OM above 1000 ng/mL, and no subjects had a predose concentration of OM >1200 ng/mL (Table 9). With a scheduled, forced titration without PK measurement, a total of 0.6% and 4.7% of patients are estimated to have C_{trough} and C_{max} >1000 ng/mL, respectively. A total of 0.2% and 1.4% of patients are estimated to have C_{trough} and C_{max} >1200 ng/mL (Table 10, population 1). In the sensitivity simulation based on the virtual population comprising 1:1 male and female patients, the proportion of patients above the 1000 ng/mL or 1200 ng/mL are expected to be slightly higher (Table 10, population 2).

Patients who are CYP2D6 poor metabolizers (PM) are expected to have about 47% higher exposure of OM compared to those who are CYP2D6 normal metabolizers (NM). As a result, CYP2D6 genotyping or PK-based titration is needed to avoid the potential for high OM concentrations in these patients. In addition, patients with some intrinsic (e.g., hepatic and renal impairment) and extrinsic (e.g., drug-drug interaction and food effect) factors would be expected to have higher OM concentration. Although these issues may be mitigated by labeling restrictions, developing a PK assay to allow for PK-based titration might be a more practical way to support dose adjustment in all patients.

Table 9. Observed Proportion of Subjects in Each Bin of OM Predose Concentration (C_{trough}) in GALACTIC-HF With PK-Guided Dosing

	C_{trough} (ng/mL) Bins					
Visit Week (n)	**<200**	**200 to <300**	**300 to <750**	**750 to <1000**	**1000 to <1200**	**1200 and above**
Week 6 (3790)	29%	28%	43%	0.2%	0%	0%
Week 12 (2613)	31%	27%	42%	0.3%	0%	0%
Week 24 (1124)	44%	24%	31%	0.5%	0.003%	0%
Week 48 (3026)	37%	22%	41%	0.7%	0%	0%

Source: FDA analysis based on adpc.xpt
Abbreviations: C_{trough}, trough concentration; HF, heart failure; n, number of subjects excluding study site 29002; OM, omecamtiv mecarbil; PK, pharmacokinetics

Table 10. Simulated Proportion of Subjects in Each Bin of OM Trough Concentration (C_{trough}) and Maximum Concentration (C_{max}) at Week 6 Following Scheduled, Forced Titration

	C_{trough} (ng/mL) Bins					
Population	**<200**	**200 to <300**	**300 to <750**	**750 to <1000**	**1000 to <1200**	**1200 and above**
Population 1. GALACTIC-HF, 79% male	13%	28%	56%	2.8%	0.4%	0.2%
Population 2. GALACTIC-HF, 50% male	11%	26%	58%	3.8%	0.6%	0.1%
	C_{max} (ng/mL) Bins					
	<200	**200 to <300**	**300 to <750**	**750 to <1000**	**1000 to <1200**	**1200 and above**
Population 1. GALACTIC-HF, 79% male	0.3%	5.4%	76%	13%	3.3%	1.4%
Population 2. GALACTIC-HF, 50% male	0.4%	4.2%	73%	16%	4.2%	2.1%

Source: FDA analysis
Population PK simulations were conducted based on two virtual populations. Population 1 was generated by sampling 4500 subjects from GALACTIC-HF preserving demographic characteristics. Virtual population 2 was generated by sampling 4500 subjects from GALACTIC-HF but including 50% of male subjects.
Abbreviations: C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; HF, heart failure; OM, omecamtiv mecarbil; PK, pharmacokinetics

Exposure-Response Relationships for Efficacy and Safety

The Applicant conducted exposure-response (E-R) analyses based on the PK, safety and efficacy data from GALACTIC-HF. The E-R analyses for efficacy showed no significant E-R relationships for the primary composite endpoint (i.e., first HF events and CV death), which might imply that an increase in OM PK exposures is not expected to improve efficacy. The E-R analysis for safety showed that higher OM PK exposures were associated with increased probability of SAEs (nominal p-value 0.0019), indicating that the higher OM PK exposures following the proposed scheduled, forced titration might lead to a higher risk of SAEs. FDA's analysis indicates that the positive E-R relationship for SAEs was largely driven by increased probability of cardiac failure SAEs. However, it should be noted that interpretation of such E-R analyses for both efficacy and safety should be cautious due to the narrow-observed PK exposures following PK-guided titration in GALACTIC-HF. In addition, meaningful inference of the E-R relationships for both efficacy and safety is unfeasible for the expected higher PK exposures following the proposed scheduled, forced titration that is beyond the observed PK exposure range in GALACTIC-HF.

3.2.3.1.2 Clinical Risk Associated With Excessive Exposure

There are limited data to evaluate clinical risk of excessive, long-term exposure of OM. In the GALACTIC-HF trial under a PK-guided dosing strategy, the median plasma concentration was maintained in the range of 250 to 300 ng/mL with limited experience in a higher exposure range. Based on the available clinical data (see Appendix 6.5.10) and nonclinical findings (see Appendix 6.3), the FDA has a concern that the excessive exposure to OM increases the risk of OM-associated cardiotoxicity including myocardial ischemia and HF in the context of a narrow therapeutic window. The FDA's analysis estimates that about 20% and 5% of patients would have C_{max} above 750 ng/mL and 1000 ng/mL, respectively, following scheduled, forced titration in the real-world setting (Table 10).

The safety signals from clinical studies raise concern that the dose-limiting cardiotoxicity of OM can be manifested as exacerbation of HF that not only impacts safety but also efficacy of OM. The FDA further conducted a concentration-response analysis based on the quintile group of the last OM concentration measured at or before Week 12 for the primary efficacy endpoint and CV death. A concentration-dependent increase in efficacy within the concentration range studied in the GALACTIC-HF trial was not observed (Table 29). Subjects who had drug concentrations in the highest category did not show benefit from OM when compared to placebo (see Appendix 6.5.14 for more details).

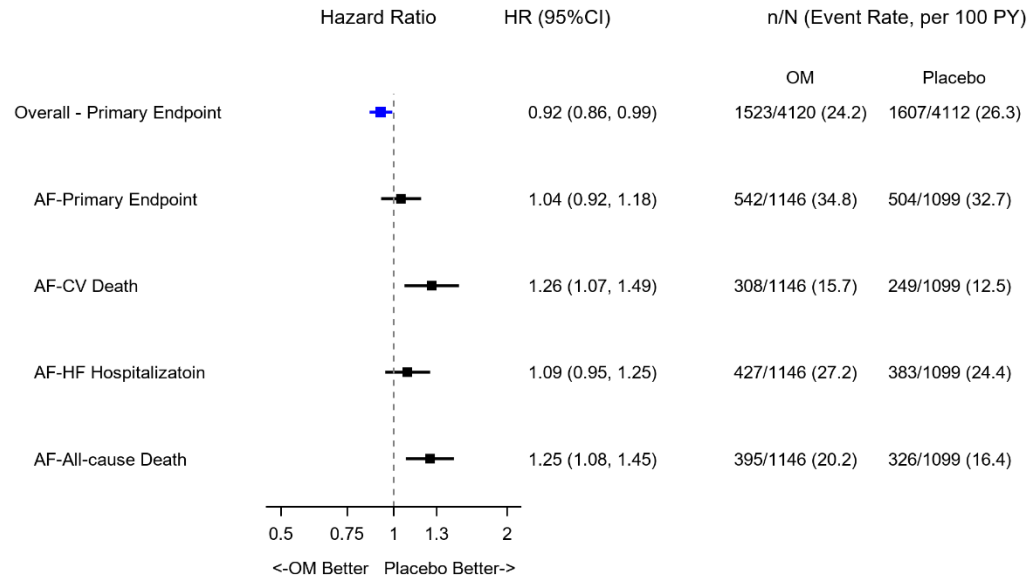
The FDA team recognizes the limitation of some of these analyses; however, the results of these analyses are not reassuring, and the review team continues to have safety concerns regarding scheduled, forced titration without required PK guidance.

3.2.3.2 Issue 2: Potential Increased Risk of CV Death in Patients With Atrial Fibrillation or Flutter

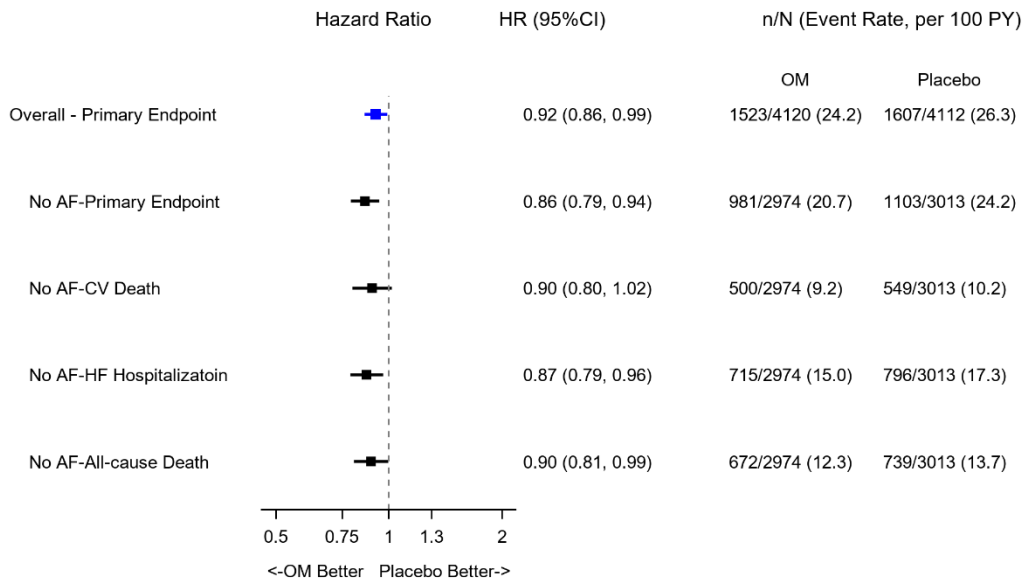
In the GALACTIC-HF trial, among subjects with AFF at baseline (27% of the GALACTIC-HF population), there was no apparent improvement on the primary efficacy endpoint (HR: 1.04; 95% CI: 0.92, 1.18) and an increased risk for CV death with OM compared to placebo (Figure 8).

Figure 8. Efficacy Endpoints by AFF at Screening: (a) Subjects With AFF (b) Subjects Without AFF, FAS, GALACTIC-HF

(a)



(b)

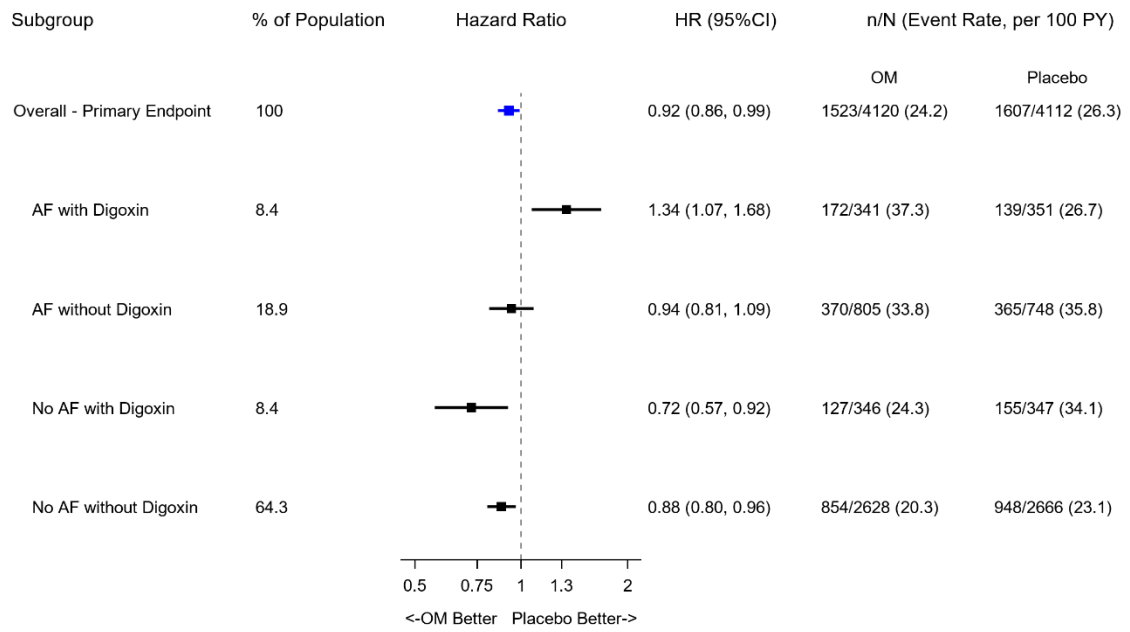


Source: Reviewer's figure; adall, date; software: SAS
Abbreviations: AF/AFF, atrial fibrillation/flutter at screening; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; FAS, full analysis set; N, number of subjects in treatment arm in the corresponding subgroup excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil, PY, patient-years

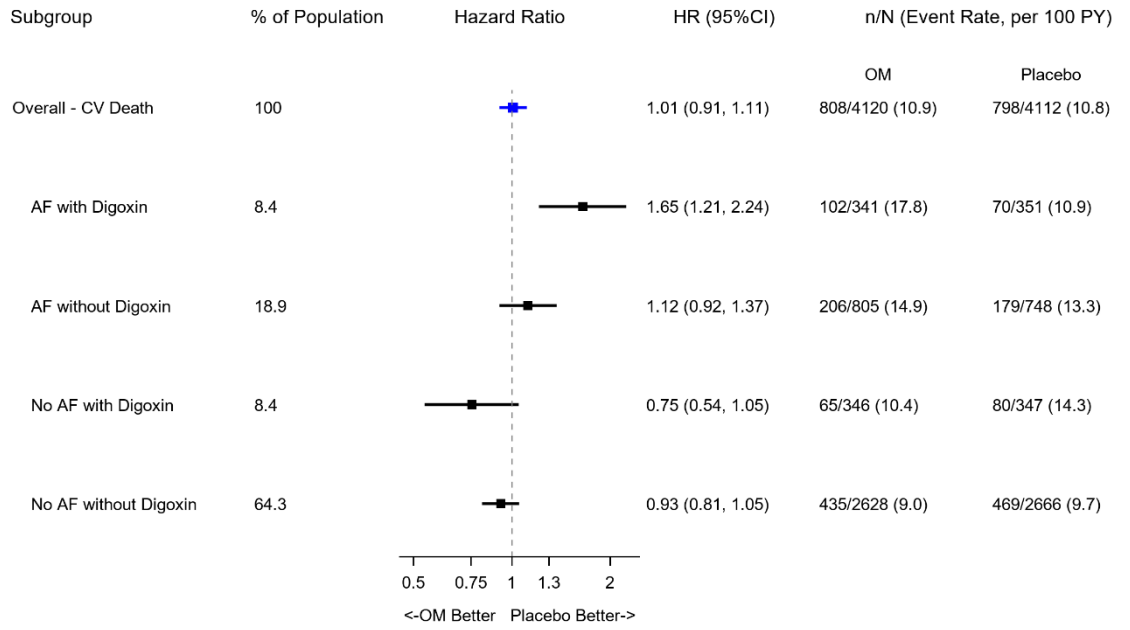
The excess in CV death in subjects with AFF was driven primarily by increased incidence of HF death as opposed to sudden cardiac death (Table 34). The mechanism for this observation is unclear but the plausibility that this finding could be associated with dose-limiting cardiotoxicity of OM cannot be ruled out. Baseline characteristics indicated that patients with AFF were older, more likely to be NYHA Class III/IV, had higher NT-proBNP and lower eGFR, and had more frequent digoxin and anticoagulant use (Table 35). The Applicant's post hoc analyses indicated that the observed treatment by AFF interaction was primarily driven by coadministration of digoxin in patients with baseline AFF (8% of the total population) (Figure 9). Hence, the Applicant argued that the adverse effects seen in AFF patients were concentrated in this subset of AFF patients treated with digoxin. However, even in the subgroup of AFF patients not treated with digoxin, OM had a numerically higher hazard ratio for CV death compared to placebo. The AFF with digoxin subgroup findings are not likely to be due to a PK interaction between OM and digoxin given that a Phase 1 study shows <8% change in digoxin exposure with OM and there were similar OM concentrations among the AFF/digoxin subgroups in the GALACTIC-HF trial.

Figure 9. Efficacy Endpoints by AFF Patients With or Without Use of Digoxin: (a) Primary Efficacy Composite Endpoint; (b) CV Death, FAS, GALACTIC-HF

(a)



(b)



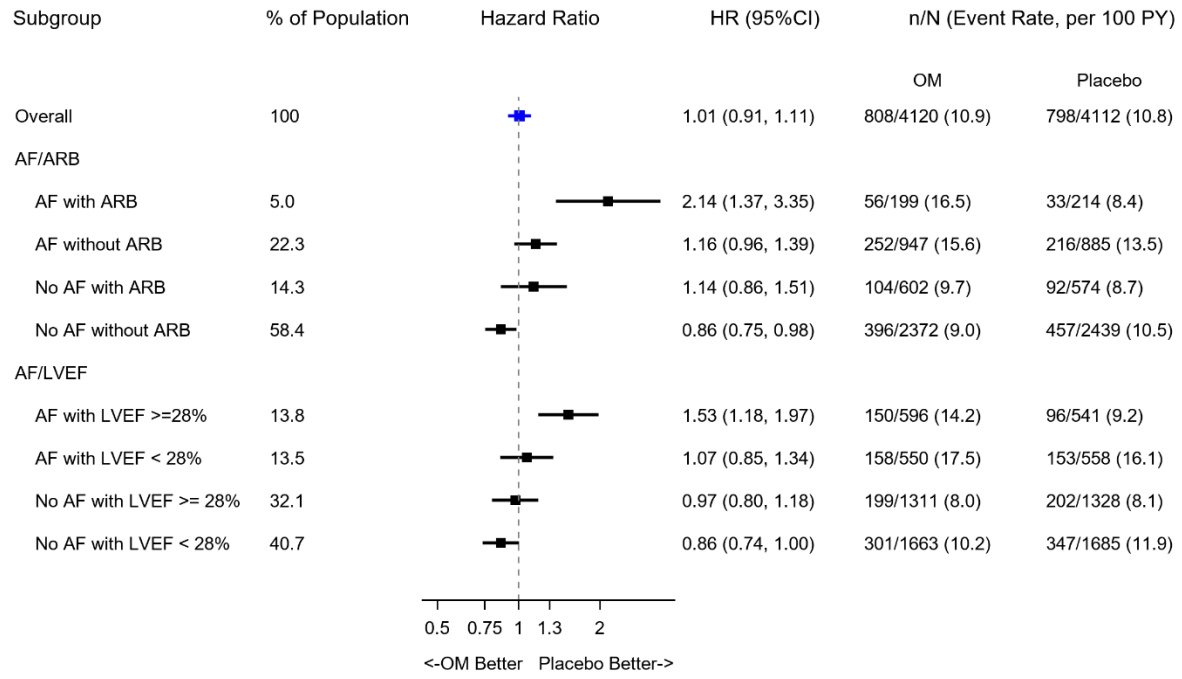
Source: Reviewer's figure; adall, adtte; software: SAS
Abbreviations: AF/AFF, atrial fibrillation/flutter at screening; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; FAS, full analysis set; OM, omecamtiv mecarbil, N, number of subjects in treatment arm in the corresponding subgroup excluding study site 29002; n, number of subjects with an event; PY, patient-years

In addition to digoxin use as a potential factor modifying the results among subjects with AFF, it is noted that subjects with ARB use at baseline and LVEF >28% (median) also modified the adverse effect of CV death observed in subjects with AFF (Figure 10). The interaction for AFF-digoxin and AFF-LVEF remained

nominally significant in a post hoc multivariate model. It should be noted that both baseline LVEF and AFF are also significant modifiers for the primary efficacy endpoint.

A plausible mechanistic hypothesis may be reasonably advanced to explain why AFF patients may not tolerate OM the same way as patients with HF and without AFF, and why a subset of AFF patients (i.e., concomitant use of digoxin and/or LVEF >28%) may have worse outcomes. However, the observed findings from these exploratory analyses, particularly sub-subgroups at risk should be interpreted with caution and require further investigations.

Figure 10. CV Death by AFF Subjects by ARB Use and by LVEF at Baseline, FAS, GALACTIC-HF



Source: Reviewer's figure; adall, adtte; software: SAS
Abbreviations: AF/AFF, atrial fibrillation/flutter at screening; ARB, angiotensin II receptor blocker; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; N, number of subjects in treatment arm in the corresponding subgroup excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil, PY, patient-years

4 Benefit-Risk Framework

Benefit-Risk Framework

Disclaimer: This predecisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	Heart failure (HF) is a chronic, progressive condition affecting 6 million individuals in the United States. About half of HF patients have HF with reduced ejection fraction (HFrEF). Despite available HF therapies, the mortality and hospitalization rates remain high. The 5-year mortality in HFrEF patients aged ≥60 years is approximately 66%. The clinical course for HFrEF patients is variable, but many patients experience acute episodes of clinical decompensation with increased symptoms requiring urgent intervention (i.e., IV diuretic treatment following hospitalization, clinic visit, emergency room visit). This worsening of chronic HF is associated with a poor long-term prognosis.	Heart failure (HF) is a chronic, progressive condition with significant morbidity and mortality. Frequent urgent interventions for clinical worsening are common during the clinical course of HFrEF and are associated with poor prognosis.
Current Treatment Options	Current treatment options for patients with HFrEF include pharmacologic and device therapies. Guideline-directed medical therapy (GDMT) and device therapy (AHA/ACC/HFSA Class I recommendations 2022) for the reduction of morbidity and mortality are: • Beta-blockers, renin-angiotensin inhibitors (ACEi, ARBs, and ARNI), MRAs, SGLT2 inhibitors (dapagliflozin and empagliflozin), hydralazine with isosorbide dinitrate (for African Americans). • Diuretics (symptomatic improvement). • Implantable cardioverter-defibrillator (ICD). • Cardiac resynchronization therapy with defibrillation (CRT-D). Additional pharmacologic therapies once GDMT is optimized: • Ivabradine, vericiguat, or digoxin.	Despite available treatment options, there is a continued need to reduce morbidity and mortality in patients with HFrEF.

	Evidence and Uncertainties	Comments to the Advisory Committee
Benefits	GALACTIC-HF was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, event-driven study in 8232 subjects with chronic HFrEF (NYHA Class II-IV, LVEF≤35%) GALACTIC-HF implemented a PK-guided dosing strategy with a target OM concentration of 300-750 ng/mL. The trial had a median follow-up of ~22 months and met its prespecified primary endpoint. Treatment with OM resulted in an 8% reduction in the risk of cardiovascular (CV) death and HF events (HF hospitalization or urgent HF visit) compared to placebo (HR: 0.92; 95% CI: 0.86, 0.99; two-sided p=0.03). The reduction in the risk of the primary composite endpoint, on the absolute scale, was 2% (or 2 per 100 PY) for OM relative to placebo (95% CI: -3.8 per 100 PY, -0.3 per 100 PY). The observed treatment effect was driven by HF events (HR: 0.93; 95% CI: 0.86, 1.00; two-sided p=0.06). The CV death component of the composite endpoint was neutral. None of the prespecified secondary endpoints in the GALACTIC-HF trial met statistical significance according to the pre-specified multiplicity hierarchy. The key secondary endpoint-time to CV death did not trend in the direction favoring OM compared to placebo (HR: 1.01; 95% CI: 0.92, 1.11; two-sided p=0.9). Subgroup analysis of the primary composite efficacy endpoint showed a generally consistent effect across baseline characteristics with the exception of left ventricular ejection fraction (LVEF) and presence of atrial fibrillation/flutter (AFF) at baseline. There was differential treatment effect of OM compared to placebo observed among (1) subjects with LVEF ≤28% (median) (HR: 0.84; 95% CI: 0.77, 0.92) vs subjects with LVEF >28% (HR: 1.05; 95% CI: 0.94, 1.16) and (2) subjects without AFF (HR: 0.86; 95% CI: 0.79, 0.94) vs subjects with AFF (HR: 1.05; 95% CI: 0.93, 1.38).	GALACTIC-HF, as a single trial serving as the basis of substantial evidence of effectiveness, demonstrated a small treatment effect where the upper limit of the 95% confidence interval approached the null for the primary efficacy endpoint and included the null for the driver of the treatment effect (i.e., HF events). <u>Requests to the AC</u> Comment on whether the GALACTIC-HF Phase 3 trial demonstrated substantial evidence of effectiveness for OM in reducing the risk of CV death and HF event in subjects with symptomatic chronic HFrEF. Comment on your interpretation of the LVEF and AFF subgroup analysis for the primary efficacy endpoint and CV death (also see risk section) in the GALACTIC-HF trial. If OM warrants a claim, how would you describe the patients in whom such benefit applies?
Risks and Risk Management	Nonclinical studies demonstrated dose-limiting cardiotoxicity of OM with a narrow safety margin for lethality and myocardial lesions. Given a less than 2-fold exposure margin of nonobserved adverse event level (NOAEL) in animals to the maximum recommended human dose of 50 mg BID, the potential risk for drug-related cardiotoxicity at the proposed clinical doses is likely to be high.	The principal safety concern of OM is the potential risk of dose-limiting cardiotoxicity including but not limited to myocardial ischemia/infarction resulting from an excessive pharmacologic effect of OM. In GALACTIC-HF, in which PK-guided dose selection strategy was implemented, the risk profile of OM was comparable to placebo with the exception among patients with AFF.

	Evidence and Uncertainties	Comments to the Advisory Committee
	Safety evaluation was primarily based on the data obtained in the GALACTIC-HF trial in which a PK-guided dose selection and PK monitoring were implemented to avoid excessive OM exposure and ensure safety. Safety assessment focused on the potential cardiotoxicity of OM, whereby excessive prolongation of systolic ejection time could lead to impaired diastolic coronary filling, resulting in cardiac adverse effects including but not limited to myocardial ischemia or infarction. In the GALACTIC-HF trial, the risks of prespecified safety endpoints – major cardiac ischemic events (HR: 1.08; 95% CI: 0.9, 1.3) and the incidence of ventricular arrhythmia SAE (~4% in each group) requiring any treatment were similar between groups. The incidence of treatment-emergent AEs and SAEs did not reveal major safety concerns. A greater incidence (risk difference of ≥0.8%) was reported in subjects on OM vs. placebo for the following AEs: • Dizziness: 8.1% vs.7.1% • Myocardial ischemia-related event: 7.4% vs. 6.6% Myocardial ischemic-related AEs include events with mild and moderate severity that did not meet the definition of major cardiac ischemic events. Treatment with OM was associated with small increases in troponin-I and CK-MB compared to placebo. The clinical significance of these increases was unclear. Subgroup findings: Subjects with AFF on OM had an increased risk of CV death compared to placebo (HR: 1.26, 95% CI: 1.1, 1.5). In particular, the excess CV death in this subset subgroup was driven by a higher incidence of HF death in OM-treated subjects. Post hoc analyses suggested that AFF patients with digoxin use and/or LVEF >28% were at a particularly high risk.	The GALACTIC-HF trial revealed that patients with AFF may be at increased risk for CV death due to worsening of HF. Given the limitations inherent in post hoc analyses, one cannot be certain about differential risk in patient subgroups, thus impacting regulatory decision-making. The Applicant originally proposed marketing OM with an untested, forced, scheduled dose titration without the need for PK guidance. With the scheduled, forced titration, higher exposures are expected compared to PK experiences in the GALACTIC-HF trial that could increase the potential risk of drug-associated cardiotoxicity that may impact both efficacy and safety of OM. The Applicant has recently proposed to implement a PK-guided dosing strategy using an LDT. This approach is deemed acceptable if measuring OM concentrations for the purpose of dose adjustment is not critical for therapeutic use of OM (nice to have vs. critical to have). <u>Requests to the AC</u> Comment on whether a PK-guided dosing strategy implemented in the GALACTIC-HF trial is critical for both safe and effective use of OM. Comment on your interpretation of subgroup analyses among AFF patients for CV death. How should this potential risk be described in the label if OM is approved?

	Evidence and Uncertainties	Comments to the Advisory Committee
	The Applicant's proposal to substitute the PK-guidance posology with a "forced titration" dosing strategy raises the following safety concerns: • PK/PD modeling simulation shows that if all patients uptitrated to 50 mg BID, 20% of patients would have OM exposure outside the target therapeutic range (C_{max} >750 ng/mL) with >5% of patients with excessive OM concentrations (C_{max} >1000 ng/mL) compared to the PK experiences in the GALACTIC-HF trial. • There is limited exposure-response data for PK >750 ng/mL. The frequency of patients with cardiotoxicity due to exaggerated pharmacologic effect of OM is expected to be increased with the scheduled, forced titration. There is evidence suggesting that OM-associated cardiotoxicity can be manifested as worsening of HF that impacts both safety and efficacy. • Patients with a poor metabolizing rate of CYP2D6 and/or other relevant intrinsic factors (e.g., low body weight) are at an increased risk of experiencing excessive OM exposure, thus increasing the risk of cardiotoxicity. • Concomitant use of CYP2D6 inhibitors with OM may increase OM exposure and increase the risk of OM-associated cardiotoxicity. During the NDA review, the Applicant subsequently agreed to use a LDT to implement a PK-guided dosing strategy that resembles a simplified version of the PK-dosing strategy that was used in GALACTIC-HF. Unlike an FDA authorized test, use of an unapproved LDT may not ensure OM concentrations are measured appropriately for the purpose of dose adjustment for every patient in the real-world setting.	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; AFF, atrial fibrillation/flutter; AHA/ACC/HFSA, American Heart Association/American College of Cardiology/Heart Failure Society of America: ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; BID, twice a day; CDx, companion diagnostics; CI, confidence interval; CK-MB, creatine kinase-myoglobin binding; C_{max}, maximum plasma concentration; CRT-D, cardiac resynchronization therapy with def brillation; CV, cardiovascular; CYP2D6, cytochrome P450 2D6; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure reduced ejection fraction; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; IV, intravenous; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NDA, New Drug Application; NOAEL, nonobserved adverse event level; NYHA, New York Heart Association; OM, omecamtiv mecarbil; PK, pharmacokinetics; PK/PD, pharmacokinetic/pharmacodynamic; SAE, severe adverse event; SGLT2, sodium-glucose cotransporter-2

Summary of Benefit-Risk

It is not certain whether the benefit of OM outweighs the risk. This uncertainty is based on both efficacy and safety considerations. The results of GALACTIC-HF showed a small treatment effect with the upper limit of the 95% confidence interval approaching the null line for the primary endpoint (i.e., 0.99) and touched it for the driving endpoint (1.00). This single trial as the basis of the NDA was not accompanied by confirmatory evidence. The treatment effect appeared to favor those with a LVEF <28%, but there is no scientific basis for this differential effect. The benefit/risk profile is further tenuous, because only 2 additional major cardiac ischemic events per 100 PY are needed to negate the potential small net benefit observed in the overall GALACTIC-HF population. The FDA review team estimated that 2% of patients may have C_{max} >1200 ng/mL following the initial proposed posology of scheduled, forced titration. This could be roughly translated to 2 additional major cardiac ischemic events per 100 PY, thus rendering OM unfavorable. This estimation does not take into account other potential risks associated with the initial proposed posology. The risk estimate for the newly proposed PK-guided dosing should be similar to that in the GALACTIC-HF trial if the PK-guided dosing is universally followed as it was in the trial.

Point(s) to Consider: Do the benefits of OM outweigh its risks for the treatment of HFrEF? If OM warranted a claim, how would you describe the patients in whom such benefit applies? Is the PK-guided posology critical for optimizing the benefit-risk profile?

Table 11. Benefit-Risk Assessment, GALACTIC-HF

		Benefit Primary Composite Efficacy Endpoint (CV Death + HF Event)				Risk Major Cardiac Ischemic Event				Net Benefit
Patient Population	% of Subjects	OM (IR)	Placebo (IR)	Delta[1] (IR)	HR	OM (IR)	Placebo (IR)	Delta[1] (IR)	HR	ΔΔ[2] (IR)
Overall	100	24.2	26.3	-2.1	0.92	2.9	2.7	0.2	1.08	-1.9
LVEF median (%)										
LVEF ≤28	54	26.1	31.2	-5.1	0.84	2.8	2.6	0.2	1.08	-4.9
LVEF >28%	46	22.2	21.3	0.9	1.05	3.0	2.8	0.2	1.07	1.1
LVEF quartile (%)										
Q1 <22%	25	28.9	36.5	-7.6	0.82	3.0	2.6	0.4	1.13	-7.2
Q2 22-27%	25	23.6	27.3	-3.7	0.84	2.4	2.3	0.1	1.01	-3.6
Q3 28-31%	24	24.3	23.2	1.1	1.09	2.8	2.6	0.2	1.09	1.3
Q4 >31%	26	20.9	20.4	0.5	1.01	3.3	3.2	0.2	1.04	0.7
AFF at baseline										
No	73	20.7	24.2	-3.5	0.86	3.3	3.0	0.3	1.12	-3.2
Yes	27	34.8	32.7	2.1	1.04	1.8	1.9	-0.1	0.94	2.0
AFF/LVEF										
No AFF with LVEF >28%	32	18.2	19.5	-1.3	0.94	3.7	3.2	0.6	1.18	-0.7
No AFF with LVEF ≤28%	41	23.0	28.4	-5.5	0.82	2.9	2.8	0.1	1.05	-5.4
AFF with LVEF >28%	14	32.7	26.0	6.7	1.22	1.4	2.0	-0.6	0.70	6.1
AFF with LVEF ≤28%	14	37.3	40.5	-3.2	0.90	2.3	1.7	0.6	1.30	-2.6

Source: FDA's table, datasets: adtte, adtte2, and adall

Observed incidence rates per 100 PY are presented under benefit and risk. Incidence rate is defined as the number of subjects with the first event divided by total patient-years at risk of experiencing the outcome.

[1] Delta is computed by the difference in IR per 100 PY comparing OM with placebo. Negative value indicates a reduction in risk on the absolute scale (per 100 PY) of the endpoint favoring OM arm compared to placebo arm.

[2] $\Delta\Delta$ (net clinical benefit) is obtained by taking the difference between the Delta under Benefit with Risk, assuming equal weight on the efficacy and safety endpoint. Negative value indicates a reduction in risk on the absolute scale (per 100 PY) of the endpoint favoring the OM arm compared to the Placebo arm.

Abbreviations: AFF, atrial fibrillation/flutter at screening; CV, cardiovascular; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; OM, omecamtiv mecarbil; PY, patient-years; Q, quarter; IR, incidence rate

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6 Appendices

6.1 Regulatory History

The initial investigational new drug (IND) application was submitted by Cytokinetics on March 31, 2006. On May 10, 2006, the IND was placed on partial clinical hold for cardiovascular (CV) safety reasons. Nonclinical studies demonstrated a steep dose-response for lethality, a narrow safety margin for myocardial lesions, and measurable amounts of cardiac troponin-I. Omecamtiv mecarbil (OM) was also found to have caused a myocardial infarction (MI) in a healthy volunteer in a non-IND study (CY 1111). The partial clinical hold was removed on July 21, 2006, after the Applicant made significant revisions to the protocol, reduced the proposed doses of OM to be studied, increased the vital sign and electrocardiographic (ECG) monitoring, and revised the informed consent document.

On September 19, 2009, the IND was transferred from Cytokinetics to Amgen. Amgen was the Applicant of the IND until it was transferred back to Cytokinetic effective May 20, 2021.

The initial pharmacokinetics (PK)/pharmacodynamics (PD) studies in healthy participants and participants with heart failure (HF) used an intravenous (IV) formulation. An immediate-release (IR) capsule was also developed and used in early Phase 1 and 2 studies. Intolerance to OM was found to be related to excessive maximum plasma concentration (C_{max}) and was associated with the development of myocardial ischemia or myocardial infarction (MI) in some study participants during short durations of exposure. To slow the absorption and reduce peak to trough fluctuation, modified release (MR) formulations with different dissolution rates were developed.

Throughout the development program, the Food and Drug Administration (FDA) voiced CV safety concerns with OM and has worked closely with the Applicant on the design of the Phase 3 trial, Study 20110203 (GALACTIC-HF), and appropriate strategies to mitigate risk to subjects (as related to the PK-guided dosing strategy and CV monitoring plan). A Special Protocol Assessment (SPA) agreement was reached with the Applicant on the design of GALACTIC-HF on July 29, 2016. SPA Modification Letters were subsequently issued on November 28, 2016, and March 13, 2018, to reflect further changes to the protocol as agreed with the FDA.

OM for the treatment of chronic heart failure with reduced ejection fraction (HFrEF) was granted Fast Track Designation on May 5, 2020. Prior to the new drug application (NDA) submission, the Division had reminded Cytokinetics that an FDA-cleared or approved companion diagnostic will be required for the PK-guided dosing strategy, if deemed essential for the safe and effective use of OM. The Applicant informed the Division that the QMS™ OM immunoassay used in the GALACTIC-HF study for PK-guided dose titration regimen will not be commercialized. The Applicant had met with the Division to discuss their approach of using a liquid chromatography-tandem mass spectrometry assay with a proposed plan to validate the assay during the review cycle of the NDA. The Division had no objections with using a liquid chromatography-tandem mass spectrometry assay but continued to state that the assay should be appropriately classified as a companion diagnostic and, thus, submission of the assay's marketing application (premarket approval application or premarket notification) should take place concurrently with the NDA submission. The NDA was submitted on November 21, 2021, with a proposed stepwise, scheduled dose titration without the need for PK guidance.

6.2 Studies Used for Efficacy and Safety Evaluation

Table 12. Clinical Studies Used for Efficacy and Safety Evaluation of OM

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
20110203 (GALACTIC-HF)	Adults with chronic HFrEF, NYHA Class II-IV, and LVEF ≤35%	Phase 3, double-blind, randomized, placebo-controlled, multicenter, PK-guided dose selection, event-driven, CV outcomes study	Drug: OM MR oral tablets of 25, 37.5, or 50 mg BID Number treated: OM: 4110; Placebo: 4101 Median Duration: 20 mo	Primary: Composite of time to CV death or first HF event Secondary: Time to CV death Change in KCCQ TSS Time to first HF hospitalization Time to all-cause death	Event-driven trial until prespecified 1590 CV death events occurred Planned: 8000 Randomized: 8256	944 centers 35 countries
20110151 (COSMIC-HF)	Adults with chronic HFrEF, NYHA Class II-III, LVEF ≤ 40%	Phase 2, double-blind, randomized, placebo-controlled, 2-phase (Dose Escalation and Expansion)	Dose-Escalation Phase: Cohort 1: OM 25 mg BID (N=37) Placebo (N=11) Cohort 2: OM 50 mg BID (N=36) Placebo (N=10) Dose-Expansion Phase (N=445) 25 mg BID (n =150) PK-guided dose titration (25 mg to 50 mg BID) (n = 146) Placebo (n=149) Treatment Duration: Dose-Escalation Phase: 7 days Dose-Expansion Phase: 20 weeks	Dose-Escalation and -Expansion Phases: Primary: PK assessment: Cmax, Ctrough, AUC Dose-Expansion Phase Secondary: Changes from baseline in SET, stroke volume, LVESD, LVEDD, HR, NT-proBNP at Week 20	Planned: 570 Randomized: Dose-Escalation Phase: Cohort 1: 49 Cohort 2: 47 Dose Expansion Phase:448	105 centers 13 countries

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
20120227	Japanese adults with chronic HFrEF, NYHA Class I-III, LVEF ≤40%	Phase 2, double-blind, randomized, placebo-controlled	Four treatment cohorts: 25 mg BID (N=21) 25-37.5 mg BID* (N=19) 25-50 mg BID* (N=20) Placebo (N=21) *PK-guided titration Treatment duration: 16 weeks	Primary Endpoint: PK assessment Secondary Endpoint: Change from baseline in SET, at Week 16	Planned: 80 Randomized:81	31 centers in Japan

Source: Reviewer's table

Abbreviations: AUC, area under the curve; BID, twice a day; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; CV, cardiovascular; HF, heart failure; HFrEF, heart failure reduced ejection fraction; HR, heart rate; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; N, number of subjects treated; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; OM, omecamtiv mecarbil; PK, pharmacokinetics; SET, systolic ejection time

6.3 Summary of Pharmacology and Toxicology Profile

Primary Pharmacology

OM is a small molecule that activates cardiac myosin and increases contraction of cardiac myocytes. In biochemical and cellular functional assays, OM exhibited high selectivity for activating ATPase of cardiac myosin (50% effective concentration [EC_{50}], 0.62µM) relative to fast skeletal (EC_{50}, 18.7µM) and smooth muscle myosin (EC_{50}, >100µM). OM activates the enzymatic domain of cardiac myosin by stabilizing its lever arm in a primed position, which results in an increase of cardiac myosin heads in the pre-power stroke state available for interaction with actin filaments during the actual power stroke period. As demonstrated in isolated rat and dog ventricular myocytes, OM over a concentration range of 0.1 to 0.3µM increased the velocity, amplitude, and duration of myocyte contraction without increasing the calcium transient. However, at higher concentrations (≥1µM), OM slowed the velocity of both myocyte contraction and relaxation, and decreased resting sarcomere length, indicative of an excessive pharmacologic effect.

OM improved cardiac function in models of HF in rats and dogs at clinically relevant plasma drug concentrations. HF was established in rats by chronic MI by ligation of the left coronary artery. IV infusion of OM for 30 minutes increased fractional shortening and ejection fraction at plasma concentrations up to 335 ng/mL. Chronic HF was induced in dogs by MI followed by rapid pacing. Intravenous infusion with OM for 15 minutes or 6 to 8 hours (plasma concentration 665 ng/mL) increased myocardial systolic wall thickening, fractional shortening, cardiac output, and stroke volume, with a concomitant decrease in heart rate and left atrial pressure. No significant changes in mean arterial pressure and coronary blood flow were observed at these plasma drug concentrations. These studies provided early proof of concept that OM may improve cardiac systolic function in HF at an appropriate dose range.

Safety Concerns Based on Nonclinical Data—Adverse Cardiac Effects

Safety pharmacology and general toxicology studies were conducted in rats and dogs for up to 26 and 39 weeks, respectively. In all studies, adverse cardiac effects were observed when OM was administered via IV infusion or by the oral route. The adverse effect on cardiac function and target organs of toxicity from these studies and their clinical relevance are discussed below.

In cardiovascular safety pharmacology studies, OM was administered by IV infusion in healthy dogs for 30 minutes to 24 hours, at doses up to 10 mg/kg. A plasma concentration of ≥1400 ng/mL was achieved.

Plasma concentrations ≤700 ng/mL increased fractional shortening, cardiac output, and stroke volume and was associated with an increase in systolic ejection time (SET).

Plasma concentration of ≥1000 ng/mL exerted adverse cardiac effects marked by increased heart rate, decreased systolic, diastolic, and mean blood pressures, decreased ventricular function (rate of ventricular contraction, relaxation, and diastolic duration), and ECG signs of ischemia (ST-depression and QRS fractionation). In addition, arrhythmias and premature ventricular contractions were observed, which developed into sporadic accelerated idioventricular rhythms.

In general toxicity studies, OM resulted in cardiac toxicities and cardiac-related mortalities in healthy rats and dogs treated for short and chronic durations. The reversibility of the cardiac lesions was not assessed in these studies. The exposures at which cardiac toxicities were observed in the pivotal

toxicology studies and the exposure multiples with respect to the clinical C_{maxss} at the maximum recommended human dose (MRHD) of 50 mg twice a day (BID) are summarized in Table 13.

Table 13. Separation Between the Plasma Concentrations at NOAEL and Dose With Toxicity

	Rat C_{max} (ng/mL)		Dog C_{max}(ng/mL)		Exposure Multiples	
Dose Levels	**Male**	**Female**	**Male**	**Female**	**334[3] ng/mL**	**573[4] ng/mL**
Dose with toxicity, mortality[2], myocardial degeneration, necrosis, and/or fibrosis 7.5 mg/kg/day	641	755[1]	944	1000	2-3	1-2
NOAEL for cardiac toxicity 5 mg/kg/day	505	590[1]	709	549	1.5-2.1	0.9-1.2
Separation[5]	**1.3**	**1.3**	**1.3**	**1.8**	N/A	N/A

Source: Reviewer's Table

[1] C_{max} value derived from female rats in 13-week toxicity study. Other C_{max} values derived from 26-week rat and 39-week dog studies.

[2] Mortalities observed in all studies conducted in rats and in the 14-day study in dogs.

[3] Clinical C_{max} at the steady state estimated for 50 mg BID based on observed PK values from the Phase 3 study at each dose level under PK-guided dosing (see Clinical Pharmacology Section 3.2.3.1.1)

[4] Clinical C_{max} at steady state based on simulation PK for all subjects receiving 50 mg BID dose under the Applicant-proposed forced titration (see Clinical Pharmacology Section 3.2.3.1.1)

[5] Separation reflects fold change between the C_{max} values associated with cardiac toxicity and the absence of cardiac toxicity.

Abbreviations: C_{max}, maximum concentration; N/A, not applicable; NOAEL, nonobserved adverse event level

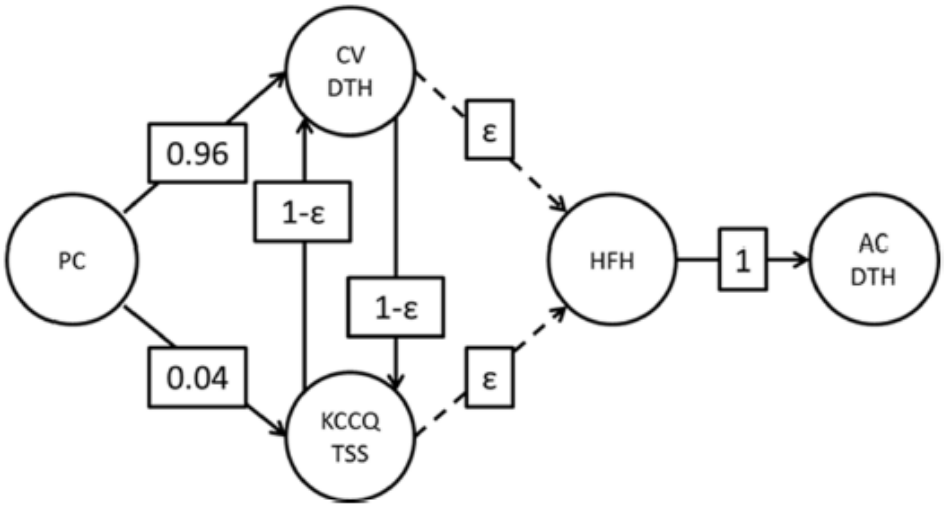
In rats, oral dosing with OM for 14 days, 13 weeks, or 26 weeks resulted in mortality and myocardial fibrosis at plasma concentrations of ≥795 ng/mL, ≥755 ng/mL, and ≥641 ng/mL, respectively. The lowest C_{max} related to cardiac toxicity was 641 ng/mL from the 26-week study, which is approximately 1.2-fold higher than the highest potential clinical C_{max} of 573 ng/mL. The dose that did not result in cardiac toxicity (5 mg/kg) in the same study was associated with a C_{max} of 505 ng/mL in males and 694 ng/mL in females, or approximately equivalent to the clinical C_{maxss} at the MRHD.

In dogs, mortality was observed in the 14-day study at doses ≥10 mg/kg/day (C_{max} of ≥897 ng/mL) but not in the longer duration studies. Myocardial degeneration/necrosis associated with fibrosis was consistently noted in 14-day, 13-week, and 39-week studies at C_{max} of ≥897 ng/mL, 985 ng/mL and 944 ng/mL, respectively. The C_{max} associated with cardiac toxicity in dogs was approximately two-fold the C_{maxss} at the MRHD while the no-observed-adverse-effect-level (NOAEL) for cardiac toxicity was 5 mg/kg in the 39-week study. The plasma concentration at the NOAEL was ~709 ng/mL in males and 549 ng/mL in females, or approximately equivalent to the clinical C_{maxss} at the MRHD.

The effect of OM on cardiac function and on cardiac toxicity appears closely related to the plasma drug concentration achieved in the nonclinical studies. Pharmacological effects considered beneficial were shown in healthy and HF dogs at plasma concentrations of ≤700 ng/mL (1.42µM) which is also similar to the drug concentrations observed at the NOAEL for cardiac toxicity (Table 13). A very modest increase in plasma drug concentrations of less than two-fold results in emergence of cardiac toxicity, including myocardial degeneration and fibrosis, and cardiac-related mortalities in both species. The Applicant reasonably proposes that at higher drug concentrations, excessive prolongation of systolic ejection time may impair cardiac relaxation and reduce ventricular filling, thus compromising diastolic coronary blood flow and predisposing to cardiac ischemia. The narrow separation between plasma drug levels considered potentially efficacious and clearly toxic in the nonclinical program is indicative of a narrow therapeutic window.

6.4 Additional Efficacy Supporting Information and Analyses

Figure 11. Multiplicity Testing Plan for the Primary and Key Secondary Endpoints, GALACTIC-HF



Source: Figure 1 of SAP version 5.0; Module 5.3.5.1
Each circle represents a hypothesis test. The values in the boxes on the arrows indicate the fraction of α propagated in the direction of the arrow to the next hypothesis test(s). A small value, ε=0.0001, is used to complete the graph while prioritizing the CV death and KCCQ TSS endpoints over the time to first heart failure hospitalization and all-cause death endpoints. Dashed arrows are used to emphasize this prioritization.
Abbreviations: AC DTH, time to all-cause death; CV, cardiovascular; CV DTH, time to CV death; HF, heart failure; HFH, time to first heart failure hospitalization; KCCQ TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; PC, primary composite endpoint

Table 14. Sensitivity Analyses Conducted for the Primary Efficacy Endpoint, FAS, GALACTIC-HF

Primary Endpoint, n(IR)	OM N=4120	Placebo N=4112	HR (95% CI)	P-value
Include investigator-reported events[1]	1787 (30.9)	1868 (33.5)	0.93 (0.87, 0.99)	0.03
Include unknown death	1589 (25.1)	1658 (27.1)	0.93 (0.87, 0.996)	0.04
Analyses addressing missing follow-up				
Worst case[2]	1548 (24.6)	1607 (26.3)	0.94 (0.87, 1.01)	0.09
Retrieved drop-out (1000 MI)[3]	1531 (24.3)	1615 (26.4)	0.92 (0.86, 0.99)	

Source: Statistical Reviewer
The number of subjects with an event and the incidence rate per 100 PY in parenthesis are reported for each arm. Incidence rate is defined by the number of subjects with the first event divided by patient-years at risk of experiencing the outcome.
[1] This analysis included all nonpositive adjudicated events based on investigator reports.
[2] A worst-case analysis was conducted by conservatively including subjects from the omecamtiv mecarbil arm who withdrew or were lost to follow-up as events for the primary endpoint while subjects from placebo who withdrew or were lost to follow-up as not considered as events for the primary endpoint. For this scenario, no imputation of future follow-up was conducted.
[3] A multiple imputation approach was used to impute missing follow-up for subjects (i.e., withdrawal of consent or lost to follow-up) based on subjects who had discontinued randomized treatment according to their randomized assignment. Off treatment data from subjects who discontinued randomized treatment but continued to be followed up was used to estimate the event rate based on a piecewise exponential model with intervals ([0, 120), [120, 360), [360, ∞)) obtained based on graphical inspection. A total of 1000 imputed datasets were obtained, and the primary statistical analysis method was applied for each of the imputed datasets. After which, Rubin's rule was used to combine the results to obtain the HR and 95% CI.
Abbreviations: CEC, clinical events classification; CI, confidence intervals; HF, heart failure; HR, hazard ratio; MI, multiple imputations; N, number of randomized subjects excluding study site 29002; OM, omecamtiv mecarbil; PY, patient-years

Table 15. Analyses of the Individual Components of the HF Endpoint Including Investigator-Reported Events,[1] FAS, GALACTIC-HF

Individual Component, n(IR)	OM N=4120	Placebo N=4112	HR (95% CI)	P-value
Time to first HF event	1462 (24.4)	1535 (26.3)	0.93 (0.87, 1.00)	0.049
Time to first HF hospitalization	1654 (28.6)	1738 (31.1)	0.92 (0.86, 0.99)	0.02
Time to urgent ER/ED or office/practice visit	426 (6.1)	446 (6.5)	0.95 (0.83, 1.08)	0.4

Source: Statistical Reviewer

The number of subjects with an event and the incidence rate per 100 PY in parenthesis are reported for each arm. Incidence rate is defined by the number of subjects with the first event divided by patient-years at risk of experiencing the outcome.

[1] This analysis included all nonpositive adjudicated events based on investigator reports.

Abbreviations: CI, confidence interval; ER/ED, emergency room/emergency department; FAS, full analysis set; HF, heart failure; HR, hazard ratio; N, number of randomized participants excluding study site 29002; OM, omecamtiv mecarbil; PY, patient-years

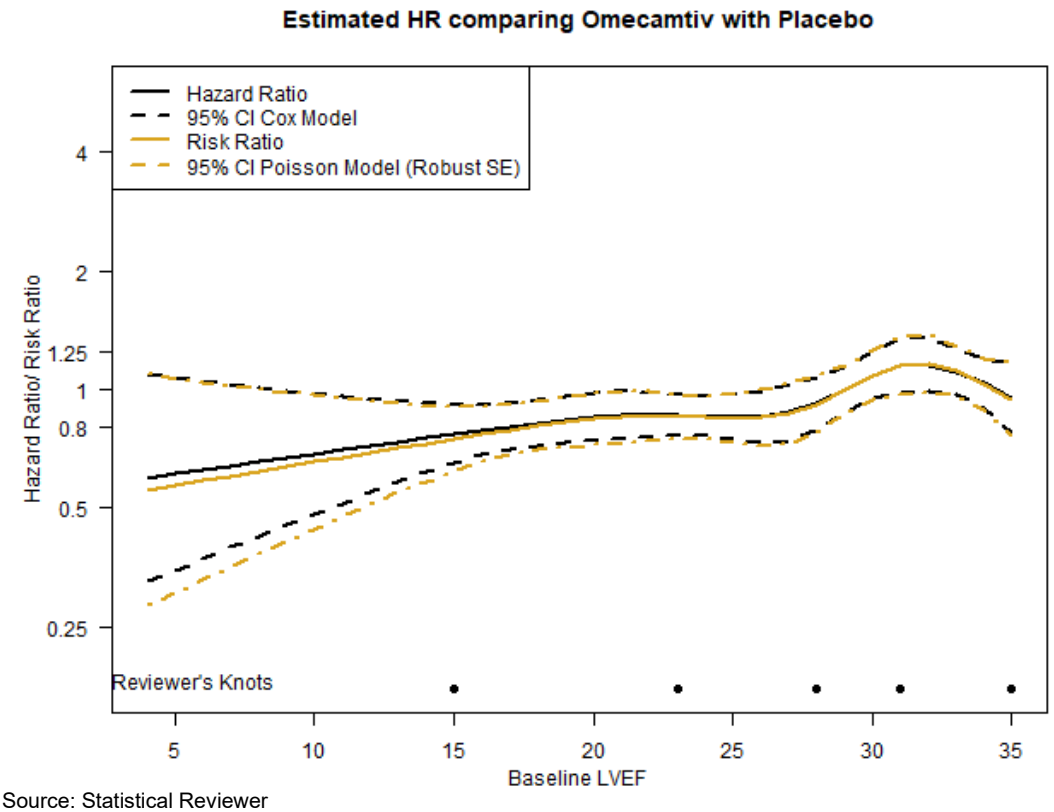
Table 16. Number of Adjudicated Primary Endpoint Events by Arm for the Baseline LVEF Grouping Based on the Reviewer's Model, FAS, GALACTIC-HF

Baseline LVEF	OM N=4120 Events/n	Placebo N=4112 Events/n
(4,15]	123/286	14 /283
(15,23]	385/979	415/943
(23,28]	342/948	407/1017
(28,31]	306/824	292/829
(31,35]	366/1080	344/1039
(35,42]	1/3	0/1

Source: Statistical Reviewer

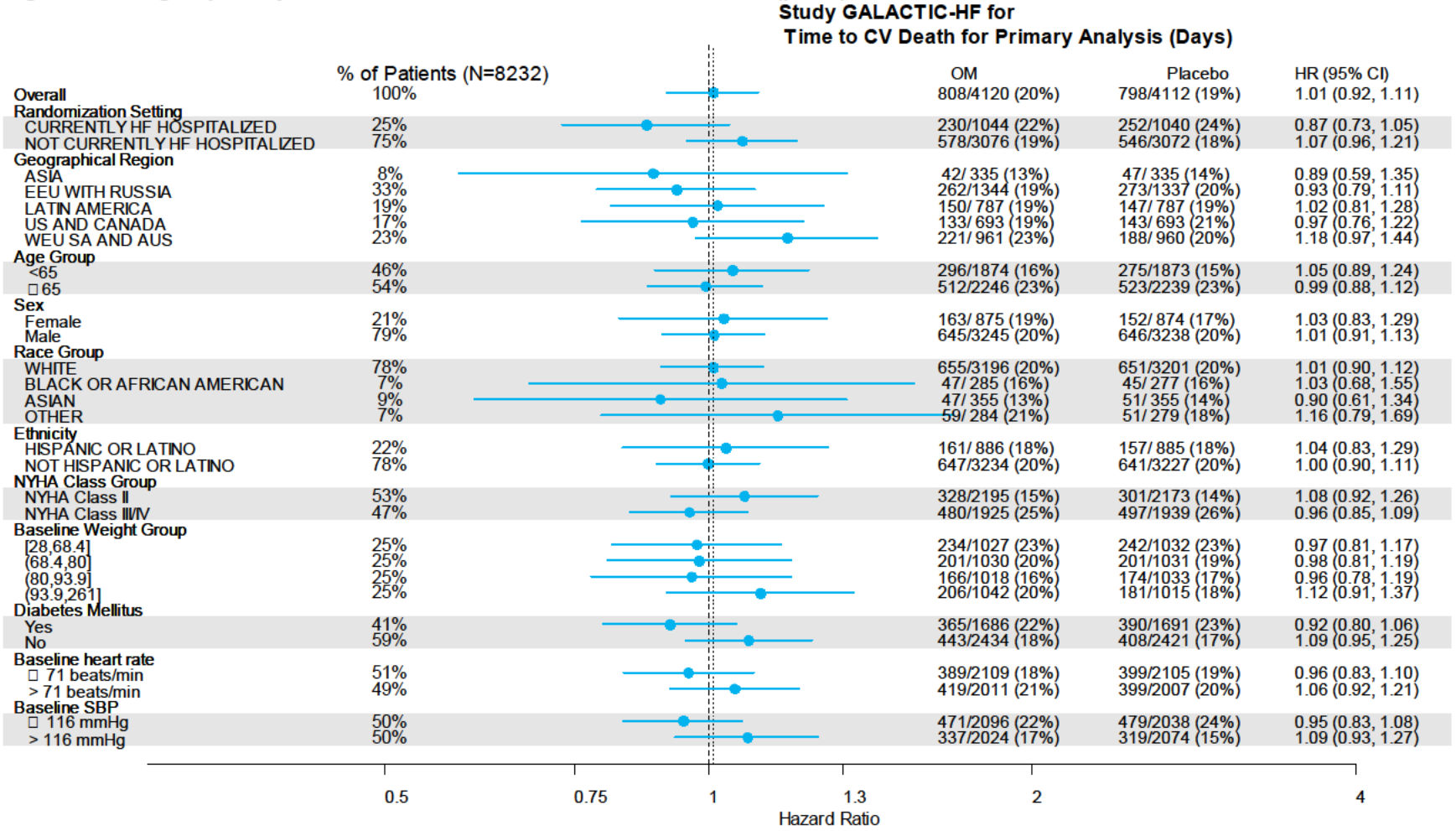
Abbreviations: FAS, full analysis set; HF, heart failure; LVEF, left ventricular ejection fraction; N, total number of randomized subjects excluding study site 29002; n, number of randomized subjects within each LVEF grouping; OM, omecamtiv mecarbil

Figure 12. FDA's Analysis of Baseline LVEF With Primary Composite Endpoint, FAS, GALACTIC-HF



Source: Statistical Reviewer
Black lines: Cox regression model including treatment, baseline LVEF modeled with a restricted cubic spline with knots chosen at 23, 28, 31 and boundary knots defined at 15 and 35, interaction of treatment with baseline LVEF splines. The black solid lines and black dotted lines correspond to the estimated hazard ratio and 95% confidence bands obtained from the Cox model.
Golden lines: Poisson regression model including treatment, baseline LVEF modeled with a restricted cubic spline with knots chosen at 23, 28, 31 and boundary knots defined at 15 and 35, interaction of treatment with baseline LVEF splines. Robust standard errors were used to obtain the standard errors. The golden solid lines and golden dotted lines correspond to the estimated hazard ratio and 95% confidence bands obtained from the Cox model.
Abbreviations: CI, confidence interval; FAS, full analysis set; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; SE, standard error

Figure 13. Subgroup Analysis for Time to CV Death, FAS, GALACTIC-HF (p. 1/2)

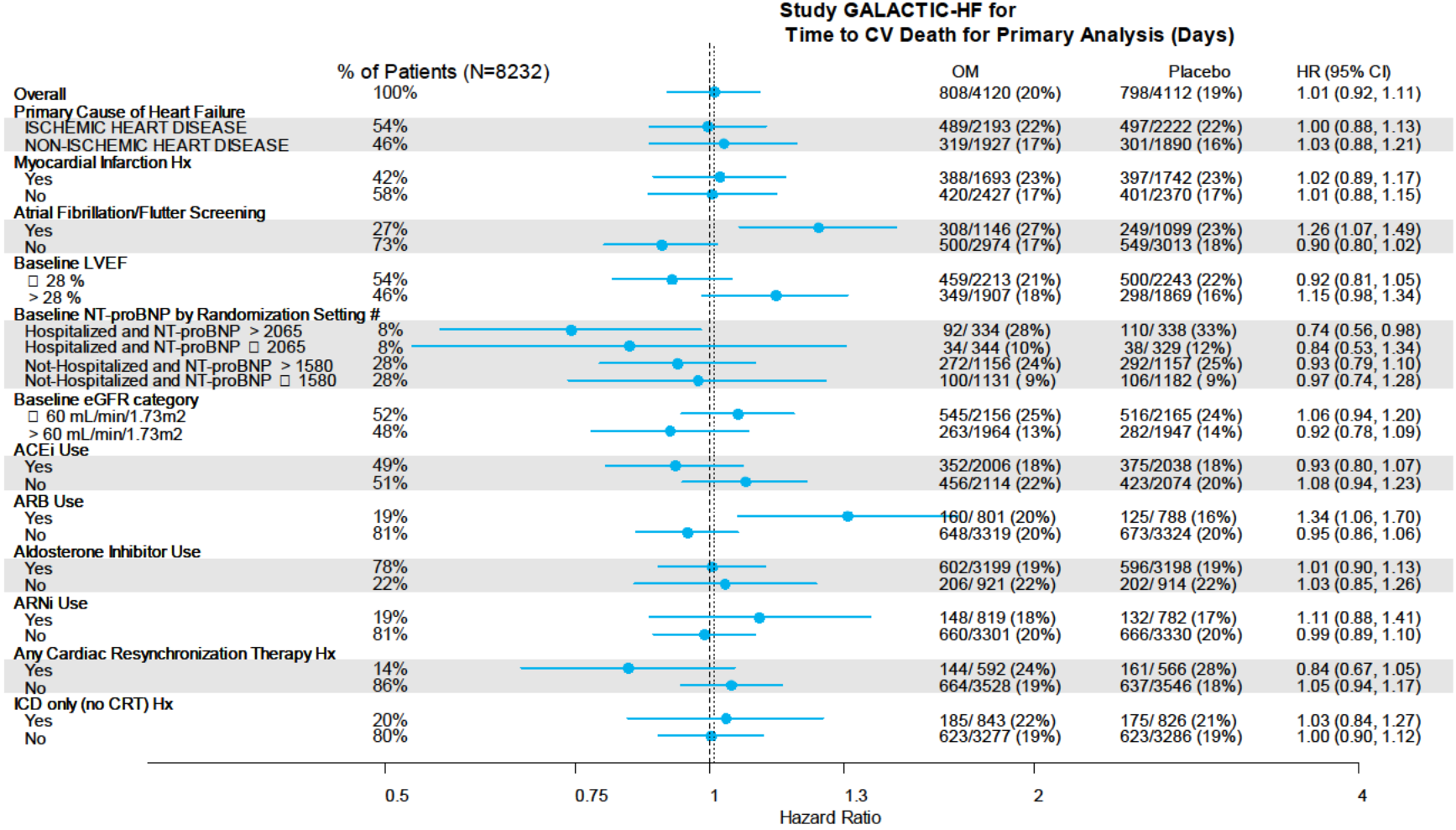


Source: Statistical Reviewer

For each arm (OM or placebo), the number of subjects with a first event/ total number of subjects within each subgroup category and percentages in parenthesis are presented.

Abbreviations: AUS, Australia; BL, baseline; CI, confidence interval/credible interval (shrinkage); CV, cardiovascular; EEU, Eastern Europe; F, female; HF, heart failure; HR, hazard ratio; M, male; N, number of subjects; NYHA, New York Heart Association; OM, omecamtiv mercabil; SA, South America; SBP, systolic blood pressure; WEU, Western Europe

Figure 14. Subgroup Analysis for Time to CV Death, FAS, GALACTIC-HF (p. 2/2)



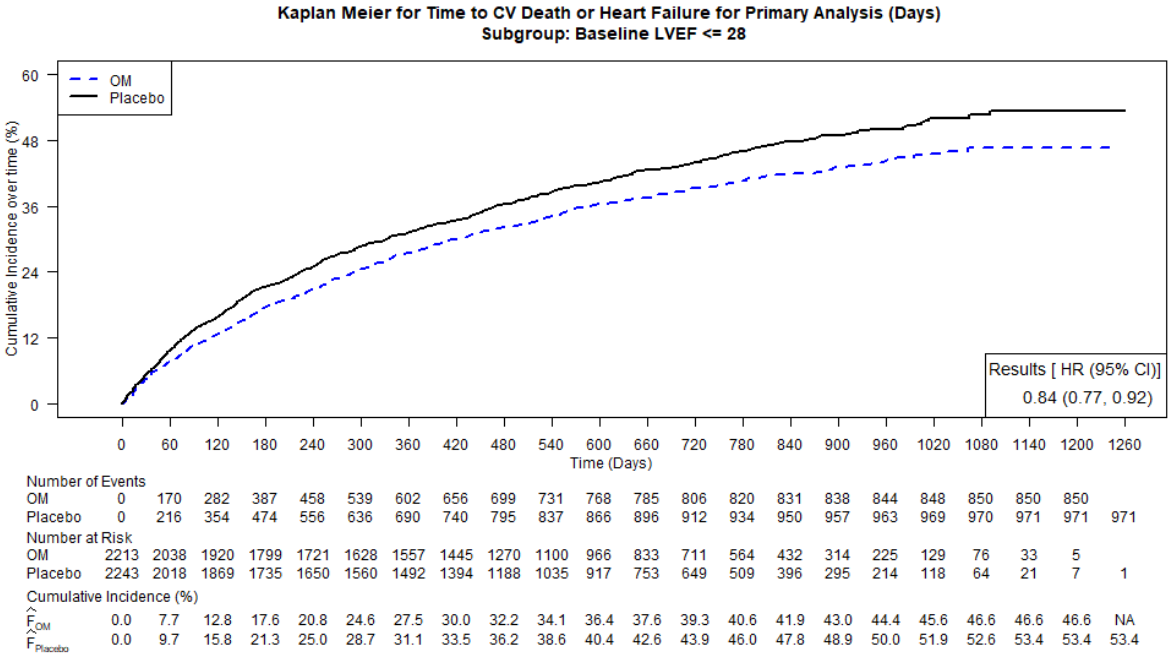
Source: Statistical Reviewer

Based only on subjects without atrial f brillation/flutter. Median NT-proBNP was obtained within each randomization setting.

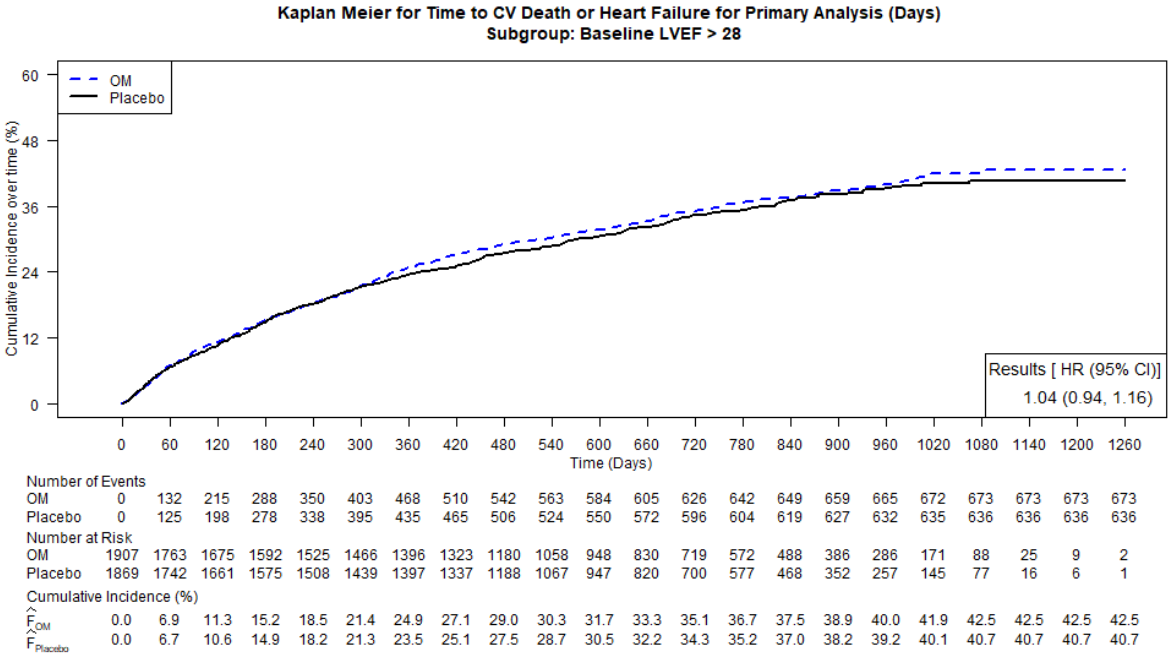
For each arm (OM or placebo), the number of subjects with a first event/ total number of subjects within each subgroup category and percentages in parenthesis are presented.

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; BL, baseline; BL HR, baseline heart rate; BL SBP, baseline systolic blood pressure; CI, confidence interval/cred ble interval (shrinkage); CRT, cardiac resynchronization therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, baseline left ventricule ejection fraction; N, number of subjects; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; OM, omecamtiv mecarbil

Figure 15. Kaplan-Meier Curves for Each Baseline LVEF Subgroup (≤28 vs. >28) for the Primary Endpoint, FAS, GALACTIC-HF



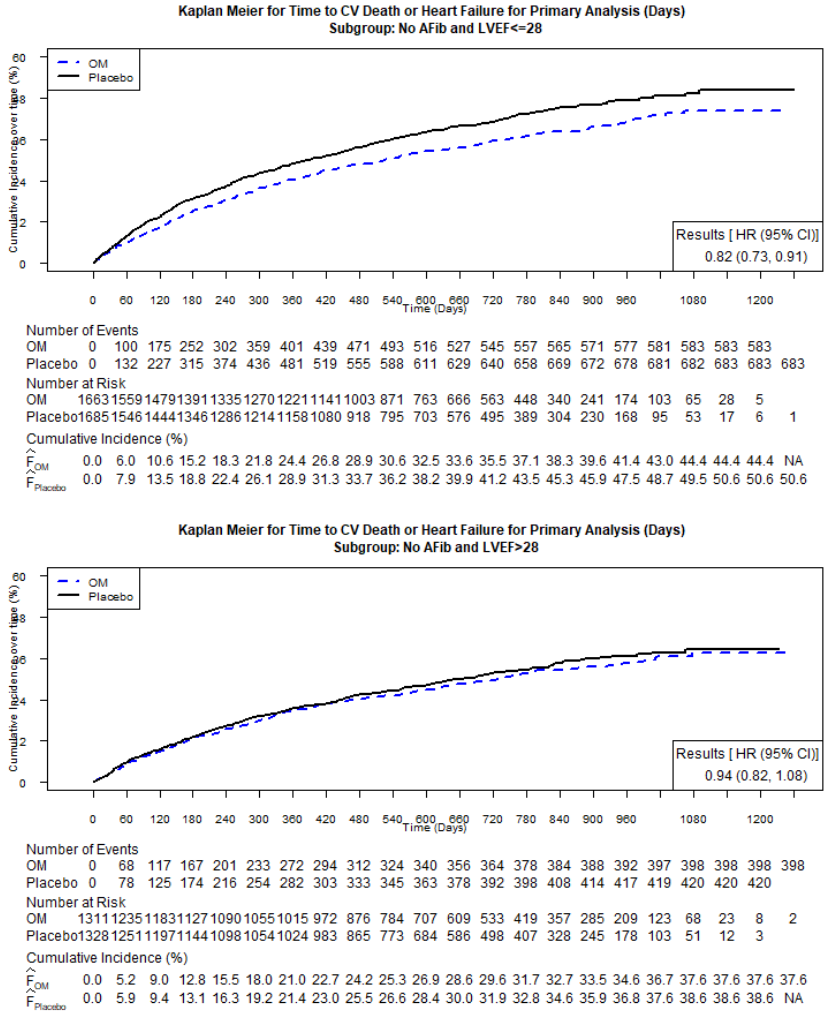
Number of Events																						
OM	0	170	282	387	458	539	602	656	699	731	768	785	806	820	831	838	844	848	850	850	850	
Placebo	0	216	354	474	556	636	690	740	795	837	866	896	912	934	950	957	963	969	970	971	971	971
Number at Risk																						
OM	2213	2038	1920	1799	1721	1628	1557	1445	1270	1100	966	833	711	564	432	314	225	129	76	33	5	
Placebo	2243	2018	1869	1735	1650	1560	1492	1394	1188	1035	917	753	649	509	396	295	214	118	64	21	7	1
Cumulative Incidence (%)																						
$\hat{F}_{OM}$	0.0	7.7	12.8	17.6	20.8	24.6	27.5	30.0	32.2	34.1	36.4	37.6	39.3	40.6	41.9	43.0	44.4	45.6	46.6	46.6	46.6	NA
$\hat{F}_{Placebo}$	0.0	9.7	15.8	21.3	25.0	28.7	31.1	33.5	36.2	38.6	40.4	42.6	43.9	46.0	47.8	48.9	50.0	51.9	52.6	53.4	53.4	53.4

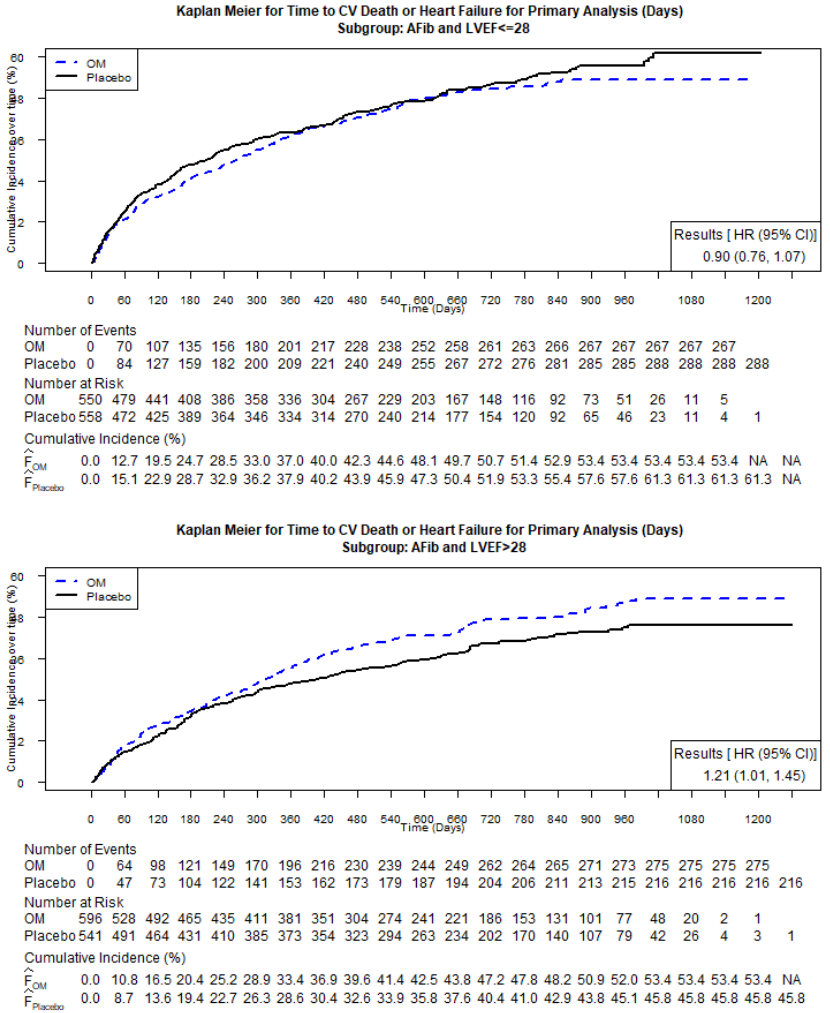


Number of Events																						
OM	0	132	215	288	350	403	468	510	542	563	584	605	626	642	649	659	665	672	673	673	673	673
Placebo	0	125	198	278	338	395	435	465	506	524	550	572	596	604	619	627	632	635	636	636	636	636
Number at Risk																						
OM	1907	1763	1675	1592	1525	1466	1396	1323	1180	1058	948	830	719	572	488	386	286	171	88	25	9	2
Placebo	1869	1742	1661	1575	1508	1439	1397	1337	1188	1067	947	820	700	577	468	352	257	145	77	16	6	1
Cumulative Incidence (%)																						
$\hat{F}_{OM}$	0.0	6.9	11.3	15.2	18.5	21.4	24.9	27.1	29.0	30.3	31.7	33.3	35.1	36.7	37.5	38.9	40.0	41.9	42.5	42.5	42.5	42.5
$\hat{F}_{Placebo}$	0.0	6.7	10.6	14.9	18.2	21.3	23.5	25.1	27.5	28.7	30.5	32.2	34.3	35.2	37.0	38.2	39.2	40.1	40.7	40.7	40.7	40.7

Source: Statistical Reviewer
Abbreviations: CI, confidence interval; CV, cardiovascular; F, cumulative incidence; FAS, full analysis set; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; N, number of randomized subjects excluding study site 29002; NA, not applicable; OM, omecamtiv mecarbil

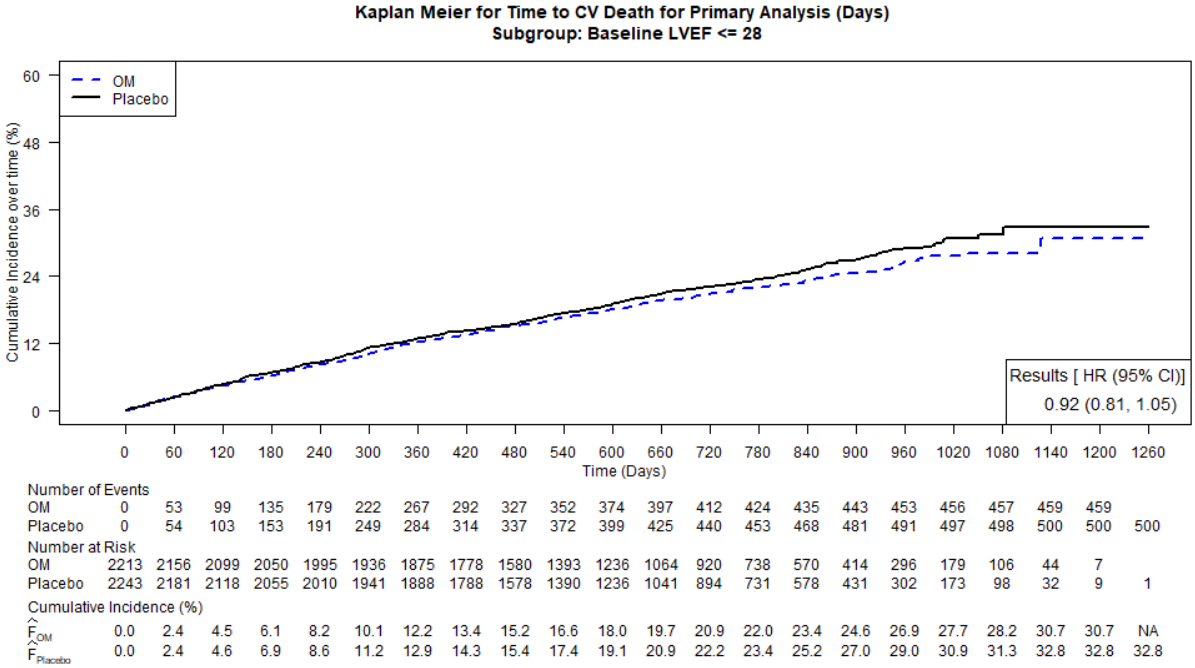
Figure 16. Kaplan-Meier Curves for Each Subgroup Combination of Atrial-Fibrillation and Baseline LVEF for the Primary Endpoint, FAS, GALACTIC-HF

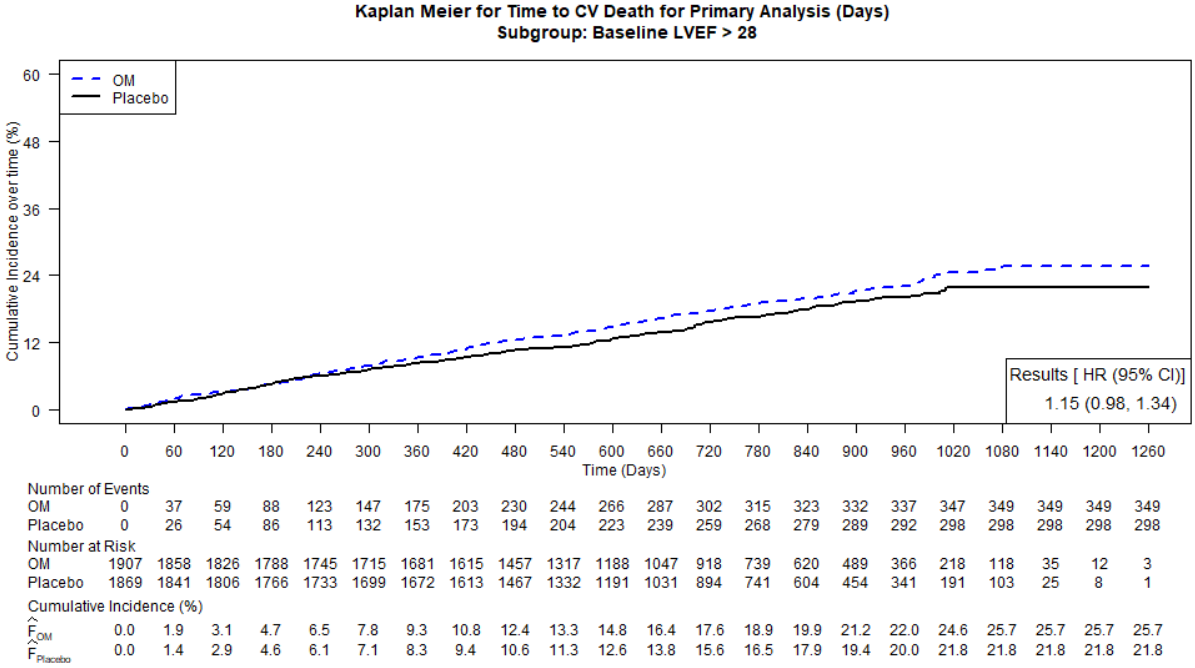




Source: Statistical Reviewer
Abbreviations: AFib, atrial fibrillation; CI, confidence interval, CV, cardiovascular; F, cumulative incidence; FAS, full analysis set; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; N, number of randomized subjects excluding study site 29002; NA, not applicable; OM, omecamtiv mecarbil

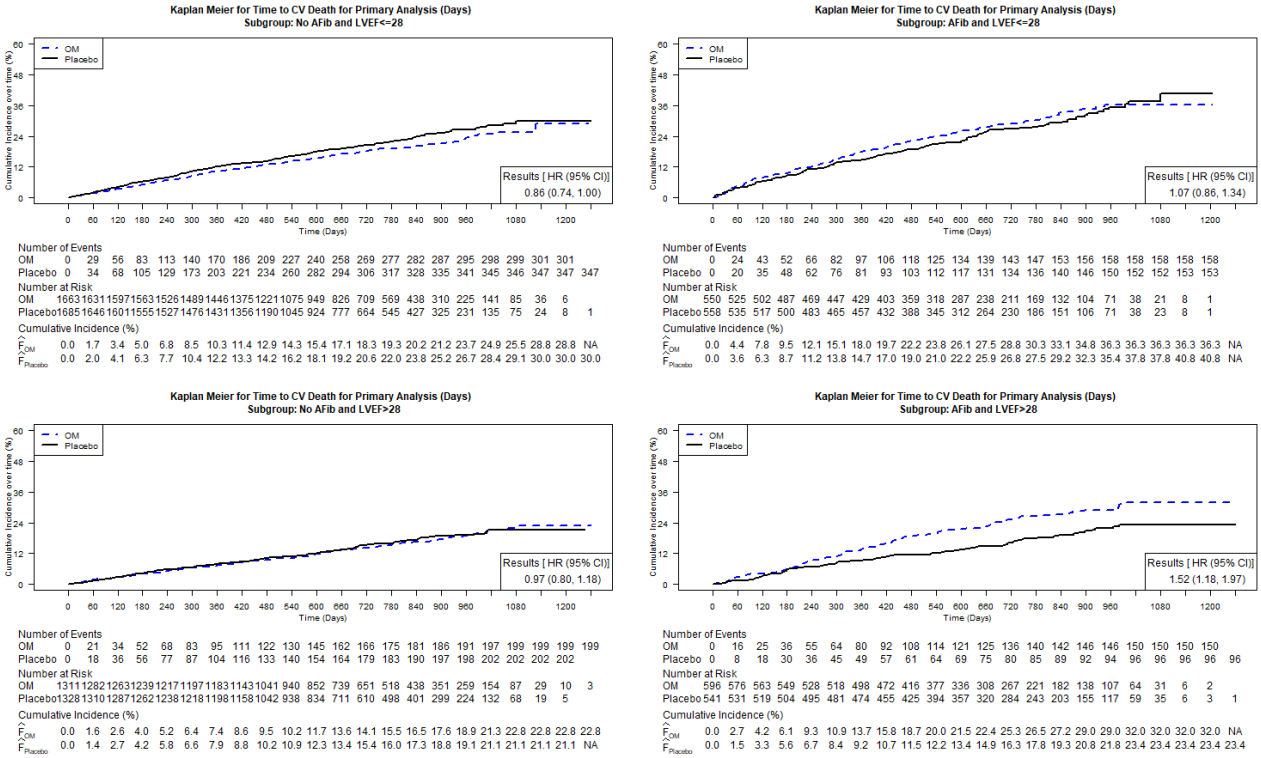
Figure 17. Kaplan-Meier Curves for Each Baseline LVEF Subgroup (≤28 vs. >28) for CV Death, FAS, GALACTIC-HF





Source: Statistical Reviewer
Abbreviations: CI, confidence interval, CV, cardiovascular; F, cumulative incidence; FAS, full analysis set; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; N, number of randomized subjects excluding study site 29002; NA, not applicable; OM, omecamtiv mecarbil

Figure 18. Kaplan-Meier Curves for Each Subgroup Combination of Atrial-Fibrillation and Baseline LVEF for the CV Death, FAS, GALACTIC-HF



Source: Statistical Reviewer
Abbreviations: CI, confidence interval, CV, cardiovascular; F, cumulative incidence; FAS, full analysis set; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; N, number of randomized subjects excluding study site 29002; NA, not applicable; OM, omecamtiv mecarbil

6.5 Safety Analysis

6.5.1 Extent of Exposure

In GALACTIC-HF, 4,110 subjects received at least one dose of OM with the median duration of exposure of 20 months. The duration of treatment exposure for GALACTIC-HF is summarized in Table 17. These durations were similar between treatment groups and sufficient to assess the safety of OM for the proposed indication.

Table 17. Duration of Exposure, Safety Population, GALACTIC-HF

Exposure	OM N=4110 n (%)	Placebo N=4101 n (%)
Duration of treatment, months		
Mean (SD)	19.5 (10.3)	19.2 (10.3)
Median (minimum, maximum)	19.9 (0.1, 41.8)	19.7 (0.0, 42.7)
Subjects treated, by duration, n (%)		
<1 month	137 (3.3%)	163 (4.0%)
≥1 month	3973 (96.7%)	3938 (96.0%)
≥3 months	3746 (91.1%)	3719 (90.7%)
≥6 months	3509 (85.4%)	3473 (84.7%)
≥12 months	3110 (75.7%)	3090 (75.3%)
≥18 months	2308 (56.2%)	2285 (55.7%)
≥24 months	1520 (37.0%)	1446 (35.3%)
≥30 months	729 (17.7%)	686 (16.7%)
≥36 months	183 (4.5%)	151 (3.7%)

Source: Reviewer's table; adsl, adexsum2; software: R
Difference is shown between OM and Placebo.
Abbreviations: CI, confidence interval; HF, heart failure; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil; SD, standard deviation

6.5.2 Death

Deaths by any cause were adjudicated efficacy endpoints and are discussed in Section 3.1.2 (Table 6). Treatment-emergent fatal adverse events (AEs) occurred with a similar incidence between treatment groups and are summarized by system organ class and preferred term in Table 18. Events within the system organ class of Cardiac Disorders comprised the most frequent causes of death (~11% in both groups). Notable treatment-emergent fatal AEs that were numerically higher (difference ≥0.5%) in the OM group compared to the placebo group was death related to cardiac failure.

Table 18. Treatment-Emergent Deaths[1] With Risk Difference ≥0.1%, Safety Population, GALACTIC-HF

Body System or Organ Class Preferred Term	OM N=4110 n (%)	Placebo N=4101 n (%)	Absolute Risk Difference (95.0% CI)[2]
Overall	837 (20.4%)	823 (20.1%)	0.3 (-1.4, 2.0)
Cardiac disorders	464 (11.3%)	452 (11.0%)	0.3 (-1.1, 1.6)
Cardiac failure (SMQ)	344 (8.4%)	324 (7.9%)	0.5 (-0.7, 1.7)
Cardiac failure acute	41 (1.0%)	28 (0.7%)	0.3 (-0.1, 0.7)
Cardiogenic shock	42 (1.0%)	30 (0.7%)	0.3 (-0.1, 0.7)
Cardiac failure congestive	24 (0.6%)	19 (0.5%)	0.1 (-0.2, 0.4)
Cardiac arrest	46 (1.1%)	42 (1.0%)	0.1 (-0.4, 0.5)
Renal and urinary disorders	14 (0.3%)	10 (0.2%)	0.1 (-0.1, 0.3)
Renal failure	3 (0.1%)	0 (0.0%)	0.1 (-0.0, 0.2)
Respiratory, thoracic and mediastinal disorders	35 (0.9%)	31 (0.8%)	0.1 (-0.3, 0.5)
Respiratory failure	8 (0.2%)	2 (0.0%)	0.1 (-0.0, 0.3)
Gastrointestinal disorders	14 (0.3%)	15 (0.4%)	-0.0 (-0.3, 0.2)
Pancreatitis acute	3 (0.1%)	0 (0.0%)	0.1 (-0.0, 0.2)
Infections and infestations	66 (1.6%)	67 (1.6%)	-0.0 (-0.6, 0.5)
Septic shock	18 (0.4%)	10 (0.2%)	0.2 (-0.1, 0.4)
COVID-19 pneumonia	4 (0.1%)	1 (0.0%)	0.1 (-0.0, 0.2)
Sepsis	16 (0.4%)	13 (0.3%)	0.1 (-0.2, 0.3)
Nervous system disorders	25 (0.6%)	27 (0.7%)	-0.1 (-0.4, 0.3)
Ischemic stroke	10 (0.2%)	6 (0.1%)	0.1 (-0.1, 0.3)
General disorders and administration site conditions	159 (3.9%)	161 (3.9%)	-0.1 (-0.9, 0.8)
Death	65 (1.6%)	49 (1.2%)	0.4 (-0.1, 0.9)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	24 (0.6%)	29 (0.7%)	-0.1 (-0.5, 0.2)
Lung neoplasm malignant	5 (0.1%)	2 (0.0%)	0.1 (-0.1, 0.2)

Source: Reviewer's table; adsl, adae; software: R
[1] This table only includes preferred terms with the difference of incidence ≥0.1% in the OM group compared to the placebo group.
[2] Difference is shown between OM and Placebo.
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HF, heart failure; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil; SMQ, Standard MedDRA Query

6.5.3 Serious Adverse Events

Overall, the incidence of serious adverse events (SAEs) was similar between treatment groups. None of the preferred terms for SAEs had a risk difference greater than 1%. SAEs of chronic obstructive pulmonary disease were reported more frequently in the OM group compared to placebo (1.5% versus 0.9%). Additional analyses revealed that this imbalance was primarily driven by the subjects with a history of chronic obstructive pulmonary disease. Among OM-treated subjects who had a SAE of chronic obstructive pulmonary disease, there were no specific patterns regarding the onset of the event nor the last OM concentration level prior to the event. No apparent safety signals were observed for other respiratory-related AEs and SAEs in GALACTIC-HF. In safety pharmacology studies, OM had no respiratory effects in rats. The totality of evidence does not indicate a major safety concern for potential adverse effects of OM on the respiratory system.

Table 19. Serious Adverse Events With Risk Difference ≥0.2%,[1] Safety Population, GALACTIC-HF

Primary System Organ Class Preferred Term	OM N=4110 n (%)	Placebo N=4101 n (%)	Absolute Risk Difference (95.0% CI)[2]
Overall	2373 (57.7%)	2435 (59.4%)	-1.6 (-3.8, 0.5)
Respiratory, thoracic and mediastinal disorders	223 (5.4%)	199 (4.9%)	0.6 (-0.4, 1.5)
Chronic obstructive pulmonary disease	63 (1.5%)	38 (0.9%)	0.6 (0.1, 1.1)
Pulmonary embolism	20 (0.5%)	13 (0.3%)	0.2 (-0.1, 0.4)
Vascular disorders	147 (3.6%)	145 (3.5%)	0.0 (-0.8, 0.8)
Hypotension	49 (1.2%)	37 (0.9%)	0.3 (-0.2, 0.7)
Gastrointestinal disorders	170 (4.1%)	168 (4.1%)	0.0 (-0.8, 0.9)
Pancreatitis acute	9 (0.2%)	2 (0.0%)	0.2 (0.0, 0.3)
General disorders and administration site conditions	250 (6.1%)	249 (6.1%)	0.0 (-1.0, 1.0)
Death	65 (1.6%)	49 (1.2%)	0.4 (-0.1, 0.9)
Metabolism and nutrition disorders	129 (3.1%)	137 (3.3%)	-0.2 (-1.0, 0.6)
Gout	14 (0.3%)	7 (0.2%)	0.2 (-0.0, 0.4)
Diabetes mellitus	15 (0.4%)	8 (0.2%)	0.2 (-0.1, 0.4)
Infections and infestations	508 (12.4%)	523 (12.8%)	-0.4 (-1.8, 1.0)
Cellulitis	34 (0.8%)	24 (0.6%)	0.2 (-0.1, 0.6)
Cardiac disorders	1713 (41.7%)	1794 (43.7%)	-2.1 (-4.2, 0.1)
Myocardial ischemia (FMQ)	222 (5.4%)	216 (5.3%)	0.1 (-0.8, 1.1)
Angina unstable	63 (1.5%)	49 (1.2%)	0.3 (-0.2, 0.8)
Acute myocardial infarction	71 (1.7%)	64 (1.6%)	0.2 (-0.4, 0.7)
Cardiogenic shock	75 (1.8%)	68 (1.7%)	0.2 (-0.4, 0.7)

Source: Reviewer's table; adsl, adae; software: R
[1] This table only includes preferred terms with the difference of incidence ≥ 0.2% in the OM group compared to the placebo group
[2] Difference is shown between OM and Placebo.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; HF, heart failure; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil

6.5.4 Adverse Events Leading to Discontinuation

The proportion of subjects who discontinued treatment due to AEs was similar between treatment groups (Table 20). A similar incidence between groups was also found for AEs of interest such as myocardial ischemia by grouping relevant terms. These data do not raise safety concerns.

Table 20. Adverse Events Leading to Discontinuation with Risk Difference ≥0.1%, Safety Population, GALACTIC-HF

Adverse Event Preferred Term	OM N=4110 n (%)	Placebo N=4101 N (%)	Risk Difference[1] (95% CI)[2]
Subjects with at least 1 AE leading to discontinuation	432 (10.5%)	447 (10.9%)	-0.4 (-1.7, 0.9)
Cardiac failure	95 (2.3%)	81 (2.0%)	0.3 (-0.3, 1.0)
Angina unstable	13 (0.3%)	7 (0.2%)	0.1 (-0.1, 0.4)
Hypotension	8 (0.2%)	3 (0.1%)	0.1 (-0.0, 0.3)
Angina pectoris	9 (0.2%)	4 (0.1%)	0.1 (-0.1, 0.3)
Fatigue	5 (0.1%)	1 (0.0%)	0.1 (-0.0, 0.2)
Pruritus	5 (0.1%)	1 (0.0%)	0.1 (-0.0, 0.2)
Dysphagia	3 (0.1%)	0 (0.0%)	0.1 (-0.0, 0.2)
Myalgia	3 (0.1%)	0 (0.0%)	0.1 (-0.0, 0.2)
Pleural effusion	3 (0.1%)	0 (0.0%)	0.1 (-0.0, 0.2)
Acute coronary syndrome	5 (0.1%)	2 (0.0%)	0.1 (-0.1, 0.2)
Renal impairment	7 (0.2%)	4 (0.1%)	0.1 (-0.1, 0.2)
Sepsis	7 (0.2%)	4 (0.1%)	0.1 (-0.1, 0.2)
Grouped preferred term			
Myocardial ischemia (FMQ)	40 (1.0%)	33 (0.8%)	0.2 (-0.2, 0.6)

Source: Reviewer's table; adsl, adae; software: R
[1] Risk difference ≥0.1.
[2] Difference is shown between OM and Placebo.
Abbreviations: AE, adverse event; CI, confidence interval; HF, heart failure; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil; FMQ, FDA Medical Query

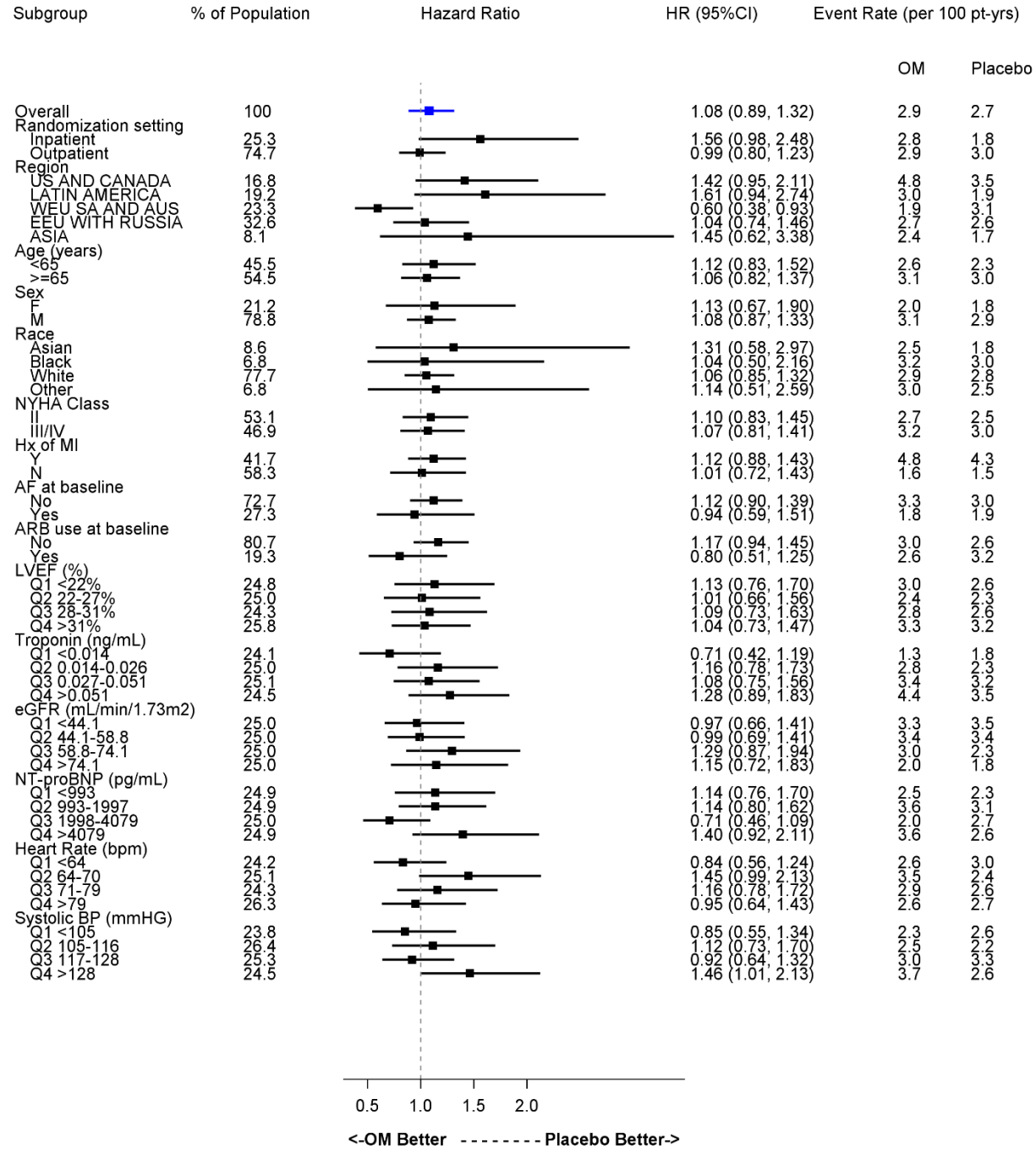
6.5.5 Safety Endpoint

6.5.5.1 Major Cardiac Ischemic Events

Major cardiac ischemic events were adjudicated in GALACTIC-HF and included fatal and nonfatal MI, hospitalization for unstable angina, and coronary revascularization (coronary artery bypass graft surgery [CABG] or percutaneous coronary intervention). During the review, we noted that not all adjudicated CV deaths due to an acute MI were included as a major cardiac ischemic event. FDA's analysis of major cardiac ischemic events was based on the revised data with addition of the previously omitted CV deaths due to MI from the original dataset. Hence the results presented in this section are slightly different from the results reported in the GALACTIC-HF clinical study report. Overall, the risk of experiencing major cardiac ischemic events was similar between treatment groups in the GALACTIC-HF study under the trial's PK-guided dosing strategy (Table 8). Additional analyses based on the on-treatment events (first dose date to last dose date +30 days) for these safety endpoints showed similar results.

Subgroup analyses of major cardiac ischemic events by baseline characteristics of interest were explored (Figure 19). Overall, the results were consistent across most of the subgroups with an hazard ratio (HR) around 1. As shown in Figure 19, subgroups that appeared to be at greater risk (HR >1.5) with OM compared to placebo included inpatient subjects (HR: 1.6 [95% confidence interval (CI): 1.0, 2.5]) and subjects from Latin America (HR: 1.6 [95% CI: 0.9, 2.7]). Both subgroups had the wide confidence intervals resulting from low numbers of events in a smaller subset. Subjects with a history of MI and a higher troponin level at baseline had a numerically higher but not markedly increased risk of major cardiac ischemic events in the OM group compared to the placebo group.

Figure 19. Subgroup Analysis for Adjudicated Major Cardiac Ischemic Event, Safety Population, GALACTIC-HF



Reviewer's Figure Source: adall, adtte2; software: SAS
Abbreviations: AF, atrial f brillation/flutter at screening; ARB, angiotensin II receptor blocker; BP, blood pressure; CI, confidence interval; EEU, Eastern Europe; eGFR, estimated glomerular filtration rate; F, female; HF, heart failure; HR, hazard ratio; Hx of MI, history of myocardial infarction; LVEF, left ventricular ejection fraction; M, male; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; OM, omecamtiv mecarbil; pt-yrs, patient-years; Q, quarter; WEU SA AND AUS, Western Europe, South Africa and Australia

6.5.5.2 *Ventricular Arrhythmias Requiring Treatment*

The incidence of SAEs of ventricular arrhythmias requiring any therapeutic intervention was similar between the OM group and the placebo group (~4% in each group) (Table 21). There were no differences between treatment groups regarding the nature or the severity of the event. Similar to the major cardiac ischemic events, the incidence of these events was slightly higher in the OM group compared to the placebo group among the inpatient subjects.

Table 21. Incidence of Serious Adverse Events of Ventricular Arrhythmias Requiring Treatment, Safety Population, GALACTIC-HF

	Inpatient		Outpatient		Total	
SAE	OM (N=1040) n (%)	Placebo (N=1034) n (%)	OM (N=3070) n (%)	Placebo (N=3067) n (%)	OM (N=4110) n (%)	Placebo (N=4101) n (%)
Number of subjects reporting SAEs of ventricular arrhythmias requiring any treatment	45 (4.3)	32 (3.1)	119 (3.9)	143 (4.7)	164 (4.0)	175 (4.3)
External electrical cardioversion/defibrillation, including ICD discharge or anti-tachycardia pacing	36 (3.5)	25 (2.4)	88 (2.9)	109 (3.6)	124 (3.0)	134 (3.3)
Initiation, reinstitution, or intensification of chronic anti-arrhythmic therapy	28 (2.7)	18 (1.7)	66 (2.1)	81 (2.6)	94 (2.3)	99 (2.4)
Ventricular arrhythmia ablation	7 (0.7)	5 (0.5)	20 (0.7)	20 (0.7)	27 (0.7)	25 (0.6)
Implantation of ICD	9 (0.9)	2 (0.2)	19 (0.6)	30 (1.0)	28 (0.7)	32 (0.8)
SAE was sustained ventricular tachycardia or fibrillation	39 (3.8)	31 (3.0)	104 (3.4)	130 (4.2)	143 (3.5)	161 (3.9)
SAE was symptomatic	39 (3.8)	32 (3.1)	97 (3.2)	126 (4.1)	136 (3.3)	158 (3.9)

Source: Reviewer's table; adsl, adtac; Software: OCS Analysis Studio, Custom Table Tool
Abbreviations: HF, heart failure; ICD, implantable cardioverter-defibrillator; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with at least one event; OM, omecamtiv mecarbil; SAE, serious adverse event

6.5.6 Adverse Events of Interest

An evaluation of AEs of interest including myocardial ischemia and arrhythmia related events using FDA Medical Queries[11] is summarized in Table 22. A numerically higher incidence of myocardial ischemia related FDA Medical Queries events was observed with OM compared to placebo. Myocardial ischemic-related AEs include events with mild and moderate severity that did not meet the definition of major cardiac ischemic events. There was no difference between groups for arrhythmia-related AEs.

[11] FDA Medical Queries (FMQs) are standardized groupings of similar AE terms intended to assist with the identification of potential safety issues during review of AE data.

Table 22. Adverse Events of Interest, Safety Population, GALACTIC-HF

FMQ (Narrow) Most Common Preferred Term	OM (N=4110) n (%)	Placebo (N=4101) n (%)	Risk Difference (95% CI)
Myocardial ischemia	306 (7.4)	271 (6.6)	0.8 (-0.3, 1.9)
Angina pectoris	118 (2.9)	87 (2.1)	0.7 (0.1. 1.4)
Arrhythmia	677 (16.5)	708 (17.3)	-0.8 (-2.4, 0.8)
Atrial fibrillation	236 (5.7)	263 (6.4)	-0.7 (-1.7, 0.4)
Tachycardia	260 (6.3)	289 (7.0)	-0.7 (-1.8, 0.4)
Ventricular tachycardia	173 (4.2)	184 (4.5)	-0.3 (-1.2, 0.6)

Source: Reviewer's table; adsl, adae; Software: OCS Analysis Studio, Custom Table Tool
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; HF, heart failure; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil

The differences in the incidence of myocardial ischemia events between groups was primarily driven by a higher frequency of angina pectoris and unstable angina reported in the OM group compared to the placebo group (Table 23). The incidence of myocardial ischemia SAEs was similar between groups.

Table 23. Myocardial Ischemia-Related TEAEs, Safety Population, GALACTIC-HF

	OM N=4110 n (%)	Placebo N=4101 n (%)	Absolute Risk Difference[1] (95.0% CI)
Myocardial ischemia (FMQ)	306 (7.4%)	271 (6.6%)	0.8 (-0.3, 1.9)
Angina pectoris	118 (2.9%)	87 (2.1%)	0.7 (0.1, 1.4)
Angina unstable	68 (1.7%)	52 (1.3%)	0.4 (-0.1, 0.9)
Acute myocardial infarction	72 (1.8%)	68 (1.7%)	0.1 (-0.5, 0.7)
Acute coronary syndrome	14 (0.3%)	12 (0.3%)	0.0 (-0.2, 0.3)
Postinfarction angina	1 (0.0%)	0 (0.0%)	0.0 (-0.0, 0.1)
Myocardial ischemia	16 (0.4%)	15 (0.4%)	0.0 (-0.2, 0.3)
Serious	222 (5.4%)	216 (5.3%)	0.1 (-0.8, 1.1)
Fatal outcome	41 (1.0%)	40 (1.0%)	0.0 (-0.4, 0.4)
Life-threatening	49 (1.2%)	68 (1.7%)	-0.5 (-1.0, 0.0)
Requiring hospitalization	193 (4.7%)	187 (4.6%)	0.1 (-0.8, 1.0)
Persist or significant disability/incapacity	9 (0.2%)	17 (0.4%)	-0.2 (-0.4, 0.0)
Other	20 (0.5%)	33 (0.8%)	-0.3 (-0.7, 0.0)
Resulting in discontinuation	40 (1.0%)	33 (0.8%)	0.2 (-0.2, 0.6)
Maximum severity			
Mild	31 (0.8%)	10 (0.2%)	0.5 (0.2, 0.8)
Moderate	56 (1.4%)	45 (1.1%)	0.3 (-0.2, 0.7)
Severe	130 (3.2%)	113 (2.8%)	0.4 (-0.3, 1.1)
Life-threatening	48 (1.2%)	63 (1.5%)	-0.4 (-0.9, 0.1)
Death	41 (1.0%)	40 (1.0%)	0.0 (-0.4, 0.4)

Source: adsl, adae; software: R
[1] Absolute risk difference >0.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; HF, heart failure; N, number of subjects in treatment arm excluding study site 29002; n, Number of subjects with an event; OM, omecamtiv mecarbil; TEAE, treatment-emergent adverse event

6.5.7 Treatment-Emergent Adverse Events

Subjects in the OM group compared to the placebo group reported more AEs (risk difference >0.5%) related to dizziness, myocardial ischemia and hypotension. The observed AEs for dizziness and hypotension were generally reported to be mild or moderate in severity. Additional information on these events is provided below.

Table 24. FDA MedDRA Queries[1] Occurring at 0.3% Higher Frequency with OM Than Placebo, Safety Population, GALACTIC-HF

System Organ Class *FDA Medical Query (Narrow)[3]* Preferred Term	OM N=4110 n (%)	Placebo N=4101 n (%)	Absolute Risk Difference (95% CI)[4]
General disorders and administration site conditions			
Dizziness	331 (8.1%)	290 (7.1%)	1.0 (-0.2, 2.1)
Dizziness	237 (5.8%)	189 (4.6%)	1.2 (0.2, 2.1)
Vascular disorders			
Hypotension[5]	394 (9.6%)	354 (8.6%)	1.0 (-0.3, 2.2)
Hypotension	309 (7.5%)	271 (6.6%)	0.9 (-0.2, 2.0)
Dehydration	55 (1.3%)	30 (0.7%)	0.6 (0.2, 1.0)
Cardiac disorders			
Myocardial ischemia	306 (7.4%)	271 (6.6%)	0.8 (-0.3, 1.9)
Angina pectoris	118 (2.9%)	87 (2.1%)	0.7 (0.1, 1.4)
Angina unstable	68 (1.7%)	52 (1.3%)	0.4 (-0.1, 0.9)
Musculoskeletal and connective tissue disorders			
Back pain	152 (3.7%)	137 (3.3%)	0.4 (-0.4, 1.2)
Nervous system disorders			
Syncope	120 (2.9%)	107 (2.6%)	0.3 (-0.4, 1.0)
Syncope	120 (2.9%)	107 (2.6%)	0.3 (-0.4, 1.0)
Renal and urinary disorders			
Acute kidney injury	256 (6.2%)	243 (5.9%)	0.3 (-0.7, 1.3)

Source: Reviewer's table; adsl, adae; software: R
[1] Absolute risk difference >0.3%.
[2] Treatment-emergent AEs defined as occurring within 30 days after last treatment.
[3] Version 2020_01_29.
[4] Difference is shown between OM and Placebo.
[5] Based on Hypotension FMQ (broad) which includes the following preferred terms: hypotension, dehydration, orthostatic. hypotension, hypovolemia, blood pressure decreased, blood pressure systolic decreased and blood pressure abnormal
Abbreviations: AE, adverse event; CI, confidence interval; FDA, Food and Drug Administration; FMQ, FDA Medical Query; HF, heart failure; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil

Dizziness

There was a greater incidence of dizziness in subjects who received OM compared to placebo (331 [8%] versus 288 [7%]). No difference was observed between the groups regarding the incidence of dizziness SAEs and the frequency of dizziness AEs resulting in discontinuation.

Hypotension/Dehydration

An imbalance in AEs for "Hypotension" FDA Medical Query (broad) was observed in the OM group compared to the placebo group (10% versus 9%). This small difference was driven by the preferred term "hypotension" (risk difference of 0.9) and "dehydration" (risk difference of 0.6). Only eight events, all hypotension, in the OM group (compared to three in the placebo group) resulted in discontinuation of study treatment.

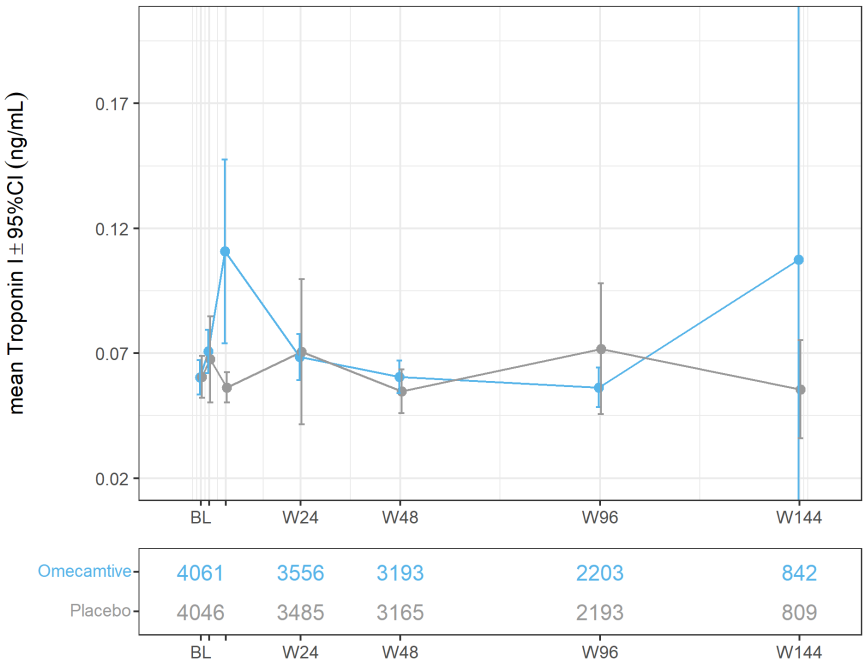
Using the narrow FDA medical query for hypotension, the difference between the groups was smaller (8.5% versus 7.9%). Blood pressure (BP) changes based on vital sign data are discussed in Section 6.5.9. Overall, the vital sign data did not suggest that OM decreases BP adversely.

6.5.8 Laboratory Findings

Cardiac Biomarkers

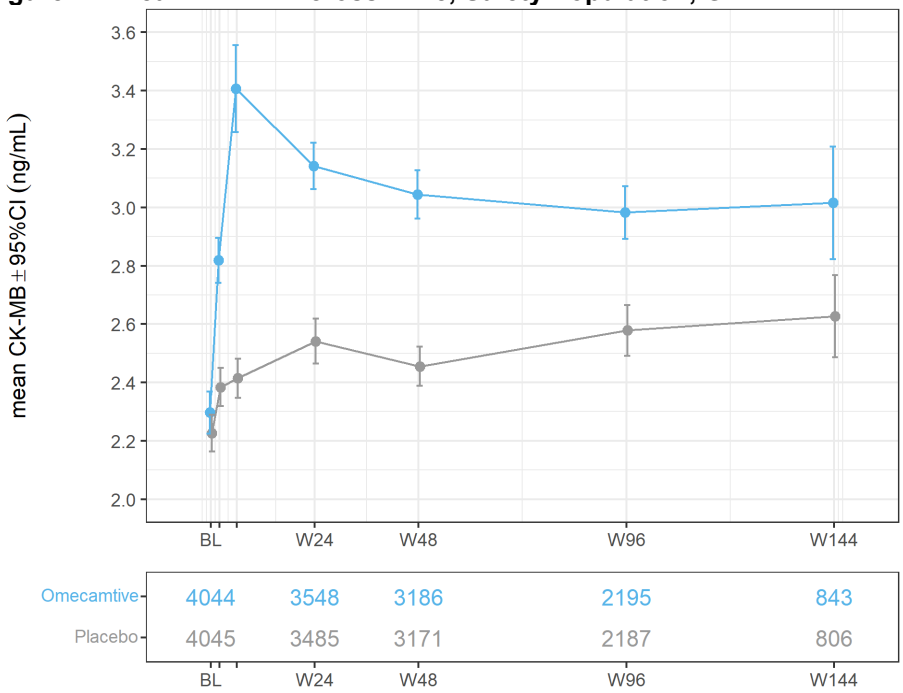
Troponin-I and creatine kinase-MB (CK-MB) were collected at baseline and at Weeks 2, 6, 24, and 48, and every 48 weeks thereafter through the duration of GALACTIC-HF. Small increases from baseline were observed in the OM group starting at Week 2 with the peak increase at Week 6 for both troponin-I and CK-MB (Figure 20 and Figure 21). It should be noted that the Week 6 measurement was the last measure before subjects could potentially be down-titrated at Week 8. The small increases in troponin-I were observed in both baseline troponin-I subgroups (>0.04 ng/mL and ≤0.04 ng/mL). In the OM group, the median changes from baseline at Week 6 were 0.017 ng/mL and 0.007 ng/mL for subjects with baseline troponin >0.04 ng/mL and ≤0.04 ng/mL, respectively.

Figure 20. Mean Troponin-I Across Time, Safety Population, GALACTIC-HF



Source: Reviewer's figure; adsl, ad b; software: R
Abbreviations: BL, baseline; CI, confidence interval; HF, heart failure; W, week

Figure 21. Mean CK-MB Across Time, Safety Population, GALACTIC-HF



Source: Reviewer's figure; adsl, ad b; software: R
Abbreviations: BL, baseline; CI, confidence interval; CK-MB, creatine kinase-myoglobin binding; HF, heart failure; W, week

Table 25 shows the group difference across study visits in troponin-I using a repeated measure model including treatment group and analysis visit as factors and troponin-I at baseline as a covariate. The increase of geometric mean ratio from baseline in troponin-I after OM treatment was about 40% greater than placebo at Week 6 and about 20 to 25% greater at other visits. Table 26 shows a similar analysis for CK-MB.

Table 25. Between-Group Comparisons of Changes From Baseline in Troponin-I Across Study Visits, Safety Population, GALACTIC-HF

	OM N=4110		Placebo N=4010		OM vs. Placebo
Analysis Visit (Week)	n	Mean Ratio to Baseline (SE)[1]	n	Mean Ratio to Baseline (SE)[1]	Geometric Mean Ratio (95% CI)[1]
Week 2	3883	1.18 (0.01)	3904	1.00 (0.01)	1.19 (1.16,1.22)
Week 6	3808	1.37 (0.01)	3828	0.97 (0.01)	1.41 (1.37,1.44)
Week 24	3523	1.23 (0.01)	3476	0.98 (0.01)	1.26 (1.23, 1.29)
Week 48	3427	1.17 (0.01)	3458	0.97 (0.01)	1.21 (1.17, 1.24)

Source: Reviewer's table; adsl, adlb; software: SAS
[1] Difference is derived from the mixed model for repeated measurement with data up to Week 48 fitted with changes from baseline in log-transformed troponin-I as a function of treatment group, scheduled visit, treatment group, interaction between treatment group and scheduled visit, and log-transformed baseline troponin-I. Results are presented after back-transformation of change from baseline in log-transformed troponin-I to original scale and hence reported as a ratio.
Abbreviations: CI, confidence interval; HF, heart failure; N, number of subjects with at least one dose of investigational product excluding study site 29002; n=number of subjects with an assessment; OM, omecamtiv mecarbil; SE, standard error

Table 26. Between-Group Comparisons of Changes From Baseline in CK-MB Across Study Visits, Safety Population, GALACTIC-HF

Analysis Visit (Week)	OM N=4110 n	OM N=4110 Mean Ratio to Baseline (SE)[1]	Placebo N=4010 n	Placebo N=4010 Mean Ratio to Baseline (SE)	OM vs. Placebo Geometric Mean Ratio (95% CI)[1]
Week 2	3958	1.27 (0.008)	3961	1.08 (0.008)	1.18 (1.16,1.20)
Week 6	3865	1.53 (0.008)	3877	1.10 (0.008)	1.39 (1.37, 1.42)
Week 24	3574	1.44 (0.008)	3521	1.16 (0.008)	1.25 (1.22, 1.27)
Week 48	3478	1.40 (0.008)	3493	1.15 (0.008)	1.21 (1.19,1.24)

Source: Reviewer's table; adsl, adlb; software: SAS
[1] Difference is derived from the mixed model for repeated measurement with data up to Week 48 fitted with changes from baseline in log-transformed CK-MB as a function of treatment group, scheduled visit, treatment group, interaction between treatment group and scheduled visit, and log-transformed baseline CK-MB. Results are presented after back-transformation of change from baseline in log-transformed troponin-I to original scale and hence reported as a ratio.
Abbreviations: CI, confidence interval; CK-MB, creatine kinase-myoglobin binding; HF, heart failure; N, number of subjects with at least one dose of investigational product excluding study site 29002; n=number of subjects with an assessment; OM, omecamtiv mecarbil; SE, standard error

Consistent with small increases observed for troponin-I and CK-MB, more subjects in the OM group met abnormality criteria for troponin-I compared to the placebo group (Table 27). There was a lower incidence of subjects meeting abnormality criteria for CK-MB in both groups, with an imbalance particularly noted for the proportion of subjects with CK-MB <3× ULN. Analyses of laboratory data for other clinical chemistry and hematology parameters from the GALACTIF-HF study did not raise safety concerns.

Table 27. Subjects Meeting Abnormality Criteria for CK-MB and Troponin-I, Safety Population, GALACTIC-HF

Abnormality Criterion	OM N=4110 n (%)	Placebo N=4101 n (%)	Absolute Risk Difference (95.0% CI)[1]
CK-MB, high, (ng/mL)			
Level 1 (>3× ULN)	56 (1.4%)	34 (0.8%)	0.5 (0.1, 1.0)
Level 2 (>5× ULN)	16 (0.4%)	8 (0.2%)	0.2 (-0.0, 0.4)
Level 3 (>10× ULN)	3 (0.1%)	1 (0.0%)	0.0 (-0.0, 0.1)
Troponin-I, high, (ng/mL)			
Level 1 (>3× ULN)	930 (22.6%)	667 (16.3%)	6.4 (4.7, 8.1)
Level 2 (>5× ULN)	470 (11.4%)	380 (9.3%)	2.2 (0.9, 3.5)
Level 3 (>10× ULN)	199 (4.8%)	172 (4.2%)	0.6 (-0.3, 1.5)
Troponin-I, high, (ng/mL)			
>0.04	2532 (61.6%)	2036 (49.6%)	12.0 (9.8, 14.1)
>0.10	1128 (27.4%)	839 (20.5%)	7.0 (5.1, 8.8)
>0.20	467 (11.4%)	380 (9.3%)	2.1 (0.8, 3.4)
>0.40	201 (4.9%)	169 (4.1%)	0.8 (-0.1, 1.7)

Source: Reviewer's table; adsl, adlb; software: R
[1] Difference is shown between OM and Placebo.
Abbreviations: CI, confidence interval; CK-MB, creatine kinase-myoglobin binding; HF, heart failure; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil; SAE, serious adverse event; ULN, upper limit of normal

6.5.9 Vital Signs

Blood Pressure

The mean baseline values were similar between the OM and placebo groups for both systolic and diastolic BP. Figure 22 shows the time-course plots for mean changes in systolic and diastolic BP values

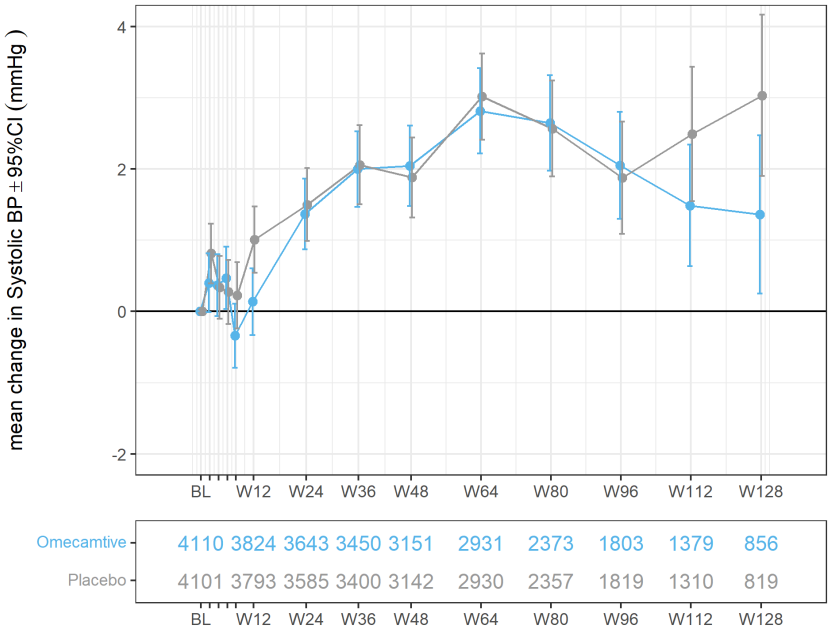
from baseline at each scheduled visit. Overall, the changes from baseline in systolic and diastolic BP were similar between groups. There were also no imbalances in systolic or diastolic BP outliers.

Heart Rate

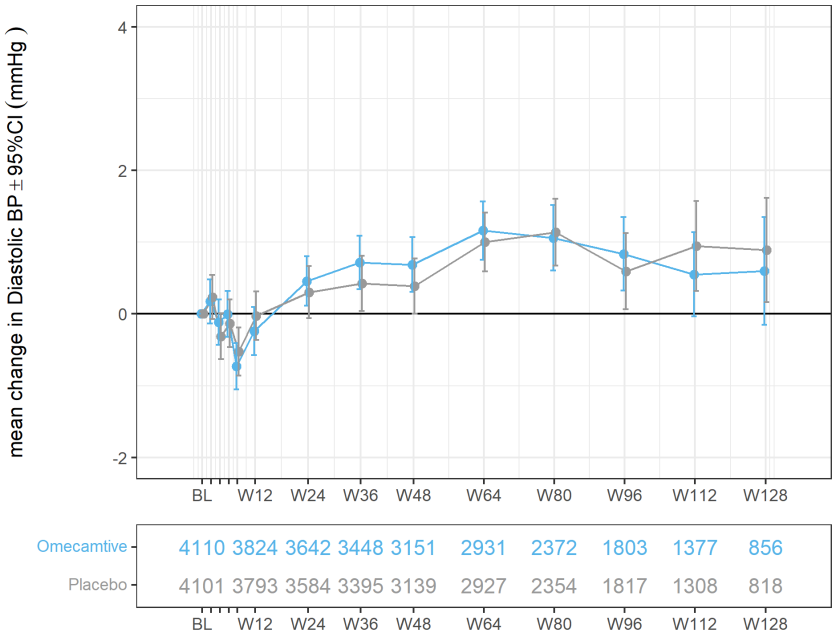
A small decrease in heart rate was observed in the OM group compared to the placebo group (Figure 23). The difference between groups across time was on average about 1 to 2 bpm.

Figure 22. Mean Change from Baseline in (a) Systolic BP and (b) Diastolic BP by the Scheduled Visits, Safety Population, GALACTIC-HF

(a)

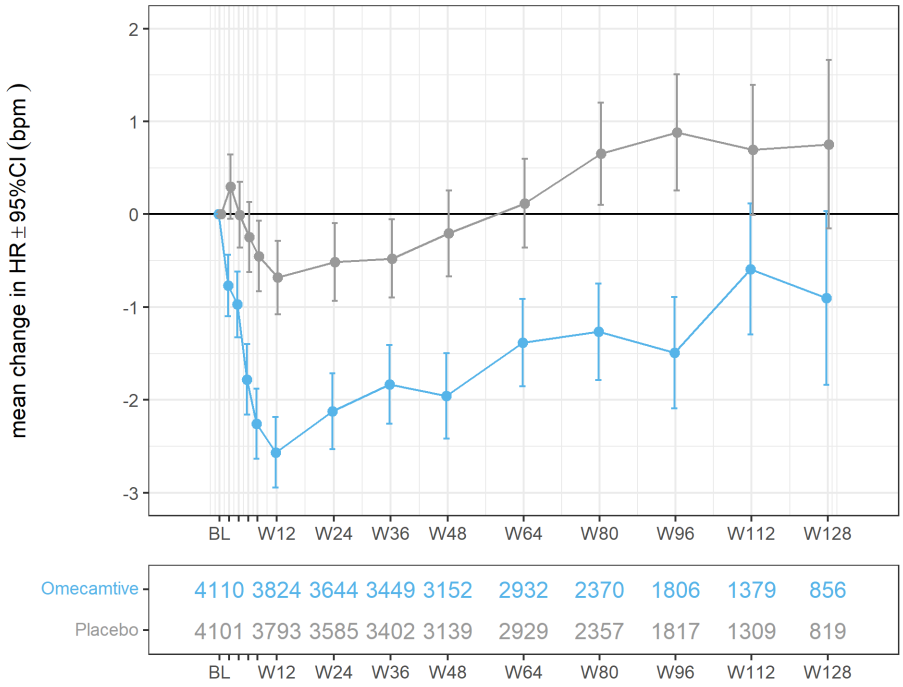


(b)



Source: adsl, advs; software: R
Abbreviations: BL, baseline; BP, blood pressure, CI, confidence interval; HF, heart failure; W, week

Figure 23. Mean Change from Baseline in Heart Rate by Scheduled Visit, Safety Population, GALACTIC-HF



Source: adsl, advs; software: R
Abbreviations: BL, baseline; CI, confidence interval; HR, heart rate; W, week

6.5.10 Clinical Findings Related to Excessive Exposure

The clinical risk associated with excessive exposure from the OM clinical program is described below.

Early Phase 1 and 2 Studies

Myocardial ischemia including myocardial infarction due to excessive concentrations of OM (C_{max} >1000 ng/mL) was reported in five participants in early clinical studies with the OM IV formulation. Three events were identified in healthy participants in the first-in-human study; the intended dose of the OM IV formulation for these participants was subsequently proven to be intolerable. The other two events were observed in subjects with HFrEF. Overall, these events occurred within hours after initiation of OM and were generally accompanied with clinical symptoms of chest pain/discomfort, palpitations, feeling hot and increased heart rate with or without elevated troponin level >0.4 ng/mL. All the events seemed to resolve soon after discontinuation of study drug and initiation of medical treatments.

Phase 2b Studies in Subjects with HFrEF

Study 2012077

This double-blind, placebo-controlled study randomized subjects into three OM groups (25 mg BID, 25 to 37.5 mg BID, or 25 to 50 mg BID) or placebo. PK-guided titration was implemented to up-titrate subjects in the 25 to 37.5 mg BID or 25 to 50 mg BID group if their OM concentration was <200 ng/mL at Week 4. We identified a 75-year-old Asian female with HFrEF who was erroneously up-titrated to 50 mg BID and had elevated plasma OM concentrations. She experienced SAEs of angina (Day 33) and cardiac failure (Day 98) during the study. Her plasma concentration of OM was measured with a value of

1050 ng/mL 4 days after hospital admission for cardiac failure SAE. Her troponin-I and NT-proBNP levels were increased in association with high OM concentrations (Figure 24). The investigator reported that there is a possibility that both SAEs of angina pectoris and exacerbation of HF may be related to OM because of the "mechanism of IP (i.e., investigational product) and high capacity exposure." (See Appendix 6.5.11 for narrative and clinical profile of this patient). There were no other subjects with a plasma concentration >750 ng/mL in this study under the PK-guided titration strategy.

COSMIC-HF

Administration of OM 50 mg BID without a PK-guided titration was studied in the COSMIC-HF trial. The COSMIC-HF trial consisted of a Dose-Escalation period in which subjects were randomized to receive 1 of 3 oral formulations of OM or placebo for 7 days in 2 Cohorts (Cohort 1: 25 mg BID; Cohort 2: 50 mg BID).

During this short study period, no SAE was reported in the placebo group in both Cohorts, and 2 possibly drug-related SAEs (2/11, 18%) were reported in the 50 mg Matrix F1 group (M-F1, the chosen MR formulation for the GALACTIC-HF trial) that led to study drug discontinuation. One SAE of unstable angina, later adjudicated as MI was associated with excessive exposure of OM (C_{trough} of 1130 ng/mL and C_{max} of 1320 ng/mL on the day of the event). This subject also had elevated troponin-I and NT-proBNP from baseline. Another SAE of myocardial ischemia with elevated troponin occurred without excessive exposure (C_{trough} of 300 ng/mL) (see Appendix 6.5.12 for more details on these two SAEs).

We noted that another subject in the OM 50 mg BID M-F1 group prematurely discontinued treatment because she met the protocol-specified criteria for drug discontinuation. She experienced a symptomatic decrease in systolic BP <80 mm Hg at three successive time points over 15 minutes. Her C_{trough} at the time of the event was 469 ng/mL. No data were available for her troponin-I and NT-proBNP level.

A higher incidence of AEs was also reported in the 50 mg M-F1 group (9/11, 82%) and pooled 50 mg group (17/36, 47%) compared to the placebo group (1/10, 10%) in Cohort 2 during the Dose-Escalation period in the COSMIC-HF trial (Table 31). Relevant AEs in addition to the two aforementioned SAEs reported in the OM 50 mg group included palpations, hypotension and increased NT-proBNP. It is noted that an AE of increased NT-proBNP (6290 pg/mL from a baseline value of 2516 pg/mL) accompanied by an elevated troponin-I level (>0.4, the baseline level was not available) occurred in a subject on Day 7 of the Dose-Escalation phase. The C_{trough} on the day of the event was 471 ng/mL and C_{max} was 601 ng/mL.

Given the safety concern, a PK-guided titration was explored in the Expansion Period (20 weeks of treatment) of the COSMIC-HF trial and the safety profile of OM under this PK-guided dosing was acceptable compared to the placebo group.

Phase 3 GALACTIC-HF Trial

Under the PK-guided dosing, the median plasma OM concentration was maintained in the range of about 250 to 300 ng/mL in the GALACTIC-HF trial and >90% of subjects had OM exposure <500 ng/mL at any study visit. There were three subjects with OM concentrations >1000 ng/mL; two subjects were on OM 50 mg BID and one patient was on OM 25 mg BID. One of these subjects had excessive OM concentrations at Week 6 that resulted in down-titration (50 mg to 25 mg). The other two subjects had excessive concentrations after Week 12 resulting in discontinuation of OM treatment. No apparent SAEs occurred ±30 days at the time when OM concentrations >1000 ng/mL were measured in these subjects. It is however noted that one subject on 50 mg BID experienced cardiac failure SAE (Day 771) during the

time when her OM concentration increased from 453 ng/mL on Day 675 to 1158 ng/mL on Day 1010. Her NT-proBNP, but not troponin-I, was also elevated during this time (Figure 25). The other subject had a concurrent hypotension AE during the time when the OM concentration was increased. The investigator thought the hypotension AE was related to OM. Her troponin-I was also elevated with the increased OM concentrations (Figure 26).

Additional Analyses:

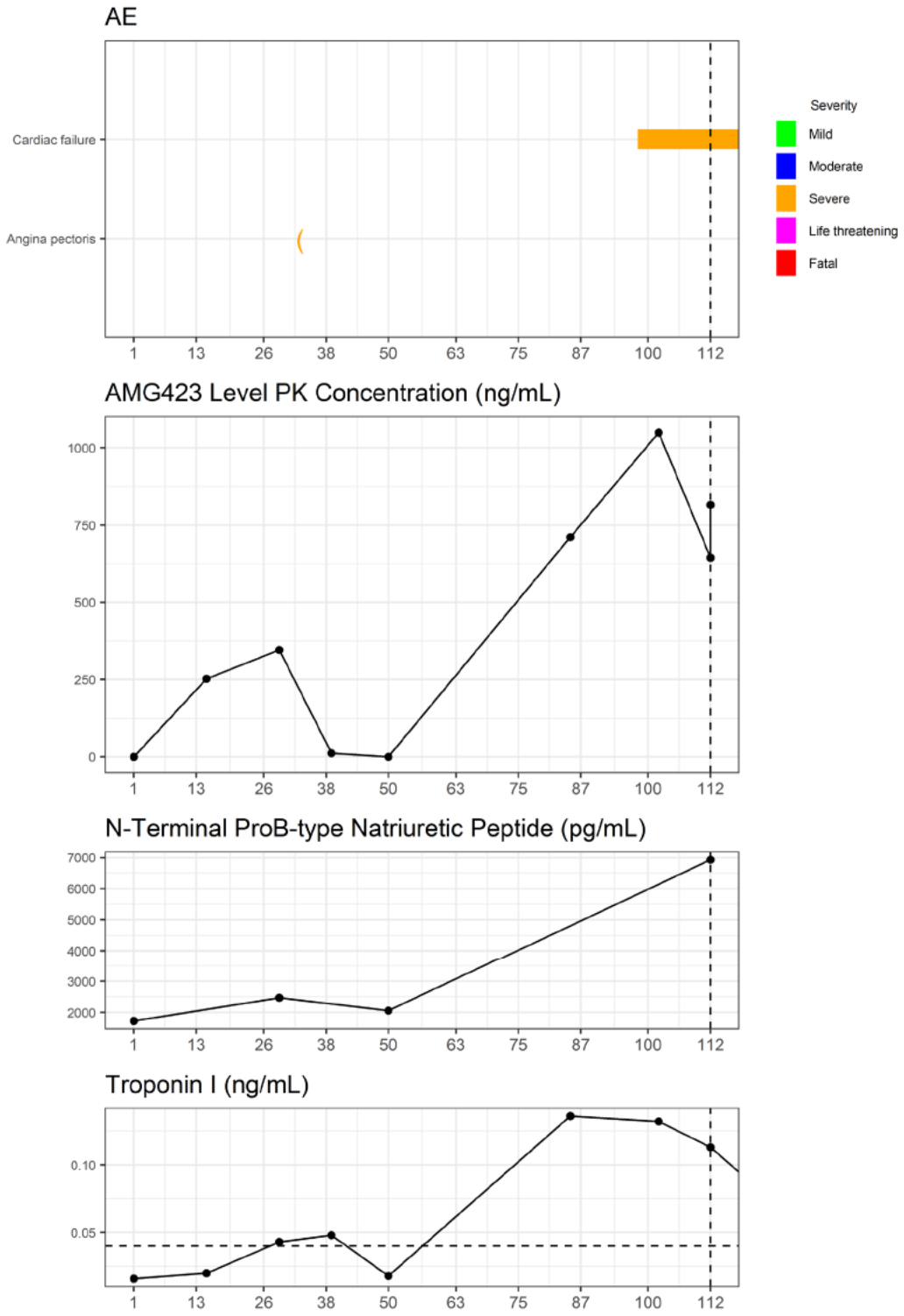
Considering safety signals observed from the Phase 2 studies, the FDA conducted exploratory analyses to evaluate the safety profile of subjects who had elevated plasma OM concentrations. The FDA identified a total of 61 subjects (1.5%) who had at least one plasma OM concentration >750 ng/mL at any point in time from the GALACTIC-HF trial. The incidence and event rates of cardiac failure AE, SAE and fatal events in this subset were higher compared to the overall trial results (Table 32). Related AEs such as hypotension and peripheral edema were also reported more frequently in this subset compared to the overall results (Table 33). The FDA further reviewed the clinical profile of these subjects with a focus on those with fatal outcome. Associations among cardiac markers (troponin-I, NT-proBNP), plasma concentrations of OM and clinical AEs (e.g., cardiac failure) were observed in many subjects. Four of fifteen fatal SAEs occurred within 6 months after the initiation of OM (see Appendix 6.5.13 Figure 27 to Figure 30 for the clinical profiles of these subjects). Among nine subjects who had a plasma concentration measured >750 ng/mL prior to Week 8 resulting in dose down-titration, a corresponding decline in troponin-I and/or NT-proBNP with decreased OM concentrations was observed.

6.5.11 Case Review in Study 20120227

Narrative Review

A 75-year-old Asian female (Baseline eGFR: 44 mL/min/1.73 m^2, troponin-I: 0.02 ng/mL, weight: 86 lb., NYHA Class III, no history of atrial fibrillation or atrial flutter [AFF]) in Study 20120227 was uptitrated to receive a dose of 50 mg BID erroneously based on an incorrect PK entry (instead of receiving the 25 mg BID) at Week 4. C_{trough} of 346 ng/mL was measured at Week 4 before the uptitration. Several days after uptitration, the patient experienced an SAE of angina pectoris with an elevated troponin-I of 1.2 pg/mL, which resulted in hospitalization and dose interruption. The OM concentration was not available at the time of the event. The study drug was interrupted, and the ischemic symptoms were considered resolved three weeks after elective percutaneous coronary intervention and stent implantation. The subject subsequently resumed OM 50 mg BID and C_{trough} at Week 12 was 711 ng/mL. Consequently, the subject experienced palpitations after light laborious work for about 1 week and was hospitalized with exacerbation of HF. Treatment with OM was not changed due to the event. An unscheduled PK was measured during hospitalization and revealed a value of 1050 ng/mL. The subject's NT-proBNP was elevated to a value of 6924 pg/mL from a baseline value of 1729 pg/mL. The event of HF did not resolve until the end of the study. Treatment included tolvaptan and febuxostat. The last C_{trough} at Week 16 was 644 ng/mL. The subject's clinical profile demonstrated that her troponin-I and NT-proBNP levels were increased in association with high OM concentrations (Figure 24). After informing the investigator of the dosing and PK information, the investigator reported that there is a possibility that both SAEs of angina pectoris and exacerbation of HF may be related to OM because of the "mechanism of IP and high capacity exposure."

Figure 24. Clinical Profile of Subject (b) (6) in Study 20120227



Source: adsl, adae, adlb; software: R; X-axis is study day
Abbreviation: AE, adverse event; AMG423, omecamtiv mecarbil; PK, pharmacokinetics

6.5.12 Case Review in COSMIC-HF

SAE of Unstable Angina in the Dose-Escalation Phase

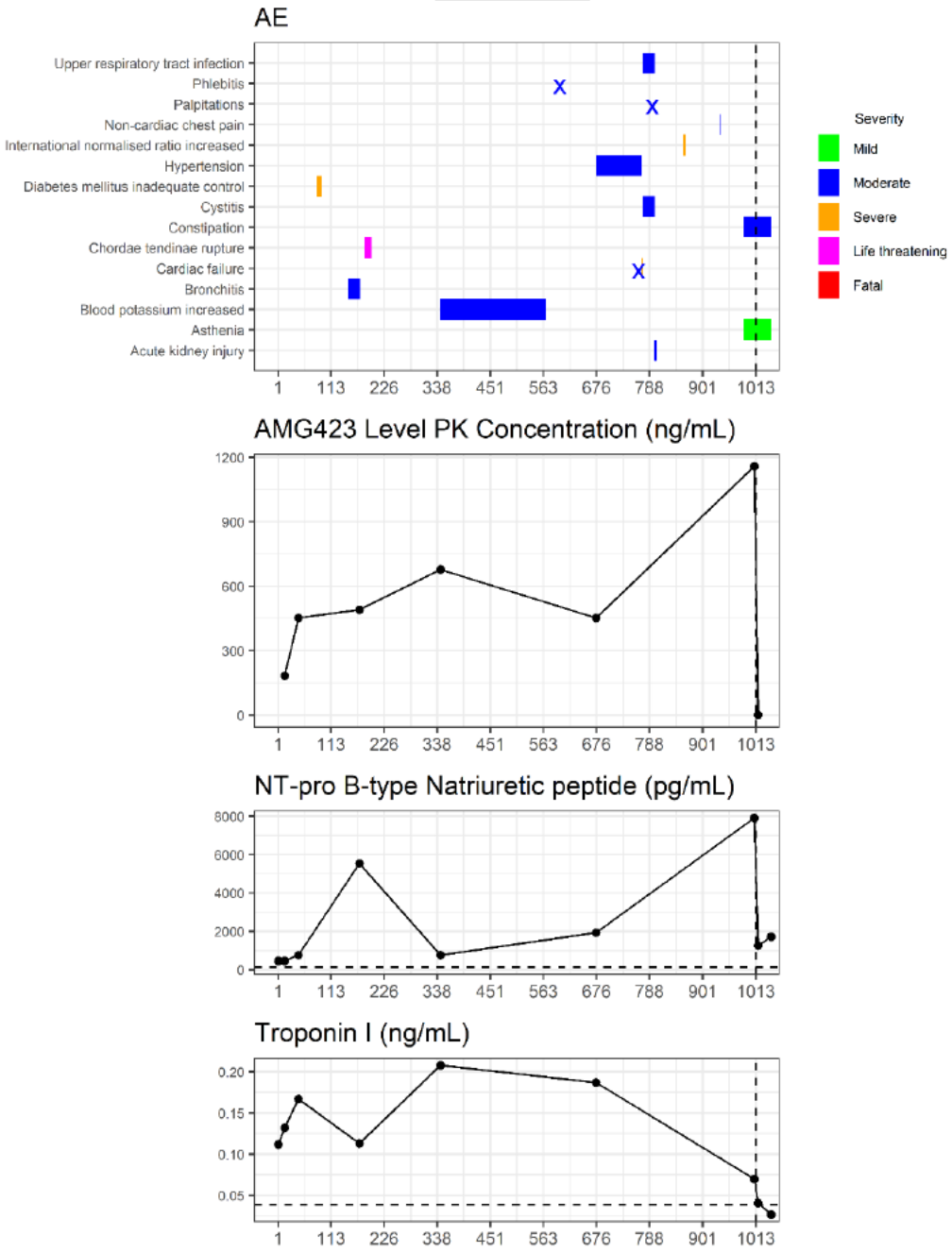
This event occurred in a 62-year-old Caucasian woman (baseline eGFR: 45 mL/min/1.73 m^2, troponin-I: 0.3 ng/mL, weight: 95 lb., NYHA Class II, no AFF at screening) who presented with sudden chest pain, accompanied by palpitations, and increased heart rate on Day 7 of the Dose-Escalation phase of the study. This SAE was later adjudicated as MI. Elevated troponin-I (>0.4) and NT-proBNP (17,662 pg/mL from baseline of 8645 pg/mL) were also reported. The subject had OM C_{trough} of 1130 ng/mL and C_{max} of 1320 ng/mL on the day of the event. OM was discontinued due to the event. The subject was hemodynamically stable after treatment and the unstable angina event was considered resolved on the same day. The subject was monitored in the cardiac intensive care for treatment and was discharged 3 days after the event.

SAE of Myocardial Ischemia in the Dose-Escalation Phase

This SAE of myocardial ischemia with elevated troponin level occurred in a 64-year-old Caucasian man (Baseline eGFR: 67 mL/min/1.73 m^2, troponin-I: 0.05 ng/mL, weight: 212 lb., NYHA Class III, no AFF at screening) on Day 5 of the Dose-Escalation phase. The subject experienced warm feeling in his body, and hot flash and subsequently developed new-onset diarrhea, mid-abdominal cramp, discomfort in his throat, and left-sided chest pain radiating to the left arm and shoulder. He was hospitalized due to suspected myocardial ischemia. OM was discontinued due to the event. This event was later adjudicated as chest pain as it did not meet the criteria for MI or unstable angina. OM C_{trough} on the day of the event was 300 ng/mL. Given the temporal relationship, the contributing role of OM in this SAE cannot be ruled out.

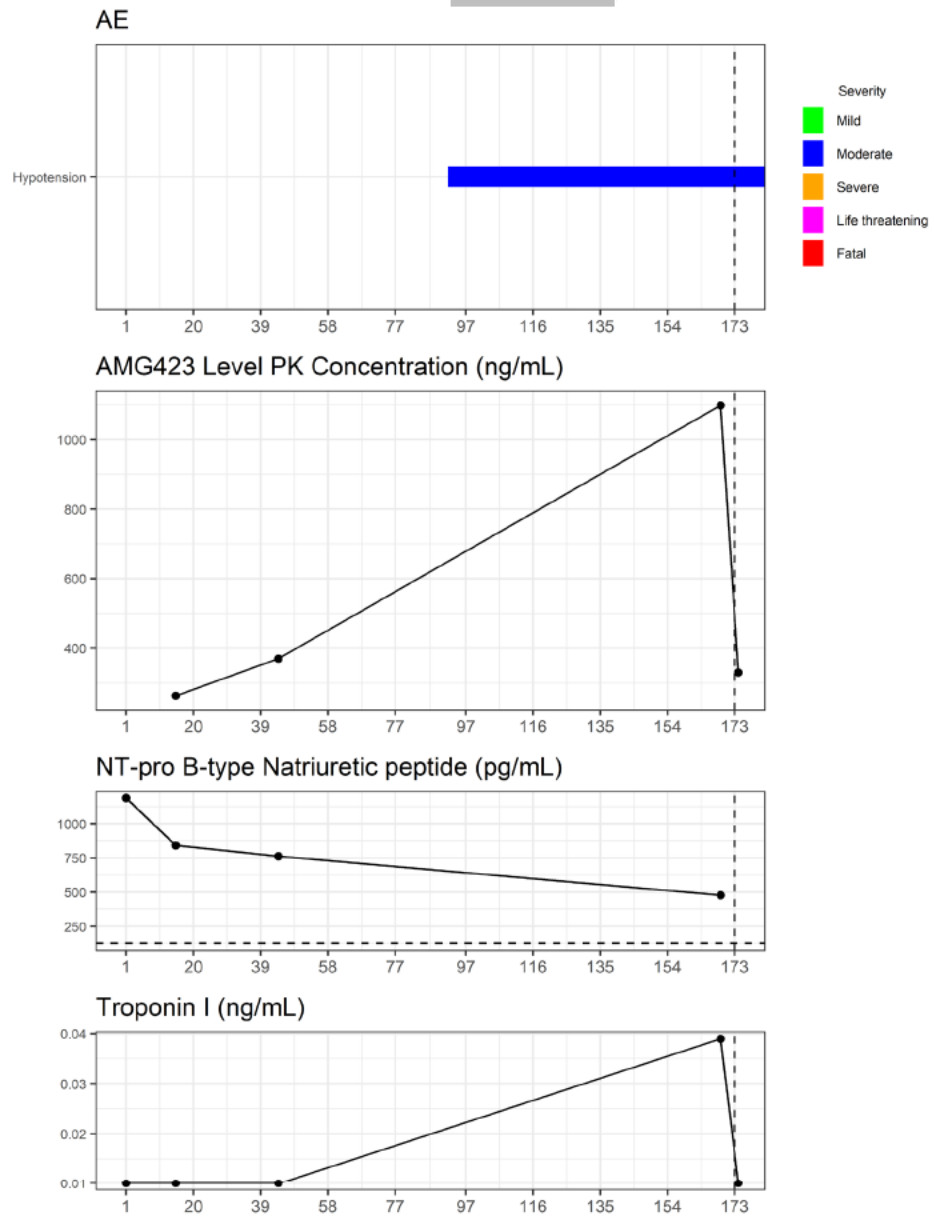
6.5.13 Case Review in GALACTIC-HF

Figure 25. Clinical Profile of Subject (b) (6) (PK >1000), GALACTIC-HF



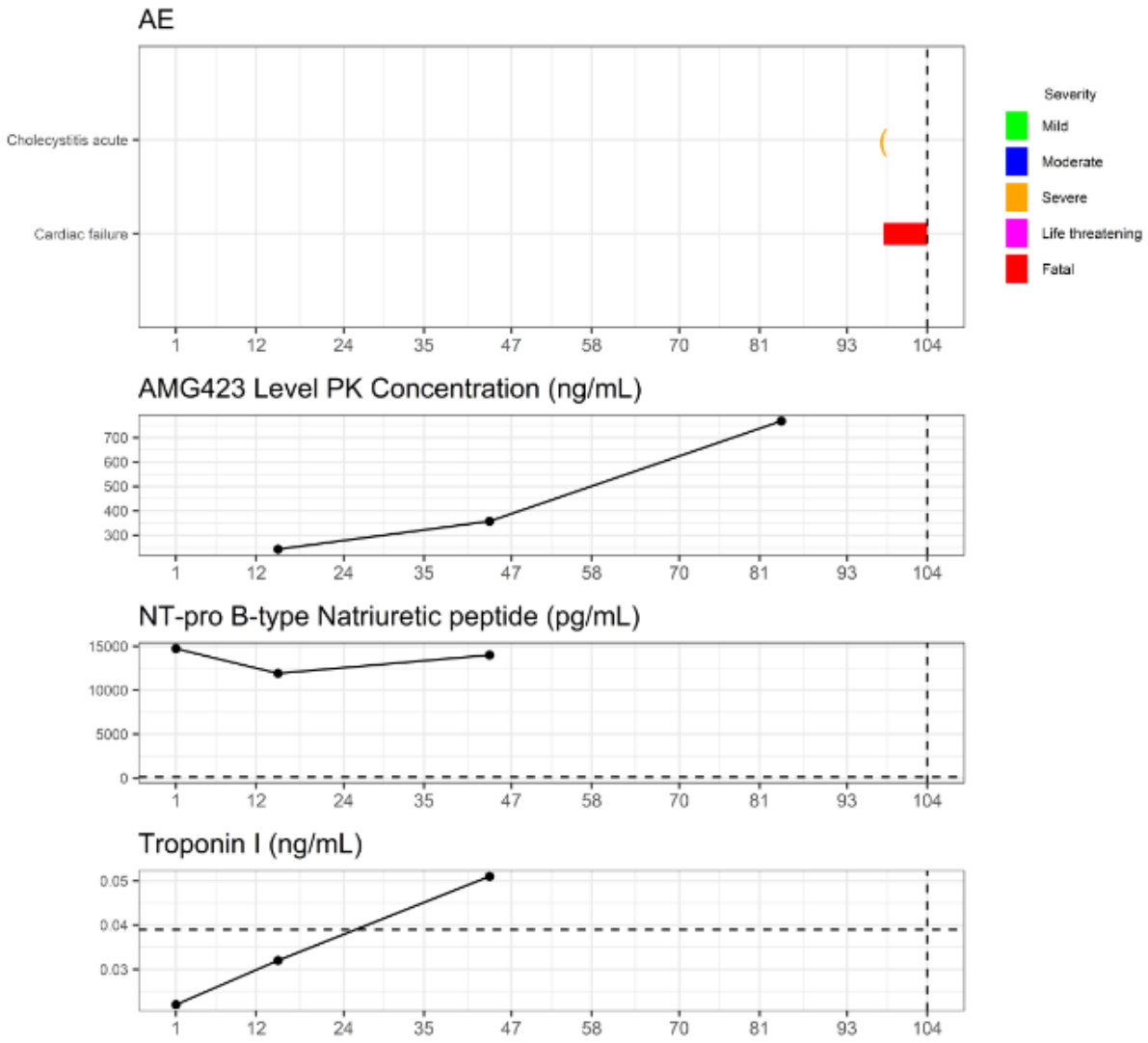
Source: adsl, adae, adlb, and adpc; software: R; X-axis is study day
This subject was a 62-year-old white female (baseline LVEF 30%, NYHA Class II, eGFR: 69 mL/min/1.73 m^2, troponin-I: 0.11 ng/mL, weight: 146 lb., no AFF at screening). She was uptitrated to 50 mg BID at Week 4 and her PK was maintained in the range of 450-600 ng/mL but had a significant elevation on Day 1013. This subject experienced a cardiac failure SAE, palpation AE, and acute kidney injury AE about seven months prior to the peak OM concentration. Her NT-proBNP increased with increasing OM concentration.
Abbreviations: AE, adverse event; HF, heart failure; PK, pharmacokinetics

Figure 26. Clinical Profile of Subject (b) (6) (PK >1000), GALACTIC-HF



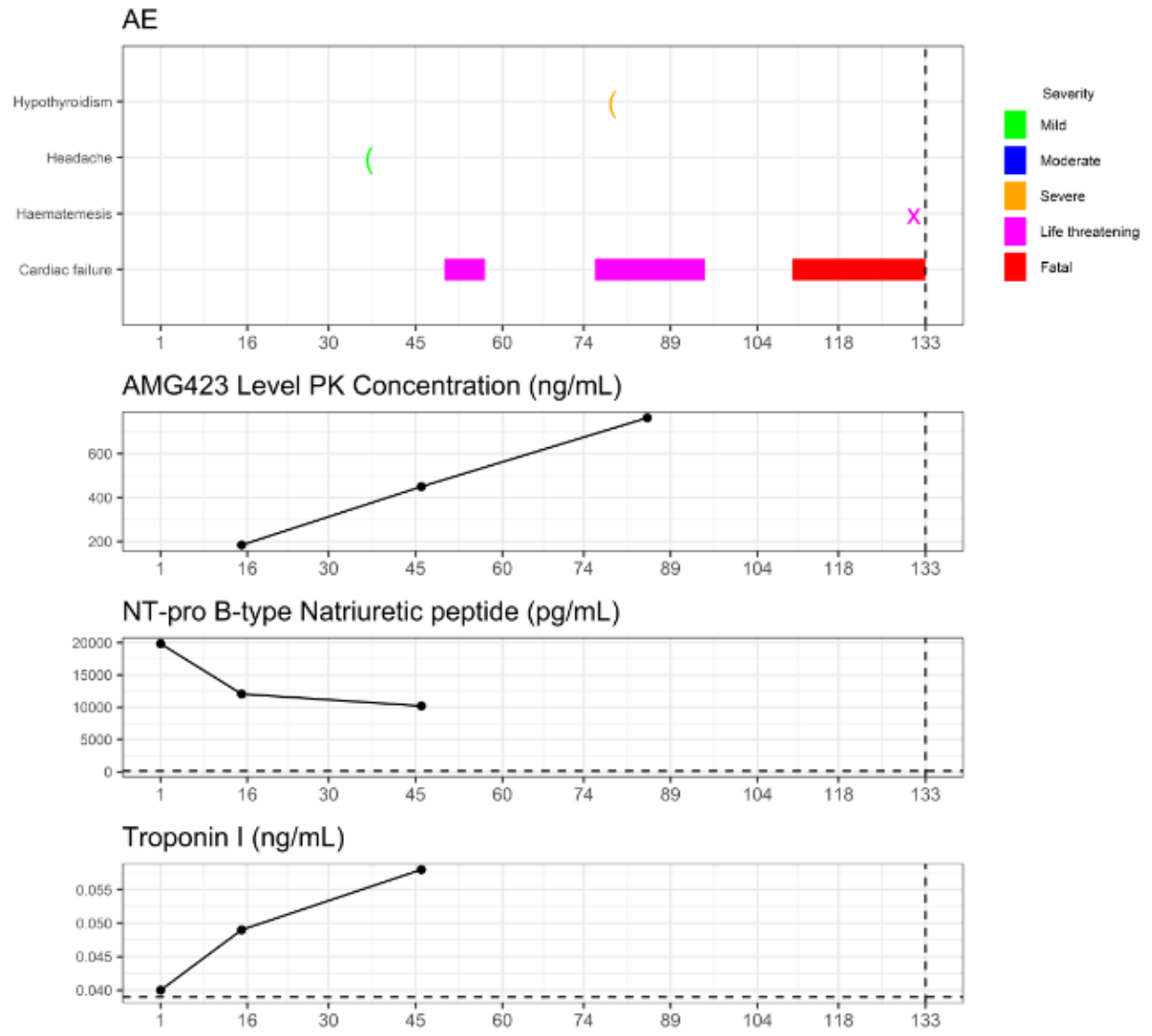
Source: adsl, adae, adlb, and adpc; software: R; X-axis is study day
This subject was a 36-year-old black female (baseline LVEF: 20%, NYHA Class III, eGFR: 49 mL/min/1.73 m^2, troponin-I: 0.01 ng/mL, weight: 187 lb, no AFF at screening) who was uptitrated to 37.5 mg BID at Week 4 and then down-titrated to 25 mg BID at Week 8. Her PK was 370 ng/mL at Week 6 and 1099 ng/mL at Week 24. This subject experienced an ongoing hypotension starting at Week 12 till the end of trial. The study drug was discontinued due to the elevated PK (>1000 ng/mL). Her troponin-I increased with increasing OM concentration.
Abbreviations: AE, adverse event; HF, heart failure; PK, pharmacokinetics

Figure 27. Clinical Profile of Subject (b) (6) (PK >750 ng/mL, Fatal Event Within 6 Months), GALACTIC-HF



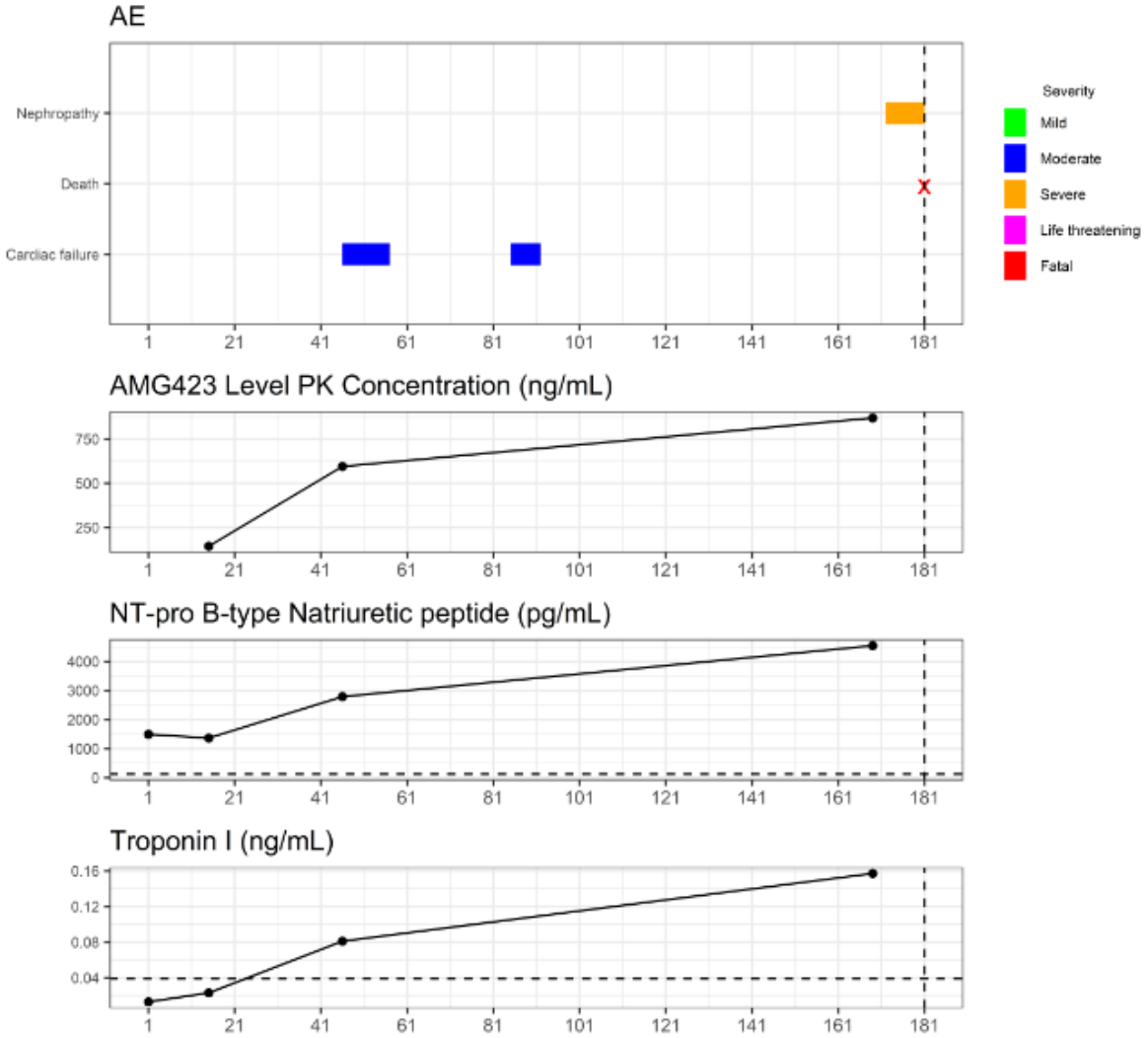
Source: adsl, adae, adlb, and adpc; software: R; X-axis is study day
This subject was a 50-year-old white female (baseline LVEF: 22%, NYHA Class III, eGFR: 52 mL/min/1.73 m^2, troponin-I: 0.02 ng/mL, weight: 121 lb, AFF at screening) who was uptitrated to 37.5 mg BID at Week 4 and her PK was 357 ng/mL at Week 6 and 768 ng/mL at Week 12. This subject experienced a cardiac failure SAE on Day 98 and died 7 days later while on the study drug.
Abbreviations: AE, adverse event; HF, heart failure; PK, pharmacokinetics

Figure 28. Clinical Profile of Subject (b) (6) (PK >750 ng/mL, Fatal Event Within 6 Months), GALACTIC-HF



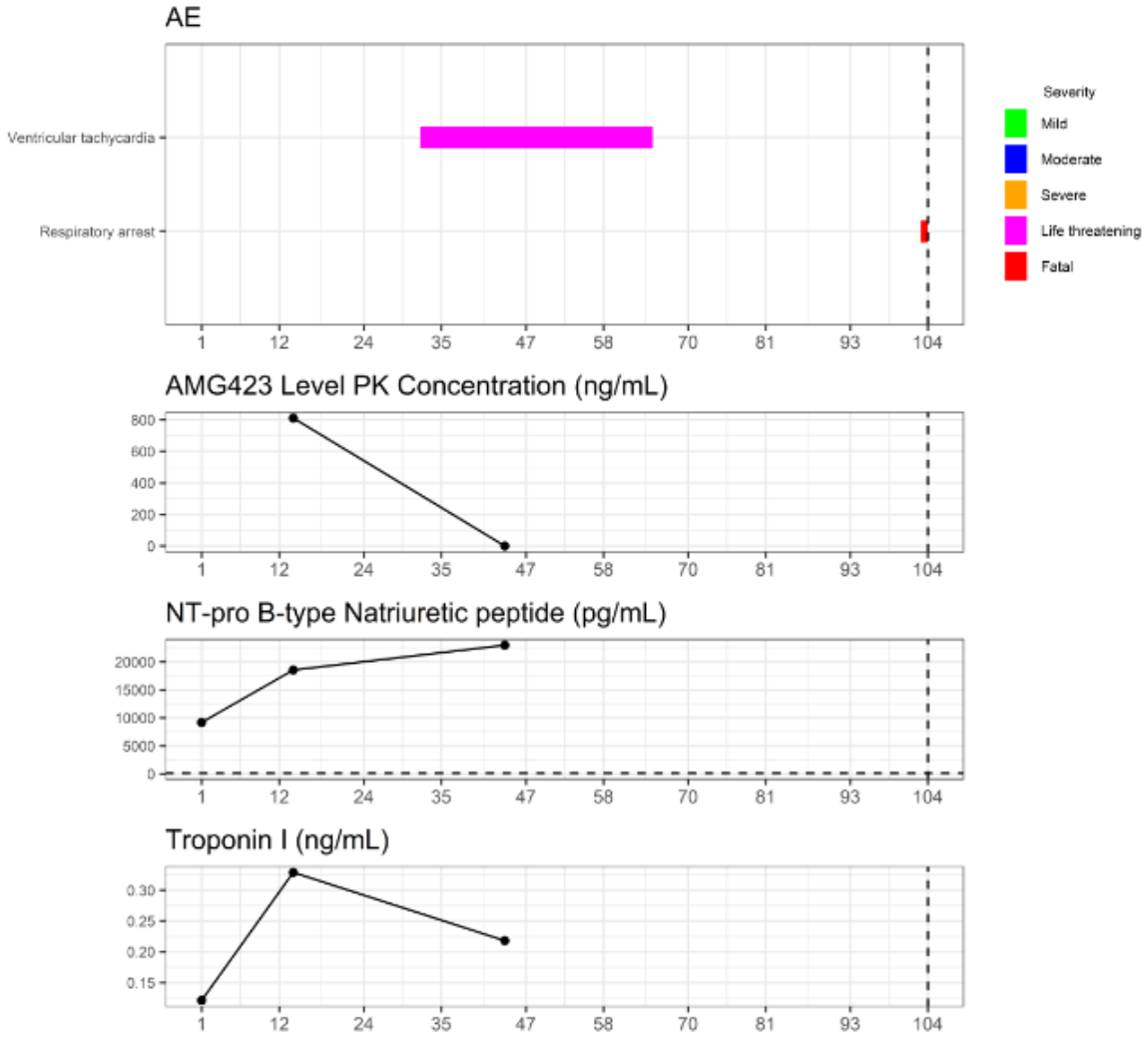
Source: adsl, adae, adlb and adpc; software: R; X-axis is study day
This subject was a 66-year-old white male (baseline LVEF: 15%, NYHA Class III, eGFR: 38 mL/min/1.73 m^2, troponin-I: 0.04 ng/mL, weight: 165 lb, AFF at screening) who was uptitrated to 50 mg BID at Week 4 and his PK was 450 ng/mL at Week 6 and 763 ng/mL at Week 12. This subject experienced life-threatening cardiac failure SAEs during the time when his plasma concentration continued to increase; no action was taken with the study drug. He experienced another cardiac failure SAE on Day 110 and died 24 days later while on the study drug. His troponin-I increased with increasing OM concentrations at Week 6 and was not available at Week 12.
Abbreviations: AE, adverse event; HF, heart failure; PK, pharmacokinetics

Figure 29. Clinical Profile of Subject (b) (6) (PK >750 ng/mL, Fatal Event Within 6 Months), GALACTIC-HF



Source: adsl, adae, adlb, and adpc; software: R; X-axis is study day
This subject was a 72-year-old white male (baseline LVEF: 31%, NYHA Class II, eGFR: 51 mL/min/1.73m^2, troponin-I: 0.01 ng/mL, weight: 185 lb, AFF at screening) who was uptitrated to 50 mg BID and his PK was 595 ng/mL at Week 6 and 869 ng/mL at Week 24. This subject experienced a cardiac failure AE at Weeks 6 and 12; no action was taken with the study drug. He experienced worsening renal disease on Day 172 and died on Day 181 while on the study drug (this event was adjudicated as an unknown death). The investigator thought the nephropathy AE and death were related to the study drug. The subject's NT-proBNP and troponin-I increased with increasing OM plasma concentrations.
Abbreviations: AE, adverse event; HF, heart failure; PK, pharmacokinetics

Figure 30. Clinical Profile of Subject (b) (6) (PK >750 ng/mL, Fatal Event Within 6 Months), GALACTIC-HF



Source: adsl, adae, adlb and adpc; software: R; X-axis is study day
This subject was a 61-year-old white male (baseline LVEF: 25%, NYHA Class II, eGFR: 52 mL/min/1.73m^2, troponin-I: 0.1 ng/mL, weight: 146 lb., AFF at screening) who received 25 mg BID and his PK at Week 2 was 812 ng/mL. This subject experienced a life-threatening ventricular tachycardia SAE on Day 32, resulting in drug interruption. He restarted 25 mg BID two months later and experienced fatal respiratory arrest (adjudicated as death due to HF) 2 weeks after readministration of OM. There were no available data for PK and cardiac biomarkers near the fatal event.
Abbreviations: AE, adverse event; HF, heart failure; PK, pharmacokinetics

6.5.14 Exploratory Analyses on Effect of Concentration in the GALACTIC-HF Trial

To explore whether there are concentration-dependent safety concerns for OM, the last plasma concentration measured prior to or at Week 12[12] was used to explore the concentration-response in the GALACTIC-HF trial. It should be noted that the lowest category of OM concentration range (<145 ng/mL) included subjects who had concentration below the quantified limit, which reflects subjects who were not on OM due to early discontinuation or other reasons. Table 28 summarizes the safety evaluation based on the categories of OM concentration ranges (quintile of concentration) compared with placebo. Overall, a higher incidence of AEs, SAEs, and fatal AEs, primarily driven by HF events, was observed in

[12] Concentration at Week 12 represents the first PK measurement after the last dose titration at Week 8

the OM group in the highest concentration group compared to other OM concentration groups and placebo. Related AEs such as hypotension and peripheral edema were also reported more frequently in the highest category of the OM concentration range compared to the other groups. There were no meaningful differences or concentration-dependent trends in AEs of interest such as arrhythmia, myocardial ischemia, and dizziness by categories of OM concentration ranges compared with placebo. It is noted that myocardial ischemia-related AEs were reported more frequently in the lowest category of the OM concentration ranges as opposed to the highest category. Further evaluation of these events noted that more myocardial ischemia events in the lowest concentration category occurred before Week 8 leading to drug discontinuation or interruption. Thus, the concentrations prior to these events were likely higher than what was measured at Week 12 and not accurately represented in this particular analysis. Overall, there was no clear concentration-dependent risk of myocardial ischemia in the GALACTIC-HF trial, likely due to the low and narrow concentration range studied.

The increased incidence of serious and fatal HF AEs in the highest category of concentration range in the OM group raises concern that the dose-limiting cardiotoxicity of OM can be manifested as exacerbation of HF that not only impacts safety but also efficacy of OM. Table 29 shows the concentration-response relationship for the primary efficacy endpoint and CV death based on the last observed OM concentrations on or before Week 12. Subjects who had OM concentrations in the highest category (>377 ng/mL) did not appear to have benefit from OM when compared to placebo. While these data suggest that the therapeutic range of OM could be lower and narrower than what the Applicant originally proposed (i.e., 300 to 750 ng/mL), it should be noted that this type of analysis is subject to potential confounding effects by other important clinical factors and is based on postrandomization information.

Table 28. Overview of Safety by Last Plasma OM Concentration up to Week 12, Safety Population, GALACTIC-HF

	OM					
	Last Concentration Prior to or at Week 12 (Quintile, ng/mL)					Placebo
	<145[a] (N=738)	145-224 (N=786)	225-300 (N=805)	301-377 (N=807)	>377 (N=801)	All (N=4101)
Any TEAE	638 (86.4)	675 (85.9)	709 (88.1)	711 (88.1)	729 (91.0)	3622 (88.3)
Any TESAE	432 (58.5)	446 (56.7)	446 (55.4)	453 (56.1)	496 (61.9)	2435 (59.4)
Cardiac failure (SMQ)	253 (34.3)	255(32.4)	247(30.7)	260 (32.2)	312(39.0)	1448 (35.3)
Any fatal AE	141 (19.1)	166 (21.1)	137 (17.0)	148 (18.3)	189 (23.6)	823 (20.1)
Cardiac failure (SMQ)	47 (6.4)	71 (9.0)	57 (7.1)	57 (7.1)	89 (11.1)	324 (7.9)
Any TEAE leading to study drug discontinuation	81 (11.0)	67 (8.5)	59 (7.3)	96 (11.9)	84 (10.5)	447 (10.9)
	AE of Interest					
Cardiac failure (SMQ)	275 (37.3)	286 (36.4)	287 (35.7)	305 (37.8)	344 (42.9)	1644 (40.1)
Hypotension (FMQ)	45 (6.1)	57 (7.3)	59 (7.3)	81 (10.0)	100 (12.5)	323 (7.9)
Peripheral edema (FMQ)	18 (2.4)	36 (4.6)	24 (3.0)	29 (3.6)	58 (7.2)	184 (4.5)
Arrhythmia (FMQ)	125 (16.9)	145 (18.4)	123 (15.3)	134 (16.6)	139 (17.4)	708 (17.3)
Myocardial ischemia (FMQ)	72 (9.8)	48 (6.1)	58 (7.2)	70 (8.7)	44 (5.5)	271 (6.6)
Dizziness (FMQ)	49 (6.6)	68 (8.7)	71 (8.8)	69 (8.6)	65 (8.1)	290 (7.1)

Source: adall, adpc, adae; software: SAS, OCS Analysis Studio, Custom Table Tool

[a] PK <145 ng/mL group included subjects who had concentration below the quantified limit due to early discontinuation of the study.

Abbreviations: FMQ, FDA Medical Query; HF, heart failure; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil; SMQ, Standard MedDRA Query; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

Table 29. Key Efficacy Endpoints by Concentration Bins (Quintile), Modified FAS, GALACTIC-HF

	OM		Placebo		
Efficacy Endpoint/Quintile of Last Concentration Prior to or at Week 12	**n/N (%)**	**ER (per 100 PY)**	**n/N (%)**	**ER (per 100 PY)**	**HR (95% CI)[1] (OM vs. Placebo)**
Primary composite endpoint (HF event + CV death)					
PK <145 ng/mL	290/738 (39.3)	25.6	1477/3897 (37.9)	25.0	1.10 (0.97, 1.25)
PK 145-224 ng/mL	265/786 (33.7)	20.5	1477/3897 (37.9)	25.0	0.86 (0.75, 0.98)
PK 225-300 ng/mL	266/805 (33.0)	21.3	1477/3897 (37.9)	25.0	0.85 (0.75, 0.97)
PK 301-377 ng/mL	278/807 (34.4)	21.7	1477/3897 (37.9)	25.0	0.84 (0.74, 0.96)
PK >377 ng/mL	316/801 (39.5)	26.8	1477/3897 (37.9)	25.0	0.99 (0.88, 1.12)
CV Death					
PK <145 ng/mL	152/738 (20.6)	11.1	707/3897 (18.1)	9.94	1.21 (1.01, 1.44)
PK 145-224 ng/mL	146/786 (18.6)	9.90	707/3897 (18.1)	9.94	1.03 (0.86, 1.23)
PK 225-300 ng/mL	119/805 (14.8)	8.08	707/3897 (18.1)	9.94	0.80 (0.66, 0.98)
PK 301-377 ng/mL	139/807 (17.2)	9.32	707/3897 (18.1)	9.94	0.91 (0.76, 1.09)
PK >377 ng/mL	169/801 (21.1)	12.0	707/3897 (18.1)	9.94	1.15 (0.97, 1.36)

Source: FDA's analysis datasets: adall, adpc, adtte

[1] This exploratory analysis was based on Cox model stratified by randomization setting and region and containing baseline eGFR as a covariate to estimate treatment effect in each concentration group.

[2] Modified FAS was defined as FAS excluding subjects who did not have a dose assigned on or prior to Week 12.

Abbreviations: CV, cardiovascular; ER, event rate; FAS, full analysis set; HF, heart failure; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event OM, omecamtiv mecarbil; PK, OM trough concentration; PY, patient-years

6.5.15 Additional Safety Tables and Figures

Table 30. PK-Guided Dose Selection Strategy, GALACTIC-HF

Study Visit	Week 2 Plasma Concentration (ng/mL)	Current Dose BID	New Dose BID
Week 4	< 200	25 mg	50 mg
	≥ 200 to < 300		37.5 mg
	≥ 300 to < 1000		no change
	≥ 1000		placebo
Study Visit	Week 6 Plasma Concentration (ng/mL)	Current Dose BID	New Dose BID
Week 8	< 750	Any	no change
	≥ 750 to < 1000	25 mg	no change
		37.5 mg	25 mg
		50 mg	37.5 mg
	≥ 1000	25 mg	placebo
		37.5 mg	25 mg
		50 mg	
Study Visit	Any Plasma Concentration (ng/mL)	Current Dose BID	New Dose
Week 12	≥ 1000	any	withdraw investigational product
Week 48			
Q48 weeks			
Unscheduled			

BID = twice a day; Q48 = every 48
Source: Applicant's CSR Table 8-1
Abbreviations: HF, heart failure; PK, pharmacokinetics

Table 31. Summary of Subject Incidence of Treatment-Emergent Adverse Events by Cohort, COSMIC-HF, Safety Population, COSMIC-HF

	Cohort 1				
	Placebo (N = 11) n (%)	25 mg M-F1 (N = 10) n (%)	25 mg M-F2 (N = 14) n (%)	25 mg SCT-F2 (N = 13) n (%)	Pooled 25 mg (N = 37) n (%)
All treatment-emergent adverse events	4 (36.4)	2 (20.0)	6 (42.9)	6 (46.2)	14 (37.8)
Grade ≥ 2	0 (0.0)	1 (10.0)	1 (7.1)	1 (7.7)	3 (8.1)
Grade ≥ 3	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (2.7)
Serious adverse events	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (2.7)
	Cohort 2				
	Placebo (N = 10) n (%)	50 mg M-F1 (N = 11) n (%)	50 mg M-F2 (N = 11) n (%)	50 mg SCT-F2 (N = 14) n (%)	Pooled 50 mg (N = 36) n (%)
All treatment-emergent adverse events	1 (10.0)	9 (81.8)	3 (27.3)	5 (35.7)	17 (47.2)
Grade ≥ 2	1 (10.0)	5 (45.5)	1 (9.1)	1 (7.1)	7 (19.4)
Grade ≥ 3	0 (0.0)	2 (18.2)	0 (0.0)	1 (7.1)	3 (8.3)
Serious adverse events	0 (0.0)	2 (18.2)	0 (0.0)	1 (7.1)	3 (8.3)
Leading to discontinuation of investigational product	0 (0.0)	2 (18.2)	0 (0.0)	0 (0.0)	2 (5.6)
Serious	0 (0.0)	2 (18.2)	0 (0.0)	0 (0.0)	2 (5.6)

N=Number of subjects in the analysis set. Percentages are based on N.
Coded using the Medical Dictionary for Regulatory Activities version 18

Source: COSMIC-HF CSR Table 12-2
Abbreviation: HF, heart failure

Table 32. Incidence and Event Rate of Cardiac Failure Adverse Event in Subjects with PK >750 ng/mL, Safety Population, GALACTIC-HF

	OM PK >750 ng/mL (N=61) n (%) ER (per 100 PY)		OM (N=4110) n(%) ER (per 100 PY)		Placebo (N=4101) n(%) ER (per 100 PY)	
Cardiac failure AE	31 (51)	37.7	1550 (38)	28.9	1644 (40)	32.2
Cardiac failure SAE	28 (46)	33.0	1378 (34)	24.7	1448 (35)	26.9
Fatal cardiac failure	10 (16)	8.9	344 (8)	5.2	324 (8)	5.0

Source: FDA's analysis datasets: adall, adpc, adae
Abbreviations: AE, adverse event; ER, event rate; HF, heart failure; N, number of randomized subjects excluding study site 29002; n, number of subjects with at least one event; OM, omecamtiv mecarbil; PK, OM trough concentration; PY, patient-years; SAE, serious adverse event

Table 33. Safety Profile for Subjects with PK>750 ng/mL, Safety Population, GALACTIC-HF

	OM PK >750 ng/mL (N=61) n(%)	OM (N=4110) n(%)	Placebo (N=4101) n(%)
Any TEAE	59 (96.7)	3594 (87.4)	3622 (88.3)
Any TESAE	41 (67.2)	2373 (57.7)	2435 (59.4)
Cardiac failure SAE	28 (45.9)	1378 (33.5)	1448 (35.3)
Fatal TEAE	15 (24.6)	837 (20.4)	823 (20.1)
Fatal cardiac failure	10 (16.4)	344 (8.4)	324 (7.9)
TEAE leading to withdrawal of IP	5 (8.2)	432 (10.5)	447 (10.9)
Adverse event of interest			
Myocardial ischemia (FMQ)	5 (8.2)	306 (7.4)	271 (6.6)
Arrhythmia (FMQ)	11 (18.0)	677 (16.5)	708 (17.3)
Cardiac failure (SMQ)	31 (50.8)	1550 (37.7)	1644 (40.1)
Hypotension	8 (13.1)	348 (8.5)	323 (7.9)
Peripheral edema	6 (9.8)	169 (4.1)	184 (4.5)

Source: FDA's analysis datasets: adall, adpc, adae
Abbreviations: FMQ, FDA Medical Query; IP, investigational product; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with at least one event; OM, omecamtiv mecarbil; PK, OM trough concentration; SAE, serious adverse event; SMQ, standard MedDRA query; TEAE, treatment emergent adverse event

Table 34. Cause of CV Death by AFF at Screening, FAS, GALACTIC-HF

	No AFF		AFF	
Cause of CV Death	**OM (N=2974)**	**Placebo (N=3013)**	**OM (N=1146)**	**Placebo (N=1099)**
CV Death	500 (16.8)	549 (18.2)	308 (26.9)	249 (22.7)
Due to heart failure	226 (7.6)	267 (8.9)	188 (16.4)	123 (11.2)
Sudden cardiac death	120 (4.0)	132 (4.4)	52 (4.5)	58 (5.3)
Presumed cardiovascular death	71 (2.4)	67 (2.2)	39 (3.4)	30 (2.7)
Presumed sudden death	41 (1.4)	39 (1.3)	14 (1.2)	15 (1.4)
Due to stroke	12 (0.4)	16 (0.5)	6 (0.5)	16 (1.5)
Due to an acute MI	15 (0.5)	13 (0.4)	4 (0.3)	2 (0.2)
Due to cardiovascular hemorrhage	3 (0.1)	1 (0.0)	2 (0.2)	1 (0.1)
Due to other cardiovascular causes	7 (0.2)	7 (0.2)	2 (0.2)	4 (0.4)
Due to cardiovascular procedure	5 (0.2)	7 (0.2)	1 (0.1)	0

Reviewer's Table Source: adall, adp; software: SAS
Abbreviations: AFF, atrial fibrillation/flutter at screening; CV, cardiovascular; FAS, full analysis set; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; N, number of subjects in treatment arm excluding study site 29002; n, number of subjects with an event; OM, omecamtiv mecarbil

Table 35. Baseline Characteristic by AFF at Screening, FAS, GALACTIC-HF

	No AF/Flutter at Baseline (n=5,987)	AF/Flutter at Baseline (n=2,245)
Demographics		
Age - yr (Mean ± SD)	63.3 ± 11.61	67.9 ± 9.89
Sex, Female - n (%)	1,340 (22.4)	409 (18.2)
Race - n (%)		
Asian	556 (9.3)	154 (6.9)
Black	487 (8.1)	75 (3.3)
Other	433 (7.2)	130 (5.8)
White	4,511 (75.3)	1,886 (84.0)
Geographic region - n (%)		
Asia	522 (8.7)	148 (6.6)
Eastern Europe/Russia	1,790 (29.9)	891 (39.7)
Latin America	1,226 (20.5)	348 (15.5)
US And Canada	1,138 (19.0)	248 (11.0)
Western Europe/South Africa/Australasia	1,311 (21.9)	610 (27.2)
Randomization setting - n (%)		
In-patient	1,361 (22.7)	723 (32.2)
Clinical Characteristics		
Atrial fibrillation or flutter at screening, n (%)	0 (0.0)	2,245 (100.0)
Hypertension Hx, n (%)	4,136 (69.1)	1,648 (73.4)
Type 2 diabetes mellitus, n (%)	2,431 (40.6)	878 (39.1)
History of stroke, n (%)	497 (8.3)	257 (11.4)
Ischemic heart failure, n (%)	3,341 (55.8)	1,074 (47.8)
History of myocardial infarction, n (%)	2,683 (44.8)	752 (33.5)
History of coronary artery bypass surgery, n (%)	950 (15.9)	367 (16.3)
History of percutaneous coronary revascularization, n (%)	1,900 (31.7)	538 (24.0)
History of ventricular tachyarrhythmia	934 (15.6)	323 (14.4)
LVEF - (%) (Mean ± SD)	26.4 ± 6.32	27.1 ± 6.10

	No AF/Flutter at Baseline (n=5,987)	AF/Flutter at Baseline (n=2,245)
NYHA Classification, n (%)		
Class II	3,353 (56.0)	1,015 (45.2)
Class III	2,473 (41.3)	1,143 (50.9)
Class IV	161 (2.7)	87 (3.9)
Median KCCQ Total Symptom Score (IQR)	70.8 (51.0 to 89.6)	63.5 (43.8 to 83.3)
Outpatient	76.0 (56.3 to 91.7)	69.8 (52.1 to 87.5)
Inpatient	55.2 (35.4 to 72.9)	47.9 (29.2 to 67.7)
SBP - mmHg (Mean ± SD)	117.0 ± 15.53	115.1 ± 14.77
Heart rate - (beats/min) (Mean ± SD)	71.3 ± 11.49	75.1 ± 13.36
Median NT-proBNP (IQR) - pg/mL	1,675.0 (812.0 to 3,579.0)	2,873.0 (1,699.0 to 5,294.0)
Median cardiac troponin I (IQR) - ng/L	25.0 (13.0 to 48.0)	31.0 (16.0 to 59.0)
Median eGFR (IQR) - mL/min/1.73m^2	60.6 (45.7 to 76.1)	53.4 (40.4 to 68.1)
Heart Failure Therapy, n (%)		
ACEi, ARB or ARNi	5,250 (87.7)	1,915 (85.3)
ARNi	1,172 (19.6)	429 (19.1)
BB	5,650 (94.4)	2,113 (94.1)
MRA	4,627 (77.3)	1,770 (78.8)
SGLT2 Inhibitors	164 (2.7)	54 (2.4)
Ivabradine	510 (8.5)	23 (1.0)
Digitalis glycosides	693 (11.6)	692 (30.8)
Amiodarone	921 (15.4)	374 (16.7)
Antiplatelet	3,662 (61.2)	546 (24.3)
Anticoagulant	1,351 (22.6)	1,498 (66.7)
Cardiac resynchronization therapy	815 (13.6)	343 (15.3)
Implantable cardioverter defibrillator	1,913 (32.0)	701 (31.2)

ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor neprilysin inhibitor; BB = beta blocker; eGFR = estimated glomerular filtration rate; IQR = interquartile range; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; n = number of participants with observed data; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure; SD = standard deviation; SGLT2 = sodium glucose transport protein 2.

Source: Applicant's CSR addendum Table 15

Abbreviations: FAS, full analysis set; HF, heart failure; Hx, history