Omecamtiv Mecarbil Efficacy and Safety

FDA Presentation

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AC Points to Consider

- Discuss the benefits of omecamtiv mecarbil (OM) and whether there is adequate evidence for concluding these benefits. Include a discussion comparing the findings for the heart failure (HF) and cardiovascular (CV) mortality components of the primary efficacy endpoint in the GALACTIC-HF trial. What role does the phase 2 trial play in your assessment of the benefits?
- If OM were approved, what should the labeling say about use as a function of left ventricular ejection fraction (LVEF)?
- If OM were approved, what should the labeling say about use in patients with atrial fibrillation or atrial flutter (AFF)?

AC Points to Consider (Cont'd)

- Whether OM is safe enough to support its proposed use; consider safety with and without pharmacokinetic-based dosing

Three Approaches for Establishing Substantial Evidence of Effectiveness (SEE)

- Two adequate and well-controlled (A&WC) trials
- One A&WC large multicenter trial
  - Clinically meaningful and statistically very persuasive effect on important outcomes (e.g., mortality, severe/irreversible morbidity)
- One A&WC clinical investigation plus confirmatory evidence (CE)
  - Examples of CE:
    - Clinical trial data in a closely related indication
    - Strong mechanistic data
  - Appropriateness of this approach depends on several factors, for example:
    - Persuasiveness of the single A&WC trial, robustness of the CE, seriousness of the disease, size of patient population, ethics/practicality of a second A&WC trial

Establishing SEE for Heart Failure Treatment

- For heart failure (HF) treatment, a single, large multicenter, A&WC, cardiovascular (CV) outcomes trial with persuasive results over standard of care therapy is considered acceptable as the basis of SEE

Considerations Regarding Using Phase 2 Data as Confirmatory Evidence

- Phase 2 trial (COSMIC-HF, randomized, double-blind, placebo-controlled)
  - The primary objectives were to (1) select an oral formulation and dose of OM and (2) to characterize OM's pharmacokinetics (PK) over 20 weeks of treatment
  - The effects of OM compared with placebo over 20 weeks of treatment on selected pharmacodynamic (PD) markers were evaluated as secondary or exploratory endpoints
    - No control for multiplicity

Considerations Regarding Using Phase 2 Data as Confirmatory Evidence (Cont'd)

- PD Results of COSMIC-HF
  - OM was associated with a varying degree of improvements in the predefined secondary endpoints
    - Systolic ejection time ($p<0.0001$), stroke volume, left ventricular end-systolic diameter, left ventricular end diastolic diameter, heart rate and NT-proBNP
  - OM was associated with a small increase in LVEF and had no effect on increasing left ventricular cardiac output (LVCO)
    - LVEF: mean increase of 1.6% ($p=0.06$) compared with placebo
    - LVCO: no treatment difference between groups: -0.047 (L/min) ($p=0.8$)

Considerations Regarding Using Phase 2 Data as Confirmatory Evidence (Cont'd)

- COSMIC-HF provides data supporting a plausible mechanism, but the degree of clinical benefits (e.g., reducing CV death or heart failure events) associated with changes of these PD markers is unclear
  - None of these PD markers were studied in Phase 3 except for heart rate and NT-proBNP
- The pivotal phase 3 trial (GALACTIC-HF) was adequately sized to detect differences in CV death (>90% power) and the primary composite endpoint of CV death or HF events (>99% power)
  - This single large multicenter trial was designed to provide an adequate basis for an efficacy claim

Outline

- Efficacy
  - Key efficacy findings from GALACTIC-HF
  - Efficacy subgroup findings
- Safety
  - Potential risk based on nonclinical data
  - Key safety findings and concerns
  - Proposed dosing strategy
- Benefit-Risk Assessment

GALACTIC-HF

- Randomized, double-blind, placebo-controlled, multi-center, event driven study conducted in adults with chronic heart failure reduced ejection fraction (HFrEF) (inclusion LVEF ≤35%)
  - Target approximately 8000 subjects to be randomized with approximately 1590 subjects experiencing CV death to ensure at least 90% power for the CV death endpoint using 2-sided Type 1 error of 0.05

- Two treatment arms:
  - OM: Starting dose of 25 twice daily (BID) titrated to 37.5 mg BID or 50 mg BID
  - Placebo: Titrated in a manner similar to OM arm

- 1:1 randomization
  - Stratification factors: Randomization setting (currently hospitalized[1] versus not) and region (five groupings: United States and Canada; Latin America; Western Europe; South Africa; and Australasia - Eastern Europe including Russia - Asia)

1: Defined as subjects currently hospitalized with primary reason as HF. This included subjects with urgent visit to emergency room (ER) for HF.

GALACTIC-HF: Key Patient Characteristics

Baseline Characteristics	Overall (N=8232)
Age, mean ± SD	65 ± 11
United States Only, n (%)	1220 (15%)
(ACEi, ARB or ARNi) + MRA + Beta Blocker, n (%)	5427 (66%)
SGLT2 inhibitors, n (%)	218 (3%)
New York Heart Association Class, n (%)	
Class II	4368 (53%)
Class III	3616 (44%)
Class IV	248 (3%)
LVEF at baseline, Mean ± SD	27% ± 6%
Median; Min – Max	28%; 4 – 42%
Atrial fibrillation/flutter at screening, n(%)	2245 (27%)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor agonist; N, number of randomized subjects excluding the site with GCP violation; SGLT, sodium glucose cotransporter 2; SD, standard deviation; LVEF, left ventricular ejection fraction; Min, minimum; Max, maximum

GALACTIC-HF: Efficacy Endpoints

- Primary Endpoint: Time to adjudicated CV death or HF event, whichever occurs first
  - CV death: Adjudicated CV death, presumed CV death, or presumed sudden death
  - HF event: HF hospitalization, urgent emergency room/emergency department/office/clinic visit
- Key Secondary Endpoint: Time to CV death
- Other Secondary Endpoints:
  - Change from baseline (CFB) in Kansas City Cardiomyopathy Questionnaire – Total Symptom score[1] (KCCQ–TSS) at Week 24
  - Time to Hospitalization for HF
  - Time to All Cause Mortality

1: The KCCQ, a disease-specific measure for HF, is a 23-item self-administered questionnaire that measures the patient's perception of their health status based on a 2-week recall period. The instrument includes questions on heart failure symptoms, physical and social function, and quality of life (QOL). The TSS averages the available summary scores from the Symptom Frequency Score and the Symptom Burden Score. The range of values is between 0 to 100, with higher values reflecting improvement.

GALACTIC-HF: Primary Endpoint

Outcomes	OM (N=4120) n (IR / 100 PY)	Placebo (N=4112) n (IR / 100 PY)	HR (95% CI) [1] (Ref = Placebo)	P-value	RD per 100 PY (95% CI) [2] (Ref = Placebo)
Primary Endpoint	1523 (24.2)	1607 (26.2)	0.92 (0.86, 0.99)	0.025	-2.1 (-3.9, -0.3)
Time to CV Death	808 (10.9)	798 (10.8)	1.01 (0.92, 1.11)	0.9 [3]	0.1 (-1.0, 1.1)
Time to HF Event	1177 (18.7)	1236 (20.3)	0.93 (0.86, 1.00)	0.06 [3]	-1.5 (-3.1, 0.0)

Source: Statistical Reviewer
Incidence rate (IR) per 100 patient years (PY) is the number of subjects with a first event divided by total PY at risk of experiencing the outcome multiplied by 100.
1: Hazard ratio (HR), confidence intervals (CI), and p-value are estimated from Cox proportional hazards regression model.
2: Difference in IR between OM with placebo. The 95% CI is based on normal approximation to Poisson rates.
3: Nominal p-values are reported for time to CV death and time to HF event outcomes.
Abbreviations: N, Total number randomized excluding study center 29002; n, number of subjects with a first event; HR, hazard ratio; RD, risk difference; CI, confidence interval; IR, incidence rate; PY, patient years

GALACTIC-HF: Key Secondary Endpoint, Causes of Cardiovascular Death

Causes of CV Death, n (% relative to N)	OM (N=4120)	Placebo (N=4112)
Total CV Death	808 (19.6)	798 (19.4)
Due to Heart Failure	414 (10.0)	390 (9.5)
Sudden Cardiac Death	172 (4.2)	190 (4.6)
Presumed Cardiovascular Death	110 (2.7)	97 (2.4)
Presumed Sudden Death	55 (1.3)	54 (1.3)
Due to An Acute Myocardial Infarction	19 (0.5)	15 (0.4)
Due to Stroke	18 (0.4)	32 (0.8)
Due to Other Cardiovascular Causes	9 (0.2)	11 (0.3)
Due to Cardiovascular Hemorrhage	5 (0.1)	2 (0.0)
Due to Cardiovascular Procedure	6 (0.1)	7 (0.2)

GALACTIC-HF: Key Secondary Endpoints

Key Secondary Endpoints	OM (N=4120)	Placebo (N=4112)	HR (95% CI) / Diff (95% CI)[1] (Ref = Placebo)	Nominal P-value	RD per 100 PY (95% CI) (Ref = Placebo)
Time to CV Death, n (IR)	808 (10.9)	798 (10.8)	1.01 (0.92, 1.11)	0.9	0.1 (-1.0, - 1.1)
CFB in KCCQ TSS at Week 24, [1] mean (SD)	9.9 (24)	9.6 (24)	0.8 (-2.6, 4.5)	0.03	NA
Time to Hospitalization for HF, n (IR)	1142 (18.0)	1179 (19.1)	0.95 (0.87, 1.03)	0.2	-1.1 (-2.6, - 0.5)
Time to All Cause Mortality, n (IR)	1067 (14.4)	1065 (14.4)	1.00 (0.92, 1.09)	>0.9	-0.0 (-1.3, - 1.2)

Source: Statistical Reviewer
Incidence rate (IR) is reported per 100 patient years
1: Mean and standard deviation are reported by arm. Estimated difference and 95% CI are based on Applicant's clinical study report. The p-value was obtained based on an omnibus F-test with 2 numerator degrees of freedom to test the OM vs. the placebo.
Abbreviations: LSM, least squares mean change from baseline; SE, standard error; SD, standard deviation; NA, not applicable

Summary of Primary Efficacy Findings

- The primary endpoint for GALACTIC-HF was met according to the prespecified alpha of 0.05. The estimated treatment effect was small.
  - On the relative scale: 8% reduction in risk of composite of CV death and/or heart failure (HR: 0.92; 95% CI: 0.86, 0.99; p=0.025)
  - On the absolute scale: Risk difference of 2 per 100 PY (95% CI: 0.3, 3.8)

- Summary of the components
  - No difference in time to CV death between arms (HR: 1.01; 95% CI: 0.9, 1.1)
  - Numerical trend in reduction in risk of HF event (HR: 0.93; 95% CI: 0.86, 1.00)

- Sensitivity analyses provide similar conclusions to the primary efficacy findings

Summary of Secondary Endpoints

- None of the secondary endpoints were formally tested because the CV death endpoint and KCCQ TSS endpoint did not meet the prespecified alpha level according to the multiplicity testing procedure
- Change from baseline in KCCQ TSS at Week 24
  - No observed difference between arms
- Time to hospitalization for HF
  - An observed numerical trend of reduction in risk
- Time to All Cause Mortality
  - No observed difference between arms

Pertinent Regulatory History

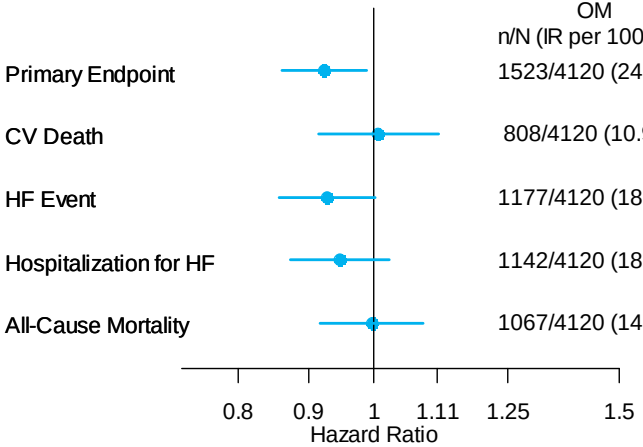
- At the end-of-phase 2 meeting, FDA stated that:
  - A single phase 3 trial using the proposed primary composite endpoint could provide adequate support for an effectiveness claim, if the primary endpoint was significant at a p-value <0.01 (and there was no adverse effect on mortality) or if CV mortality was significant at p-value <0.05

- Considerations:
  - The primary endpoint was significant. HR: 0.92; 95% CI: 0.86, 0.99; p=0.025 (p >0.01).
  - No difference in CV death or all cause mortality

Pertinent Regulatory History

- At the end-of-phase 2 meeting, FDA stated that
  - If the p-value for the primary composite endpoint were driven by “urgent heart failure visits” (i.e., ED/office visit), a single trial with a p-value of 0.05 would probably not be sufficient for approval in the absence of at least strong trends for the other components of the composite endpoint

- Considerations



	OM n/N (IR per 100 PY)	Placebo n/N (IR per 100 PY)	Hazard Ratio (95% CI); p-value	RD per 100 PY (95% CI)
Primary Endpoint	1523/4120 (24.2)	1607/4112 (26.3)	0.92 (0.86, 0.99); 0.03	-2.1 (-3.9, -0.3)
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HF Event	1177/4120 (18.7)	1236/4112 (20.3)	0.93 (0.86, 1.00); 0.06	-1.5 (-3.1, 0.0)
Hospitalization for HF	1142/4120 (18.0)	1179/4112 (19.1)	0.95 (0.87, 1.03); 0.2	-1.1 (-2.6, 0.5)
All-Cause Mortality	1067/4120 (14.4)	1065/4112 (14.4)	1.00 (0.92, 1.09); >0.99	-0.0 (-1.3, 1.2)

Outline

- Efficacy
  - Key efficacy findings from GALACTIC-HF
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Applicant's Proposal

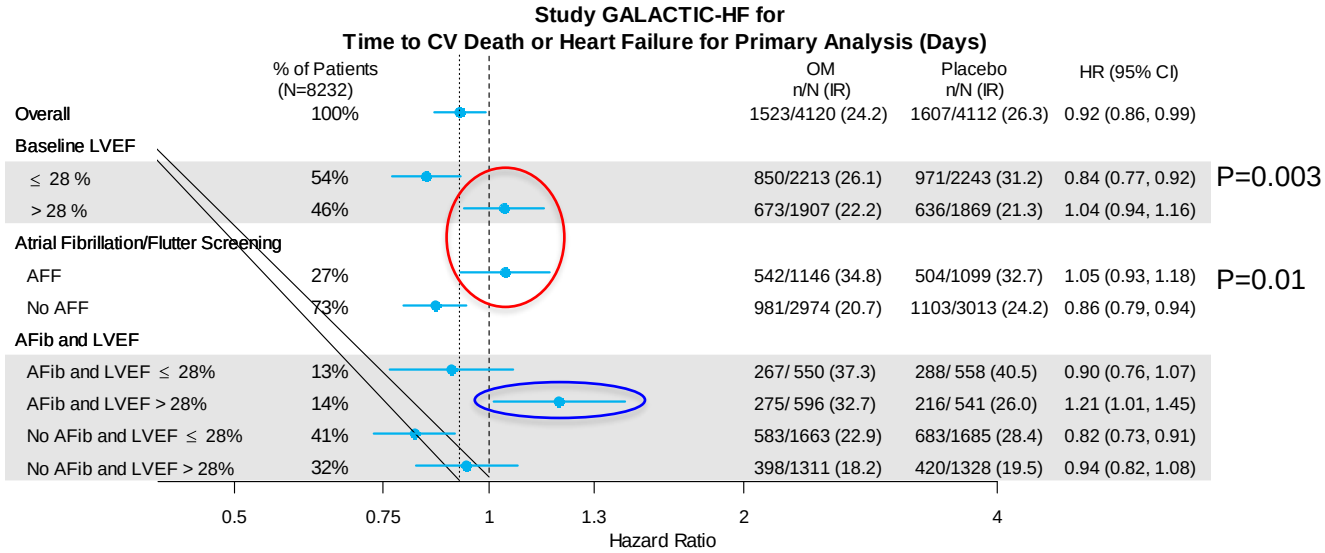
- Proposed language for the Indication section of labeling
  - *"Benefits are increasingly evident the lower the left ventricular ejection fraction (LVEF)."*

Subgroup Findings - Disclaimer

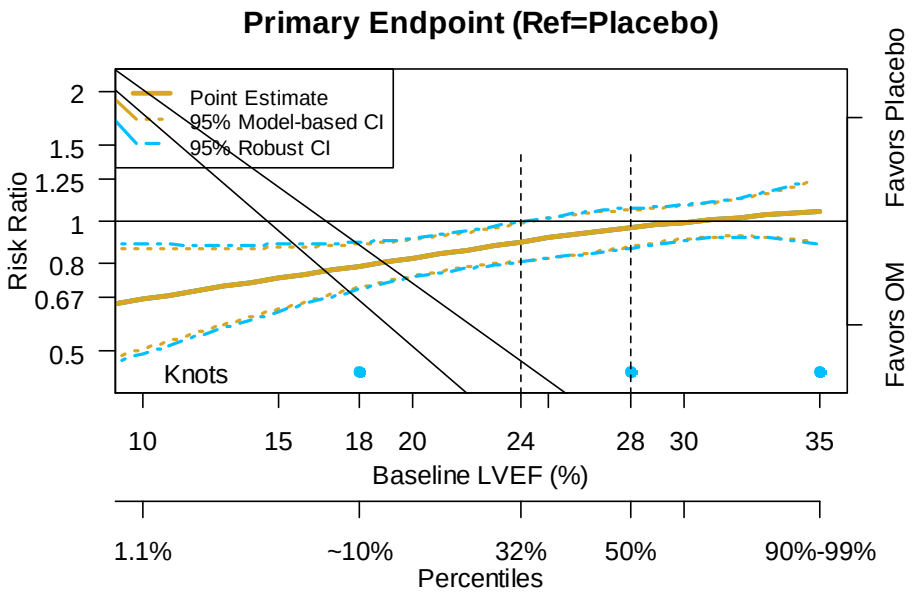
- These subgroup analyses are exploratory, not definitive evidence for or against a treatment effect within particular subgroup(s)

Subgroup Findings

- Heterogeneity of treatment effects seen in the prespecified subgroups defined by LVEF and atrial fibrillation/flutter (AFF)
- Exploratory subgroup analysis conducted for combination of LVEF and AFF



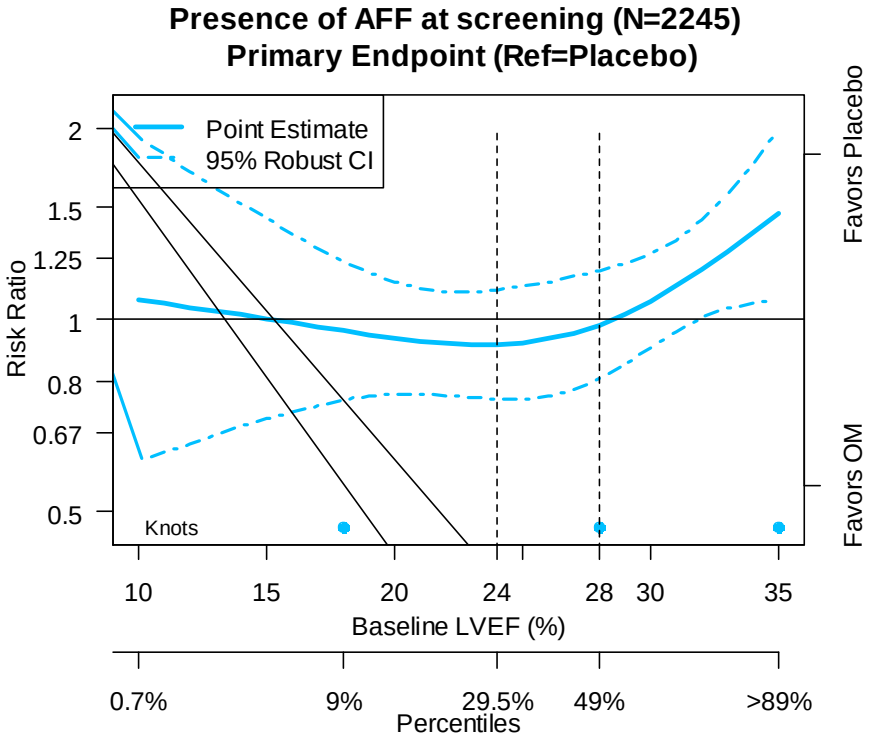
Applicant's Analysis: Primary Endpoint Versus Baseline LVEF

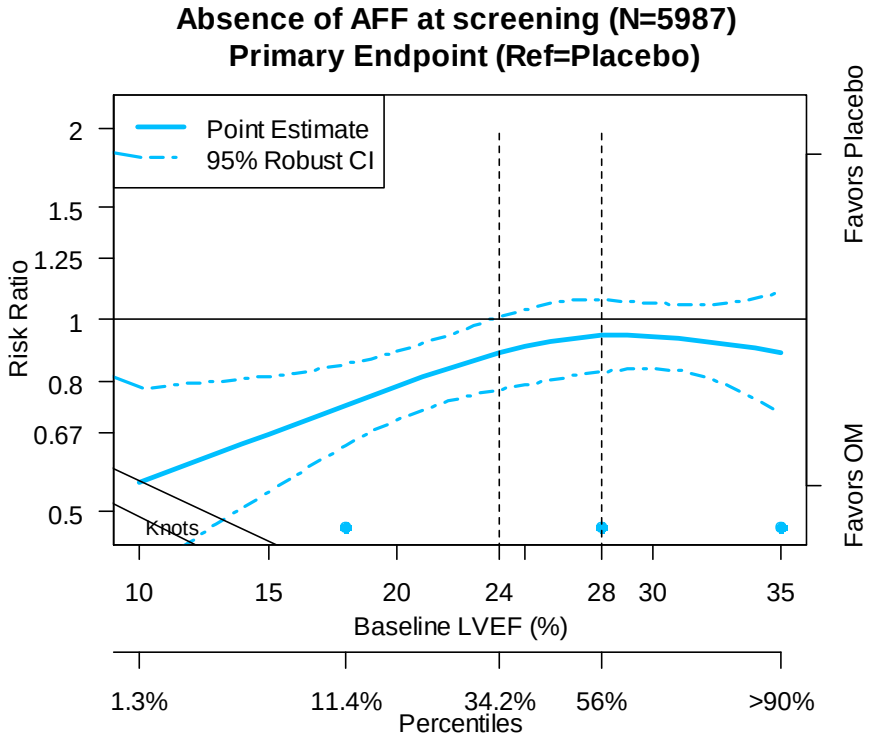


- Observed trends of benefit for lower range of LVEF
- Model limitations
  - Rationale for the placement and number of knots is unclear
  - Different models provide different interpretation

Source: Statistical Reviewer
Model-based confidence interval (CI) was based on the Applicant's Poisson regression model adjusting for treatment variable, LVEF (using restricted cubic splines with knots at 18, 28, 35), and interaction of the LVEF with treatment.
Robust CI was based on the Applicant's Poisson regression model but a Huber-white sandwich variance was used to relax the mean variance assumption.

FDA's Analysis: Primary Endpoint Versus Baseline LVEF by Presence/Absence of AFF at Screening





Within each AFF subgroup, the Applicant's Poisson regression model, with Huber White sandwich errors, adjusting for treatment variable, LVEF (using restricted cubic splines with Applicant's knots at 18, 28, 35), and interaction of the LVEF with treatment.

Summary of Issues

- Using baseline LVEF to determine the subjects who may benefit
  - Limitations of the model used to describe the relationship
  - "*Benefits are increasingly evident the lower the left ventricular ejection fraction (LVEF)*" is vague and not clearly actionable for health care providers
  - Does not account for the uncertainty in the LVEF measurement
- AFF
  - Detrimental treatment effect observed for OM in exploratory subgroup with AFF and LVEF >28%

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Potential Risk Based on Nonclinical Data

- **Dose-limiting cardiotoxicity**[1] observed in both rats and dogs
  - Myocardial fibrosis/degeneration/necrosis and mortality following short and chronic treatment
  - Cardiac toxicity appears closely related to plasma OM concentrations
- **Narrow therapeutic window in rats/dogs**
  - Separation between the maximum OM concentration (C_{max}) associated with cardiac toxicity and the Cmax associated without cardiac toxicity: **~1.3 fold**
- **Minimal safety margin in rats/dogs** when comparing the estimated C_{max} at the maximum recommended human dose (MRHD)[3] of 50 mg BID to the C_{max} at dose without cardiac toxicity: **~2 fold**

	Rat C_{max} (ng/mL)		Dog C_{max} (ng/mL)		**Safety Margin** for the C_{max} at MRHD[3]
	Male	Female	Male	Female	
Dose with cardiac toxicity[2] (7.5 mg/kg/day)	641	755	944	1000	
Dose without cardiac toxicity (5 mg/kg/day)	505	590	709	549	**1.5-2.1**
Separation	**1.3**	**1.3**	**1.3**	**1.8**	---

1. The functional changes following acute dose treatment include increased heart rate, decreased blood pressure, decreased ventricular function, and ECG signs of ischemia.
2. Data presented were from chronic and 13-week toxicity studies;
3. Clinical Cmax of 334 ng/mL at the steady state estimated for 50 mg BID based on observed PK value from the phase 3 under PK-guided dosing

Pertinent Regulatory History

- During the course of development, FDA expressed concerns about CV safety in association with dosing of OM
  - Myocardial ischemia including myocardial infarction (MI) occurred in healthy volunteers and patients with HFrEF during short durations of exposure
- PK-guided titration was tested in phase 2 studies and a refined PK-guided posology was used in GALACTIC-HF to mitigate the risk
  - The strategy in GALACTIC-HF used PK measurement at set timepoints to adjust the OM dose and was designed to achieve the target plasma concentrations (300-750 ng/mL), while minimizing the frequency of excessive exposure (>1,000 ng/mL)

Pertinent Regulatory History (Cont'd)

- Prior to the NDA submission,
  - the Applicant informed the Division that the QMS™ OM immunoassay used in the GALACTIC-HF study for PK-guided dose titration regimen would not be commercialized
  - The Applicant proposed to develop and validate a LC-MS/MS assay during the review cycle of the NDA
- The Applicant subsequently submitted the NDA proposing scheduled, forced dose titration without the need for PK guidance

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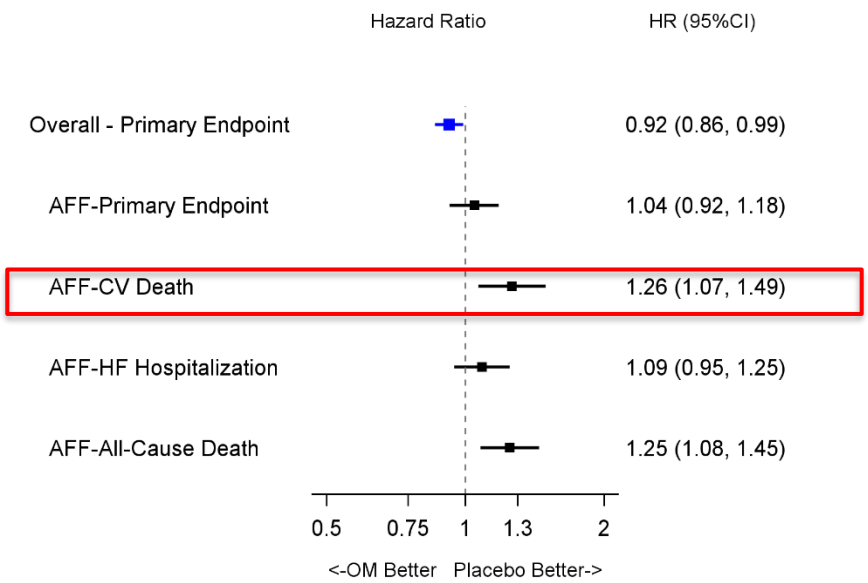
Overview of Safety Results in GALACTIC-HF

- Under a PK-guided dosing strategy, the risk profile of OM is generally acceptable except for patients with atrial fibrillation/flutter (AFF)
- The risk of myocardial ischemia is contained
  - Adjudicated major cardiac ischemic event[1] [HR: 1.1 (0.9, 1.3)]
- Small increase in troponin-I and creatine kinase-MB but clinical significance of these findings is unclear
- Subgroup analysis indicated an increased risk of CV death in patients with AFF on OM compared to placebo

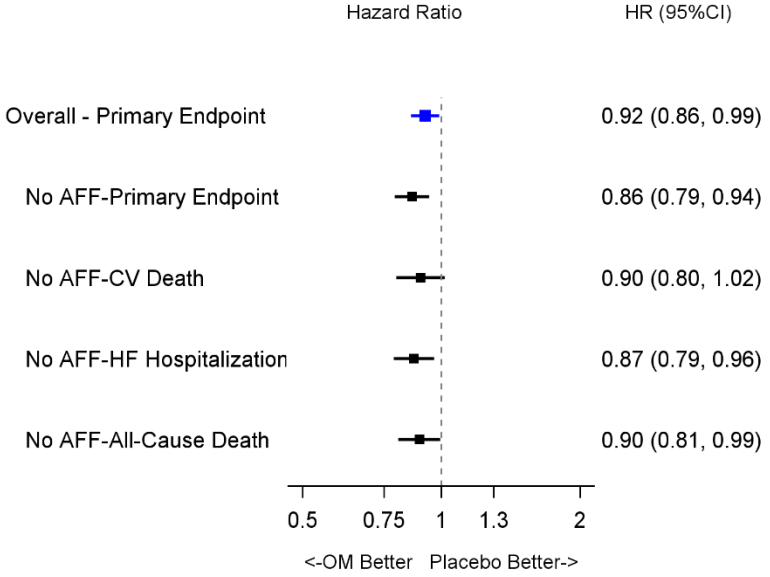
1. Fatal and non-fatal MI, hospitalization for unstable angina, and coronary revascularization

Efficacy Endpoints by Baseline AFF Subgroup

Atrial fibrillation/flutter at screening
(N = 2,245, 27%)



No atrial fibrillation/flutter at screening
(N =5,987 , 73%)



Potential Increased Risk of CV Death in Patients with AFF

- The excess in CV death was driven by increased incidence of HF death
  - A higher incidence of cardiac failure adverse events among AFF patients on OM compared to placebo (50% versus 46%)
- Unclear mechanism but patients with AFF could be more susceptible to the potential cardiotoxicity related to OM
- Post-hoc analyses suggest subsets of AFF patients had worse results for CV death
  - AFF patients with digoxin use [8% of the total population, HR= 1.7 (1.2, 2.2)]
  - AFF patients with LVEF ≥28% [14% of the total population, HR=1.5 (1.2, 2.0)]
- Unclear whether AFF patients at risk could be prospectively identified

Clinical Risks and Uncertainties

- The principal safety concern of OM is the potential risk of dose-limiting cardiotoxicity in the context of a narrow therapeutic window
  - The risks of OM appear to be contained in GALACTIC-HF under a PK-guided dosing strategy
- The Applicant identified the risk of myocardial ischemia due to excessive exposure in early clinical studies and proposed a safety threshold of 1,000 ng/mL
  - The threshold is arbitrary and mainly based on limited data from clinical studies with an intravenous (IV) formulation following short-term exposure
- There are limited data to assess the clinical risk associated with long-term, excessive exposure of OM because of the PK-guiding dosing strategy
  - In GALACTIC-HF, median exposure was maintained in the range of 250-300 ng/mL

Clinical Risks and Uncertainties (Cont'd)

- There is evidence indicating that excessive exposure to OM increases the risk of myocardial ischemia and HF
  - A positive exposure-response relationship for SAEs, primarily driven by cardiac failure SAEs
  - Case findings suggest correlations between increased concentration of OM/increased troponin-I and/or NT-proBNP in connection with cardiac AEs such as myocardial ischemia and HF
- Optimal therapeutic range has not been well established
  - The Applicant's proposed therapeutic range of 300-750 ng/mL is rather wide and not supported by the available data
  - No apparent exposure-response relationship for the primary efficacy composite endpoint

Main Safety Concern

- The potential risk of OM-associated cardiotoxicity is likely to increase without a mandatory requirement of measuring plasma concentration for the purpose of dose adjustment in the real-world setting
- The potential increased risk of CV death due to worsening of HF among patients with AFF

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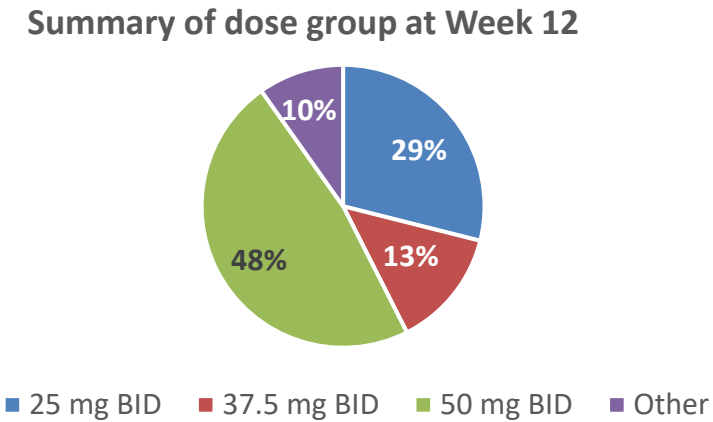
PK-guided Dosing Titration in GALACTIC-HF

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
	≥ 1,000		placebo
	Week 6 Plasma Concentration		
Week 8	< 750	Any	No change
	≥ 750 to < 1,000	25 mg	No change
		37.5 mg	25 mg
		50 mg	37.5 mg
	≥ 1,000	25 mg	Placebo
		37.5 mg	25 mg
		50 mg	
	Any Plasma Concentration		
Week 12	≥ 1,000	Any	Withdraw omecamtiv mecarbil
Week 48			
Q 48 weeks			
Unscheduled			

BID = twice a day; Q 48 = every 48



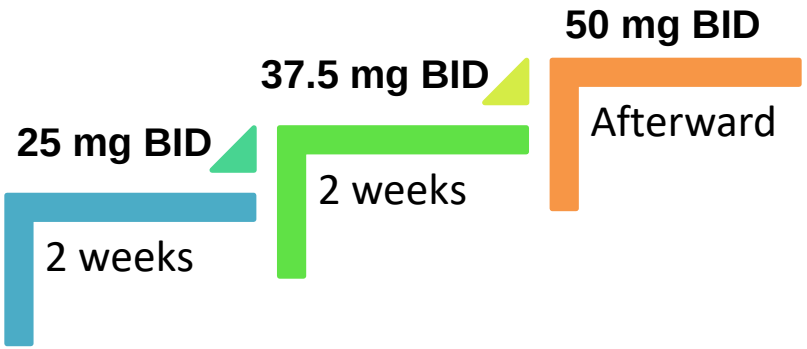
Other includes discontinued investigational product (8.4%), no investigational product box dispensed (0.4%), and visit did not occur (1%)

Source: Table 11-1, Study 20110203 CSR

- Target trough OM plasma concentration (C_{trough}) range: 300-750 ng/mL.
- Avoiding an excessive C_{trough} of >1000 ng/mL.
- PK-guided dosing posology was effective in limiting high OM plasma concentrations.

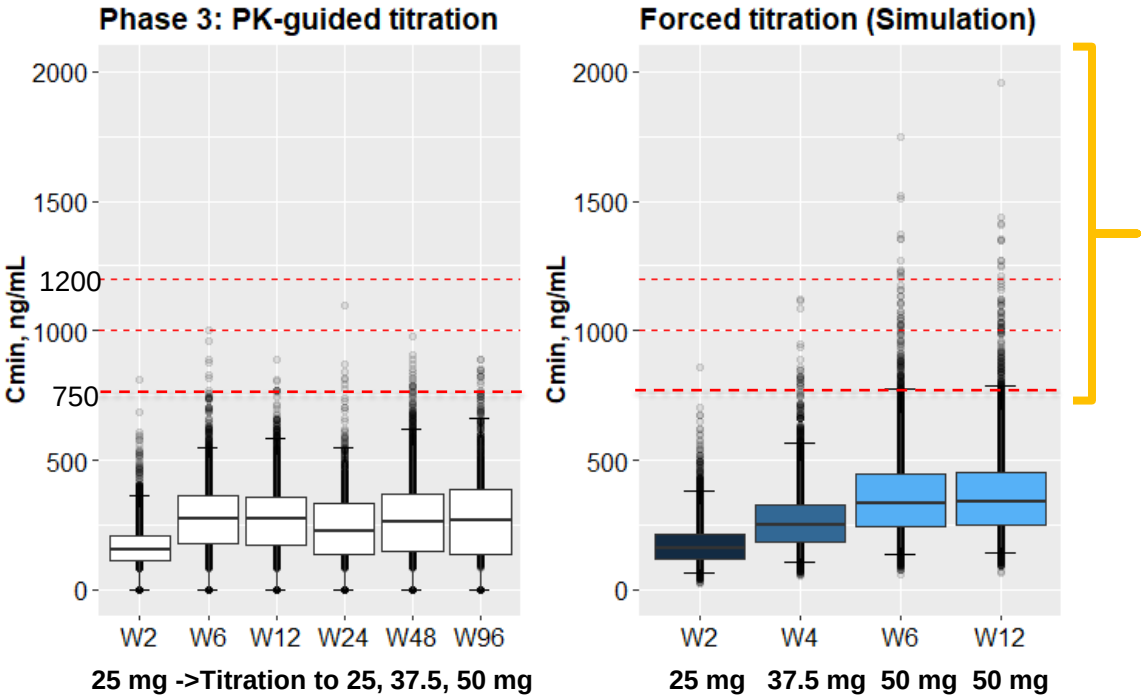
Scheduled, Forced Dosing Titration

- The Applicant initially proposed scheduled, forced dose titration, which was not tested in the GALACTIC-HF trial



OM concentrations would not be required to guide dose titration with this approach

Higher PK Exposures Anticipated with Scheduled, Forced Titration (vs. Phase 3 PK Experience)



- Increased risk of myocardial ischemia with drug level >1000 ng/mL based on Phase 1 and 2 safety data
- Limited exposure-response experience for Ctrough (Cmin) >750 ng/mL

Error bar: 2.5th – 97.5th percentile

Source: FDA's analysis

Note: Simulations for scheduled, forced titration were conducted in 4500 patients sampled from GALACTIC-HF preserving demographic characteristics.

An Example to Demonstrate the Impact of Intrinsic/Extrinsic Factors on PK of OM

- CYP2D6 genotype
  - Cytochrome P450 CYP2D6 is the most extensively characterized polymorphic drug-metabolizing enzyme where some people have no CYP2D6 activity and are poor metabolizers.
  - Subjects with CYP2D6 poor metabolizer (PM) genotype exhibited higher OM exposure ($AUC_{0-\infty}$ ↑47%) compared to those with CYP2D6 normal metabolizer genotype.
  - Patients who are CYP2D6 PMs may have an increased risk of high drug exposure without the use of a PK-guided titration.

Summary of Effect of Different Titration Regimen

- A scheduled, forced titration is expected to lead to high OM concentrations (>1000 ng/mL) in some patients.
- OM concentrations were well controlled with PK-guided titration in the phase 3 trial.
- PK-guided titration is also helpful to address potential safety concerns with elevated OM exposure due to intrinsic/extrinsic factors.

The Applicant's Newly Proposed Posology

- New proposal during the NDA review
  - Implement a PK-guided dosing strategy that resembles a simplified version of the PK-dosing strategy in GALACTIC-HF
  - PK will be measured using a Labcorp LC-MS/MS method, a laboratory-developed test not authorized by FDA, instead of the immunoassay used in GALACTIC-HF

Outline

- Efficacy
  - Adequacy of the GALACTIC-HF trial to demonstrate substantial evidence
  - Efficacy Subgroup findings
- Safety
  - Potential risk based on nonclinical data
  - Key safety findings and concern
  - Proposed dosing strategy
- Benefit-Risk Assessment

Benefit-Risk Assessment

- It is not certain whether the benefit of OM outweighs the risk
  - The small, not statistically persuasive, treatment effect from the single pivotal trial may not be adequate to establish effectiveness
  - The risk could vary depending on whether or how well a PK-guided dosing strategy is followed
  - Benefit-risk assessment is complicated by differential results in certain subgroups (i.e., LVEF and AFF)

Benefit-Risk Assessment (Cont'd)

- The potential small net benefit in the overall GALACTIC-HF population is uncertain given the issues discussed and the limitation of the analysis. This assessment only considered the first event, not all CV deaths.
- The benefit-risk profile is unacceptable under the initial proposed posology of scheduled titration
- The benefit-risk profile under the newly proposed PK-guided dosing with the LC-MS/MS assay should be similar to that in GALACTIC-HF if the PK guided dosing is universally followed as it was in the trial

Incidence Rate (IR)	Benefit Primary Composite Efficacy Endpoint (CV death +HF event)			Risk Major Cardiac Ischemic Event			Overall Benefit-Risk[2]		
	OM (per 100 PY)	Placebo (per 100 PY)	Delta[1] (per 100 PY) (95% CI)	OM (per 100 PY)	Placebo (per 100 PY)	Delta[1] (per 100 PY) (95% CI)	OM (per 100 PY)	Placebo (per 100 PY)	Delta[1] (per 100 PY) (95% CI)
GALACTIC-HF	24.2	26.3	-2.1 (-3.9, -0.3)	2.9	2.7	0.2 (-0.3, 0.8)	26.1	28.5	-2.4 (-4.2, -0.5)

[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] Overall benefit risk was calculated based on time to first of primary composite efficacy endpoint or major cardiac ischemic event

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Correction to the Briefing Document

- On p. 53, Table 16, the first line currently reads:

Baseline LVEF	OM N=4120 Events/n	Placebo N=4112 Events/n
(4,15]	123/286	14 /283

- This should read (revisions in red):

Baseline LVEF	OM N=4120 Events/n	Placebo N=4112 Events/n
[4,15]	123/286	148/283


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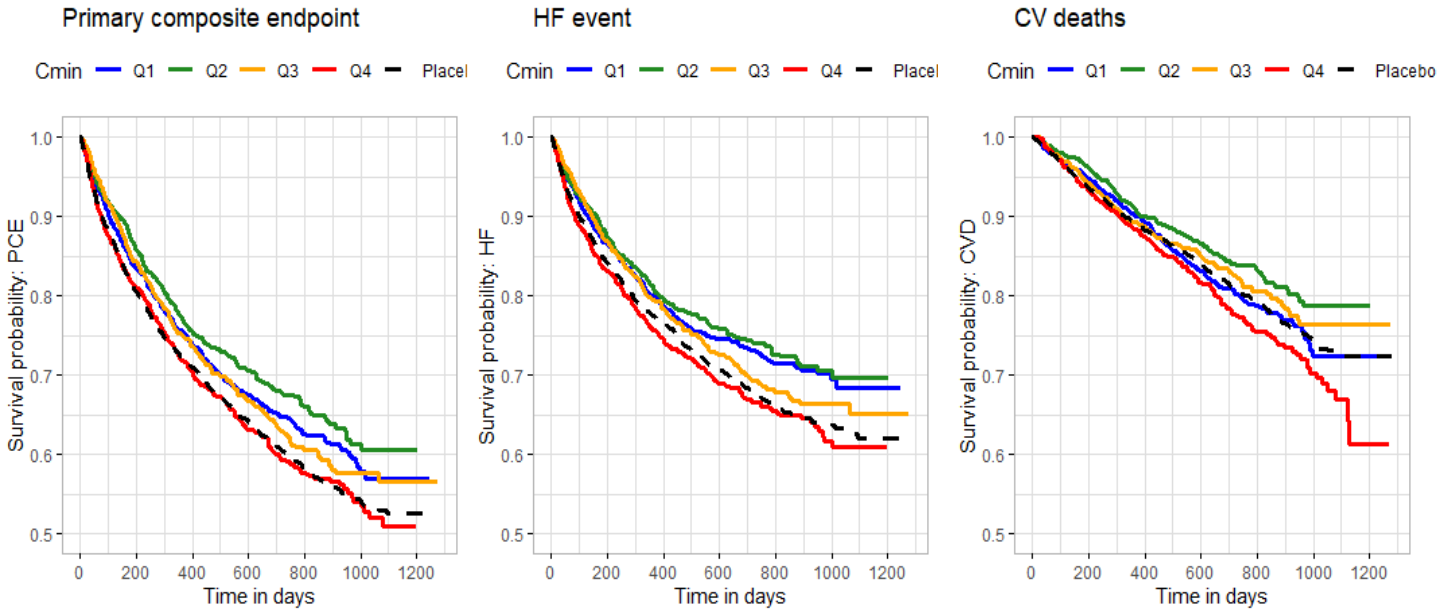
ADMINISTRATION

Backup Slides Shown
NDA 216401
Omecamtiv Mecarbil

Reviewer's analysis confirmed no apparent E-R relationship for primary composite endpoint, HF event or CV deaths

- **KM survival curves are largely overlapping across four quartiles of OM trough concentrations at Week 12**



Source: Reviewer's analysis

No Evidence of Concentration-Dependent Increase in Efficacy in GALACTIC-HF

Efficacy Endpoint/Quintile of Last Concentration Prior to or at Week 12	OM		Placebo		HR (95% CI)[1] (OM vs. Placebo)
	n/N (%)	ER (per 100 PY)	n/N (%)	ER (per 100 PY)	
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)

[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.

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

GALACTIC-HF: Summary of First Primary Endpoint Events

Events, n (%)	OM (N=4120)	Placebo (N=4112)
Cardiovascular death as first event	346 (8)	371 (9)
Cardiovascular death	239 (6)	277 (7)
Presumed cardiovascular death	71 (2)	54 (1)
Presumed sudden death	36 (<1)	40 (1)
Heart failure events as first event	1177 (29)	1236 (30)
Hospitalization for heart failure	1107 (27)	1133 (28)
Urgent heart failure ER/ED visit	45 (1)	74 (2)
Urgent heart failure office/practice visit	25 (1)	29 (1)