21 March 2024
EMA/400270/2024
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Kinharto

omecamtiv mecarbil

Procedure No. EMEA/H/C/006112

Applicant: Cytokinetics (Ireland) Limited

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. CHMP Recommendation

Based on the review of the data and the applicant's response to the list of questions on quality, safety, and efficacy, the application for omecamtiv mecarbil (KINHARTO) in the treatment of

KINHARTO is indicated for the treatment of adult patients with symptomatic chronic heart failure and reduced ejection fraction less than 30% (see section 5.1).

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the list of outstanding issues.

1.1. Questions to be posed to additional experts

N/A

1.2. Inspection issues

1.2.1. GMP inspection(s)

N/A

1.2.2. GCP inspection(s)

N/A

1.3. New active substance status

Based on the review of the data, it is considered that the active substance omecamtiv mecarbil contained in the medicinal product KINHARTO could be qualified as a new active substance.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The applicant proposed the following indication:

KINHARTO is indicated for the treatment of adult patients with symptomatic chronic heart failure and reduced ejection fraction less than 30% (see section 5.1).

Heart failure (HF) with reduced ejection fraction (HFrEF) is a chronic, progressive condition characterised by impaired cardiac contractility, in which the presence and severity of signs and symptoms of heart failure are categorised according to the American College of Cardiology Foundation/American Heart Association Stages of HF and the New York Heart Association (NYHA) Functional Classification (Yancy 2013). The natural history of HFrEF is often punctuated by frequent recurrent hospitalisations and, ultimately, a cardiovascular (CV) death.

2.1.2. Epidemiology and risk factors, screening tools/prevention

HF is a major global health concern, which affects approximately 64 million people worldwide (James 2018). In developed countries, approximately 1% to 2% of the adult population has HF, with the

prevalence rising to >10% among those 70 years of age or older (McDonagh, 2021; Groenewegen, 2020). In the United States (US) alone, an estimated 6.2 million people ≥20 years of age have HF, and the prevalence is predicted to increase by 46% by 2030 (Virani, 2020). In Europe, it is estimated that 15 million people have HF (Dickstein, 2008), with prevalence ranging from 1% to 2% in countries such as Portugal, Spain, Germany, Sweden, and Italy (Savarese, 2022). Approximately 50% of all HF cases are HFrEF (Savarese 2022), meaning that 32 million patients worldwide have HFrEF, based on current global prevalence estimates.

2.1.3. Aetiology and pathogenesis

HFrEF is a clinical syndrome characterised by cardiac systolic dysfunction. Over time, in an attempt to preserve cardiac output (CO), a series of compensatory changes can occur characterised by increased sympathetic tone, peripheral vasoconstriction, and the activation of various neurohormonal pathways. Common causes of HF include coronary artery disease, previous myocardial infarction, hypertension and diabetes.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

HF is a clinical syndrome associated with a range of LV abnormalities and is categorised based on EF. HFrEF is commonly used to describe HF patients with an EF <40%, and heart failure with preserved ejection fraction (HFpEF) is used to describe HF patients with an EF ≥50% (Ponikowski et al. 2016).

The clinical course for HFrEF patients is variable, with periods of stability punctuated by acute episodes of clinical decompensation with increased symptoms such as dyspnea, fatigue, and oedema. Even after successful recompensation, these events result in a worsening long-term prognosis as the risk for future decompensations increases, quality of life declines, and each recovery becomes less complete, which ultimately can result in CV death. HF is the leading cause of hospitalisations in patients >65 years and accounts for 1–2% of all hospitalisations in the Western world (Savarese, 2022).

Despite guideline-directed medical therapy, substantial residual risk remains, as illustrated by the results of recent large, randomised, placebo-controlled CV outcomes studies. Results from 4 such recent interventional clinical trials in patients with HFrEF, 1 evaluating an ARNi (sacubitril-valsartan), 2 evaluating SGLT2 inhibitors (dapagliflozin and empagliflozin), and 1 evaluating a soluble guanylate cyclase inhibitor (vericiguat) are presented in Table 1. In the PARADIGM-HF trial, which had a median duration of follow-up of 27 months, the incidence of CV death or hospitalisation for HF was 21.8%, the incidence of CV death was 13.3%, and the incidence of all-cause mortality was 17.0% in patients receiving valsartan sacubitril (McMurray, 2014). Importantly, in a population of worsening HF patients enrolled in the recently completed VICTORIA trial, the event rate for CV death or hospitalisation for HF was 33.6 per 100 patient-years, and the event rate for CV death was 12.9 per 100 patient-years in patients receiving vericiguat (Armstrong, 2020). Clearly, there remains a need for additional treatments with mechanisms that are complementary (and, therefore, potentially additive) to the existing GDMTs.

Furthermore, optimal doses of standard of care therapies are often not well tolerated due to their adverse events (AEs). Many existing treatment options are associated with intolerable AEs, including bradycardia, hypotension, hyperkalemia, and renal insufficiency, often leading to underuse and underdosing. Ultimately this leaves many patients with HF suboptimally treated and at risk for worse outcomes than patients who are optimally treated (Greene, 2018). Moreover, treatment with cardiac inotropes, such as dobutamine and milrinone, has been associated with increased mortality (Ahmad, 2019). Omecamtiv mecarbil has the potential to be an important addition to GDMT, not only because of its benefit in reducing the risk of HF outcomes but also because of its neutral impact on blood

pressure, renal function, and electrolyte balance, which are frequently compromised in patients with worsening HFrEF and further exacerbated by GDMT.

Outside the context of a clinical trial, in a large registry of hospitalised patients with HF (OPTIMIZE HF, n=25,245) and in the broader US Medicare population (Curtis, 2009), mortality rates at 1-year were more dire (37.2% and 35.7%, respectively). Thus, there remains a high unmet medical need for HF patients, particularly those with features of higher risk.

Table 1. Events Rates in Recent Clinical Trials in Patients With HFrEF

	PARADIGM-HF (N=8,442)		**DAPA-HF (N=4,744)**		**VICTORIA (N=5,050)**		**EMPEROR-Reduced (N=3,730)**	
	ARNi (n=4,187)	**Enalapril (n=4,212)**	**Dapagliflozin (n=2,373)**	**Placebo (n=2,371)**	**Vericiguat (n=2,526)**	**Placebo (n=2,524)**	**Empagliflozin (n=1,863)**	**Placebo (n=1,867)**
Publication Year	2014		2019		2020		2020	
Median Duration of Follow-up (months)								
	27		18.2		10.8		16	
Annualised Event Rate (Events per 100 patient-years at risk)								
Primary Composite Endpoint	10.5	13.2	11.6	15.6	33.6	37.8	15.8	21.0
CV Death	6.0	7.5	6.5	7.9	12.9	13.9	7.6	8.1
First HF Event[a]	NA	NA	6.9	9.8	25.9	29.1	10.7	15.5
All-cause Death	NA	NA	7.9	9.5	16.0	16.9	10.1	10.7

ARNi=angiotensin receptor/neprilysin inhibitors; CV=cardiovascular; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; N=number of participants in the analysis set; n=the number of participants with observed data; NA=not applicable.

[a] In VICTORIA and EMPEROR-Reduced, HF event refers to hospitalisation for HF

2.1.5. Management

Long-term goals of HF therapy include reducing death and hospital readmission rates in patients with HFrEF.

Several interventions have been shown to reduce the rate of HFrEF hospitalisations and improve mortality, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor/neprilysin inhibitors (ARNi), β-adrenergic blockers, mineralocorticoid receptor antagonists (MRAs), cardioverter devices, and cardiac resynchronisation therapy (CRT) (Yancy 2013; Zannad 2013), with the sodium-glucose cotransporter-2 (SGLT2) inhibitors now joining the list of these guideline-directed medical therapies (GDMTs) (Packer 2020; McMurray 2019; McDonagh 2021). However, none of these therapies directly address the underlying problem in HFrEF, namely cardiac contractile dysfunction.

Despite excellent background therapy, the morbidity and mortality for HF patients remain high in contemporary interventional clinical trials. Thus, there remains a great unmet medical need for HF patients, particularly in those with features of higher risk.

2.2. About the product

Mode of action

Omecamtiv mecarbil (also known as AMG 423 and CK-1827452) is a selective cardiac myosin activator that increases cardiac contractility by specifically binding to myosin at an allosteric site stabilising its lever arm in a primed position, increasing the number of myosin heads that can bind to actin filaments and undergo a power stroke once the cardiac cycle starts. As a cardiac myotrope, omecamtiv mecarbil increases the contraction of cardiac myocytes by direct action on the sarcomere in the absence of changes in the cardiac myocyte calcium transient or the rate of contractility. Instead, omecamtiv mecarbil increases the extent and duration of cardiac contraction without a significant increase in myocardial oxygen consumption.

The proposed indication is:

KINHARTO is indicated for the treatment of adult patients with symptomatic chronic heart failure and reduced ejection fraction less than 30% (see section 5.1).

The proposed posology is:

The recommended starting dose of KINHARTO is 25 mg twice daily. KINHARTO can be started in outpatients or inpatients hospitalised for heart failure, whose condition has been stabilised.

KINHARTO is administered at doses of 25 mg twice daily, 37.5 mg twice daily, or a maximum dose of 50 mg twice daily. After 2 weeks at the starting dose of 25 mg twice daily, the dose should be increased to 37.5 mg twice daily, and after another 2 weeks, increased to the maximum dose of 50 mg twice daily.

Withhold KINHARTO if signs or symptoms of acute myocardial ischaemia or myocardial infarction occur and initiate appropriate assessment and treatment of the patient (see section 4.4).

If the ischaemic event is judged to be related to KINHARTO, consider decreasing the dose or discontinuing KINHARTO. If the ischaemic event is determined to be unrelated to KINHARTO, then KINHARTO can be resumed at the physician's discretion, at the same dose prescribed prior to discontinuation.

2.3. The development programme/compliance with guidance/scientific advice

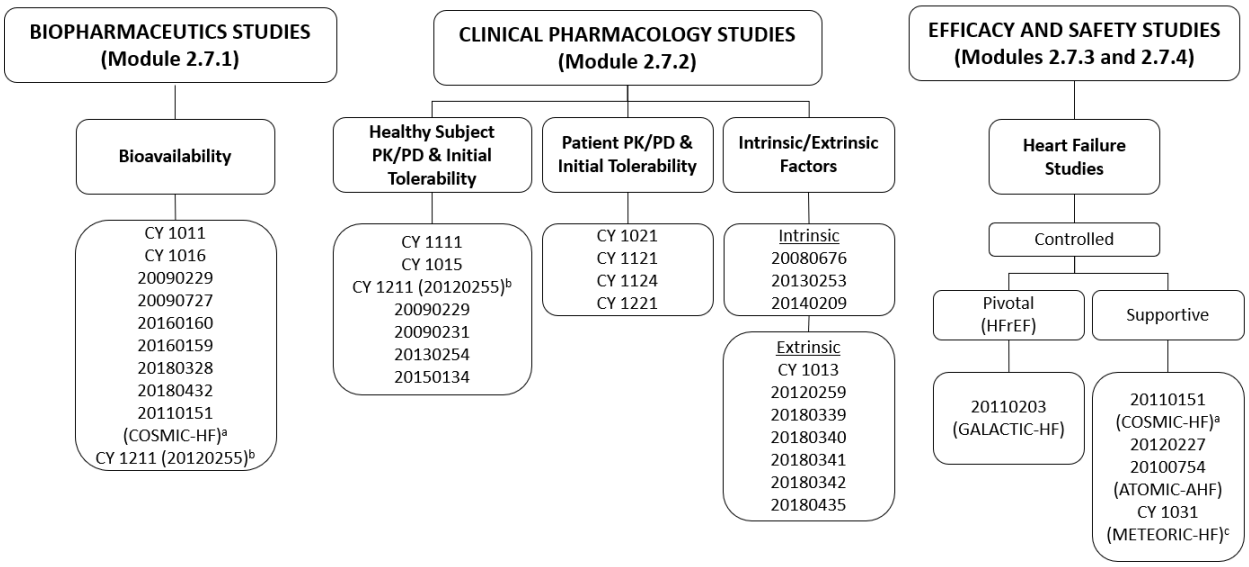
Development programme

The clinical development programme for omecamtiv mecarbil comprises 33 completed clinical studies (Error! Reference source not found.), all included in this marketing application, enrolling approximately 10,500 participants evaluating healthy participants, participants with chronic HF, participants with acute HF, and participants with other conditions such as renal and hepatic impairment.

The PK, PD, and safety and tolerability profile of omecamtiv mecarbil were first evaluated in healthy participants (CY 1111, n=35 randomised, 34 treated) and then in participants with HF (CY 1121, n=45 randomised and treated) using an IV formulation with infusions up to 72 hours in duration. The effects of chronic oral dosing with omecamtiv mecarbil and the implementation of a PK-guided dose selection strategy informing the transition into Phase 3 were evaluated in the Phase 2 Study 20110151 (COSMIC HF, Expansion Phase, n=448 randomised, 445 treated).

The clinical efficacy and safety profile of omecamtiv mecarbil in support of the proposed indication in participants with chronic HFrEF is based primarily on data from the completed Phase 3 CV outcomes study, 20110203 (GALACTIC-HF, n=8,256 randomised, 8,211 treated).

Other studies in chronic HF (CY 1021, CY 1221, CY 1124, 20120227, and CY 1031 [chronic HF and reduced exercise capacity]) and acute HF (20100754 [ATOMIC-AHF]) contributed to the overall development programme. A comprehensive array of biopharmaceutic and clinical pharmacology studies were also completed as part of the development programme.



HFrEF=heart failure with reduced ejection fraction; PD=pharmacodynamics; PK=pharmacokinetics.

Figure 1. Omecamtiv Mecarbil Clinical Studies Included in the Marketing Authorisation Application

Compliance with CHMP guideline

The most relevant CHMP guidelines applied:

Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure (CPMP/EWP/235/95, Rev.2. July 2017)

Scientific Advice

During the course of development, the applicant sought regulatory and scientific advice from the following agencies:

- European Medicines Agency (EMA) (April 2016, June 2019)

EMEA/H/SA/3243/1/2016/III

The applicant raised questions concerning pre-clinical and clinical development, focussing on the GALACTIC-HF study.

- It was stated that the proposal to include admission to ED/urgent care centres for HF as part of the PEP is questioned. The EMA recommended excluding such events from the primary endpoint definition. This advice has not been pursued by the applicant.
- The EMA did not support the secondary endpoints (components of the composite), the endpoint time to first HF hospitalisation. The informative censoring of patients who die before hospitalisation creates the potential for this analysis to be misleading. The information about time to first hospitalisation is already adequately captured by the primary composite (if CV death is considered a severe HF hospitalisation). The applicant has not pursued this advice. The other secondary outcomes, time to CV death and time all-cause mortality, are acceptable. Furthermore, the chosen exploratory outcomes are reasonable and acceptable, and in line with the advice, time to recurrent hospitalisations has also been included as an exploratory outcome.

The key advice points and compliance with these points are tabulated in Table 2.

Table 2. Key Advice Points of EMEA/H/SA/3243/1/2016/III

Advice point:	Compliance:
The addition of an additional Ctrough measurement at Week 6 to guide potential down-titration at Week 8.	Compliant
Excluding admission to the emergency department/urgent care centre for HF from the primary endpoint definition.	Not complaint, with rationale
Including analysis for recurrent hospitalisations	Compliant
The endpoint time to first HF hospitalisation is not supported. The informative censoring of patients who die before hospitalisation creates the potential for this analysis to be misleading.	Non-compliant, with rationale.
A composite of time to first HF hospitalisation or all-cause mortality should be added as a secondary endpoint.	Compliant
It is critical to maintaining the blind after PK sampling and dose titration in order to maintain the integrity of the trial.	Compliant

At interim-analysis, the applicant will only claim statistical significance if the time to CV death is statistically significant too	Compliant, but not applicable.
It is important to predefine and justify the Minimal Clinically Important Difference for KCCQ	Not compliant, no rationale

- EMEA/H/SA/3243/2/2019/III

  The applicant raised questions concerning quality and clinical development. Their questions focused on the choice of regulatory starting materials, other quality aspects and IVIVC (not pursued).

- The applicant was advised to redefine one starting material to ensure consistent quality.
- The applicant was advised that one starting material could be acceptable provided that a detailed discussion on impurities is provided, along with analytical data for further confirmation.

- Medicines and Healthcare products Regulatory Agency (MHRA) (July 2019)

2095/Omecamtiv mercarbil

The applicant raised questions concerning the conduct of the TQT study.

- The MHRA agreed with the proposed plan to conduct the TQT study but mentioned that the potential risk of myocardial ischeaemia, TQT endpoints, and the omecamtiv mecarbil action on ion channels needed further consideration.

2.4. General comments on compliance with GMP, GLP, GCP

GMP: No pre-approval inspections to verify GMP compliances are deemed necessary.

GLP: No GLP inspections are deemed necessary.

GCP: No GCP inspections are deemed necessary.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

2.5.2. New active substance status

Based on the review of the data, it is considered that the active substance omecamtiv mecarbil contained in the medicinal product KINHARTO could be qualified as a new active substance.

2.5.3. Orphan designation

N/A

2.5.4. Similarity with orphan medicinal products

N/A

2.5.5. Information on paediatric requirements

A paediatric investigation plan (PIP) for omecamtiv mecarbil, with a deferral and a waiver, was adopted by the Paediatric Committee (PDCO) in 2015 in the condition 'Treatment of heart failure'. A decision with annexes (P/0197/2015) was issued on 4 September 2015, at this time the development of omecamtiv mecarbil was under Amgen's sponsorship.
A modification to the PIP (EMEA-001696-PIP01-M01) was submitted on 19 December 2019 and adopted by the PDCO on 29 March 2019. The Decision with annexes (P/0172/2019) was issued on 15 May 2019. Cytokinetics resumed the role of global sponsor and another PIP modification (EMEA-001696-PIP01-14-M02) was submitted on 21 March 2022. A positive PDCO opinion was adopted on 24 June 2022. The decision with annexes (P/0260/2022) was issued on 15 July 2022.

The PIP comprises 3 studies, including:

- Study 1: Quality-related study to develop an age-appropriate formulation
- Study 2: Two-part clinical study consisting of an open-label, multiple-dose safety, PK and PD study followed by a randomised, double-blind, placebo-controlled, multicentre PK, PD, safety and tolerability study in paediatric patients with chronic heart failure
- Study 3: An extrapolation study to extrapolate the clinical efficacy data from adults to paediatric chronic heart failure patients.

EMA confirmed, as part of the presubmission interaction, that all 3 studies are deferred until after the MAA submission, no data need to be submitted, and consequently, a compliance check is not required.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as prolonged-release tablets containing 25 mg, 37.5 mg or 50 mg omecamtiv mecarbil as an active substance.

Other ingredients are fumaric acid, hypromellose, lactose monohydrate, magnesium stearate and microcrystalline cellulose as part of the tablet cores and macrogol, polyvinyl alcohol, talc, titanium dioxide and iron oxides (red and/or yellow) as part of the film-coating.

The product is available in PVC/PCTFE/Aluminium blisters in an outer carton.

3.1.2. Active Substance

3.1.2.1. General Information

International non-proprietary name (INN):	omecamtiv mecarbil
United States Adopted Name (USAN):	omecamtiv mecarbil
Chemical names:	methyl 4-[[2-fluoro-3-[(6-methylpyridin-3-yl)carbamoylamino]phenyl]methyl]piperazine-1-carboxylate
Other name:	1-piperazinecarboxylic acid, 4-[[2-fluoro-3-[[[(6-methyl-3-pyridinyl)amino]carbonyl]amino]phenyl]methyl]-, methyl ester,
CAS registry number:	873697-71-3 (free base)
Laboratory code:	AMG 423 CK-1827452 (CK-452)
Molecular formula:	$C_{20}H_{24}FN_5O_3$
Relative molecular mass:	401.44 g/mol

Physical characteristics (description):	White to off-white powder	
Solubility:		
pKa-value:	5.11 ± 0.02 and 6.25 ± 0.0	
pH		
Partition coefficient:	2.9	
Thermal properties:	Weight loss above 229°C due to thermal decomposition. (thermogravimetric analysis) 255.2°C due to decomposition (differential scanning calorimetry)	
Solubility	Solvent	Solubility (mg/mL)
	Ethanol	2.37
	DMSO	25.0
	PEG 400	1.89
Hygroscopicity:	Slightly hygroscopic	
Stereochemistry:		

Full information on the active substance is provided in the dossier.

3.1.2.2. Manufacture, process controls and characterisation

The proposed starting materials are acceptable, and the selection of these starting materials is in line with previous scientific advice. All limits have been adequately justified using spike and purge studies where relevant, and suitability of the analytical methods has been demonstrated.

The manufacturing process has been described in sufficient detail, and a flow chart representing the process has been provided. The process parameters and in-process controls are adequate in combination with the process manufacturing narrative and the intermediate specifications. Process validation studies have been conducted for three batches on a commercial scale, which is sufficient for a non-sterile active substance. Potentially mutagenic impurities have generally been well investigated and controlled.

The drug substance structure has been adequately elucidated. The active substance does not contain any chiral centres. Polymorphism has been adequately investigated.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The inclusion of the selected tests in the proposed specification are acceptable, and the specification is in line with ICH Q6A and batch analytical data at release and during stability.

The analytical methods have been described, and validation has been adequately performed in line with ICH Q2A. Batch analytical data has been provided for 27 batches, including three batches manufactured with the current process , and complies to the proposed specification. Sufficient information has been provided on the reference standards.

3.1.2.4. Stability

Stability data on the active substance has been provided. The used conditions are in line with ICH guidelines and are acceptable. The batches were stored in a smaller version of the proposed container closure system.

The stability studies show that omecamtiv mecarbil is stable with little to no changes in all monitored parameters for the studied period. The proposed re-test period is supported.

Photostability studies have been conducted in line with ICH Q1B as per the requirements. Forced degradation studies were carried out. The stability indicating nature of the related substances/assay test method has been demonstrated.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and pharmaceutical development

Description of the product

The drug products are prolonged-release tablets in three different strengths containing 25 mg, 37.5 mg and 50 mg omecamtiv mecarbil.

The different tablet strengths are described.

Sufficient information on the description and composition of the drug products has been provided.

The excipients are well-known and widely used in oral pharmaceutical preparations.

Pharmaceutical development

Multiple solid dosage formulationswere used during phase 1 clinical development. Different modified-release technologies were evaluated.

Multivariate studies have been performed to further optimise the most promising phase 3 formulation.

Based on further optimisation studies, minor changes were implemented for the commercial formulation compared to the phase 3 formulation. Furthermore, the film-coating was changed. Similar dissolution profiles (f2 >50) were demonstrated.

The dissolution method development has been adequately described, and the choices made are justified. The discriminatory power of the QC dissolution method was demonstrated. The manufacturing process development has been adequately described. The development was guided by prior experience and risk analysis. Where applicable the results of the development studies support process parameter settings (target and ranges) and in-process control acceptance criteria as laid down in the manufacturing process description.

Packaging

The drug products are packed in blisters. The suitability of this packaging material has been sufficiently confirmed by the formal stability studies.

3.1.3.2. Manufacture of the product and process controls

Manufacture

The manufacturing process has been described in sufficient detail. The proposed process parameter settings are supported.

Supportive studies and adequate details on the container closure system have been provided.

Process controls

The in-process control tests and acceptance criteria are acceptable and are in line with general Ph.Eur. requirements or development and validation data.

Process validation

The drug product is a prolonged-release tablet and is considered a specialised pharmaceutical dose form (prolonged-release tablet). Therefore, the method of manufacture is considered non-standard.

The manufacturing process has been adequately validated on three full-scaled batches per strength.

3.1.3.3. Product specification, analytical procedures, batch analysis

The drug product specification includes tests for description, identification (by HPLC retention time and UV spectrum), assay, organic impurities, content uniformity, dissolution and microbial limits.

An adequate elemental impurities risk assessment has been performed. However, the provided nitrosamine risk evaluation is not acceptable yet (major objection [MO]).

Analytical procedures and reference standards

The analytical procedures have been described in sufficient detail, and the in-house analytical procedures have been adequately validated. In addition, the stability indicating nature of the HPLC methods for assay and organic impurities was demonstrated through forced degradation studies.

Batch analysis

Batch analysis data have been provided for drug product batches consistently demonstrating compliance with the drug product specification.

Container closure

The container closure system has been described in sufficient detail. The control of the blister materials is adequate and the materials of the PVC/PCTFE (Aclar) forming foil and aluminium lidding foil comply with the relevant Ph.Eur. monograph and/or regulation on food contact materials.

3.1.3.4. Stability of the product

Stability data have been provided. The stability conditions were according to ICH guidelines.

All parameters were well within the specification limits.

The claimed shelf-life is acceptable.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

A major objection on the nitrosamines control strategy is outstanding as well as some other concerns that need to be resolved before the drug product can be accepted.

3.2. Non-clinical aspects

3.2.1. Introduction

Omecamtiv mecarbil is a novel small-molecule cardiac myotrope that directly activates cardiac myosin and is intended for patients with heart failure. For the non-clinical programme, a complete package of studies was submitted by the applicant, covering pharmacodynamics, pharmacokinetics and toxicology with the appropriate *in vitro* and *in vivo* studies. Most pivotal studies were performed in rats and dogs, with specific studies (also) performed in mice, monkeys and rabbits.

The assessment of the non-clinical dossier differs slightly from the standardised procedure. The applicant proposes a dose in humans resulting in C_{max} between 350 and 750 ng/mL and warns not to exceed the C_{max} of 1200 ng/mL. In the clinic, C_{max} values of 330 ng/mL (+/- 80 ng/mL) were obtained with 50 mg omecamtiv mecarbil BID at the lower spectrum of the pharmacological active concentration (300-1000 ng/mL). Since this broad range in C_{max} target concentration in heart failure patients, the following classes were used in order to evaluate the non-clinical findings: class I) <-500 ng/mL for the average clinical C_{max} and lower spectrum of the PD active concentration; class II) 500-750 ng/mL for the upper spectrum of the PD active concentration relevant for patients with elevated Cmax values; and class III) 750-1200 ng/mL for the concentration that may show toxicity and exaggerated PD relevant for patients with very high C_{max} values.

3.2.2. Pharmacology

Omecamtiv mecarbil (OM, also referred to as AMG 423 or CK-1827452) is a first-in-class small molecule cardiac myotrope, indicated for adult patients with symptomatic chronic heart failure with reduced ejection fraction (HFrEF) less than 30%. The proposed maximum dose is 50 mg twice daily, aiming at a plasma concentration of 300-750 ng/mL in humans.

3.2.2.1. Primary pharmacodynamic studies

In general, OM appears to increase the transition rate of cardiac myosin from the weak actin-binding conformation to the strong actin-binding conformation, thereby increasing cardiac contractility. It can bind to myosin at an allosteric site, stabilising the lever arm in the primed position, increasing the number of myosin heads that can bind to actin filaments and undergo a power stroke once the cardiac cycle starts. OM appears to increase cardiac contractility without increasing cardiac myocyte intracellular calcium or myocardial oxygen consumption.

Myosin activation (in vitro)

The pharmacological potency of OM and some of its metabolites was evaluated in multiple *in vitro* studies. In the first study (Study NCD05-026), the effect of OM on the ATPase rate at the 50% point of the calcium activation curve was evaluated. OM increased the ATPase rate in the bovine cardiac regulated system (consisting of S1, actin, troponins and tropomyosin, but lacking structure of the sarcomere) and skinned bovine myofibrils (in which the architecture of the cardiac sarcomere is preserved) with an EC50 of 0.62 µM. Isothermal titration calorimetry experiments confirmed the direct binding of OM to bovine cardiac S1. In addition, transient kinetics experiments with bovine cardiac S1 demonstrated that OM did not affect ATP binding or ADP release, but inhibited phosphate release from bovine cardiac S1 in the absence of actin. In conclusion, OM appears to activate the cardiac myosin ATPase in the myofibril or regulated thin filament and inhibits the myosin ATPase in the absence of actin.

In a second study (Study NCD11-118), OM and metabolites M1, M2, M3, M4 and M5 were evaluated in skinned bovine cardiac myofibrils, measured by the effect on ATPase rate at the 25% point of the calcium activation curve. These metabolites were detected in human hepatocytes (Study 112319), but it should be noted that no major metabolites (>10%) were identified in humans. OM and metabolite M5 were potent activators with an EC50 of 0.9 µM and 1.7 µM, respectively. Since M5 is only present at <3% in humans and not considered a major metabolite, the clinical relevance of this finding is limited. Metabolites M4 and M3 were relatively weak activators with EC50 values of 11 µM and 36 µM, respectively. In humans, M3 and M4 were the most abundant metabolites at 6% and 3.3%, respectively. At the proposed posology, these metabolites are considered pharmacologically inactive. Finally, metabolites M1 and M2 were very weak activators with a EC50 >100 µM.

Cardiac muscle selectivity (in vitro)

To evaluate the selectivity of OM, similar systems of other sources (rabbit skeletal and chicken smooth muscle) were also evaluated (Study NCD05-026). OM had no effect on the ATPase rate in any smooth muscle system. Similar as in the cardiac system, OM increased the ATPase rate in the skeletal skinned myofibrils, although at an EC50 of 18.65 µM (30-fold higher compared to cardiac system). Additionally, OM increased ATP hydrolysis in a heterologous system of cardiac S1 myosin and cardiac thin filament, but when the cardiac S1 myosin was replaced with skeletal S1 myosin, this effect was abolished. Furthermore, OM had no effect on ATP hydrolysis in a heterologous system of skeletal S1 myosin and skeletal thin filament, but when the skeletal S1 myosin was replaced with cardiac S1 myosin, ATP hydrolysis was increased.

In a secondary pharmacodynamics study (NCD05-030), the effect of 10 µM OM on isometric force production in skinned skeletal muscle fibres was evaluated. At low calcium concentrations (pCA >6, equivalent to that in resting muscle), OM had no effect on the relative tension of skeletal muscle fibres. A modest calcium-sensitising shift was observed at intermediate calcium concentrations (pCa 5.25-6, equivalent to that in contracting muscles). The maximal isometric tension was slightly blunted at saturating calcium conditions (pCa 4-5). The applicant states that this effect occurs at plasma drug concentrations exceeding clinical concentration; however, since only one concentration was tested, no

No Observed Effect Level (NOEL) was determined. It is acknowledged that there was no effect on motor function in the safety pharmacology study in the Albino rat (Study NCD05-018).

Effect on contractility (ex vivo)

The effect of OM on cardiac contractility in isolated adult rat ventricular myocytes was evaluated in multiple studies at concentrations between 0.08-3 µM OM. In addition, studies with isolated dogs (healthy and with heart failure) ventricular myocytes were performed at concentrations between 0.1-10 µM OM. In addition, an exploratory study in human atrial and ventricular trabeculae was performed at concentrations between 0.1-3 µM OM.

In the first study in rat myocytes (Study 123960), increasing contraction amplitude, velocity and duration were observed at 0.1 and 0.3 µM OM, indicative of enhanced contractility. However, at concentrations of ≥1 µM OM, these parameters were decreased. In addition, resting sarcomere length was decreased in a concentration-dependent manner at ≥0.3 µM OM, indicative of relaxation impairment. These results indicate that OM can have a dual effect on contractility.

In the second study in rat myocytes (Study NCD05-027), qualitatively similar results to the previous study were observed (Study 123960). Fractional shortening was increased at ≥0.2 µM, but was significantly decreased at 0.8 µM. At ≥0.4 µM OM, diastolic cell length was shortened and contraction and relaxation velocities were decreased. When the pacing frequency was lowered, fractional shortening was further increased while the effects on diastolic cell length were less pronounced. Conversely, fractional shortening and cell length were further decreased when the pacing frequency was increased to 3 Hz, which clearly demonstrates the effect of the pacing frequency on contractility parameters after OM exposure.

In the first study in dog myocytes (Study 151983), concentration-dependent increased contraction amplitude, velocity and duration and relaxation velocity were observed at ≥0.1 µM OM, indicative of enhanced contractility. However, at ≥1 µM OM, contraction and relaxation velocity were decreased, which was most pronounced at 3 µM. In addition, resting sarcomere length was decreased concentration-dependent at ≥0.3 µM OM, indicative of relaxation impairment. In general, these findings are in line with the study in rat ventricular myocytes (Study NCD05-027, Study 123960), demonstrating the dual effects on contractility.

In the second study in myocytes from a healthy dog (Study 123962), increasing contraction amplitude and duration was observed, indicative of enhanced contractility. In addition, contraction velocity decreased in a concentration-dependent manner at ≥1 µM OM. Relaxation velocity was increased at concentrations up to 1 µM, but decreased at ≥3 µM OM. Together with a concentration-dependent decrease in resting sarcomere length at ≥1 µM, this could be indicative of relaxation impairment. In general, these findings are in line with the studies in isolated rat ventricular myocytes (Study 123960, Study NCD05-027) and isolated dog ventricular myocytes (Study 151983). In ventricular myocytes from a dog with heart failure, OM appeared more potent, and enhanced contractility was already observed at the lowest tested dose of 0.1 µM. It should be noted that basal levels of the measured parameters from myocytes of healthy and heart failure myocytes were not reported nor compared in the study report, hampering the interpretation of the results.

In a final exploratory *ex vivo* study with human atrial and ventricular trabeculae (Study 123685), OM increased the maximum amplitude of contraction in both atrial and ventricular human trabeculae at ≥1 µM OM, as expected from a positive inotrope. In addition, OM increased the duration of contraction transient at 10%, 50% and 90% relaxation in both trabeculae at 3 µM OM.

Effect on calcium transient (ex vivo)

The magnitude and kinetics of the cellular calcium transient were explored in isolated rat and dog cardiac myocytes. In rat myocytes (Study NCD05-027), OM did not affect the calcium levels and

kinetics at 0.2 µM, which could indicate that OM-induced cardiac contractility is not due to effects on the Ca transient. It should be noted that it would have been more informative when a relevant concentration range of OM was evaluated (instead of a single concentration of 0.2 µM) to determine the effect on Ca transient (without the addition of a myosin inhibitor to correct for large diastolic cell length changes at 10 µM OM).

In dog myocytes (Study 151983), OM prolonged Ca-transient duration at ≥1 µM, and at 3 µM, the velocity of diastolic Ca-transient was also decreased. In general, this suggests that OM directly interacts with the cardiac sarcomere, and not via a transient calcium mechanism at clinically relevant concentrations, although this effect cannot completely be excluded for patients with higher exposure levels (≥400 ng/ml). In addition, Ca transient was only evaluated in "healthy" systems, not in non-clinical disease models.

In vivo activity

The *in vivo* activity of OM was evaluated in multiple studies with rats and dogs using (bolus and continuous) intravenous administration in both healthy animals as in animals with induced heart failure.

In the study in rats (Study NCD05-032), healthy rats with plasma levels of ≥173 ng/ml (0.43 µM) demonstrated a dose-dependent increase in fractional shortening and ejection fraction and decreased systolic diameter, indicative of increased contractility. At the highest dose, animals with plasma levels of 666 ng/ml (1.66 µM) displayed diastolic relaxation impairment (as indicated by decreased left ventricle dimensions), which can be considered exaggerated pharmacology. No clear effect was observed on mean arterial- diastolic- and systolic pressure or heart rate. A similar response on fractional shortening and ejection fraction was obtained in rats with induced heart failure and sham-operated animals. In contrast, high-dose rats with induced heart failure, reaching plasma levels of 1136 ng/ml (2.83 µM), did not demonstrate a sharp decrease in diastolic and systolic diameter as compared to sham-operated animals with plasma levels of 947 ng/ml (2.36 µM). The applicant hypothesises that this could be due to stiffness of the ventricle, perhaps from scar tissue and fibrosis. Additionally, a significant decrease in heart rate was observed at the highest tested dose in both sham control animals and animals with heart failure. No additional haemodynamic parameters were monitored in these animals. Finally, it should be noted that two animals with heart failure died during or immediately following drug treatment at the highest dose; however this was not discussed by the applicant. In conclusion, the intended pharmacological response was observed at exposure levels of ≥173 ng/ml in healthy rats and rats with heart failure, while signals of impaired relaxation were observed at exposure levels of ≥666 ng/ml, which is within the proposed clinical range, demonstrating a narrow therapeutic window.

In the first study in healthy dogs (Study NCD05-025), a dose-dependent increase in fractional shortening and ejection fraction was observed at ≥0.1 mg/kg/h, resulting in plasma exposure levels of ≥68 ng/ml (0.17 µM). At doses of ≥0.3 mg/kg/hr, with plasma exposure levels of ≥225 ng/ml (0.56 µM), this was accompanied by decreased systolic diameter, reflecting increased contractility of the ventricle. In general, these changes were still observed 1 hour after the 60-minute infusion. No effect was observed on diastolic diameter or heart rate. In contrast to the study in rats (NCD05-032), no exaggerated pharmacology was observed at the highest tested dose which resulted in exposure levels of 763 ng/ml (1.9 µM).

In the first phase of a second study in dogs (Study CV04-0058), dogs with normal cardiac function displayed a dose-dependent increase of cardiac contractility 5 minutes after bolus dosing, indicated by increased myocardial wall thickening and fractional shortening starting at the lowest tested dose of ≥0.25 mg/kg OM. This resulted in increased cardiac output and stroke volume at 0.5 mg/kg, but these parameters returned towards pre-dose levels at 1 mg/kg. However, coronary blood flow (a surrogate

for myocardial oxygen demand) was increased at ≥0.5 mg/kg, and this was accompanied by increased Weiss tau (index for diastolic function) and mean arterial pressure at the highest test dose of 1 mg/kg. Total peripheral resistance decreased at 0.5 mg/kg but returned towards pre-dose levels at 1 mg/kg. Heart rate was not affected by OM. No plasma exposure levels were determined in this phase.

In the second phase of this study, 15 minutes after the start of dosing (0.5 mg/kg bolus, followed by 0.5 mg/kg/hr continuous infusion), healthy dogs and dogs with congestive heart failure had plasma exposure levels of 425 ng/ml (1.06 µM) and 341 ng/ml (0.85 µM), respectively. It should be noted that there was high variability in exposure and the observed parameters between animals. Both healthy dogs and dogs with congestive heart failure displayed increased stroke volume, myocardial wall thickening, and fractional shortening. Similar as in the first phase, both groups also demonstrated increased Weiss tau and increased coronary blood flow, although less pronounced. In this phase, heart rate and left atrial pressure were also decreased. In dogs with congestive heart failure, the increase in stroke volume and fractional shortening was more pronounced, which resulted in increased cardiac output. In healthy dogs, this was not evident, which is in contrast with the observations of the first phase of this study. 7-8 hours after the start of dosing, dogs with congestive heart failure demonstrated a sustained effect in which fractioning shortening, myocardial wall thickening, cardiac output and stroke volume were further increased, and heart rate and left atrial pressure were further decreased. In addition, the total peripheral resistance was decreased. This could reflect a reflex-mediated response to the increase in cardiac output. The plasma concentration after 8 hours was 542 ng/ml (1.35 µM). In general, these findings were similar to the study in rats with heart failure (Study NCD05-032) and demonstrated the pharmacological activity OM in this model.

To evaluate the possible waning of the pharmacological effect of OM after repeated exposure, and to compare the PK-PD profile after oral vs intravenous administration, a final *in vivo* study was conducted in dogs (Study NCD05-049). The pharmacological response did not appear to be blunt, and no accumulation of the drug or metabolites had appeared. In addition, the fractioning shortening and plasma levels were similar after the IV dose and oral dosing, indicating that PK/PD relationship was similar between different administration routes.

3.2.2.2. Secondary pharmacodynamic studies

To exclude important potential off-target interactions, OM was screened *in vitro* against a panel of 26 (Study CV04-0069) or 60 (Study 119745) off-target receptors, channels, and transporters at a single concentration of 10 µM. In the first study, there was no significant inhibition (>50%) of specific radioligand binding at any of the receptors tested. In the second study, only significant competition was observed for the serotonin receptor 7 (5-hydroxytryptamine receptor 7 [5HT7R]) (58% inhibition). In a confirmatory study (Study 119877) in Chinese Hamster Ovary cells stably transfected with human 5HT7R, OM had no antagonistic activity in a concentration range of 0.03-100 µM. However, OM weakly inhibited the activity of serotonin (IC50= 56 µM). This finding is likely not relevant, since this concentration is far above clinical concentrations.

To evaluate the potential inhibition of human platelet phosphodiesterase type 3 (PDE3), PDE3 activity (measured by [3H]AMP formation) was evaluated after incubation with 10 or 30 µM OM (Study CV04-0070). At these tested concentrations, OM displayed no PDE3 inhibitory activity. This is also in line with the findings in isolated adult rat cardiac myocytes (Study NCD05-027).

Since increased fractional shortening may be secondary to afterload reduction produced by vasodilation, the effect of 0.1-100 µM OM on vascular tone (isometric tension) was evaluated in cross-sectional rings of rat aorta stimulated with phenylephrine (Study NCD05-031). OM was a weak vascular relaxant in rat aortic rings (estimated IC50=25.7 µM), which exceeds clinical concentrations and is therefore not considered relevant.

3.2.2.3. Safety pharmacology programme

Safety pharmacology parameters of OM were assessed in GLP-compliant study for the central nervous-, cardiovascular-, respiratory- and renal systems. At doses of up to 6 mg/kg/day OM (continuous IV infusion for 6-hours), which was the maximum tolerated dose in acute toxicology studies (see section 4.1), there were no neuropharmacologic and behavioral (Study NCD05-018), respiratory (Study NCD05-019), or renal (Study NCD05-021) functional effects. No plasma concentration levels were determined in these studies, but in an acute dose range finding study (Study NCD05-009), this high dose resulted in plasma concentrations of 898 ng/ml, which is not far above the intended clinical concentrations.

The cardiovascular safety pharmacology of OM was evaluated in a series of *in vitro*, *in vivo*, and *in silico* studies.

hERG, Cav1.2 and Nav1.5 channel current inhibition

In a GLP compliant study with OM (Study NCD05-022), concentration-dependent inhibition of the hERG potassium channel current in HEK293 cells was observed at ≥10 µM OM, with 43.6% inhibition at 100 µM. The IC50 for hERG current inhibition was estimated to be 125.5 µM. In another GLP-compliant study M4 (Study 121085), significant inhibition (16,3%) was observed at 300 µM. Additionally, concentration-dependent inhibition of peak tetrodotoxin-resistant voltage-gated sodium channel Nav1.5 current was observed at ≥30 µM OM, and for the voltage-gated L type calcium Cav1.2 current, inhibition was only observed at 300 µM OM (Study 152017, non-GLP). Metabolite M4 did not demonstrate any significant inhibition on the hERG and Cav1.2 current, and only slight inhibition of the Nav1.5 current at the highest concentration tested (300 µM). In conclusion, the clinical relevance of hERG, Cav1.2 and Nav1.5 channel current inhibition are considered limited since they were observed at concentrations far above the clinical concentrations of both OM and M4.

To assess potential OM-induced ventricular myocyte repolarisation abnormalities, an *in silico* model of the human ventricular action potential was used, based on current channel inhibition values obtained in previous *in vitro* studies (Study NCD05-022 and Study 152017). In this model, OM prolonged action potential duration at ≥10 µM, but did not induce early after depolarisations. In conclusion, the pro arrhythmic risk was considered low, since a similar ProA score was obtained as the negative control compound verapamil.

Cardiovascular safety studies (ex vivo)

In both isolated rat hearts (Study 123959) and isolated rabbits hearts (Study 123447), QTc and JTc intervals were shortened, indicative of shortened ventricular repolarisation, however the mechanism behind these findings remains unknown. This was observed at ≥40 ng/ml (0.1 µM, lowest tested dose) in rat hearts, and at ≥401 ng/ml (1 µM) in rabbit hearts. No clear effect on the PR or QRS interval was observed, which indicates that ventricular depolarisation and excitation conduction was not altered at concentrations up to 1204 ng/ml (3 µM, highest tested dose). In addition, a concentration-dependent decrease in heart rate was observed in both species, although this effect was more pronounced in the isolated rat hearts. Ventricular contractility was decreased concentration-dependently at ≥401 ng/ml in both species.

In a GLP-compliant study with isolated canine Purkinje fibres (NCD05-023), OM induced shortening of cardiac action potential duration ADP at 60, and 90% repolarisation at all tested concentrations (3-30 µM) and stimulus intervals (2s simulating bradycardia, 1s simulating normocardia and 0.5s simulating tachycardia), but the changes were relatively small and not concentration-dependent. The shortening of the action potential duration could be due to the shortened QTc interval as observed in isolated rabbit and rat hearts (Study 123959, Study 12344). In conclusion, OM did not prolong action potential

repolarisation at concentrations which are above the clinical concentrations (≥1200 ng/ml), and no relevant signals were observed in the clinic.

Cardiovascular safety studies (in vivo)

In an exploratory GLP-compliant escalating dose range finding study (NCD05-013), conscious male beagle dogs receiving ≥3 mg/kg/hr, resulting in plasma levels of 1399-1442 ng/ml, displayed a slowly decreasing dP/dt accompanied by decreased systolic, diastolic and mean blood pressure and increased left ventricular end-diastolic pressure. In addition, the ECG-derived heart rate was increased. ST segment changes were indicative of myocardial ischaemia, and cardiac output was reduced. At the highest tested dose of 10 mg/kg/hr, with plasma concentrations of 3172-3488 ng/ml, these findings further progressed and were accompanied by clinical signs (decreased activity, cold to touch, decreased muscle tone, partially closed eyes and pallid skin) and a prolonged systolic ejection period, indicative of impaired cardiac relaxation. One animal showed decreased CO2 saturation and increased pH and O2 saturation. Dosing was stopped after 17 minutes because of the poor condition of the animals, and the animals showed signs of recovery within 90 minutes after the dosing was stopped. These findings can be defined as exaggerated pharmacology and occur at plasma levels exceeding clinical concentrations. The NOAEL was considered 1 mg/kg/hr OM (plasma levels of 378-394 ng/mL), which is in the lower range of the intended clinical concentrations. The animals receiving a continuous 24-hour infusion of 0.5 mg/kg/hr did not demonstrate any treatment-related cardiovascular effects, while plasma levels reached 649-715 ng/ml, which falls within the higher range of the intended clinical concentrations.

In a definitive GLP-compliant study in conscious male dogs (Study NCD05-020), treatment-related findings were limited to animals receiving 6 mg/kg/day, with 1232 ng/ml plasma concentrations. These animals displayed an increased heart rate, accompanied by shortened PR, QRS and QT intervals and decreased systolic, diastolic and pulse pressures. The decrease in the QT interval did not result in any change in the QTc. The NOAEL was considered 1.8 mg/kg/day, resulting in plasma levels of 269 ng/ml, slightly below the intended clinical concentrations.

An additional non-GLP exploratory cardiovascular safety study (Study 121105) in anaesthetised male beagle dogs with low (normal) and high (paced, 120 bpm) heart rates was performed. In non-paced dogs, contractility parameters (systolic duration, ejection time and cardiac output) were increased dose-dependently at ≥0.49 mg/kg (plasma exposure levels of 532 ng/ml), as expected based on the pharmacodynamic properties of OM. However, the heart rate significantly increased at the highest dose of 2.945 mg/kg (plasma exposure levels of 1360 ng/ml), reducing stroke volume. In the paced dogs with higher heart rates, OM exposure reduced stroke volume, cardiac output, and mean arterial pressure due to reduced diastolic filling time and end-diastolic volume. This was already observed at ≥0.89 mg/kg, resulting in plasma levels of 567 ng/ml. The changes in ECG parameters were attributed to the increased heart rate. Finally, ST segment changes (indicative of cardiac ischaemia) were observed in OM-treated paced dogs (cumulative OM dose of 1.35 mg/kg), and non-paced OM-treated dogs (cumulative OM dose of 2.07 and 2.945 mg/kg) with intermittent high heart rate.

In a final non-GLP cardiovascular safety study in conscious male beagle dogs (Study 121515), dose-dependent prolongation of the systolic ejection time, Weiss tau and increased systole-to-diastole duration ratio were observed, which is in line with the pharmacodynamic properties of OM. At the highest dose level, resulting in plasma concentrations of 1,090 ng/mL, mechanical alternans (early), electrocardiographic ischaemic signs (ST-depression and QRS fractionation), and arrhythmias (later) were observed. During the 24-hour recovery period, electromechanical abnormalities were still observed, but mechanical parameters and cardiac timing showed a trend towards recovery. (outstanding concern [OC]).

In conclusion, OM demonstrates a dual effect on cardiac contractility with the intended pharmacological response (cardiac contractility) at clinically relevant plasma levels, while adverse signals of impaired relaxation were observed at the upper range of the intended clinical concentrations. In addition, at plasma levels slightly above clinical concentrations, animals displayed observations indicative of cardiac ischaemia, demonstrating a narrow therapeutic window. This is further discussed in Section 3.2.4.2 Repeat dose toxicity.

3.2.2.4. Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies have been conducted, and insufficient information on PD interactions was provided in the dossier's clinical part. This is not acceptable, and the applicant is requested to provide information on pharmacodynamic interactions with other medicinal products or substances (see clinical AR).

3.2.3. Pharmacokinetics

A comprehensive package of non-clinical pharmacokinetic studies was presented by the applicant. The complete ADME profile of omecamtiv mecarbil was characterised for both rats and dogs (*in vivo* distribution only in dogs) for the intravenous and oral route of administration. Additional pharmacokinetic data were available for monkeys (single-dose) and mice (repeat-dose). It is unfortunate, however, that the applicant only performed a complete pharmacokinetic analysis in a limited number of studies and the rest of the studies usually only reported plasma concentrations. Nevertheless, in the pivotal studies, complete pharmacokinetic analysis was available.

Methods

Appropriate validated analytical methods have been developed and validated for plasma analysis of all pivotal animal species used in the pre-clinical studies.

The method validation was performed in two facilities in Canada and the US. Both facilities are GLP-compliant facilities. The reports on validating methods for rat, rabbit and dog plasma included a GLP compliance statement. This statement was absent for the mouse studies and partial validation of omecamtiv in rabbit plasma.

Analytical methods were developed for mouse, rat, rabbit and dog plasma. All methods were LC-MS/MS based methods for the detection of omecamtiv mecarbil and metabolites M1, M3 and M4 in rats and M1 and M3 in dogs. In dog plasma, the linear range for omecamtiv mecarbil was 2.0-1000 ng/mL for M1, and M3 was 5.0-500 ng/mL. In rat plasma, the linear range was 2.0-1000 ng/mL for omecamtiv mecarbil, 5.0-500 ng/mL for M1 and M3 in the first study and 1.0-100 ng/mL for M3 and M4 in a second study in a different testing facility. In mice plasma, the linear range for omecamtiv was 2 ng/mL-1,000 ng/mL. In rabbit plasma, the range was 5 ng/mL-2500ng/mL. Stability was assessed and found to be appropriate for the conduction of the analyses (24-144 hours at RT in mouse and rabbit plasma) and 14-295 days in a frozen matrix in rat and dog plasma). It was also found to be stable for 3-6 thaw cycles.

Single-dose pharmacokinetics

The single-dose pharmacokinetics of omecamtiv mecarbil were studied in three species; rats, dogs and monkeys. Rats (males and females) were dosed IV and PO with doses ranging from 0.2-10 mg/kg. For dogs and monkeys only male animals were studied, with doses of 0.5 mg/kg IV and 1.0 mg/kg PO.

After IV administration, clearance was comparable between rats and monkeys (18.6-23.64 mL/min/kg and 20.1 mL/min/kg, respectively), but lower in dogs with 7.25 mL/min/kg. The volume of distribution (V_{ss}) was comparable across species, ranging from 2.99-3.77 L/kg in rats, 3.61 L/kg in dogs and 7.72 L/kg in monkeys (and approx. 6.2 L/kg in humans of 70 kg). Half-life was comparable between IV and PO dosing in monkeys, with $t_{1/2}$ of 102 minutes and 105 minutes for IV and PO administration, respectively. In rats, there was a more pronounced difference between 126 minutes (IV) and 390 minutes (PO), ranging from 155-764 minutes between individual animals after PO administration. In dogs, the $t_{1/2}$ was slightly longer, with 408 minutes after IV and 340 minutes after PO administration. In humans, the half-life is 20-23 hours, which is substantially longer than observed in the non-clinical animal species (about 3-fold compared to PO administration in dogs and rats).

In general, absorption after PO administration was fast in all species, with T_{max} ranging from 30-60 minutes in rats, 30 minutes in dogs and 85 minutes in monkeys. The difference in Tmax between animals was substantial in monkeys, ranging from 15-180 minutes. C_{max} values are variable between individual animals. Since only a small number of animals was used in most single-dose studies, this leads to variable results between studies performed in the same animal species. However, keeping the individual variability in mind, the mean values are rather consistent across the different animal species. In rats, up to doses of 5 mg/kg, C_{max} increases approximately dose proportional. The increase is less than dose-proportional from 7.5 (5.6) mg/kg to 10 mg/kg. For the AUC_{inf} the increase is also dose proportional for the low doses (0.2-1.0 mg/kg). For the higher doses (2.5-10 mg/kg) there appears to be a more than dose-proportional increase for 1.0-2.5 mg/kg, but not from 2.5-5.6 mg/kg. From 5.6 mg/kg to 10 mg/kg, the increase appears dose proportional for male animals but more than dose-proportional for females. There seems to be a trend towards higher exposures in female rats, compared to male rats, with gender differences of 1.65-fold at 2.5 mg/kg, 1.41-fold at 5.6 mg/kg and 2.50-fold at 10 mg/kg.

The mean bioavailability ranged from 65.1-80.3% in rats, 79.0% in dogs and 59.5% in monkeys (range 40.8-76.3% between individual monkeys). In humans, the bioavailability was high (F=94% in study 20090229 for an oral solution). The absolute bioavailability of the Phase 3 formulations of omecamtiv mecarbil at 25 mg and 50 mg doses ranged from 75% to 100%, respectively.

Repeat-dose pharmacokinetics

In non-pregnant animals, the repeat-dose pharmacokinetics of omecamtiv mecarbil were investigated in mice, rats and dogs. The monkey was not used in the (pivotal) toxicology studies and was not included in further pharmacokinetic assessment. Kinetics were assessed after oral gavage (in mice and rats as a liquid, in dogs in capsules), and dosing was done twice daily (usually an AM and PM dose). A continuous intravenous infusion was performed in rats and dogs for 14 days.

In mice, omecamtiv mecarbil was administered twice daily for up to 177 days PO. T_{max} was approx. 7 hours, although some early peaks at 1 hour were also reported. Over time, following repeated administration, no marked (<2 fold) accumulation of omecamtiv mecarbil upon twice daily dosing was observed. There was only a trend towards higher exposure (AUC increase approx. 1.3-1.7 fold). After 27 days, the exposure to omecamtiv mecarbil (AUC_{last}) increased approximately 3.6-fold for males and 3.3-fold for females for a 3.0-fold increase in the dose (2.5 to 7.5 mg/kg/day). Overall, both increases in AUC and C_{max} were dose proportional, and this did not change over time. Female mice had a lower exposure than male animals; however, the gender difference was <2-fold and therefore not considered clinically relevant.

In rats, after PO administration for 182 days, there seemed to be only a slight increase in C_{max} (<2-fold difference) in both male and female animals. Regarding exposure, there was limited accumulation

in the high-dose groups with an AUC accumulation ratio of approx. 2.3 in both genders. Exposure overall was slightly higher in females than in male animals; however, these differences were also <2-fold. Plasma concentrations and exposure to omecamtiv mecarbil generally increased proportionally with increasing dose levels for males and females. The M3 metabolite concentrations (C_{max}) were overall about 10-15% of the parent. After 14 days of continuous intravenous infusion, mean concentrations were only reported at day 15. At the same dose level, mean concentrations in female animals were approx. 1.5-fold higher than in male animals (540 ng/mL versus 751 ng/mL at the highest dose level of 12 mg/kg/day).

Several repeat-dose studies were performed in dogs, both IV (1.2-12 mg/kg/day) and PO (1.5-7.5 mg/kg/day). After continuous infusion in dogs, there was slight accumulation over time for the mean plasma concentration of approx. 1.5 fold increase over 14 days. No gender differences were observed. After PO administration for 268 days, no substantial accumulation was observed in dogs. Increases in C_{max} were minor, and for AUC, the increase was approx. 1.5-fold in the high dose of 7.5 mg/kg/day. Plasma concentrations and exposure to omecamtiv mecarbil generally displayed proportional increases with increased dose levels at all included time points. No substantial differences in pharmacokinetics were observed between male and female animals after oral administration. It was noted, however, that plasma concentrations of omecamtiv mecarbil were very variable between individual animals (up to 25-fold) at the same sampling time and also substantial differences (up to approx. 10-fold) in plasma concentrations at different sampling times (1h AM vs 1h PM) were seen within individual animals. Metabolites M1 and M3 were detectable in the higher dosing groups, but concentrations were low compared to the parent compound (<10%).

In both pregnant rats and pregnant rabbits, the pharmacokinetic profile (C_{max} and AUC) appear comparable to the profiles observed in non-pregnant pre-clinical species. However, T_{max} and $T_{1/2}$ values could only be compared to single-dose data in non-pregnant animals. Half-life in rabbits was short, ranging from 1.78-3.63 hours. No studies have been performed in non-pregnant rabbits, but this is similar to the half-life of approx. 2h observed in rats and monkeys after a single dose of omecamtiv mecarbil. There was some slight accumulation in rabbits between GD7 and GD19 for C_{max} (approx. 2-fold increase) and AUC (2-3 fold increase over time). In pregnant rats, C_{max} and AUC values between GD7 and GD20 are comparable, trending more towards a decrease over time than toward an increase.

Distribution

Protein binding of omecamtiv mecarbil was determined in rat, dog, and human plasma by equilibrium dialysis for 24 hours at 10 µM. The plasma protein binding for omecamtiv mecarbil *in vitro* was comparable between rat, dog, and human plasma, with binding values of 82.1%, 70.4%, and 81.5%. The applicant concludes that the non-covalent plasma protein binding was independent of the concentrations tested in all species. However, concentration-dependent binding could not be assessed in the study provided by the applicant, as only one concentration (10uM) was applied in this study.

Blood-to-plasma ratios of omecamtiv mecarbil in rat and human plasma were determined at 500, 5,000, and 15,000 ng/mL following a 30-minute incubation at 37°C. The mean omecamtiv mecarbil blood-to-plasma partition ratios in rats and humans were 1.06 and 0.918, respectively. At later time points (96h) (assessed in the *in vivo* rat distribution study), the blood: plasma ratio shifted to 2.05, indicating a slower elimination from blood components than from plasma. Since omecamtiv mecarbil did not preferentially distribute into red blood cells at time-points <96h and C_{max} is the main indicator for pharmacodynamic effect and toxicity, plasma concentrations are suitable to assess omecamtiv mecarbil exposure.

In vivo tissue distribution of omecamtiv mecarbil was determined in male and female Long Evans rats after a single IV (1 mg/kg) or PO dose (2.5 mg/kg) of [^{14}C]-omecamtiv mecarbil administration and in male and female Sprague Dawley rats after a single PO dose (2.5 mg/kg) of [^{14}C]-omecamtiv mecarbil. Samples were collected to 840 hours for LE rats and 96 hours for SD rats. Samples were analysed for radioactivity with LSC and quantitative whole-body autoradiography.

In partially pigmented LE rats, a strong association with melanin-containing tissues was observed (uveal tract, eye, meninges and pigmented skin), which was reversible but with a long half-life. Eye uveal tract AUC_{inf} for omecamtiv mecarbil in male LE rats after a single 2.5 mg/kg PO administration was 18400000 ng-eq[^{14}C]*h/g, with a C_{max} of 23700 ng-eq[^{14}C]/g and a half-life of 799 hours. For pigmented skin, the AUC_{inf} was 199000 ng-eq[^{14}C]*h/g with a C_{max} of 2000 ng-eq[^{14}C]/g and a half-life of 149 hours. In male SD rats, after a single 2.5 mg/kg PO administration, AUC_{inf} for the eye uveal tract was 4540 ng-eq[^{14}C]*h/g, with a C_{max} of 500 ng-eq[^{14}C]/g and a half-life of 9.82 hours. For non-pigmented skin, the AUC_{inf} was 13100 ng-eq[^{14}C]*h/g with a C_{max} of 687 ng-eq[^{14}C]/g and a half-life of 44 hours. Exposure (AUC_{inf}) was 4053 times higher in LE compared to SD rats in the eye uveal tract and 15.2 times higher for pigmented skin than non-pigmented skin. Differences in C_{max} were 47.4-fold for the eye uveal tract and 2.9-fold for the skin between LE and SD rats. The applicant points out the melanin binding is reversible; however, since omecamtiv mecarbil is administered twice daily and the half-life in the tissues is very long, on a chronic basis, it is unlikely the concentrations in the eye uveal tract and other melanin-containing tissues will decrease over time. Other organs that contained smaller, yet still substantial, concentrations of omecamtiv mecarbil were the liver, myocardium, adrenal gland and cortex and muscles, and to a lesser extend, the kidneys. In non-pigmented SD rats, highest exposures were seen in the liver. Distribution to the other tissues was comparable to the LE rats. Omecamtiv mecarbil did not distribute to the brain.

No studies were performed in foetuses or pups from pregnant and lactating rats. Therefore it is unknown if omecamtiv crosses the placenta. Also, no analysis was performed to determine the excretion of omecamtiv mecarbil in milk.

Metabolism

The metabolic pathway of omecamtiv mecarbil was assessed *in vitro* using enzymes and hepatocytes from mice, rats, dogs and human origin. In hepatocytes, omecamtiv mecarbil was the most abundant form found in all species (70.2-89.0%) except in male rats (28.5%). Metabolite M3 was the most important metabolite formed in human hepatocytes (13.4% in men and 6.0% in women hepatocytes). M3 was also present in the hepatocytes of mice and dogs in comparable amounts. In rats, the amount in females was comparable to human males (13.9%), but in male rats, it was higher (38.6%). These large gender differences were only observed in rats and not observed for all metabolites. Metabolite M3 was also formed in enzyme studies, where it was formed only when incubated with human recombinant CYP2D6, but not with CYP3A4, CY2J2, or CYP2C8. The metabolite M15 (a putative alcohol) was only formed by human recombinant CYP3A4 and was not seen in other species.

In vivo, the omecamtiv parent compound was the major component (87.56-91.12%) in rat plasma after 1mg/kg IV or 2.5 mg/kg PO [^{14}C]-omecamtiv mecarbil in male SD rats. The major biotransformation pathway of omecamtiv mecarbil in rats was the hydrolysis of the piperazine amide bond on omecamtiv mecarbil to form M3. Oxidation on the piperazine benzylic position generated another metabolite, M1. However, no information was available on the plasma concentrations of M1, M3 and M5 in the *in vivo* rat studies. M1, M3 and M5 were only determined in rat urine, faeces and bile, in which M1 and M3 were the main metabolites. Since the study was only performed in male rats, there is no data on gender differences in metabolism as was observed in the repeat-dose toxicokinetic

study. In the repeat-dose studies, M3 was measured in rat plasma at approx. 15% of the dose in male rats and 6% in female rats.

In dogs (3 males and 3 females per group) [^{14}C]-omecamtiv mecarbil was dosed at 0.75 mg/kg IV or 2 mg/kg PO. Omecamtiv mecarbil circulated in plasma mainly as a parent compound (81.2% to 84.5%) with M5 (7.9% to 9.5%) and M3 (5.2% to 6.8%) as the main metabolites. No gender differences were observed.

Similar to the metabolism in dogs, omecamtiv mecarbil was the most abundant component (83.8%) in human plasma after a single oral dose of 35 mg, with M3 and M4 (lactam metabolite of M3) as the most abundant metabolites at 6.0%, and 3.3% of total drug-related AUC, respectively (averaged for IV and PO). The metabolite M4 that was observed in human plasma is also formed in small amounts in dogs and rats. However, plasma concentrations were not available. Nevertheless, up to 1% of the dose is excreted as M4 in dogs, and up to 6% of the dose is excreted as M4 in rats.

Excretion

The excretion of omecamtiv mecarbil was studied after intravenous and oral dosing at 1 mg/kg IV in rats and 0.75 mg/kg IV in dogs and 2.5 mg/kg in rats PO, and 2.0 mg/kg PO in dogs. In rats, the IV and PO dose contained a combination of non-radiolabeled omecamtiv mecarbil and [^{14}C]-omecamtiv mecarbil to achieve the target dose of 1 mg/kg and 2.5 mg/kg, respectively. The overall recovery of [^{14}C]-omecamtiv mecarbil-derived radioactivity was 94.2% and 90.2% in IV-dosed females and PO-dosed male rats, respectively. Faecal excretion accounted for 60.4% and 51.8% after IV or PO dosing. A mean of 32.8% and 31.9% of the administered omecamtiv mecarbil dose was recovered in urine within 24 hours post-dose. In bile duct cannulated rats administered a PO dose, a mean of 36.6% of the dose was recovered in bile. An average of 12.9% of the dose was recovered in faeces, and 43% of the dose was recovered in urine. Initially the 12.9% recovered omecamtiv was proposed to be unabsorbed drug, but further analysis revealed only 1.68% was parent drug. The other radioactivity was due to metabolites, suggesting first-pass metabolism, rather than unabsorbed drug, influenced the bioavailability of omecamtiv in the rat study. Estimation of the bioavailability by hepatic excretion ratio predicted a bioavailability of 74.3% (1.04-fold lower than the actual 77.4%) confirming this hypothesis.

Metabolism of omecamtiv mecarbil was the main clearance mechanism, with low amounts (≤7% of dose) of parent excreted into the urine, bile, or faeces. M3 was secreted into urine, faeces, and bile. M3 accounted for 17.16% in urine and 32.25% in faeces after IV administration; 16.24% in urine and 24.09% in faeces after PO administration to non-cannulated rats; and 27.31% in urine, 7.51% in bile, and 3.53% in faeces after PO administration to bile duct cannulated rats. Therefore, the faecal excretion of M3 was 24.09% in non-cannulated rats versus 11.04% in cannulated rats. This difference was not seen for other metabolites, such as M1 (9.99% in non-cannulated rats versus 11.47% in cannulated rats). Alterations such as reduced bile flow and expression (both up-and downregulation) of several hepatic and renal transporters were observed in literature studies in bile-duct cannulated and bile-duct ligated rats. These alterations could have occurred in the BDC rats used for the omecamtiv mass balance study and may provide an explanation for the shift from faecal to urinary excretion in BDC compared to intact rats. Since M1 is eliminated into the bile via a different mechanism compared to M3, the effect of altered bile elimination in BDC rats may differ between those two metabolites.

In dogs, overall mean recoveries of [^{14}C]-omecamtiv mecarbil-derived radioactivity in male and female dogs were 86.8% and 87.9%, respectively, after IV administration, and 89.5% and 90.8%, respectively, after PO administration. No sex-dependent differences were observed. Faecal excretion

accounted for 72.8% and 75.6% in males and females after IV dosing. Urinary excretion accounted for a mean of 11.0% and 10.5%. After PO dosing, faecal excretion was at 76.0% and 77.4% in male and female dogs, respectively. Urinary excretion was low, accounting for 11.2% and 12.2% in males and females. M3 was the major metabolite in excreta and accounted for 19.5% to 23.1% of administered radioactivity (eliminated mostly in faeces), followed by M31 at 16.8% to 20.1%, and M11 at 15.9% to 18.3%.

The excretion was comparable after IV and PO dosing. Overall recoveries were high in both species (>85%), which was also seen in human male volunteers (86.6%). Faecal excretion was higher in dogs (approx. 75% of dose) compared to rats (approx. 55%) and humans (38%). Urinary excretion was approx. 33% in rats and approx. 11% in dogs, which was both lower than urinary excretion in humans (49%). In all species, clearance was primarily as metabolites, with M3 as the main metabolite in dogs, rats and humans. In dogs omecamtiv was also converted to and excreted as M11 and M31 in a substantial amount (16-21% and 16-18% of the dose for M11 and M31, respectively).

3.2.4. Toxicology

3.2.4.1. Single-dose toxicity

The applicant submitted 5 single-dose toxicity studies conducted in Sprague Dawley rats and beagle dogs. Omecamtiv mecarbil was administered by the intravenous (IV) or the oral route (PO) to both species, consistent with the therapeutic routes of administration evaluated in clinical studies.

In the rat, single PO doses were tolerated up to 5 mg/kg (C_{max} ~1,035 ng/mL). At 10 mg/kg/day (C_{max} of 1,372 to 1,596 ng/mL), mortality occurred, and clinical signs, including decreased activity, decreased muscle tone, uncoordinated movement, and unsteady gait, were observed. Consequently, a dose of 5 mg/kg/day was the maximum tolerated dose in rats for oral dosing. The acute toxicity profile was similar in the IV infusion study, in both IV studies, the dose that resulted in a 1 mg/kg/hour infusion (C_{max} ~800 ng/mL) of omecamtiv mecarbil was well tolerated. A dose that resulted in 3 mg/kg/hour infusion (C_{max}>2000 ng/mL) led to mortality. This suggests that the safety of this product is related to the C_{max}.

In the oral dog single-dose escalation study, omecamtiv mecarbil was tolerated up to 4 mg/kg with emesis as the only clinical sign. At ≥8 mg/kg (C_{max} of 2,053 to 3,040 ng/mL), salivation, pale gums, decreased activity, and laboured breathing were observed. Ventricular dysrhythmias were observed in association with elevations in troponin I, which correlated with the light microscopic finding of myocardial degeneration/necrosis. In the 6-hour IV infusion study, at 6 mg/kg/day (1 mg/kg/hour, C_{max} of 938 to 1212 ng/mL), there were no treatment-related changes noted. Mortality occurred at 12 mg/kg/day (C_{max} of 2506 to 3215 ng/mL), treatment-related changes were observed in the heart (degeneration/necrosis and inflammation), the liver (moderate intracytoplasmic accumulation of eosinophilic material of variable size, and hepatocellular vacuolation), and the lungs (bronchoalveolar inflammation, haemorrhage and oedema). Elevations of troponin I and creatine kinase were seen at 18 mg/kg/day, and liver enzymes were also elevated, as was blood urea nitrogen.

In summary, omecamtive mecarbil-induced heart toxicity was observed in dogs (but not in rats) in acute toxicity studies, and it seemed to be related to the excessive pharmacological effects of omecamtiv mecarbil. The toxicity was similar regardless of the route of administration and was associated with plasma C_{max} levels above 2000 ng/mL. In addition, mortality and associated agonal effects were observed in the rat at C_{max} levels above 1372 ng/mL and in dogs from 2506 ng/ml.

3.2.4.2. Repeat-dose toxicity

The repeat-dose toxicity studies consisted of exploratory (n=5) and GLP-compliant studies (n=8) with omecamtiv mecarbil that were conducted in CbyB6F mice, albino rats, and beagle dogs. The administration was performed through oral gavage (rat and mouse), oral capsule (dog), and IV continuous infusion (rat and dog). Studies involving continuous intravenous infusion for up to 14 days were conducted in rats and dogs to support phase 1 and 2 clinical trials. However, the intravenous route of administration (RoA) was not further developed due to the potential risk of cardiac ischaemia. Repeat oral dosing toxicology studies were conducted in the rat for up to 26 weeks and in the dog for up to 39 weeks, as the oral route was the intended route of administration for the pivotal phase 3 study and anticipated for commercial use.

In the mouse study (OG 28-day), except mortality and clinical signs prior to death, no other test article related toxicity was observed. This study is not further discussed here. The rat and the dog were the main species chosen for repeated dose toxicity evaluation, which is accepted. In general, there were no omecamtiv mecarbil-related effects on body weight, clinical observations, food consumption, haematology, urinalysis, organ weight or ECG (only performed in dogs). Heart toxicity and adrenal changes were the main article-related findings. These findings are summarised per target organ below.

PK-guided dose selection was employed in clinical trials to attain target steady-state plasma concentrations of omecamtiv mecarbil (300 to 750 ng/mL) while reducing the risks associated with excessive omecamtiv mecarbil concentrations (>1,200 ng/mL). On average, the C_{max} in humans would be 330 ± 80 ng/mL; however, elevated (500-750 ng/mL) and high (750 - 1200 ng/mL) plasma concentration may also be expected in certain groups of patients. In order to evaluate the non-clinical findings, as they were C_{max} related, three categories are proposed: class I) <500 ng/mL for the average clinical C_{max} and lower spectrum of the PD active concentration; class II) 500-750 ng/mL for the upper spectrum of the PD active concentration relevant for patients with elevated C_{max} values; and class III) 750-1200 ng/mL for the concentration that may show toxicity and exaggerated PD relevant for patients with very high C_{max} values.

Heart:

Myocardial toxicity was the primary and dose-limiting adverse effect of omecamtiv mecarbil. This was presented as histopathologic findings of myocardial degeneration, necrosis, and/or fibrosis in both rats (oral) and dogs (oral and IV).

In rats, minimal to moderate myocardial degeneration/necrosis and fibrosis were observed in all oral studies (14 days, 13 and 26 weeks) but not in IV studies (14 days). It occurred in the highest treated groups at dose level of ≥7.5 mg/kg/day, and corresponding to C_{max} ≥641 ng/mL. Although 8 out of 24 male rats were found dead at this level, the results of the histopathological evaluation did not show a direct connection between mortality and heart changes. The observed heart degeneration/fibrosis remained minimal to moderate and was not present in all deceased animals. As a result, the underlying cause of death could not be determined or attributed to the observed myocardial degeneration, necrosis, and/or fibrosis. Furthermore, there was no clear evidence of progression in the severity or incidence of the heart injury with increasing doses or prolonged exposure time. Therefore, the cause of the mortality in rats remains unclear.

In 14-day dog IV studies, minimal to moderate myocardial degeneration associated with or without fibrosis and mortality (1/6 animals) was found at a dose level 12 mg/kg/day (0.5 mg/kg/hour), correlated with C_{max} ≥996 ng/mL. In the deceased animal, evidence of market myocardial degeneration/necrosis, minimal cardiac haemorrhage and moderate to severe inflammation was identified, and was suggested as the cause of mortality. In dog oral studies (13 and 39 weeks), minimal to slight myocardial degeneration/necrosis with fibrosis and myocardial fibrosis occurred at

doses ≥5 mg/kg/day, correlated with C_{max} ≥870 ng/mL. No mortality was observed in the GLP oral studies, whereas it was observed in the non-GLP exploratory studies.

ECG evaluations were conducted in dog studies but not in rat, and effects were limited to electrical alternans during periods of sinus tachycardia found in one dog study (14 day IV, NCD05-012). In all other repeated dose toxicity studies in the dog, there were no article-related qualitative abnormalities, and quantitative ECG parameters (heart rate, PR, QRS, QT, QTc and RR) unaffected. Consequently, the analysis of ECG results failed to identify any early indications of the adverse effects on cardiac function caused by omecamtiv mecarbil in repeated dose toxicity studies. It can be claimed that the ECG effects seen in healthy animals are not expected to be relevant for patients. However, it should be noted that in safety pharmacology studies, excessive dosing of omecamtiv mecarbil resulted in ECG changes such as increased heart rate with corresponding decreases in PR and QT intervals, as well as changes in the ST segment in both paced and non-paced dogs (study NCD05-020, NCD05-013). Besides, ECG ST segment depression was found in healthy participants indicating myocardial ischaemia or infarction when excessively high omecamtiv mecarbil (>1,200 ng/mL) plasma concentration was achieved in phase I clinical trials. The reason for the discrepancy in these ECG results is not understood.

Troponin I levels, which could indicate heart toxicity, were evaluated only in dog studies. Cardiac Troponin I elevation was observed in one male dog in a 14-day IV study at the highest dose level (12/mg/kg). It is questionable to use troponin I as an earlier biomarker for predicting heart toxicity in the dog studies, as troponin I elevation was observed in a limited number of studies (animals). Furthermore, these elevated levels were seen at dose levels where cardiac necrosis/fibrosis had already occurred.

Adrenal

In the 13- and 26-week rat oral studies, minimal to moderate adrenal cortical vacuolation was observed, which was correlated with an increase in adrenal gland weights at ≥5 mg/kg/day. Similarly, an increase in adrenal gland weight associated with cortical hypertrophy was found in dogs after 39 weeks of oral dosing at ≥5 mg/kg/day. This finding was neither observed in IV studies nor short-term (14-day) oral studies (non-GLP). The adrenal changes (5 mg/kg/day) were likely a chronic stress response (Everds, 2013); however, whether it was due to myocardial toxicity is doubtful since it happened before the myocardial fibrosis (7.5 mg/kg/day). The applicant conducted a thorough examination of animal studies and concluded that there is no potential correlation between the observed adrenal toxicity and mortality. While the precise cause of this observed adrenal toxicity remains uncertain, it is hypothesised that the adrenal stress response may be a secondary effect associated with omecamtive mecarbil, as the adrenal gland is the key organ for stress reactions. Besides, it seems that clinical studies did not uncover treatment-related changes associated with adrenal alterations. Consequently, these non-clinical findings may have limited relevance to clinical applications.

Liver

Minimal cytoplasmic rarefaction and minimal single-cell necrosis were found in the liver of the dog in the 39-week oral study at 7.5mg/kg/day. In addition, minimal accumulation of eosinophilic material in hepatocytes and slight centrilobular hepatocellular vacuolation were found in one male dog after 14 day IV dosing. The absence of a recovery analysis makes it impossible to determine the reversibility of the findings. However, since elevated levels of liver enzymes were absent, liver toxicity is not likely a concern.

Kidney

Microscopic changes of tubular degeneration/regeneration in the kidney were found in male dogs given 7.5 mg/kg/day and in female dogs given ≥5 mg/kg/day for 39 weeks. Although there were no

associated changes in measures of renal function such as serum creatinine and proteinuria, the absence of information on the reversibility makes it difficult to conclude on the severity of the effects.

3.2.4.3. Genotoxicity

A standard battery of genotoxicity tests showed that omecamtiv mecarbil has no genotoxic potential.

3.2.4.4. Carcinogenicity

Carcinogenicity was evaluated in a 26-week Tg.rasH2 mouse study and a 2-year rat study. There were no relevant increases in tumour incidence in either study. Toxicity findings are in line with the findings in the repeated dose studie and are pharmacology-related or stress induced.

3.2.4.5. Reproductive and developmental toxicity

In a combined male and female fertility and early embryonic development study in rats, no adverse effects on any of the parameters were seen. No formal TK analyses were performed; however, the concentration at 1 hour postdose at the high dose of 5 mg/kg/day was 604 ng/ml in males and 660 ng/ml in females and appeared somewhat higher than the Cmax measured in the repeated dose toxicity study in rats (505 ng/ml in males and 376 ng/ml in females). Therefore, exposure in terms of plasma concentration was in the elevated clinical range.

It can be concluded that omecamtiv mecarbil does not affect male or female fertility at a dose resulting in exposures in the elevated clinical range in terms of Cmax.

Embryo-fetal development was tested in rats and rabbits. In rats, the high dose of 10 mg/kg/day was not tolerated, resulting in dam mortality. This dose group was terminated early without fetal or litter examinations. At the mid-dose of 3 mg/kg/day, no adverse effects were observed on dams, embryo-fetal development, or pregnancy. The 3 mg/kg/day dose resulted in a plasma concentration of 508 ng/ml at GD6 and 401 ng/ml at GD17.

In rabbits, no adverse effects on dams, embryo-fetal development, or pregnancy was observed at any dose level. The high dose of 10 mg/kg/day resulted in a plasma concentration of 750 ng/ml at GD7 and 1922 ng/ml at GD19.

It can be concluded that omecamtiv mecarbil has no effect on embryo-fetal development or pregnancy at a dose resulting in exposures in rats within the elevated clinical range, and in rabbits around 1.5-fold higher than patients with a very high Cmax.

In a pre-and postnatal study in rats, no adverse effects were seen in the offspring of rats, including reproductive performance, when dosed up to lactation day 20. At the high dose, the exposure was 679 ng/ml, which is in the elevated clinical range in terms of Cmax.

Overall conclusion on reproductive toxicity: Omecamtiv mecarbil had no adverse effects on fertility, embryofetal or pre-postnatal development in rats or rabbits. However, since higher doses were not tolerated, the highest doses tested in rats resulted in plasma concentrations within the elevated range of the clinical Cmax. Higher doses could be tested in rabbits, resulting in plasma concentrations 1.5-fold the maximum Cmax anticipated in patients. Although these studies are reassuring, there is no sufficient safety margin; therefore, a risk for the fetus cannot be ruled out. This should be reflected in the SPC section 4.6.

3.2.4.6. Toxicokinetic data

Toxicokinetics were studied in mice, rats, dogs and rabbits. An extensive overview of the kinetics of omecamtiv mecarbil can be found in Section 3 Pharmacokinetics in this assessment report. Since toxicology of omecamtiv mecarbil appears to be C_{max} driven, only the toxicokinetic studies that reported a C_{max} value are presented here. Other studies often only reported plasma concentrations at a certain time point (for example, pre- and post-dose), and it is not clear if the concentration at this post-dose time point is the maximum achieved concentration. However, these reported concentrations were compared to the C_{max} values in other toxicokinetic studies and were found to be very similar (usually lower).

Exposure multiples were not calculated because the therapeutic range of the C_{max} in humans, as provided by the applicant, is very broad. On average, the C_{max} in humans would be 330 ± 80 ng/mL, however, elevated (500-750 ng/mL) and high (750 - 1200 ng/mL) may also be expected in certain groups of patients. Due to this broad range, it can only be concluded that the C_{max} values reached in mice, rats, dogs and rabbits are all within this broad window and exposure multiples would be very small for the average patient and non-existent (<1) in the worst-case scenario. With the provided non-clinical toxicology studies, it remains, therefore, partially unclear what the consequences are for the patients when they reach high omecamtiv plasma concentrations.

3.2.4.7. Tolerance

Several local tolerance studies were performed. Omecamtiv mecarbil did not induce hemolysis, contact sensitisation or skin irritation and was a mild eye irritant. These studies, however, are not relevant to the current application of oral use.

3.2.4.8. Other toxicity studies

All potential genotoxic impurities in the drug substance and drug product are adequately controlled.

Impurities fumarate (3352519) and L-urea (2539889) which are specified above the qualification threshold are sufficiently qualified in dedicated repeated dose studies.

Omecamtiv mecarbil has no phototoxic potential.

3.2.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): KINHARTO			
CAS-number (if available): 873697-71-3			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD 107	Log D_{ow} values: -0.89 at pH 4 0.21 at pH 5 2.78 at pH 7 2.85 at pH 9	Potential PBT (N)
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log D_{ow}	2.78 at pH 7 2.85 at pH 9	not B

Persistence	DegT50	Dissipation $DT_{50, water(r)}$=10.1 d/20.5 d (l/l) $DT_{50, sediment(r)=}$>1000 d (both systems; l/l) $DT_{50, system(r)}$=>1000 d (both systems; l/l)			l=lake DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	9.2 mg/L 2.3 mg/L 1.7 mg/L			not T
	CMR	not investigated			potentially T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	Value	Unit			Conclusion
$PEC_{surface\ water}$, default	0.5	µg/L			>0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$=347 and 420 L/kg $K_{oc\ soil}$=9360, 5710 and 825 L/kg			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Dissipation $DT_{50, water(r)}$=4.7 d/9.6 d (l/l) $DT_{50, sediment(r)=}$>1000 d (both systems; l/l) $DT_{50, system(r)}$=>1000 d (both systems; l/l) Sediment shifting 19-83%			l=lake DT_{50} values at 20°C; Significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Raphidocelis subcapitata*	OECD 201	NOEC EC10	9.2 26.5	mg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC EC10	2.3 3.4	mg/L	reproduction
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	1.7	mg/L	post-hatch survival
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC/ EC10	≥1000	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC EC10	64 874	mg/kg_{dw}	Not normalised to 10% o.c.

3.2.6. Discussion on non-clinical aspects

In general, OM appears to increase the transition rate of cardiac myosin from the weak actin-binding conformation to the strong actin-binding conformation, thereby increasing cardiac contractility. It can bind to myosin at an allosteric site, stabilising the lever arm in the primed position, increasing the number of myosin heads that can bind to actin filaments and undergo a power stroke once the cardiac cycle starts. OM appears to increase cardiac contractility without increasing cardiac myocyte intracellular calcium or myocardial oxygen consumption.

No non-clinical pharmacodynamic drug interaction studies have been conducted, and insufficient information on PD interactions was provided in the dossier's clinical part. This is not acceptable (see clinical AR).

Single-dose pharmacokinetics were evaluated in rats, beagle dogs and cynomolgus monkeys after IV and PO administration. No relevant differences were observed between non-clinical animal species, although half-life was longer in dogs (approx. 6 hours) compared to monkeys (approx. 2 hours). In humans, however, half-life is substantially longer, with 20-23 hours. Repeat-dose studies were performed in mice, rats and dogs. Overall, no relevant interspecies differences were observed. In general, C_{max} and AUC increased approx. Dose-proportionally, omecamtiv mecarbil did not substantially (>2-fold), and gender differences were not observed. A strong association with melanin-containing tissues was observed in partially pigmented LE rats. Omecamtiv mecarbil was the most abundant form found *in vitro* and *in vivo* in all species, and metabolite M3 was the most important metabolite formed in all animals and humans. There were no unique human metabolites and no major metabolites in humans.

The excretion of omecamtiv is primarily as metabolites. First-pass metabolism, rather than unabsorbed drug, influenced the bioavailability of omecamtiv. Metabolite M3 was secreted into urine, faeces, and bile. M3 accounted for 17.16% in urine and 32.25% in faeces after IV administration; 16.24% in urine and 24.09% in faeces after PO administration to non-cannulated rats; and 27.31% in urine, 7.51% in bile, and 3.53% in faeces after PO administration to bile duct cannulated rats. Therefore, the faecal excretion of M3 was 24.09% in non-cannulated rats versus 11.04% in cannulated rats. This difference was not seen for other metabolites, such as M1 (9.99% in non-cannulated rats versus 11.47% in cannulated rats). A shift from bile to urinary elimination can occur as a result of bile duct cannulation and could have occurred in the BDC rats used for the omecamtiv mass balance study. This may provide an explanation for the shift from faecal to urinary excretion in BDC compared to intact rats. Since M1 is eliminated into the bile via a different mechanism compared to M3, the effect of altered bile elimination in BDC rats may differ between those two metabolites.

In the repeated dose toxicity studies, the myocardial lesion was the primary and dose-limiting toxic effect of omecamtiv mecarbil. This was presented as histopathologic findings of myocardial degeneration, necrosis, and/or fibrosis in both rats (oral) and dogs (oral and IV). In rats, heart toxicity occurred in the highest treated groups at a dose level of ≥7.5 mg/kg/day, which is also the lethal dose. There was no clear evidence of progression in the severity or incidence of the heart lesion with increasing doses or prolonged exposure time. Since the histopathological evaluation did not show a direct connection between mortality and heart changes, the cause of the mortality remains unclear. In the dog, heart toxicity was found at doses ≥5 mg/kg/day (oral dosing, no mortality) and 12 mg/kg/day (IV dosing, lethal dose). ECG changes were not found in any of the repeated dose toxicity studies despite the observed heart toxicity. The applicant suggested that only high plasma concentrations exceeding 1200 ng/mL(human) or 1000 ng/ml (dog) are associated with myocardial ischaemia that is sufficient to produce changes on the ECG. This can be agreed. Omecamtiv mecarbil resulted in ECG changes such as ST segment depression found in dogs in safety pharmacology studies and in healthy participants indicating myocardial ischaemia or infarction in phase I clinical trials. However, in several dog toxicity studies, when severe heart effects were observed, no ECG morphology changes were found. For instance, in the 14-day IV infusion study (NCD05-012), marked myocardial degeneration/necrosis was observed at a dosage of 12 mg/kg/day. Besides, no ECG changes were observed in any of the IV studies (NCD05-012, CV04-0071, CV04-0062), where clear heart toxicity and mortality were evident at doses of 12 or 24 mg/kg/day, with Cmax levels exceeding 1,000 ng/mL. The absence of ECG changes despite observing severe heart effects and C_{max} levels exceeding 1,000 ng/mL in these studies remains unresolved. The complexity of correlating ECG results with heart ischaemia in repeat dose toxicity studies is acknowleged. Given that ECG changes are often more predictive for acute cardiac ischaemia, their reliability in reflecting heart ischaemia during repeated dose toxicity studies may be limited due to the chronic nature of exposure and potential adaptation of the cardiovascular system over time. Besides, there is abundance of warnings regarding

overdose and potential ischaemic events in clinical practice. Consequently, this issue will not be further persued.

Troponin I elevation was observed in a limited number of studies (animals), and these elevated levels were seen at dose levels where cardiac necrosis/fibrosis had already occurred. Therefore, using troponin I as an earlier biomarker for predicting heart toxicity is questionable.

The toxic heart effects found in animal toxicity studies appeared closely related to plasma drug concentration. Pharmacological effects of omecamtiv mecarbil considered beneficial were shown in healthy and HF dogs at plasma concentrations of ≤700 ng/mL, which was similar to the drug concentrations observed at the NOAEL (505-694 ng/mL in rat, 549-709 in dog). A very modest increase in plasma drug concentrations of less than two-fold resulted in the emergence of myocardial degeneration, necrosis/ fibrosis (641-694 ng/mL in rat, 944-1000 ng/mL in dog), and mortalities (641-694 ng/mL in rat, 996-1293 ng/mL in dog). The close proximity between plasma drug levels that are potentially effective and those that are clearly toxic (causing lethality) in the nonclinical programme indicates a narrow therapeutic window. Given that reliable biomarker for early detection of cardiac toxicity were absent in the current animal studies and that lethality occurred at similar plasma concentrations as the cardiac lesions, there might be a risk of lethal overdosing in the clinic. Hence, it is imperative that the clinical plasma concentration remains below 1000 ng/mL, and it should be monitored frequently in patients. A clinical MO on the therapeutic range is posed in the clinical efficacy/methodology section.

In the 13- and 26-week rat oral studies and 39-week dog oral studies, minimal to moderate adrenal cortical vacuolation was observed, which was correlated with an increase in adrenal gland weights at ≥5 mg/kg/day. This was likely a chronic stress response (Everds, 2013); however, whether it was due to myocardial toxicity is doubtful since it happened before the myocardial fibrosis (7.5 mg/kg/day). In addition, unexplained mortality was noted. The applicant conducted a thorough examination of animal studies and concluded that there is no potential correlation between the observed adrenal toxicity and mortality. While the precise cause of this observed adrenal toxicity remains uncertain, it is hypothesised that the adrenal stress response may be a secondary effect associated with omecamtive mecarbil, as the adrenal gland is the key organ for stress reactions. Besides, it seems that clinical studies did not uncover treatment-related changes associated with adrenal alterations. Consequently, these non-clinical findings may have limited relevance to clinical applications.

Carcinogenicity was evaluated in a 26-week Tg.rasH2 mouse study and a 2-year rat study. In the mouse, there was a slight increase in alveolar bronchiolar adenomas in high-dose males. However, the incidence was still within the historical control range, and this is therefore considered a chance finding.

In the rat, there was an increase in pheochromocytoma in the adrenal medulla in high-dose males. This is a common finding in ageing rats. Although. the incidence is slightly above historical control range, no increase was seen in females, and therefore it is likely that this finding is a chance finding and not related to treatment.

Further non-neoplastic findings not mentioned by the applicant include angiecstasis, which is likely not treatment-related since it is not associated with inflammation, atrophy or degeneration. However, a slight increase in cortical vacuolation also occurred in the high-dose males, similar to findings in the repeated dose toxicity studies and could be stress related. Thrombus of the heart, seen in high dose males, is likely a consequence of cardiac toxicity which is pharmacologically-related and to which rats are more sensitive than humans. It is unlikely that patients wil develop cardiac thrombus.

Omecamtiv mecarbil had no adverse effects on fertility, embryofetal development or pre- postnatal development in rats or rabbits. However, since higher doses were not tolerated, the highest doses tested in rats resulting in plasma concentrations that were within the elevated range of the clinical

Cmax. In rabbits higher doses could be tested, resulting in plasma concentrations 1.5-fold the maximum Cmax anticipated in patients. Although these studies are reassuring, there is no sufficient safety margin, and therefore a risk for the fetus cannot be ruled out. This should be reflected in the SPC section 4.6.

All potential genotoxic impurities in the drug substance and drug product are adequately controlled.

Regarding the environmental risk assessment, omecamtiv mercabil is considered not to be PBT nor vPvB. Therefore, a risk to the STP, surface water and groundwater compartment is not anticipated based on the prescribed use of omecamtiv mercabil.

3.2.7. Conclusion on non-clinical aspects

In general, OM appears to increase the transition rate of cardiac myosin from the weak actin-binding conformation to the strong actin-binding conformation, thereby increasing cardiac contractility. It can bind to myosin at an allosteric site, stabilising the lever arm in the primed position, increasing the number of myosin heads that can bind to actin filaments and undergo a power stroke once the cardiac cycle starts. In *ex vivo* and *in vivo* preclinical models, OM demonstrated a dual effect on cardiac contractility with the intended pharmacological response (cardiac contractility) at clinically relevant plasma levels, while adverse signals of impaired relaxation were observed at the upper range of the intended clinical concentrations. The precise mechanism of action is not completely clear, as some contradictory findings (with regard to oxygen consumption and effects on calcium transient) are described in the literature, and the applicant should provide further clarification.

From a pharmacokinetic point of view, the applicant provided an adequate amount of information. The rat and dog can be considered relevant species for non-clinical efficacy and safety studies. No substantial interspecies differences in pharmacokinetic parameters were observed, and pharmacokinetics were also relatively comparable to human values. No unique human metabolites were observed, and there were no major metabolites.

In the animal toxicity studies, myocardial degeneration, necrosis, and/or fibrosis observed in both rats and dogs was the primary toxic effect of omecamtiv mecarbil, and it appeared closely related to the plasma drug concentration. The close proximity between plasma drug levels (≤700 ng/mL) that are potentially effective and those that are clearly toxic (641-694 ng/mL in rat, 996-1293 ng/mL in dog) in the nonclinical programme indicates a narrow therapeutic window. Due to the absence of reliable biomarkers for early detection of cardiac toxicity in the current animal studies, and the lethality can occur at similar plasma concentrations as cardiac lesions, there is a potential risk of lethal overdosing in the clinic.

3.3. Clinical aspects

3.3.1. Clinical pharmacology

The initial studies exploring PK and PD of omecamtiv mecarbil in healthy participants and participants with HF were performed with an IV formulation. These studies and early studies of orally administered immediate-release formulations resulted in high peak plasma concentrations of omecamtiv mecarbil in some participants due to rapid absorption of omecamtiv mecarbil. Because these studies showed that high plasma concentrations of omecamtiv mecarbil (>1,200 ng/ml) can be associated with the development of myocardial ischaemia or myocardial infarction, likely as a result of an exaggerated pharmacological effect, modified release (MR) formulations with different dissolution rates were developed to slow the rate of absorption and minimise high plasma concentrations of omecamtiv mecarbil.

Prototype MR tablets using the anhydrous freebase form of drug substance were used in early Phase 1 and Phase 2 development. The drug substance was subsequently changed from the anhydrous freebase to the dihydrochloride hydrate salt, a more physically stable form with higher solubility and used to develop several newer MR formulations. Following their evaluation in healthy participants (study 20090727) and participants with HF (study 20110151, escalation phase), final MR tablet formulations of omecamtiv mecarbil in strengths of 25, 37.5, and 50 mg (free-base equivalent, referred to as the MR Phase 3 tablet formulation) were selected for BID dosing in the pivotal Phase 3 Study 20110203. For the intended commercial drug product, further changes were implemented to the MR Phase 3 tablet formulation to differentiate the 3 strengths and further optimise the manufacturing process.

3.3.1.1. Pharmacokinetics

The pharmacokinetics of omecamtiv mecarbil were investigated in 28 clinical studies in healthy volunteers and patients. In addition, *in vitro* studies were conducted investigating the plasma protein binding, blood-to-plasma ratio, human hepatic metabolism, CYP enzyme identification, transporter substrate specificity, CYP and transporter inhibition and induction via AhR, CAR and PXR.

Methodology

Validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods were used to quantify plasma concentrations of omecamtiv mecarbil and its metabolites (except for 20110203) in plasma and urine. The plasma concentrations of omecamtiv mecarbil in 20110203 were quantified using the omecamtiv mecarbil immunoassay (QMS). Standard pharmacokinetic and statistical analyses were applied.

The population pharmacokinetic model included available PK data from 4269 subjects, with the vast majority (87.9%) coming from study 20110203. The initial population pharmacokinetic model consisted of a two-compartment model with first-order absorption and first-order elimination. The initial model had unstable parameter estimates and for the covariate search only 2 formulations were used. A redevelopment of the model was performed, including a renewed base model building and the covariate selection was done with stepwise forward addition / backward elimination. During the structural model development, data for the phase 3 study 20110203 (GALACTIC-HF) was excluded as for that study only pre-dose levels were assessed. The final model included all data, including data from the phase 3 study. Absorption parameters were fixed, to aid model stability. In the update of the model, presence of dose-dependent bioavailability and non-linear elimination were both tested. Incorporating these effects did not improve model fit, thus presence of dose-dependent bioavailability or non-linear elimination is not supported by the data.

The population pharmacokinetic model demonstrates a tendency to underpredict omecamtiv mecarbil plasma concentrations. In the update of the model, presence of dose-dependent bioavailability and non-linear elimination were both tested. Incorporating these effects did not improve model fit, thus presence of dose-dependent bioavailability or non-linear elimination is not supported by the data.

With the current model, it can be concluded that the inter-individual variability of omecamtiv mecarbil is high (reflected by the high estimates of the interindividual variability estimates). For instance, the interindividual variability on the apparent central volume of distribution is >100%. The model simulations account for this large interindividual variability, and therefore, the conducted simulation methodology is appropriate. Simulation results are discussed in the relevant sections of the assessment report, but it should be noted that these results could be biased by the tendency of the

model to underpredict high plasma concentrations. In the (model-predicted) steady-state exposure, relatively high standard deviations were observed.

Two exposure-response analyses were submitted to support the current procedure. In the first, the relationship between omecamtiv mercabil concentration and systolic ejection time (SET) was evaluated. In the second analysis, the relationship between omecamtiv mercabil exposure parameters ($C_{max,ss}$, $C_{min,ss}$ and AUC_{ss}) and several clinical outcomes (both efficacy and safety) was evaluated in patients included in study 20110203.

The modelling estimates that patients have a maximum of 39% change from baseline for SET. The EC50 values indicated that the EC50 is presumably in the range of 400 to 600 ng/ml. Within- and between-subject variability is relatively moderate compared to the pharmacokinetic parameters of omecamtiv mecarbil in the dose and SET range studied. No indication of hysteresis was found for the relationship between pharmacokinetics and SET.

Based on the exposure-response modelling, it is considered unlikely that the exposure-response relationship can be considered flat with the proposed posology. It is important that the target exposure range is well-defined, based on the PD parameter SET and it's relation to the clinical outcomes.

A minimal PBPK model was developed using the Simcyp simulator in order to predict the CYP3A4 induction (midazolam), CYP2C8 inhibition (repaglinide) and BCRP inhibition (rosuvastatin) potential to impact omecamtiv mecarbil PK at the clinically untested scenarios of multiple dosing. The development and verification of the OM compound file was performed using clinical PK data available from single and multiple dosing of formulation MR-F1. The omecamtiv PBPK model was verified by comparison of model predicted PK parameters to the observed PK parameters from studies 2018-0339 and 2018-0334. The model was considered verified as the predicted Cmax, tmax and AUC fell within 2-fold of the observations. The model was further verified to the CYP2C8 inhibition potential of omecamtiv mecarbil by using repaglinide as the CYP2C8 clinical probe substrate (compound file with the published clinical data). The CYP3A4 induction potential of omecamtiv at higher 50 mg dose and the BCRP inhibition potential of omecamtiv at steady state was assessed by using *in vitro* and clinical DDI data with clinical probe substrates (midazolam and rosuvastatin, respectively) as well as compound files with published clinical data. Nevertheless, the qualification of PBPK model on simulation CYP2C8 inhibition and CYP3A4 induction+inhibition at maximal dose could not be considered sufficient.

Physiological-chemical properties

Omecamtiv mecarbil has a molecular formula of $C_{20}H_{24}FN_5O_3$ and a relative molecular mass of 401.44 g/mol (free base). Omecamtiv mecarbil is highly permeable based on *in vitro* studies. Based on clinical DDI study, co-administration of omecamtiv mecarbil with a proton pump inhibitor (omeprazole) does not translate into significant changes in omecamtiv mecarbil absorption or exposure, hence, omecamtiv mecarbil may be administered with acid-reducing agents.

Absorption

After oral administration of the commercial omecamtiv mecarbil tablets, C_{max} was achieved in approximately 6-8 hours. Absolute bioavailability was characterised in 3 studies with a direct comparison of oral and intravenous administration. Overall, the oral bioavailability of omecamtiv mecarbil is relatively high. Omecamtiv mecarbil, either as an oral solution or immediate-release

formulation, is estimated to have an absolute bioavailability of more than 90%. Bioavailability of the modified release formulations is markedly lower, estimated in the range of 60-80%.

Throughout most of the clinical development programme, earlier formulations were used. The proposed commercial formulation has only been used in studies 20160160, 20180432 and 20180328. There is no bioequivalence study between the phase 3, or commercial formulation. An indirect comparison of pharmacokinetic parameters obtained from different studies in which these formulations were administered indicated that the C_{max} and t_{max} are expected to be within the same range for both formulations. However, the mean AUC and the range of the mean AUC are higher for the commercial formulation than for the Phase 3 formulation. Since patients are titrated to the optimal therapeutic range, the anticipated increased exposure from the commercial formulation is not irrelevant.

The effect of a high-fat meal on the bioavailability of each strength of the PR commercial formulation was assessed in two crossover studies. Exposure was estimated to be higher in the fed state compared to the fasted state, between 13 and 22% (AUC_{inf}) and 31 and 40% (C_{max}). Therefore, patients should take omecamtiv mecarbil consistently under the same fed, or fasting conditions. In combination with the proposed PK-guided dosing, this method of administration is considered the most optimal for a patient taking omecamtiv mecarbil.

Distribution

The *in vitro* plasma protein binding is ~82% at a concentration of 10 µM (4900 ng/ml). The observed *ex vivo* plasma protein binding in subjects with normal renal function was ~91%. A free fraction (f_u) of 0.18 is used for calculations of the drug-drug interaction risks as worst case scenario.

The blood-to-plasma ratio was ~0.9 *in vitro*, indicating no significant distribution into blood components.

Omecamtiv mecarbil has a large volume of distribution of over 438 L, as estimated by the PopPK.

Metabolism

The *in vitro* metabolism in human liver microsomes and human hepatocytes was low, with 65% remaining after 1.5 h and ~85% remaining after 2 h, respectively. M3 was the major metabolite formed in human hepatocytes.

The *in vivo* metabolism and metabolic profile of omecamtiv mecarbil was investigated in the human mass balance study following IV and oral administration. The major metabolic pathway was decarbamylation of omecamtiv mecarbil to M3 followed by further biotransformation to M4 (Figure 2). Omecamtiv mecarbil was also metabolised to several other metabolites. The parent compound was the most abundant component in plasma, with M3 and M4 present at 6.8% and 3.3% of total drug-related AUC, respectively. No other metabolites individually constituted more than 3% of circulating radioactivity. In urine and faeces, only a small proportion was omecamtiv mecarbil, while M3 and M4 were the major metabolites (M3 and M4 were 10.5 and 7.8% in urine and 17.2 and 3.1% in faeces). M3 and M4 are considered pharmacologically inactive.

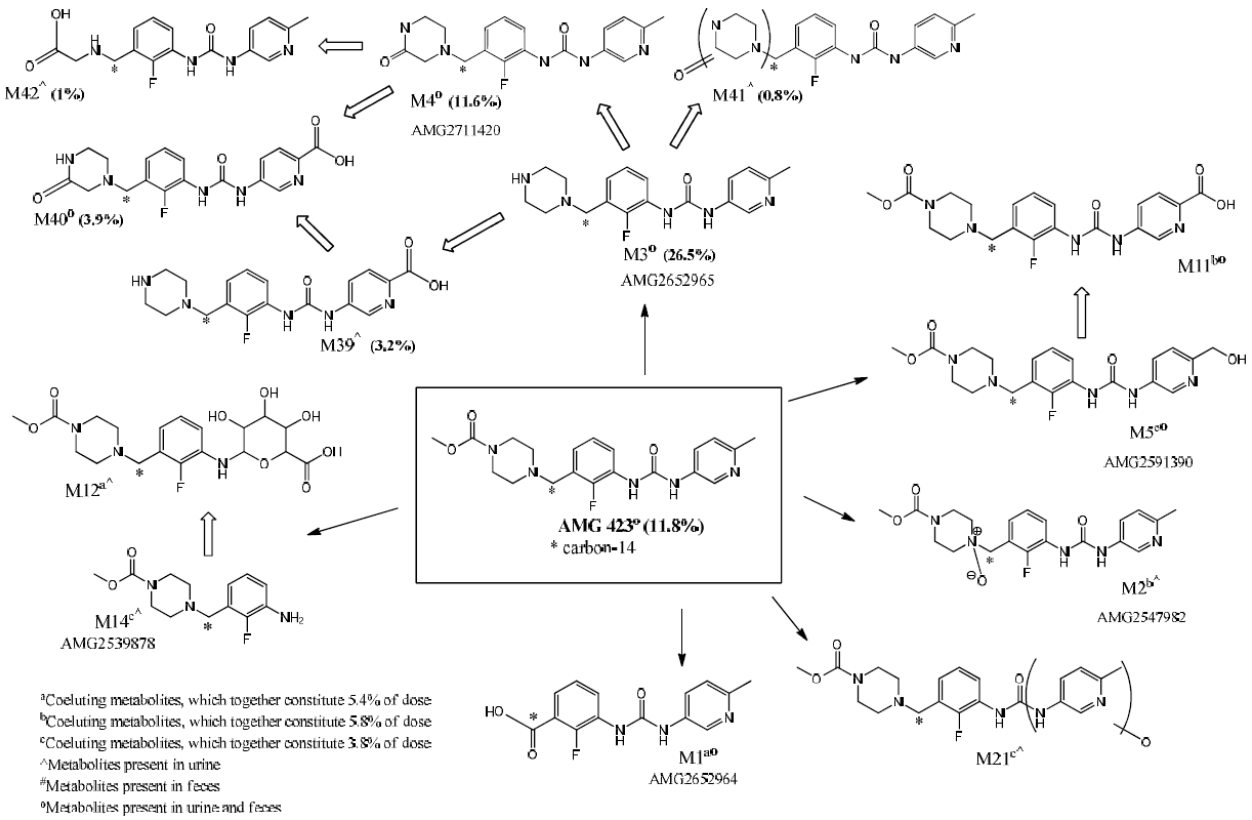


Figure 2. Proposed Biotransformation P of Omecamtiv Mecarbil in Humans

In vitro data indicates that M3 is mainly formed by CYP4A11 and CYP4F2 and most likely to a lesser extent by CYP2D6 *in vivo*. Based on the effect of genetic polymorphism in CYP2D6 , mass balance data and ketoconazole inhibition data, multiple enzymes are involved in the metabolism of omecamtiv mecarbil. CYP3A4 is involved up to 14% in the overall metabolism, CYP2D6 up to 32% to the overall metabolism, CYP4A11 up to 28% of the overall metabolism, CYP4F up to 19% of the overall metabolism and 7% is excreted unchanged.

Transporters

Omecamtiv mecarbil is a substrate of P-glycoprotein and BCRP, and it is not a substrate of OATP1B1 and OATP1B3. Since omecamtiv mecarbil is highly permeable and mainly eliminated as a metabolite, no other transporters need to be investigated.

Elimination

Following oral administration, 48% of the dose was recovered in urine and 38% in faeces. Thus, of the absorbed dose, around 2/3rd is eliminated via urine and 1/3rd via faeces. The mean elimination half-life for oral omecamtiv mecarbil was 27.4.9 has estimated with the final popPK model. The clearance of omecamtiv mecarbil is predominantly by metabolism with an apparent clearance of 12.1 L/h.

Dose proportionality and time dependencies

It can be concluded that the pharmacokinetics of omecamtiv mecarbil demonstrate a linear behaviour, and systemic exposure increases proportionally over the clinical dose range. Furthermore, there is no relevant variation of strength for the commercial formulation, i.e. two tablets of the 25 mg strength only demonstrate slightly higher exposure compared to one tablet of the 50 mg strength.

Results of study CY 1015 demonstrate that following 10 mg and 30 mg doses, in a comparison of AUC_{tau} at steady state and AUC_{inf} at a single dose, the pharmacokinetics of omecamtiv mecarbil were time-dependent, with AUC_{tau} being approximately 35% higher than following a single dose.

The accumulation following twice daily administration was investigated with a prototype MR formulation in study CY 1021. A comparison of AUC0-12 at steady state and AUC0-12 (Day 1) indicated that multiple-dose administration of 50 mg MR BID in Cohort 1 resulted in a mean accumulation ratio of omecamtiv mecarbil of approximately 4.4. Steady state of omecamtiv mecarbil was achieved by Day 7 (CY 1021) following multiple-dose administration of the 50 mg MR prototype tablet BID and with PopPK modelling it was predicted that 94.6% of the subjects achieved steady-state omecamtiv mecarbil concentrations by Day 14.

The peak-to-trough fluctuations in omecamtiv mecarbil plasma concentrations are low, with a mean $Cmax/C_{predose}$ ratios between 1.2 to 1.3 at steady state (2015-0134, CY 1211, 2013-0254).

Pharmacokinetics in the patient's population

There is no clear indication that a difference between healthy participants and patients with heart failure is expected with regard to the pharmacokinetics of omecamtiv mecarbil. For the dose of 50 mg twice daily, an AUC of 3860 ± 958 ng × h/mL and a C_{max} of 331 ± 80.8 ng/mL can be expected.

All PK data for patients included in the population PK analysis are derived from clinical studies (Phase 2 studies 2012-0227 and 2011-0151; pivotal Phase 3 study 2011-0203) where PK-guided dosing for omecamtiv mecarbil was employed per study protocol. As vast majority of population PK dataset is comprised of patients, the proposed popPK model-based predictions on omecamtiv mecarbil pharmacokinetics are biased by controlled dosing (i.e. measured plasma concentrations do not adequately reflect omecamtiv mecarbil dose-exposure relationship). It is currently not clear whether the current popPK model could be considered optimal for estimating the number of subjects with high plasma concentrations with the proposed posology (scheduled dose titration without PK-guidance) or for describing the effect of intrinsic/extrinsic factors on omecamtiv mecarbil PK parameters or on steady state exposures in patients on proposed dosing regimen.

Special populations

Genetic polymorphism

The effect of CYP2D6 genetic polymorphism on the PK of omecamtiv mecarbil was investigated in study CY1013. CYP2D6 is involved up to 32% to the overall metabolism. Lack of CYP2D6 activity would lead to a 1.5-fold increase in exposure. No adjustment of the starting dose or other warnings are needed since patients have an individualised PK-based dose titration strategy to reach and maintain the target therapeutic range.

No dedicated study was conducted investigating the effect of genetic polymorphisms in CYP4A11 on the PK of omecamtiv mecarbil. CYP4A11 is involved up to 28% of the overall metabolism. Lack of

CYP4A11 activity would lead to a 1.4-fold increase in exposure at the highest. No adjustment of the starting dose or other warnings are needed since patients have an individualised PK-based dose titration strategy to reach and maintain the target therapeutic range.

Renal impairment

The effect of renal impairment on the pharmacokinetics of omecamtiv mecarbil was investigated in a dedicated clinical study. Results from study 20080676 indicate comparable exposure of omecamtiv mecarbil in patients with End Stage Renal Disease (ESRD) subjects and healthy subjects. Multi-fold differences of exposure to metabolites of omecamtiv mecarbil are estimated in patients with ESRD. There is no notable difference between patients on- or off-haemodialysis. In study 20140209, exposures of omecamtiv mecarbil (as measured by AUC and Cmax) in subjects with mild, moderate, or severe renal impairment or ESRD appear to be comparable to subjects with normal renal function. However, broad ranges of the estimated ratio of geometric least squares means (GLSMs 90% CI) exist. The effect of renal impairment was also estimated based on data from the pivotal Phase 3 study 20110203, which included patients with mild, moderate, and severe renal impairment. Increases of 42-58% in the PK of omecamtiv mecarbil were noted in participants with moderate or severe renal impairment.

Thus, patients with reduced renal function demonstrate higher exposure than patients with normal renal function. However, the exposure difference is within limits and contained within the currently targeted therapeutic concentration range, by the proposed PK-guided dosing.

Of note, the exposure to metabolite M4 was estimated to increase 12-fold in patients with ESRD in study 20080676, compared to healthy subjects. However, the expected exposure to M4 is within safety limits as established in the non-clinical part of the dossier.

Hepatic impairment

Omecamtiv mecarbil, M3, and M4 exposure are likely to be similar in participants with normal liver function and participants with mild and moderate hepatic impairment (Child-Pugh Class A and B), as no statistically significant difference was observed in the dedicated hepatic impairment study. Although the number of subjects included was small, and thus study power was low, this conclusion can be supported. No studies were conducted in participants with severe hepatic impairment (Child-Pugh Class C). Therefore, a reduced starting dose (25mg QD) is recommended for patients with severe hepatic impairment.

Other intrinsic factors

Based on the results of the popPK, no clinically relevant effect of sex, age, weight or race on the pharmacokinetics of omecamtiv mecarbil are expected. Exposure was estimated to increase with lower body weight by about 28% when comparing the highest (>94 kg) with the lowest body weight (<67 kg) included in the analysis. A Phase 1 study directly comparing immediate release formulation of omecamtiv mecarbil demonstrated that pharmacokinetics are similar between males and females. A direct comparison Japanese and Caucasian healthy participants demonstrated a slightly higher exposure in the Japanese participants, however, this difference is presumably largely related to the lower body weights in the Japanese participants. The effect of age on the pharmacokinetics on omecamtiv mecarbil is limited, and differences between age groups are likely a reflection of lower eGFR and body weight in older patients.

Drug-drug interactions

Omecamtiv mecarbil as victim

In vitro data indicate that omecamtiv mecarbil is metabolised to its main metabolite M3 mainly formed by CYP4A11 and CYP4F2, and most likely to a lesser extent by CYP2D6 *in vivo*. The fraction metabolised attributable to CYP2C8, CYP3A, and CYP2J2 is approximately 14, and attributable to CYP4A/4F family approximately 48%.

Clinical DDI studies were conducted to investigate the effect of a weak CYP2D6 inhibitor and a strong and moderate CYP3A4 inhibitor on the PK of omecamtiv mecarbil, but no clinical studies were conducted to investigate the effect of a strong CYP2D6 inhibitor and CYP4A11 and CYP4F2 inhibitors on the PK of omecamtiv mecarbil. The effect of co-administration with a CYP2D6 strong inhibitor is expected to be similar to the effect of CYP2D6 poor metabolising status, i.e. a 1.2-fold increase in C_{max} and 1.5-fold increase in AUC. Considering the possible importance of CYP4A11 and 4F2 on the metabolism of omecamtiv mecarbil, clinical consequence of concomitant medication with weak, moderate and strong CYP2D6 inhibitors should be discussed (OC).

Omecamtiv mecarbil as perpetrator

Based on the *in vitro* studies, omecamtiv mecarbil is an inhibitor of P-glycoprotein and BCRP at maximal intestinal concentrations but not of CYP3A4. However, omecamtiv mecarbil is a time-dependent inhibitor of CYP3A4 in the intestine. A clinical DDI study with rosuvastatin (BCRP substrate) resulted in an increase in C_{max} of 1.5-fold. This would indicate that omecamtiv mecarbil is a weak inhibitor towards BCRP.

At maximal portal vein concentrations, omecamtiv mecarbil is an inhibitor of OATP1B1 and 1B3. A clinical DDI study with rosuvastatin (OATP1B1/1B3 substrate) resulted in an increase in C_{max} of 1.5-fold.

At maximal systemic concentrations, omecamtiv mecarbil is an inhibitor of CYP2C8, but not of CYP1A2, 2B6, 2C9, 2C19, 2D6, and 3A4. In addition, omecamtiv mecarbil is an inhibitor of the transporters P-glycoprotein, BCRP, MATE1 and MATE2-K at maximal systemic concentrations, and not OAT3. Omecamtiv mecarbil may be an inducer at clinically relevant systemic concentrations via CAR and PXR. The applicant investigated the net-effect of intestinal time-dependent inhibition and induction via PXR on the PK of midazolam (sensitive CYP3A4 substrate). The net effect was weak induction, however, the study was not conducted at maximal clinical dosing.The applicant provided a PBPK model to exclude the clinical relevance of the observed *in vitro* CYP2C8 inhibition potential of omecamtiv mecarbil. However the PBPK model is not sufficiently qualified to exclude the clinical relevance of the inhibition potential. Therefore, a clinical DDI study following a single dose of omecamtiv mecarbil investigating the inhibition potential towards CYP2C8 should be performed (OC). In addition, the applicant did not investigate the clinical induction potential towards CAR (CYP2B6). A clinical DDI study following multiple dosing to investigate the induction potential towards CAR using bupropion as sensitive substrate (including measurement of hydroxybupropion) should be performed (OC). Until the study results become available, a warning on potential induction via CAR is included in section 4.5 of the SmPC.

No DDI study was performed to investigate the interaction potential with oral contraceptives, since the target population is older, not taking contraceptives. However, it cannot be excluded that some younger women may take omecamtiv mecarbil. A warning is included in the SmPC that no dedicated DDI study was conducted but that plasma exposure may be decreased which may result in decreased efficacy of oral contraceptives.

3.3.1.2. Pharmacodynamics

Mechanism of action

Omecamtiv mecarbil (also known as AMG 423 and CK-1827452) is a selective cardiac myosin activator that increases cardiac contractility by specifically binding to myosin at an allosteric site and stabilising its lever arm in a primed position, increasing the number of myosin heads that can bind to actin filaments and undergo a power stroke once the cardiac cycle starts. As a cardiac myotrope, omecamtiv mecarbil increases the contraction of cardiac myocytes by direct action on the sarcomere, in the absence of changes in the cardiac myocyte calcium transient or the rate of contractility, which is in contrast to other positive inotropes such as β-adrenergic agonists, phosphodiesterase inhibitors, and cardiac glycosides. Instead, omecamtiv mecarbil increases the extent and duration of cardiac contraction without a significant increase in myocardial oxygen consumption.

Primary pharmacology

Echocardiography was the primary modality employed to assess the pharmacodynamics of OM in healthy participants and participants with HF. Key metrics of cardiac function assessed included systolic ejection time (SET; the most sensitive echocardiographic measure of the effect of OM), stroke volume (SV), cardiac output (CO), fractional shortening (FS), left ventricular ejection fraction (LVEF) and left ventricular dimensions and volumes.

First-in-man single ascending IV dose study in healthy subjects (Study CY 1111)

Study CY 1111 was a first-in-man, phase I, double-blind, randomised, four-way crossover, placebo-controlled, dose-escalation, PK/PK study in 4 cohorts of healthy subjects (N=34). Healthy male subjects received four 6-hour IV infusions: 3 doses of OM and 1 placebo. The OM IV dose levels were 0.005, 0.015, 0.025, 0.0625, 0.125, 0.25, 0.5, 0.625, 0.75 and 1 mg/kg/hr iv. The highest dose in each of the first three cohorts was administered as the lowest dose in the next cohort. There was a washout of at least seven days between Day 1 of each period.

OM produced significant concentration-related increases in SET associated with increases in LVEF and FS (Figure 3, Figure 4, and Figure 5), with a half maximal effective concentration (EC50) of approximately 400 ng/mL for SET and EF. Statistically significant effects were achieved at doses higher than 0.125 mg/kg/h. OM increased atrial contractile function, and there were no clinically relevant changes in diastolic function. The dose-limiting toxicity was myocardial ischaemia occurring at plasma concentrations exceeding 1,200 ng/mL in 3 individuals (two subjects treated with 0.75 mg/kg/h and 2 subjects treated with 1.0 mg/kg/h), likely due to excessive prolongation of the SET (by more than 110 msec in each case), and reduction of time during diastole for coronary perfusion.

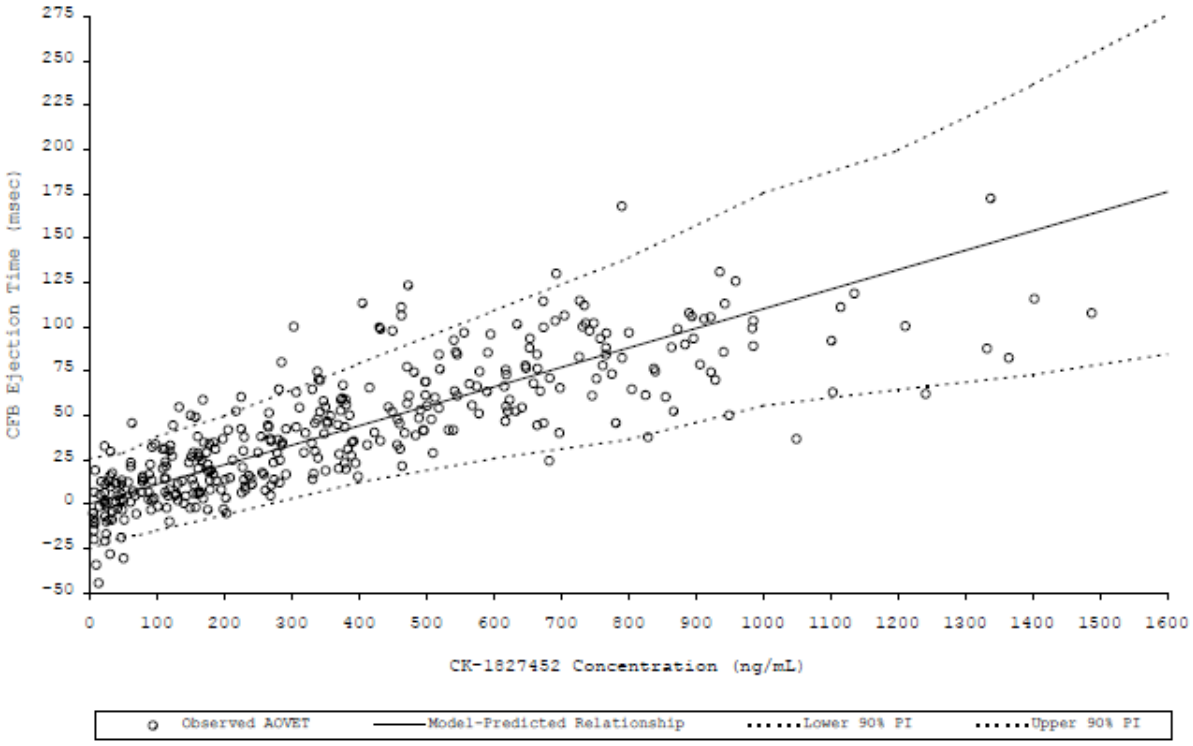


Figure 3. Relationship of Change from Baseline Ejection Time (msec) versus Plasma Concentration (ng/mL): Linear Model

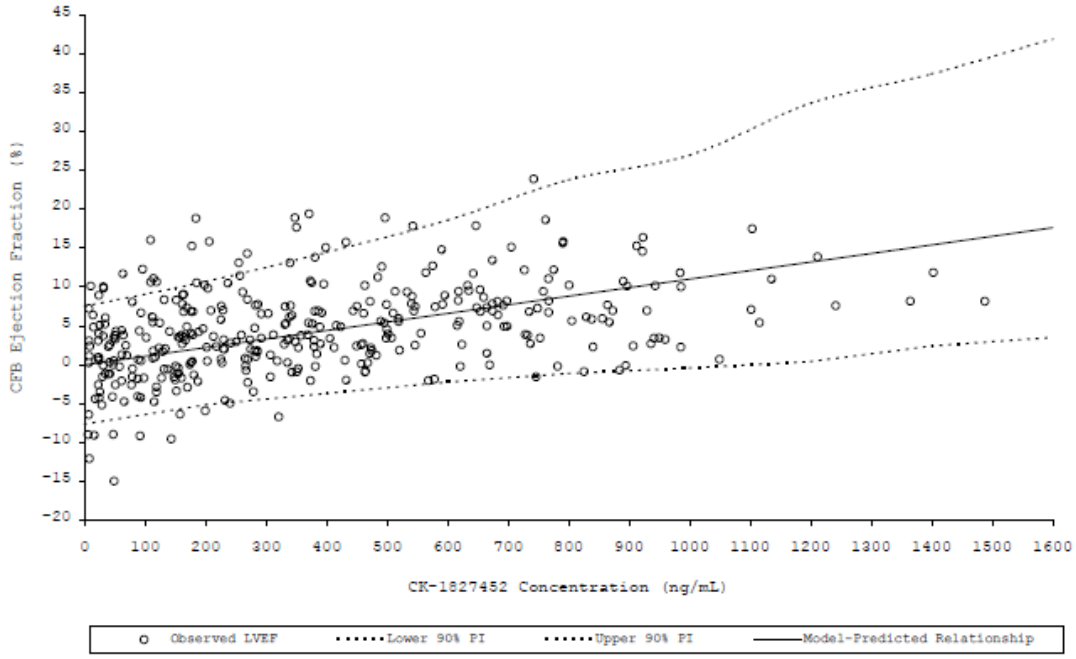


Figure 4. Relationship of Change from Baseline Ejection Fraction (%) versus Plasma Concentration (ng/mL): Linear Model

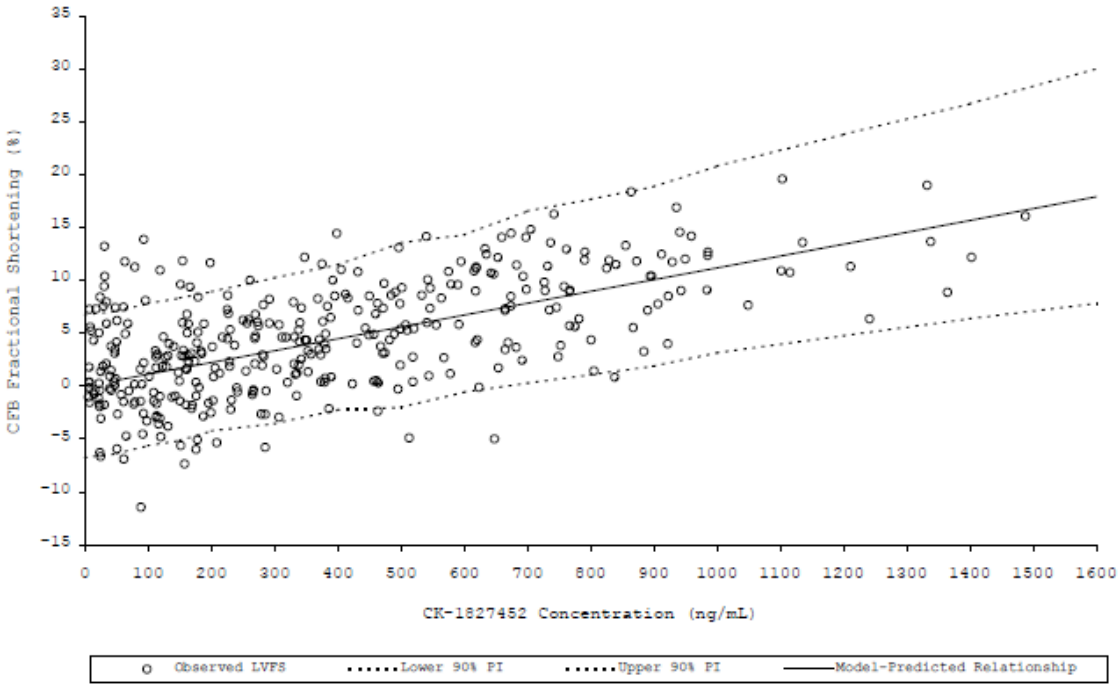


Figure 5. Relationship of Change from Baseline Fractional Shortening (%) versus Plasma Concentration (ng/mL): Linear Model

Multiple IV dose escalation study in patients with stable HF (Study CY 1121)

Study CY1121 was a phase II, multi-centre, double-blind, randomised, placebo-controlled, dose-escalation, crossover, PK/PD study in patients with stable HF. The study consisted of 5 cohorts (N=45). Participants in Cohorts 1 to 4 underwent 4 treatment periods, each consisting of 3 active treatments and 1 placebo treatment that was randomised into the dose escalation sequence (Table 3). Each active treatment consisted of 2 sequential infusions for Cohorts 1 to 3 and 3 sequential infusions for Cohort 4. Participants in Cohort 5 underwent 2 treatment periods, each consisting of 1 active treatment (3 sequential infusions) and 1 placebo treatment in random order. There was a washout period of at least 1 week between the start of each treatment period for all cohorts.

Table 3. Doses of Omecamtiv Mecarbil Administered to Cohorts 1 to 5 (Study CY 1121)

Cohort	Treatment	IV Infusion 1	IV Infusion 2	IV Infusion 3
1	B	0.125 mg/kg/h (1 h)	0.0625 mg/kg/h (1 h)	-
1	C	0.25 mg/kg/h (1 h)	0.125 mg/kg/h (1 h)	-
1, 2	D	0.5 mg/kg/h (1 h)	0.25 mg/kg/h (1 h)	-
2	E	0.75 mg/kg/h (1 h)	0.375 mg/kg/h (1 h)	-
2	F	1.0 mg/kg/h (1 h)	0.5 mg/kg/h (1 h)	-
3	I	0.25 mg/kg/h (1 h)	0.025 mg/kg/h (23 h)	-
3	J	0.50 mg/kg/h (1 h)	0.05 mg/kg/h (23 h)	-
3	K	1.0 mg/kg/h (1 h)	0.1 mg/kg/h (23 h)	-
4	M	0.25 mg/kg/h (1 h)	0.125 mg/kg/h (1 h)	0.025 mg/kg/h (22 h)
4	N	0.5 mg/kg/h (1 h)	0.25 mg/kg/h (1 h)	0.05 mg/kg/h (22 h)
4	O	1.0 mg/kg/h (1 h)	0.5 mg/kg/h (1 h)	0.1 mg/kg/h (22 h)
5	Q	1.0 mg/kg/h (1 h)	0.5 mg/kg/h (1 h)	0.1 mg/kg/h (70 h)
5	R	0.75 mg/kg/h (1 h)	0.375 mg/kg/h (1 h)	0.075 mg/kg/h (70 h)

Concentration-dependent improvements in cardiac function, including SET, SV, CO, FS, and LVEF were observed, associated with a modest decline in heart rate (Table 4, Figure 6). Among the PD parameters, SET was the most sensitive indicator of drug effect in that increases in SET became statistically significant at OM concentrations >100 ng/ml, with an EC_{50} of 293 ng/ml. These increases in SET remained statistically significant for up to 24 hr of infusion and for up to 24 hr after the termination of infusion.

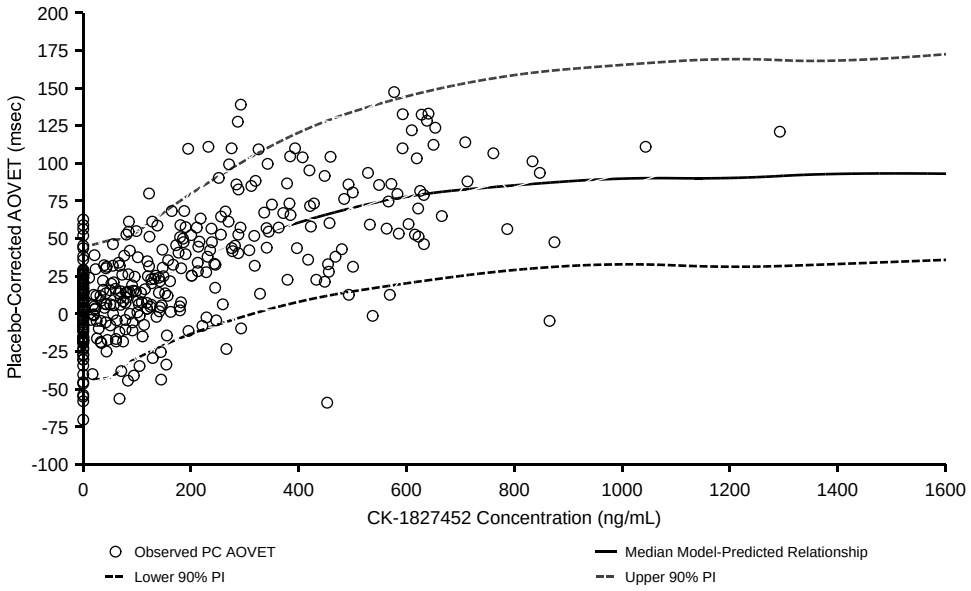
Higher plasma concentrations were also associated with reductions in end-systolic and diastolic volumes that may have been more pronounced with longer-term infusion. As in healthy participants, cardiac ischaemia emerged at plasma concentrations exceeding 1,200 ng/mL in some but not all individuals (Cleland, 2011). In this study, the PD response across most PD markers, in particular LVEF and CO, was statistically significant at plasma concentrations of omecamtiv mecarbil above 300 ng/mL.

Table 4. Summary of Results of Echocardiographic Pharmacokinetic/Pharmacodynamic Relationship from Bin Analysis (Study CY 1121)

	Plasma Concentration of Omecamtiv Mecarbil (ng/mL)						
	Baseline	**0 to 100**	**>100 to 200**	**>200 to 300**	**>300 to 400**	**>400 to 500**	**>500**
Variable	LS Mean Difference from Baseline (Test – Placebo) (p-value)						
SET (msec)	315.5	0.573 (0.8842)	18.4 (<0.0001)	47.1 (<0.0001)	58.1 (<0.0001)	59.2 (<0.0001)	80.0 (<0.0001)
LVOTVTI (cm)	32.6	-0.012 (0.9780)	0.408 (0.3676)	1.48 (0.0049)	2.77 (<0.0001)	2.46 (0.0004)	2.65 (<0.0001)
LVOTSV (mL)	18.1	-0.321 (0.8510)	0.701 (0.6981)	5.36 (0.0104)	10.5 (<0.0001)	8.95 (0.0013)	9.74 (<0.0001)
LVOTCO (mL/min)	68.5	-32.5 (0.7798)	52.1 (0.6714)	180 (0.2032)	408 (0.0191)	400 (0.0344)	330 (0.0202)

	Plasma Concentration of Omecamtiv Mecarbil (ng/mL)						
	Baseline	**0 to 100**	**>100 to 200**	**>200 to 300**	**>300 to 400**	**>400 to 500**	**>500**
LVFS (%)	243.4	0.591 (0.3665)	1.49 (0.0357)	2.93 (0.0004)	2.56 (0.0086)	2.39 (0.0320)	4.58 (<0.0001)
LVVOLS (mL)	167.7	0.835 (0.8391)	3.40 (0.4311)	-4.99 (0.3039)	-10.7 (0.0770)	-12.6 (0.0556)	-14.8 (0.0026)
LVVOLD (mL)	4423.3	0.846 (0.8722)	5.33 (0.3331)	-1.66 (0.7881)	-14.2 (0.0659)	-15.3 (0.0676)	-16.2 (0.0096)
LVEF (%)	32.1	-0.185 (0.7604)	0.225 (0.7258)	0.813 (0.2578)	1.12 (0.2151)	0.151 (0.8761)	1.64 (0.0232)
LVEF2 (%)	17.8	0.265 (0.8321)	1.25 (0.3462)	2.73 (0.0738)	7.93 (<0.0001)	6.82 (0.0009)	10.2 (<0.0001)

LS=least-square; LVEF=left ventricular ejection fraction by 2D method of discs; LVEF2=the ratio of stroke volume as determined from Doppler of the left ventricular outflow tract to the LV end diastolic volume as calculated from the 2D method of discs; LVFS=left ventricular fractional shortening; LVOTCO=Doppler-derived cardiac output; LVOTSV=left ventricular outflow tract stroke volume; LVOTVTI=left ventricular outflow tract velocity time integral; LVVOLD=left ventricular end-diastolic volume; LVVOLS=left ventricular end-systolic volume; SET=systolic ejection time (also abbreviated as aortic valve ejection time [AOVET]).



AOVET=aortic valve ejection time=systolic ejection time; CK-1827452=omecamtiv mecarbil; Emax=maximum effect; PC=placebo corrected; PI=prediction intervals.

Figure 6. Relationship of Placebo-corrected Systolic Ejection Time Versus Plasma Concentration: Sigmoidal E_{max} Model (Study CY 1121)

Dose escalation study in patients with HFrEF using oral formulation (Study 20110151; COSMIC-HF)

Study 20110151 was a double-blind, randomised, placebo-controlled, multi-centre study consisting of a Dose Escalation Phase (N=96) to select 1 of 3 omecamtiv mecarbil oral MR tablet formulations (MR MTX-F1, MR MTX-F2, and MR SCT-F2) in 2 dose escalation cohorts (25 mg BID Cohort 1; 50 mg BID Cohort 2, or placebo BID for 7 days), followed by an Expansion Phase (N = 448) to evaluate 20 weeks of administration of the selected omecamtiv mecarbil formulation at dose levels of 25 to 50 mg BID

compared with placebo in participants with chronic HFrEF. The Expansion phase included transthoracic echocardiographic assessments.

In the Expansion Phase, subjects were randomised into 1 of the 3 treatment groups to receive 25 mg oral omecamtiv mecarbil BID (fixed dose group), 25 mg BID titrated to 50 mg BID guided by PK (PK-titration group), or placebo for 20 weeks. The dose in the PK-titration group was increased from 25 to 50 mg BID at week 8 if the plasma concentration of omecamtiv mecarbil was <200 ng/mL at steady state. Following PK-guided titration using the MR F1 tablet formulation at doses of 25 and 50 mg BID, the highest Cmax in the PK-guided titration group observed was 831 ng/mL.

Statistically significant improvements were observed for all the pre-specified efficacy endpoints of SET, SV, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), heart rate, and NT-proBNP over 20 weeks of oral dosing with omecamtiv mecarbil, with larger apparent effects in the PK titration group (see also section 3.3.4 “3.3.4. Clinical efficacy’: Table 30 and Table 31).

Secondary pharmacology

Effect on cardiac depolarisation

Omecamtiv mecarbil was subjected to an extensive nonclinical and clinical evaluation of its potential to prolong the QT interval. Nonclinical studies included the Comprehensive *in vitro* Proarrhythmia Assay (CiPA) protocol human ether-á-go-go-related gene (hERG), Nav1.5, and Cav1.2 channels, action potential duration in dog Purkinje fibres, and *ex vivo* cardiac functional parameter assessments in isolated rat and rabbit hearts, and a safety pharmacology study in the dog. The half maximal inhibitory concentration (IC50) for inhibition of hERG current was estimated to be 125.5 µM (NCD05-022), far exceeding (>350-fold) the therapeutic free concentration range (0.09 to 0.35 µM, corresponding to the unbound concentration of the therapeutic range of 200 to 750 ng/mL); omecamtiv mecarbil had no activity on sodium channel protein type 5 subunit alpha (Nav1.5) or calcium channel, voltage-dependent, L type, alpha 1C subunit (Cav1.2) at relevant concentrations (Study 152017). Omecamtiv mecarbil also did not prolong action potential repolarisation in isolated canine Purkinje fibres at concentrations up to 10 µM (NCD05 023, CV04-0067) and did not prolong action potential duration in isolated canine Purkinje fibres.

A modified TQT study (20090231) was conducted in which supratherapeutic doses of omecamtiv mecarbil were not administered due to the risk of toxicity related to an exaggerated pharmacologic effect at excessive plasma concentrations. Omecamtiv mecarbil at the single studied dose of 50 mg did not have a clinically relevant effect on the QT interval or on cardiac conduction, consistent with the ICH E14 definition of a negative thorough QT/QTc study. More specifically, after a single dose of 50 mg OM, the Cmax values ranged between 220 to 801 ng/mL. The mean change from baseline QTcF (ΔQTcF) after the administration of omecamtiv mecarbil generally followed the placebo pattern across postdose time points. Mean placebo-corrected ΔQTcF (ΔΔQTcF) after omecamtiv mecarbil ranged from -6.7 ms at 1 hour postdose to -0.8 ms at 4 hours postdose (Table 5). The highest upper bound of the 1-sided 95% CI (equivalent to the 2-sided 90% CI) was 0.7 ms at 4 hours postdose.

After dosing with 400 mg oral moxifloxacin, a clear increase of mean ΔΔQTcF was observed with a peak value of 13.1 ms (90% CI: 11.71, 14.57) at 3 hours. The lower bound of the 1-sided 95% CI (equivalent to the 2-sided 90% CI) was larger than 5 ms at all 3 of the prespecified timepoints (11.13, 11.71, and 11.37 ms at 2, 3, and 4 hours, respectively), thereby demonstrating assay sensitivity.

Table 5. Placebo-corrected Change-From-Baseline QTcF **(ΔΔQTcF)** at Each Timepoint (QT/QTc Analysis Set) (Study 20090231)

Day	Time point	50 mg Omecamtiv Mecarbil Oral Solution	Moxifloxacin
Day 1	0.25 h Postdose	-2.6 (0.79) [-3.87; -1.24]	2.2 (0.80) [0.89; 3.53]
	0.5 h Postdose	-4.9 (0.89) [-6.40; -3.45]	8.6 (0.89) [7.11; 10.05]
	0.75 h Postdose	-5.8 (0.96) [-7.34; -4.18]	10.1 (0.96) [8.51; 11.67]
	1 h Postdose	-6.7 (0.86) [-8.13; -5.29]	10.2 (0.86) [8.74; 11.58]
	1.5 h Postdose	-4.5 (0.90) [-5.95; -2.98]	11.1 (0.90) [9.61; 12.59]
	2 h Postdose	-2.7 (0.92) [-4.21; -1.18]	12.7 (0.92) [11.13; 14.17]
	3 h Postdose	-1.5 (0.86) [-2.96; -0.10]	13.1 (0.86) [11.71; 14.57]
	4 h Postdose	-0.8 (0.92) [-2.35; 0.70]	12.9 (0.92) [11.37; 14.42]
	8 h Postdose	-2.2 (1.16) [-4.10; -0.24]	9.7 (1.17) [7.75; 11.62]
	12 h Postdose	-1.9 (1.27) [-3.98; 0.22]	9.0 (1.27) [6.85; 11.06]
	24 h Postdose	-1.2 (0.90) [-2.68; 0.30]	5.3 (0.90) [3.78; 6.76]

Pharmacodynamic interactions with other medicinal products or substances

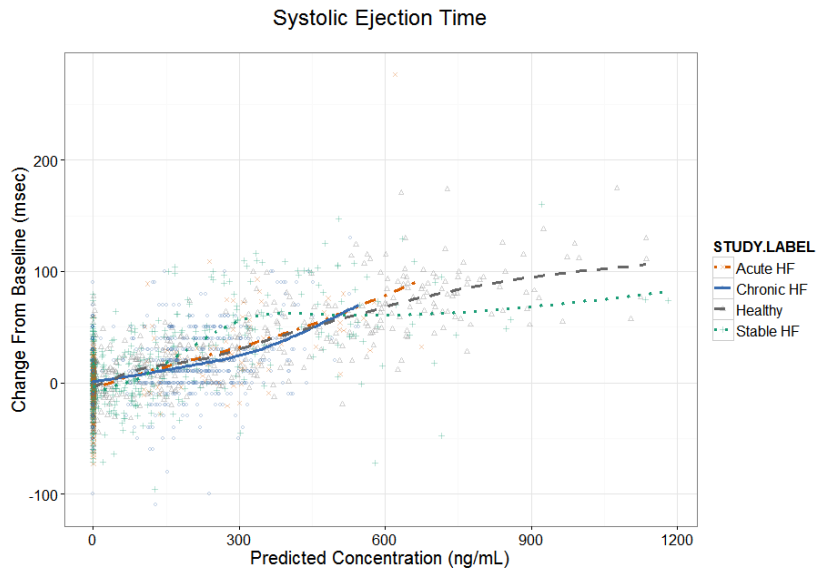
Clinical studies have not been conducted to evaluate pharmacodynamic interactions between omecamtiv mecarbil and other medicinal products or substances. However, the potential for omecamtiv mecarbil to induce off-target pharmacological effects on other unrelated proteins was investigated *in vitro*. Omecamtiv mecarbil was evaluated *in vitro* for binding to a larger panel of pharmacological targets (Studies CV04-0069, 119745, 119877, CV04-0070). The results indicate that omecamtiv mecarbil does not interact with over 80 pharmacological targets at therapeutically relevant concentrations.

Genetic differences in PD response

No information on genetic differences in PD response was available.

Relationship between plasma concentrations and effect

A direct-effect relationship exists between plasma omecamtiv mecarbil concentrations and SET over a wide range of plasma omecamtiv mecarbil concentrations (Figure 7). The omecamtiv mecarbil development programme sought to maintain pharmacodynamically active omecamtiv mecarbil plasma concentrations (eg, >200 ng/mL), but with the understanding that excessive omecamtiv mecarbil plasma concentrations (eg, >1,200 ng/mL) lead to exaggerated pharmacology potentially resulting in cardiac ischaemia presumably due to reduced coronary perfusion during diastole.



HF=heart failure.
Acute HF from 20100754; Chronic HF from 20110151; Stable HF from CY 1121; Healthy from CY 1111.

Figure 7. Relationship between Omecamtiv Mecarbil Concentrations and Change from Baseline in Systolic Ejection Time (ER118755)

3.3.2. Discussion on clinical pharmacology

Pharmacokinetics

Overall the pharmacokinetics of omecamtiv mecarbil have been adequately characterised.

Omecamtiv mecarbil is highly permeable based on *in vitro* studies but its solubility is pH-dependent. Bioavailability of the modified release formulations is markedly lower, estimated in the range of 60-80%. Exposure was estimated to be higher in the fed state compared to the fasted state, patients should take omecamtiv mecarbil consistently under the same fed, or fasting conditions.

The major metabolic pathway was decarbamylation of omecamtiv mecarbil to metabolite M3, followed by further biotransformation to M4 (both considered pharmacologically inactive). Multiple enzymes are involved in the metabolism of omecamtiv mecarbil and it is metabolised to several other metabolites. However, the parent compound was the most abundant component in plasma.

In vitro data indicates that M3 is mainly formed by CYP4A11 and CYP4F2 and most likely to a lesser extent by CYP2D6 *in vivo*. CYP3A4 is involved up to 14% in the overall metabolism, CYP2D6 up to 32% to the overall metabolism, CYP4A11 up to 28% of the overall metabolism, CYP4F up to 19% of the overall metabolism and 7% is excreted unchanged.

Following oral administration, 48% of the dose was recovered in urine and 38% in faeces. The mean elimination half-life for oral omecamtiv mecarbil was 27.4.9 has estimated with the final popPK model. The clearance of omecamtiv mecarbil is predominantly by metabolism with an apparent clearance of 12.1 L/h.

There is no clear indication that a difference between healthy participants and patients with heart failure is expected with regard to the pharmacokinetics of omecamtiv mecarbil.

Regarding genetic polymorphisms on the PK of omecamtiv mecarbil, lack of CYP2D6 activity would lead to a 1.5-fold increase in exposure, lack of CYP4A11 activity would lead to a 1.4-fold increase in

exposure at the highest. No adjustment of the starting dose or other warnings are needed since patients have an individualised PK-based dose titration strategy to reach and maintain the target therapeutic range.

Patients with reduced renal function demonstrate higher exposure than patients with normal renal function. However, the exposure difference is within limits and contained within the currently targeted therapeutic concentration range, by the proposed PK-guided dosing. The exposure is similar in participants with mild and moderate hepatic impairment (Child-Pugh Class A and B). No studies were conducted in participants with severe hepatic impairment (Child-Pugh Class C). Therefore, a reduced starting dose (25mg QD) is recommended for patients with severe hepatic impairment.

No clinically relevant effect of sex, age, weight or race on the pharmacokinetics of omecamtiv mecarbil are expected.

Clinical DDI studies were conducted to investigate the effect of a weak CYP2D6 inhibitor and a strong and moderate CYP3A4 inhibitor on the PK of omecamtiv mecarbil, but no clinical studies were conducted to investigate the effect of a strong CYP2D6 inhibitor and CYP4A11 and CYP4F2 inhibitors. The effect of co-administration with such inhibitors is expected to be within limits.

Omecamtiv mecarbil can be an inhibitor of P-glycoprotein and BCRP, and time-dependent of CYP3A4 in the intestine. At maximal portal vein concentrations, omecamtiv mecarbil is an inhibitor of OATP1B1 and 1B3. At maximal systemic concentrations, omecamtiv mecarbil is an inhibitor of CYP2C8, but not of CYP1A2, 2B6, 2C9, CYP1A2, 2B6, and 2C19, respectively 2D6, and 3A4. In addition, omecamtiv mecarbil is an inhibitor of the transporters P-glycoprotein, BCRP, MATE1 and MATE2-K, and not OAT3.

Omecamtiv mecarbil may be an inducer at clinically relevant systemic concentrations via CAR and PXR. A clinical DDI study following a single dose of omecamtiv mecarbil investigating the inhibition potential towards CYP2C8 should be performed (OC). A clinical DDI study following multiple dosing to investigate the induction potential towards CAR using bupropion as sensitive substrate (including measurement of hydroxybupropion) should also be performed (OC).

No DDI study was performed to investigate the interaction potential with oral contraceptives, a warning is included in the SmPC that plasma exposure may be decreased which may result in decreased efficacy of oral contraceptives.

Pharmacodynamics

Omecamtiv mecarbil (OM) is a first-in-class cardiac myosin activator. Myosin activation increases cardiac contractility by specifically binding to myosin at an allosteric site stabilising its lever arm in a primed position, increasing the number of myosin heads that can bind to actin filaments and undergo a power stroke once the cardiac cycle starts. OM increases cardiac contractility in the absence of changes in the cardiac myocyte calcium transient and oxygen consumption.

The pharmacodynamic effects of OM were evaluated after single and multiple dose administrations in healthy subjects (Study CY 1111) and in subjects with heart failure (Study CY 1121 and Study 20110151). Study CY 1111 was a first-in-man four-way crossover, single ascending IV dose phase I study in 34 healthy subjects evaluating a six-hour continuous IV infusions of 0.005, 0.015, 0.025, 0.0625, 0.125, 0.25, 0.5, 0.625, 0.75 and 1 mg/kg/hr iv. In this study, OM resulted in a dose and plasma concentration-related increase in systolic ejection time (SET), ejection fraction (EF), and fractional shortening (FS). Regarding SET (the most sensitive indication of drug effect), significant effects were observed at doses higher than 0.125 mg/kg/h. Study CY 1121 was a cross-over multiple IV dose-escalation phase II study in 45 patients with stable heart failure in which subjects received continuous infusions of 0.0625 – 1.0 mg/kg/h for 1h, 0.025-0.1 mg/kg/h for 22 h, 0.025 – 0.1 mg/kg/h for 23h, 0.075 and 0.1 mg/kg/h for 70h. OM infusion resulted in dose and plasma

concentration-related increases in cardiac function, including SET, stroke volume (SV), cardiac output (CO), EF, and FS. Significant effects in SET were observed at OM concentrations >100 ng/ml. PK/PD modelling of data from CY 1111 and CY 1121 found the EC50 increase in SET was 410 and 293 ng/mL, respectively. Importantly, in both Study CY1111 and CY 1121, myocardial ischaemia due to an excessive concentration of OM (⩾1200 ng/ml) was observed (n=3 in CY 1111 and n=2 in CY 1121)(see also Clinical safety). Study 20110151 was a phase II study evaluating oral OM tablet formulations. In the expansion phase of this study, oral administration of OM resulted in significant increases in SET, LVEF, SV, and FS and reductions in left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), and heart rate, with larger effects in highest OM dose group.

Overall, the different phase I and II studies showed a clear concentration-response relationship between OM plasma concentration and changes in PD markers of cardiac function, including SET, EF, and FS, which were significant at OM concentrations >100 ng/ml with the risk of cardiac toxicity at OM concentrations ⩾1200 ng/ml due to exaggerated pharmacology.

Any QT-prolonging potential for OM is unlikely based on the absence of any QT-prolonging effect *in vitro*, pre-clinical, modified QT study and phase III ECG data.

Clinical studies have not been conducted to evaluate pharmacodynamic interactions between omecamtiv mecarbil and other medicinal products or substances. However, the potential for omecamtiv mecarbil to induce off-target pharmacological effects on other unrelated proteins was investigated *in vitro*. Omecamtiv mecarbil was evaluated *in vitro* for binding to a larger panel of pharmacological targets (Studies CV04-0069, 119745, 119877, CV04-0070). The results indicate that omecamtiv mecarbil does not interact with over 80 pharmacological targets at therapeutically relevant concentrations.

The applicant acknowledges that genetic variation could result in differences in drug response (safety and/or efficacy). No genetic variation data was available in the GALACTIC-HF trial. The applicant is proposing to implement a PK-based dosing titration that will enable patients to achieve therapeutic concentrations of omecamtiv mecarbil and will minimise the risk of exceeding concentrations >1200 ng/mL that have been associated with the risk of ischaemia. The applicant states that this individualised dosing paradigm will circumvent any potential difference in the pharmacodynamic response due to genetic variability. This is not fully endorsed, as it is still possible that at the same concentration, genetic differences can lead to differences in efficacy and/or safety. However, this issue is not further pursued, given the lack of specific signals and lack of available data.

Several published articles demonstrated that omecamtiv mecarbil increased calcium sensitivity in slow (Type I) but not fast (Type II) skeletal muscle fibers (Malik 2011, Nagy 2015 and Lindqvist 2019). While at a tissue level omecamtiv mecarbil activates slow skeletal muscle fibres, it is unlikely to have any impact on overall skeletal muscle performance in humans, given the larger dynamic range of skeletal muscles and the fact that skeletal muscles are under neural feedback whereby the nerve input into muscle is modified in real time to achieve the desired force output.

3.3.3. Conclusions on clinical pharmacology

Overall the pharmacokinetics of omecamtiv mecarbil has adequately been characterised.

Generally, the pharmacodynamics of OM have been sufficiently evaluated. However, there are some points for clarification concerning pharmacodynamic interactions with other medicinal products and genetic differences in PD response. Furthermore, the applicant has made some claims without any justification that need to be addressed, i.e., OM increases cardiac contractility without changes in the

cardiac myocyte calcium transient and oxygen consumption and that OM is a selective cardiac myosin activator (so without affecting skeletal myosin).

3.3.4. Clinical efficacy

The proposed indication is based upon the efficacy results of Phase 3 Study 20110203 (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure [GALACTIC-HF]). Study 20110203 is a global, double-blind, placebo-controlled, multicentre, CV outcomes study that assessed the efficacy and safety of omecamtiv mecarbil on mortality and morbidity in participants with chronic HfrEF (8,256 randomised and 8,211 dosed). A Final Clinical Study Report (CSR) was completed on 16 Apr 2021, and a CSR Amendment 1 was completed on 21 Sep 2021, both based on a database relock of 10 Mar 2021. CSR Addendum v2 dated 19 Aug 2022 provided supplemental analyses that further characterise the efficacy and safety profile of omecamtiv mecarbil in the total cohort and higher-risk subgroups and describe the profile of the pharmacokinetic (PK)-guided dose titration strategy.

Additional studies that provide supportive efficacy data were also included:

- Two Phase 2b studies, Studies 20120227 and 20110151 Expansion Phase (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure [COSMIC-HF]) in participants with chronic HfrEF, provide supporting efficacy data.
- Study 20100754 (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure [ATOMIC-AHF]), a Phase 2, dose-finding, randomised, double-blind, placebo-controlled study of intravenous (IV) omecamtiv mecarbil in participants with left ventricular systolic dysfunction hospitalised for acute HF, which informed the inclusion of patients in 20110203.

All the abovementioned clinical studies were conducted in compliance with Good Clinical Practice (GCP). An overview of the studies supporting efficacy is shown in Table 6 and Table 7.

Table 6. Efficacy Studies in Participants with Chronic Heart Failure With Reduced Ejection Fraction Supporting the Proposed Indication.

Type of Study	Study Identifier/ Protocol No.	Study Design and Type of Control	Study Objectives	Test Products; Dosage Regimens; Route of Administration	No. of Participants Enrolled/ Treated	Study Population and Key Entry Criteria	Duration of Omecamtiv Mecarbil Treatment	Study Status; Type of Report/ Location
Pivotal CV outcomes	20110203 (GALACTIC-HF)	Phase 3, double-blind, randomized, placebo-controlled, multicenter, parallel-group, event-driven, CV outcomes study	Effect of omecamtiv mecarbil vs. placebo on time to CV death or first HF event, whichever occurred first, in participants with chronic HFrEF receiving SoC therapy	Oral, MR tablets 25, 37.5, or 50 mg, BID[a]	8,256/8,211	Participants with chronic HFrEF, NYHA Class II-IV, and LVEF ≤ 35% who were either currently hospitalized with the primary reason of HF or had 1 of the following events within 1 year of screening: hospitalization or urgent visit to the emergency department with primary reason of HF; 18 to 85 years of age	Up to 4 years, until prespecified 1,590 CV death events occurred	Completed; Final CSR/ (20110203) /5.3.5.1 CSR Addendum (20110203 CSR Addendum v2)/5.3.5.1

Efficacy	20110151 (COSMIC-HF)	Phase 2b, double-blind, randomized, placebo-controlled, 2-Phase (Dose Escalation and Dose Expansion)	Dose Escalation Phase: Dose selection of 1 of 3 oral formulations in participants with HF and LVSD Dose Expansion Phase: Evaluation of selected formulation at 2 target dose levels vs. placebo (PK, cardiac structure and function, NT-proBNP, HR)	Dose Escalation Phase: 3 tablet formulations (MR MTX-F1, MR MTX-F2, and MR SCT-F2), 25 mg (cohort 1) or 50 mg (cohort 2), BID, oral or placebo Dose Expansion Phase: MR MTX-F1 tablet, oral 3 dose cohorts; 25 mg BID; PK-guided dose titration (25 to 50 mg BID); or placebo	Dose Escalation Phase: Cohort 1: 49/48 Cohort 2: 47/46 Dose Expansion Phase: 448/445	Participants with chronic HFrEF, NYHA Class II-III, stable pharmacological therapy, and LVEF ≤ 40%; 18 to 85 years of age	Dose Escalation Phase: 7 days Dose Expansion Phase: 20 weeks	Completed; Final CSR/ (20110151) /5.3.5.1
Efficacy	20120227	Phase 2b, double-blind, randomized, placebo-controlled	Safety, PK, efficacy (SET), in Japanese participants with HFrEF	MR MTX-F1 tablet, oral 4 dose cohorts: 25 mg, BID; 25 mg then 37.5 mg[b], BID; 25 mg then 50 mg[b] BID; or Placebo	81/81	Participants with chronic HFrEF, stable optimal pharmacological therapy, LVEF ≤ 40%; 20 to 85 years of age	16 weeks	Completed; Final CSR/ (20120227) /5.3.5.1

BID=twice a day; COSMIC-HF=Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure; CSR=clinical study report; Cpredose=plasma concentration before investigational product administration; CV=cardiovascular; GALACTIC-HF=Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; HF=heart failure; HfrEF=heart failure with reduced ejection fraction; HR=heart rate;LVEF=left ventricular ejection fraction; LVSD=left ventricular systolic dysfunction; MR=modified-release; MR MTX-F=MR matrix formulation; MR SCT=MR swellable core technology; NT-proBNP=N-terminal prohormone brain-type natriuretic peptide; NYHA=New York Heart Association; PK=pharmacokinetic; SET=systolic ejection time: SoC=standard of care. A Dose selection based on Week 2 and potentially Week 6 steady-state Cpredose values. B Dose selection based on Week 2 steady-state Cpredose value.

Table 7. Efficacy Study in Participants with Acute Heart Failure

Type of Study	Study Identifier/ Protocol No.	Study Design and Type of Control	Study Objectives	Test Products; Dosage Regimens; Route of Administration	No. of Participants Enrolled/Treated	Healthy Participants or Diagnosis of Participants and Key Entry Criteria	Duration of Omecamtiv Mecarbil Treatment	Study Status; Type of Report/ Location
Efficacy	20100754 (ATOMIC-AHF)	Phase 2b, double-blind, randomized, placebo-controlled	Efficacy (dyspnea response), safety and tolerability, PK in participants with LVSD hospitalized for acute HF	Solution for injection, 1 mg/mL, IV, 2 sequential infusions (4 h loading dose and 44 h maintenance dose): 7.5 mg/h for 4 h then 1.5 mg/h for 44 h; 15 mg/h for 4 h then 3.0 mg/h for 44 h; 20 mg/h for 4 h then 4.0 mg/h for 44 h; or Placebo	613/606	Current hospitalization for a primary reason of worsening HF and requiring IV therapy for HF; History of chronic HF and LVEF ≤ 40%; Persistent dyspnea at rest or with minimal exertion, at least 2 h after receiving an IV diuretic and within 24 h after their initial IV diuretic dose; 18 to 85 years of age	48 hours	Completed; Final CSR/ (20100754) /5.3.5.1

ATOMIC-AHF = acute treatment with omecamtiv mecarbil to increase contractility in acute heart failure; CSR = clinical study report; h = hour; HF = heart failure; IV = intravenous; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; PK = pharmacokinetic.

ATOMIC-AHF=acute treatment with omecamtiv mecarbil to increase contractility in acute heart failure; CSR=clinical study report; h=hour; HF=heart failure; IV=intravenous; LVEF=left ventricular ejection fraction; LVSD=left ventricular systolic dysfunction; PK=pharmacokinetic.

3.3.4.1. Dose-response studies

Intravenous and immediate-release oral formulations of omecamtiv mecarbil were evaluated early in the clinical programme. Omecamtiv mecarbil was found to produce concentration-dependent improvements in echocardiographic parameters of systolic function (SET, fractional shortening, stroke volume, cardiac output, and LVEF), with changes evident at plasma concentrations ⩾200 to 300 (depending on the PD marker) ng/mL.

Excessive plasma concentrations (⩾1200 ng/mL) of omecamtiv mecarbil have been shown to result in acute myocardial ischaemia and MI in 6 out of 16 participants. With excessive plasma concentrations of omecamtiv mecarbil, an exaggerated pharmacological effect on systolic ejection time results in decreased diastolic filling, potentially leading to impaired diastolic coronary blood flow, which can cause myocardial ischaemia or infarction. Given the rapid absorption of omecamtiv mecarbil and the desire to avoid excessive plasma concentrations of omecamtiv mecarbil, a BID dosing regimen and formulation that controlled the release of omecamtiv mecarbil to blunt Cmax to minimise peak to-trough fluctuations were was considered optimal for continued development. To address these issues, several modified-release formulations were developed.

Three formulation prototypes were selected to be tested in the Phase 2b Study 20110151 (which is discussed in detail under section 3.3.4.7). These 3 modified-release formulations were evaluated during the dose escalation phase, then the selected formulation was further studied during a 20 week expansion phase. Pharmacokinetic data from the Dose Escalation Phase of Study 20110151 enabled the selection of matrix a formulation 1 (MTX-F1) as the formulation for further evaluation due to relatively low peak to trough fluctuations and lower inter-participant variability compared with the other modified release formulations and the immediate release formulation.

One participant in cohort 2 (50 mg BID) of the dose escalation phase of Study 20110151 experienced a serious cardiac adverse event (preferred term angina unstable) temporally associated with an excessive plasma concentration of omecamtiv mecarbil (Cmax=1,320 ng/mL); the event was positively adjudicated as an MI. The occurrence of this case, in addition to population PK modelling indicated that using a fixed dose of 50 mg BID could rarely result in excessive exposure to omecamtiv mecarbil and led to the incorporation of a PK-guided dose selection group into the study design of the dose expansion phase of Study 20110151 to maintain plasma concentrations under 1,000 ng/mL.

The MTX-F1 formulation was evaluated at 2 dose levels, a fixed dose of 25 mg BID and a PK-guided dose selection strategy employing doses of 25 mg BID and 50 mg BID, in approximately 448 participants in the Dose Expansion Phase of Study 20110151. The PK-guided dose selection with an oral modified-release tablet ensured participant safety while maximising the therapeutic potential of omecamtiv mecarbil. Data from the Dose Expansion Phase showed that the PK-guided dose selection was effective at maintaining plasma concentrations of omecamtiv mecarbil under 1,000 ng/mL; no participant had a plasma concentration ⩾812 ng/mL. Pharmacodynamic effects of omecamtiv mecarbil on cardiac function and structure were generally dose and concentration-dependent, ie, participants with plasma concentrations of omecamtiv mecarbil <200 ng/mL after 2 weeks of dosing with 25 mg BID, increasing the dose to 50 mg BID resulted in greater pharmacodynamic effects compared to those who remained on 25 mg BID.

Thus, Study 20110151 established that the PK-guided dose selection scheme effectively kept participants in the desired therapeutic range. However, a substantial fraction of participants (39.7%) in

the study did not have their dose of omecamtiv mecarbil increased to 50 mg BID. Pharmacokinetic/PD model simulations were conducted to evaluate the potential to optimise exposure and the proportion of participants experiencing an increase in the SET of 25 msec. The modelling found that with the inclusion of an intermediate dose of 37.5 mg BID and an additional titration threshold, more participants would achieve pharmacodynamically active concentrations of omecamtiv mecarbil.

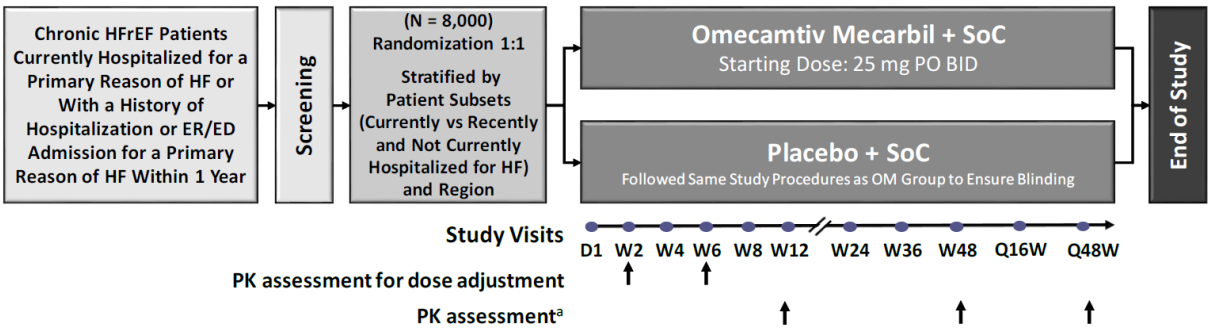
Thus, the PK-guided dose titration strategy for the pivotal Phase 3 Study 20110203 targeting the therapeutic omecamtiv mecarbil plasma concentration range of 300 to 750 ng/ml was adapted from the Dose Expansion Phase of Study 20110151. Participants would start at 25 mg BID and escalate to 50 mg BID if the Cpredose was <200 ng/mL as in Study 20110151. Additionally, if Cpredose was between 200 and 300 ng/mL, participants would escalate to the new intermediate dose of 37.5 mg BID. Given this individualised dosing strategy, achieved concentrations of omecamtiv mecarbil (including maximum and overall distributions) across the 3 doses were expected to be similar, and the percentage of participants predicted to exceed 1,000 mg/mL less than 0.1% overall.

3.3.4.2. Main study(ies)

The efficacy is primarily based on the pivotal phase 3 study 20110203 (GALACTIC-HF), a double-blind, randomised, placebo-controlled, multicentre study to assess the efficacy and safety of omecamtiv mecarbil on mortality and morbidity in subjects with chronic heart failure with reduced ejection fraction. The study is also known as GALACTIC-HF: Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure.

Study 20110203 (GALACTIC-HF)

Methods



BID = twice a day; D = day; ED = emergency department; ER = emergency room; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; OM = omecamtiv mecarbil; PK = pharmacokinetics; PO = by mouth; Q16W = every 16 weeks; Q48W = every 48 weeks; SoC = standard-of-care; W = week
Note: Planned enrollment period 2 years, total study period/follow-up 4 years.
[a] PK assessment was done at week 24 rather than week 12 for subjects who enrolled before protocol amendment 1.

Figure 8. Study flowchart

Study Participants

Key inclusion criteria:

- Male or female, ≥18 to ≤85 years of age at signing of informed consent
- History of chronic HF (defined as requiring treatment for HF for a minimum of 30 days before randomisationisation)

- LVEF ≤35%, per the subject's most recent medical record, within 12 months prior to screening. The most recent qualifying LVEF must be at least 30 days after any of the following, if applicable: 1) an event likely to decrease EF (e.g., myocardial infarction, sepsis); 2) an intervention likely to increase EF (e.g., cardiac resynchronisation therapy, coronary revascularisation); or 3) the first ever presentation for HF.
- NYHA class II to IV at the most recent screening assessment
- Oral SoC therapies for chronic HF (e.g., beta-blockers, renin-angiotensin-aldosterone system inhibitors) should be present if not contraindicated. Subjects enrolled during either HF hospitalisation or early after HF hospitalisation discharge can be reinitiating or titrating oral SoC chronic HF therapies at the same time of randomisationisation with the goal of achieving optimised therapy on the study.
- Currently hospitalised with the primary reason of HF OR one of the following events within 1 year to screening: 1) hospitalisation with the primary reason of HF; 2) urgent visit to ED with primary reason of HF.
- B-type natriuretic peptide (BNP) level ≥125 pg/mL or an NT-proBNP level ≥400 pg/mL at the most recent screening assessment (subjects receiving angiotensin receptor-neprilysin inhibitor [ARNi] must use NT-proBNP assessment; for subjects in atrial fibrillation/flutter at screening, the cut off levels are: BNP ≥375 pg/mL or NT-proBNP ≥1200 pg/mL)

Key exclusion criteria:

- Receiving mechanical hemodynamic support (e.g., intra-aortic balloon pump counterpulsation), or invasive mechanical ventilation ≤7 days prior to randomisationisation
- Receiving IV inotropes (e.g., dobutamine, milrinone, levosimendan) or IV vasopressors (eg, epinephrine, norepinephrine, dopamine, or vasopressin) ≤3 days prior to randomisationisation
- Receiving IV diuretics or IV vasodilators, supplemental oxygen therapy, or non-invasive mechanical ventilation (e.g., bilevel positive airway pressure [BiPAP] or continuous positive airway pressure [CPAP] ≤12 hours prior to randomisationisation.
- Acute coronary syndrome (ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, unstable angina), stroke, or transient ischaemic attack, major cardiac surgery or cardiac intervention (i.e., implantation of cardiac closure devices, cardiac resynchronisation therapy, or catheter ablation), percutaneous coronary intervention, or valvuloplasty/other cardiac valve repair or implantation within the 3 months prior to randomisationisation
- Insertion of other cardiac devices (e.g., implantable cardioverter defibrillator, permanent pacemaker, monitoring devices) within 30 days prior to randomisationisation
- Severe uncorrected valvular heart disease, hypertrophic or infiltrative cardiomyopathy, active myocarditis, constrictive pericarditis, or clinically significant congenital heart disease
- Chronic antiarrhythmic therapy, except for amiodarone. Note: for the purposes of this exclusion criterion, digoxin, calcium channel blocker, and beta-blocker therapy are not considered to be chronic antiarrhythmic therapies
- Symptomatic bradycardia or second or third-degree heart block without a pacemaker
- Systolic blood pressure >140 mmHg or <85 mmHg, or diastolic blood pressure>90 mmHg, or heart rate >110 beats per minute, or <50 beats per minute at screening

- Estimated glomerular filtration rate (eGFR) <20 mL/min/1.73m2 or receiving dialysis at screening
- Hepatic impairment defined by a total bilirubin (TBL) ≥2 times the upper limit of normal (ULN), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 times ULN at screening

Locations: This study was conducted at 944 study centres in 35 countries worldwide.

Time period: The study ran from 22 December 2016 – 27 August 2020

Treatments

The investigational products used in this study were OM, administered in doses of 25, 37.5, and 50 mg BID, and matching placebo. Omecamtiv mecarbil and placebo tablets were identical in both appearance and packaging (14-count blister packs).

OM was administered orally twice daily in the morning and evening by the subjects and can be taken under fasted or fed conditions. The investigational product (IP) will be swallowed whole (not chewed, crushed, or split). Each morning and evening administration should be taken at approximately the same time of day.

Subjects randomised to OM initiated administration at 25 mg BID. All subjects had predose PK assessed at Week 2 to guide the dose adjustment for subjects randomised to OM. See Table 11 for a summary of dose adjustment rules. At Week 6, another predose PK was assessed to reflect the PK results of the previous adjustment and potentially change the dose at Week 8. Pharmacokinetics was assessed on Weeks 12 and 48 and then every 48 weeks throughout the study. A new IP supply will be provided to all subjects at the Week 4 and Week 8 study visits regardless of the randomised treatment group and outcome of the PK assessment in order to maintain the blind. If the Week 2 PK value is not available in time for dose adjustment, subjects randomised to OM will continue with the 25 mg BID dose assignment pending the Week 6 PK assessment. If the Week 6 PK value is not available in time for the dose adjustment, subjects randomised to OM will be assigned to the lower dosage regimen (25 mg BID).

At Weeks 12, 48, and then every 48 weeks, PK will be assessed and are not part of the PK-based dose adjustment approach. Subjects with plasma concentration ≥1000 ng/mL at assessments after the Week 8 visit will be requested to stop IP administration, regardless of signs or symptoms. An extra visit will be scheduled, and the subject's treatment assignment will be unblinded.

Subjects randomised to placebo will receive placebo throughout the study but will undergo identical PK and resupply procedures.

If a subject experienced clinical signs or symptoms consistent with acute myocardial ischaemia or infarction, the subject received immediate medical attention according to the institution's usual SoC, and the IP administration was withheld. Serial cardiac ischaemic markers and ECGs should be analyzed locally. Results from local laboratory assessment of Troponins (I or T), CK-MB, and BNP or NT-proBNP should be recorded in the CRF. A central laboratory PK sample, Troponin I, CK-MB, and NT-proBNP should be collected in all subjects experiencing such events as close as possible to the event, and the time the last IP was taken. The results of the PK assessment, when present, will routinely remain blinded to the sponsor and investigators. The Data Monitoring Committee (DMC), however, will receive unblinded PK data. Amgen should be notified of suspected acute myocardial ischaemia or infarction within 24 hours of knowledge of the event. Restarting IP after a cardiac ischaemic event may be considered after appropriate management of the case and assessment of the likely cause of the event and the potential relatedness of the event to IP. The subject, investigator, and Amgen should discuss

and agree upon the decision to reinitiate the subject after a cardiac ischaemic event. Subjects experiencing acute cardiac ischaemic events suspected to be related to IP should not be rechallenged. When restarting, subjects initiate OM 25 mg BID or placebo BID, according to initial group allocation. A new predose PK assessment will be conducted after 2 weeks from IP reinitiation, and dose adjustment will occur at the next IP dispensation visit. The adjustment follows the same procedures as for study visit Week 4, limiting the maximum dose to what was assigned before the event. Subjects reinitiating IP after withholding for reasons other than cardiac ischaemic events will restart on the same IP dose as established before the event.

Table 8. PK-guided OM dosing scheme

Study Visit	Week 2 Plasma Concentration (ng/mL)	Current Dose BID	New Dose BID
Week 4	< 200	25 mg	50 mg
	≥ 200 - < 300		37.5 mg
	≥ 300 - < 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 - < 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	New Dose
Week 12	≥ 1000	Any	Withdraw IP
Week 48			
Q 48 weeks			
Unscheduled			

BID = twice a day; IP = investigational product; Q 48 = every 48

The study is event-driven and will conclude when approximately 1590 CV death events have occurred. Subject accrual is planned for 24 months. After signing the informed consent, subjects should be randomised within 8 weeks. The expected treatment length after subject accrual completion and until the number of required CV death events has been reached is 24 months. Therefore, it is anticipated that follow-up for the first randomised subjects will reach approximately 48 months (4 years), and for the last randomised subjects, approximately 24 months (2 years). The actual duration of study for an individual subject may be longer or shorter based on the amount of time required to reach the specified number of events. Experiencing a nonfatal primary endpoint does not end study participation for a study subject. Subjects will continue treatment and follow-up procedures until the study ends, as described above. All subjects will be followed from randomisationisation through the date of study termination unless the subject has withdrawn consent, irrespective of whether the subject is continuing to receive study treatment.

The follow-up visits are displayed graphically in Figure 8. Follow-up visits are at W2, W4, W6, W8, W12, W24, W36, W48 and after that every 16 weeks till the end of the study, which is event driven as described above.

Objectives

The primary objective was to evaluate the effect of treatment with omecamtiv mecarbil (OM) compared with placebo on time to cardiovascular (CV) death or first heart failure (HF) event, whichever occurs first, in subjects with chronic HF with reduced ejection fraction (HfrEF) receiving standard of care (SoC) therapy.

Secondary objectives are to evaluate the effects of omecamtiv mecarbil on time to CV death, time HF hospitalisation, time to all-cause mortality, and the effects of treatment with OM on change in patient-reported outcomes. The objectives can also be found in the combined objectives and endpoints table; see Table 9.

The primary hypothesis was that when added to SoC, OM is well tolerated and superior to placebo in reducing the risk of CV death or HF events in subjects with chronic HfrEF. Secondary hypotheses were that OM reduces the individual risks of CV death, HF hospitalisation, and all-cause death and improves symptoms in subjects with chronic HfrEF compared with placebo.

Secondary hypotheses are that OM reduces the individual risks of CV death, HF hospitalisation and all-cause mortality and that omecamtiv mecarbil improves symptoms in subjects with chronic HfrEF compared to placebo.

Outcomes/endpoints

The primary endpoint is the composite of time to CV death or first HF event, whichever occurs first.

An overview of all objectives and endpoints is tabulated in Table 9.

At the time of study protocol development, only hospital admission for HF had typically been used as a component of the primary endpoint; however, more recent heart failure guidelines support the inclusion of urgent outpatient interventions as a component of the primary endpoint (EMA, 2017; FDA, 2019). As noted in a European Society of Cardiology Heart Failure Association consensus statement (Zannad, 2013), care for worsening HF will increasingly be provided in the outpatient setting. Analyses from the MADIT-CRT and PARADIGM-HF studies (Skali, 2014; Okumura, 2016) demonstrated similar CV mortality risks following outpatient HF events and inpatient HF admissions. A recently completed pivotal clinical trial of dapagliflozin in patients with HfrEF (DAPA-HF) used a similar endpoint (McMurray, 2019) and supported marketing authorisation in the European Union (EU) for treatment of symptomatic chronic HfrEF. The inclusion of HF events in the outpatient setting as a component of the primary composite endpoint is consistent with the increased transition from inpatient to outpatient care and the predictive risk of these outpatient events.

Table 9. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of treatment with OM compared with placebo on the time to CV death or first HF event, whichever occurred first, in subjects with chronic HfrEF receiving SoC Therapy.	Composite of time to CV death or first HF event, whichever occurred first: • A death was defined as a CV death endpoint if the death was positively adjudicated as a

• An HF event was defined as presentation of the patient for urgent, unscheduled clinic/office/ED visit, or hospital admission, with primary diagnosis of HF, where the patient exhibited new or worsening symptoms of HF on presentation, had objective evidence of new or worsening HF, and received initiation or intensification of treatment specifically for HF (Hicks et al, 2015). Changes to oral diuretic therapy did not qualify as initiation or intensification of treatment.	CV death, presumed CV death, or presumed sudden death. • An HF event was defined as an urgent, unscheduled clinic/office/ED visit, or hospital admission, with a primary diagnosis of HF, where the patient exhibited new or worsening symptoms of HF on presentation, had objective evidence of new or worsening HF, and received initiation or intensification of treatment specifically for HF (Hicks et al, 2015). Changes to oral diuretic therapy did not qualify as initiation or intensification of treatment.
Secondary	
To evaluate the effects of OM on time to: • CV death • HF hospitalisation • All-cause death	• Time to CV death • Time to first HF hospitalisation • Time to all-cause death
To evaluate the effects of treatment with OM on change in patient-reported outcomes (PROs)	Change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) from baseline to week 24 (stratified by randomisationisation setting)
Safety	
To evaluate the safety of OM as measured by subject incidence of reported adverse events, including serious adverse events of ventricular arrhythmias requiring treatment and adjudicated major cardiac ischaemic events (myocardial infarction [MI], unstable angina hospitalisation, and coronary revascularisation)	• Subject incidence of reported adverse events • Subject incidence of reported serious adverse events of ventricular arrhythmias requiring treatment • Subject incidence of positively adjudicated major cardiac ischaemic events (Adjudicated major cardiac ischaemic adverse events are: MI, hospitalisation for unstable angina, percutaneous coronary intervention (PCI)/coronary artery bypass graft (CABG)) • Time to first positively adjudicated MI • Time to first positively adjudicated MI or investigator final diagnosis of MI • Time to first positively adjudicated MI or investigator final diagnosis of MI or potential endpoint (PEP) type of MI
Exploratory	
To evaluate the effect of OM on the risk for HF events and HF hospitalisation in subjects	• Incidence of HF events within the first 30 days and the first 60 days after index

randomised during hospitalisation for HF during the first: • 30 days after discharge • 60 days after discharge	hospitalisation in subjects randomised during HF hospitalisation • Incidence of HF hospitalisations within the first 30 days and the first 60 days after index hospitalisation in subjects randomised during HF hospitalisation
To evaluate the effect of OM on NT-proBNP changes	Change in NT-proBNP from baseline to each assessment
To evaluate the effect of OM on first and recurrent HF events	• Time to first HF event • Times to recurrent HF events
To evaluate the effect of OM on recurrent HF hospitalisations	Times to recurrent HF hospitalisations
To evaluate the effect of OM on the composite time of CV death or HF hospitalisation, whichever occurred first	Composite of time to CV death or first HF hospitalisation, whichever occurred first
To evaluate the effect of OM on the composite of time to all-cause death or HF hospitalisation, whichever occurred first	Composite of time to all-cause death or first HF hospitalisation, whichever occurred first
To evaluate the effect of OM on resting heart rate	Change in resting heart rate from baseline to each assessment
To evaluate the effect of OM on KCCQ TSS changes over time	Changes in KCCQ scores from baseline to each assessment
To evaluate the effect of treatment with OM on the composite of time to CV death, HF event, MI, hospitalisation for unstable angina, coronary revascularisation, and stroke, whichever occurred first	Composite of time to CV death, HF event, MI, hospitalisation for unstable angina, coronary revascularisation, and stroke, whichever occurred first
To further characterise the pharmacokinetics (PK) of OM	OM concentration at week 2 and week 6

Sample size

The sample size calculation is based on the CV mortality component of the primary composite endpoint. The control group event rate is assumed to vary by randomisationisation setting. Subjects randomised in a hospital setting are assumed to have a greater risk in the first year of 19% followed by the constant yearly outpatient setting rate of 7%. Assuming 25% of subjects will be randomised in the hospital setting, the CV mortality rate in the first year is expected to be 10% overall subjects and 7% for each year thereafter.

A 24 month enrollment period is assumed, and the total study duration is set to 48 months. The hazard ratio for CV death alone is assumed to be 0.8 after a 3-month treatment lag at the beginning of the trial, where the hazard ratio is assumed to be 1. Additionally, assume 10% of subjects discontinue therapy per year and 10% of subjects over the course of the trial will be lost to endpoint determination. The overall type I error is 0.05 for 2-sided testing. After accounting for these factors, a

total sample size of approximately 8000 subjects with approximately 1590 subjects experiencing CV death events is required to ensure a power of 90% for testing superiority for CV death (Shih [1995]). Assuming the rates for experiencing either a heart failure event or CV death are double those for CV death alone and the same other assumptions as for CV death alone; the primary composite endpoint is expected to have >99% power when the primary analysis is triggered.

Randomisation and blinding (masking)

Subjects who meet the eligibility requirements will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups (OM or placebo) in a double-blind manner. Randomisationisation will be stratified by randomisationisation setting (currently hospitalised for HF or recently and not currently hospitalised for HF) and region (5 strata: US and Canada; Latin America; Western Europe, South Africa, and Australasia; Eastern Europe including Russia; Asia). Subjects can only be randomised 1 time for this study. Subjects in the recently and not currently hospitalised for HF setting who meet all eligibility criteria at the end of screening will return to the study site for randomisationisation and day 1 procedures. Subjects in the currently hospitalised HF setting who meet all eligibility criteria at the end of screening should be randomised prior to discharge, with day 1 procedures occurring during the hospitalisation.

Subjects could only be randomised 1 time for this study. The study centres used an interactive voice response system/interactive web response system (IVRS/IWRS) to assign a unique randomisationisation number to each eligible subject.

Several measures were undertaken to maintain blinding. The OM and matching placebo tablets used in this study were identical in appearance, presented in identical containers, and stored and packaged in the same manner. Investigators were blinded to treatments and doses. To further protect the blind, subjects randomised to placebo underwent all the same protocol procedures as those randomised to OM, including providing the predose blood samples for the PK plasma concentrations required for the dose selections.

Statistical methods

Estimands

Post-hoc an estimand was defined, based on the efficacy estimation in the analysis plan (Table 10).

Table 10 Attributes of the Estimands for the Overall Population and the Subgroup with Baseline LVEF <30%

Estimand	Attributes	Detail Description
The primary estimand for the overall population	Population[a]	Subjects with chronic heart failure with reduced ejection fraction receiving SoC therapy and potentially treatable with omecamtiv mecarbil (see eligibility criteria in the 20110203 protocol for detail)
	Treatment	Omecamtiv mecarbil + SoC versus placebo + SoC
	Variable	Time (days) to CV death or first HF event, whichever occurred first from randomisation
	Intercurrent Events (ICEs) and Handling	ICEs - a. Discontinuation of treatment b. Withdrawal consent or lost to follow-up c. Non-CV death Treatment policy strategy was used for ICEs a and b. Therefore, data collected after ICEs a and b will be used for the determination of the primary endpoint. Hypothetical strategy was used for ICE c. If ICE items b and c would cause data to be missing after ICEs for the primary endpoint. The primary endpoint would be censored at the time when the ICE occurred.
	Population-level Summary	Hazard ratio for omecamtiv mecarbil versus placebo and its 95% CI using the Cox proportional hazards model. Therefore, missing data will be treated as missing at random (MAR).
The primary estimand for the subgroup of baseline LVEF <30%	Population[a]	Subjects with chronic heart failure with reduced ejection fraction with LVEF less than 30% at baseline receiving SoC therapy and potentially treatable with omecamtiv mecarbil
	Treatment	Omecamtiv mecarbil + SoC versus placebo + SoC
	Variable	Time (days) to CV death or first HF event, whichever occurred first from randomisation
	Intercurrent Events (ICEs) and Handling	ICEs - a. Discontinuation of treatment b. Withdrawal consent or lost to follow-up c. Non-CV death Treatment policy strategy was used for ICEs a and b. Therefore, data collected after ICEs a and b will be used for the determination of the primary endpoint. Hypotherical strategy was used for ICE c. If ICE items b and c would cause data to be missing after ICEs for the primary endpoint. The primary endpoint would be censored at the time when the ICE occurred.
	Population-level Summary	Hazard ratio for omecamtiv mecarbil versus placebo and its 95% CI using the Cox proportional hazards model. Therefore, missing data will be treated as MAR.

CI=confidence interval; CV=cardiovascular; HF=heart failure; ICE=intercurrent event; MAR=missing at random; SoC=standard of care.

[a] Subjects at the Hungarian study site 29002 are excluded due to GCP violation as they are anticipated to not represent patients from a treatable population defined as patients who would meet the eligibility requirements of this study and are capable and wiling to be dosed.

Analysis sets

Efficacy analyses were performed on the full analysis set, which included all randomised subjects except for subjects at study centre 29002 (major GCP violation). Subjects were analyzed according to their randomised treatment group assignment.

Safety analyses were performed on the safety analysis set, which included all randomised subjects who received at least 1 dose of the investigational product while in the study. Unless otherwise specified, for safety analyses, subjects were grouped according to their randomised treatment group assignment with the following exception. If a subject received treatment throughout the study that was different from the randomised treatment group assignment, then that subject was grouped by the actual treatment.

Primary analysis

The primary analysis, which was also the final analysis, occurred after the primary completion milestone of 1590 CV deaths was achieved and included estimation for time-to-event endpoints up to the analysis cut-off date using the final analysis data and other efficacy and safety endpoints using the final data. Unless otherwise specified, all hypothesis tests are reported as 2-sided, and the full study had an overall type I error rate of 0.05.

Subject disposition, demographics, baseline characteristics, and exposure to the investigational product were summarised. Continuous variables were summarised using descriptive statistics, including the number of observations (n), mean, standard deviation or standard error, median, first and third quartile, minimum, and maximum. Categorical variables were summarised using the number and percentage of subjects.

The primary endpoint was the composite of time to CV death or first HF event, whichever occurred first. The composite endpoint was assessed using a Cox model stratified by randomisationisation setting and region. The Cox model included terms for baseline eGFR and treatment group. The treatment effect was tested using a likelihood ratio test, and 95% Cis for the model parameters were computed. Intervals and parameters were exponentiated to display on the hazard ratio scale.

Kaplan-Meier estimates of cumulative incidence of the composite endpoint were computed by randomisationisation setting and overall. Associated 95% pointwise Cis were estimated using the log transformation.

The Cox model was fit for subgroups of each stratification factor and the other prespecified subgroups.

The following sensitivity analyses were conducted:

- Stratified log-rank test (no use of baseline eGFR)
- Repeat of the Cox model, including events only up to the minimum of the last nonfatal potential endpoint collection date (LPEPD), EOS date, and analysis cut-off date
- Tipping point analysis (sensitivity) where subjects who discontinued the study early (not ending the study due to death or COVID-19) have five randomly drawn exponentially distributed time-to-event variables multiply imputed with specified hazard ratios. The hazard ratio for imputing where the p-value crosses alpha will be determined.

Analyses for secondary endpoints time to CV death, time to first HF hospitalisation, and time to all-cause death used the same model as for the primary composite endpoint. Overall, Kaplan-Meier estimation used the same approach as the primary composite endpoint. For time to CV death and time to all-cause death, an additional analysis including all events up to the last confirmed survival status

date (including any after the analysis cut-off date) and including all undetermined cause deaths as CV deaths were conducted using the same Cox model.

Changes in KCCQ TSS from baseline to week 24 were assessed using a mixed-model fit within each randomisationisation setting containing the baseline TSS value, region, baseline eGFR, scheduled visit, treatment group, and the interaction of treatment group with a scheduled visit. Only the planned visits at weeks 12 and 24 were included. Associated 95% Cis for change from baseline were reported for each visit within each randomisationisation setting. An omnibus F-test with 2 numerator degrees of freedom was used to test the treatment effect of OM versus placebo. The test used the marginalised mean differences to placebo within each randomisationisation setting at week 24. An overall pooled estimate for the KCCQ TSS treatment difference to placebo will also be calculated using a likelihood-based approach of Hardy and Thompson (1996). Similarly, for each component of the KCCQ TSS, Symptom Frequency Score and Symptom Burden Score, the change in score from baseline to week 24 will also be assessed using the mixed model.

For HF Events and Hospitalisations separately, counts and proportions of subjects in the full analysis set randomised in the hospital setting and discharged from the hospital with an event in $\leqslant$30 and $\leqslant$60 days were reported, along with Kaplan-Meier estimates and associated 95% Cis.

Summary statistics for change from baseline in NT-proBNP at each scheduled visit by treatment group and randomisationisation setting were reported, and mean differences between treatment groups and associated 95% Cis were provided.

Times to recurrent HF events and recurrent HF hospitalisations were assessed separately by:

- A semiparametric joint frailty model of recurrent HF events/hospitalisations and CV death as a terminal event as described in Liu et al. (2004). The 2 component models (recurrent HF events/hospitalisation model and CV death) had baseline functions stratified by randomisationisation setting and region and contained terms treatment group and a common mean 1 gamma-distributed frailty random variable to handle correlation between the 2 processes.
- A negative binomial regression where HF events/hospitalisations and CV death were considered as events. If an event/hospitalisation occurred on the same day as a CV death, only 1 event contributed to the count. The model included terms for the stratification factors and treatment group.
- Mean cumulative rate function estimates as described in Ghosh and Lin (2000), where all-cause death is considered a terminating event. Estimation was by treatment group and randomisationisation setting. These estimates estimated the expected number of events/hospitalisations where a subject who died cannot have additional events/hospitalisations.

For each approach, point estimates and associated 95% Cis were computed.

Summary statistics for change from baseline in resting heart rate as measured by ECG at each scheduled visit and by treatment group and randomisationisation setting were reported for subjects in the ECGAS. Mean differences between treatment groups and associated 95% Cis were provided by randomisationisation setting.

Summary statistics for change from baseline in each KCCQ score at each scheduled visit by treatment group and randomisationisation setting were reported. The empirical cumulative distribution function for changes in KCCQ TSS from baseline to week 24 was estimated and plotted by treatment group, randomisationisation setting, and by categories defined by the baseline Patient Global Rating Severity (PGR-S, moderate or greater vs less than moderate). Empirical cumulative distribution functions for

changes in KCCQ TSS from baseline to week 24 using the fractionally imputed data were also provided by treatment group and randomisationisation setting. The proportion of subjects within each treatment group achieving an increase from baseline of 5, 8, 10, 12, and 15 points or more in the KCCQ TSS were reported overall, by randomisationisation setting, and by baseline PGR-S. The risk difference for each threshold was estimated using the minimum risk weights of Mehrotra and Railkar (2000) and Newcombe interval as described in Yan and Su (2010). Summary statistics for the individual questions included in the KCCQ TSS score by treatment group and randomisationisation setting were reported. Mean differences between treatment groups and associated 95% Cis were provided.

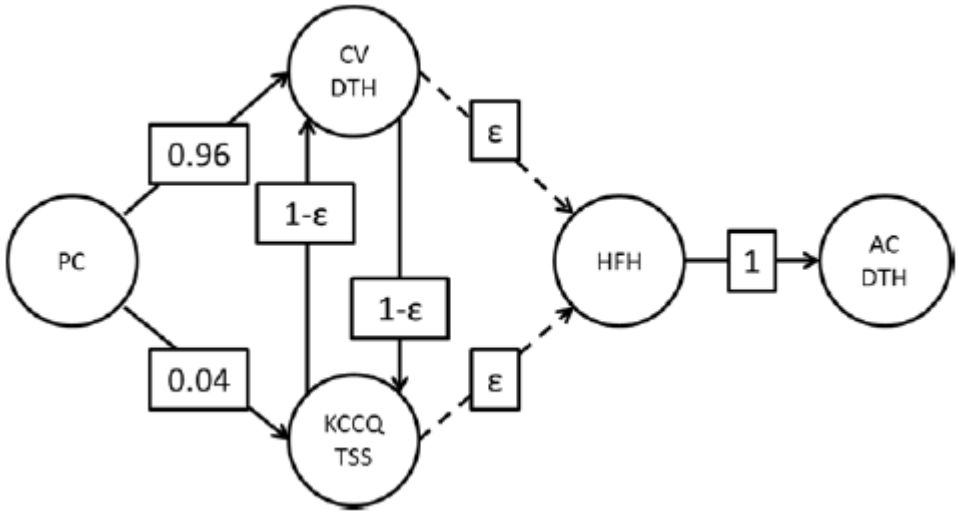
Additional analyses were conducted to assess the impact of COVID-19, including supportive analyses for the primary composite endpoint and secondary endpoints as described in Table 8-3 and for the exploratory endpoint of time to CV death or first HF hospitalisation as described in the SAP.

Interim analyses

Futility for the primary endpoint was assessed when approximately one-third and two-thirds of the overall required CV deaths were observed. Efficacy was assessed when approximately two-thirds of the overall required CV deaths were observed. An alpha of 0.001 (Haybittle-Peto approach; Haybittle, 1971; Peto et al, 1976) was used to assess superiority. The DMC could recommend stopping the trial if the primary composite endpoint and the secondary endpoint time to CV death reached statistical significance. The remainder of the secondary endpoints were assessed with an overall alpha of 0.001 following the testing diagram if the study was stopped early. Interim futility and efficacy assessments were conducted by the Independent Biostatistical Group (IBG) and reviewed by the DMC.

Multiplicity

To preserve an overall type I error rate of 0.05 for the primary and secondary endpoints, a multiplicity adjustment was performed. A total alpha of 0.05 was used to test the primary analysis triggered based on observing approximately 1590 CV deaths. Within the primary analysis, the total alpha was applied to all primary and secondary endpoint hypothesis tests. The primary endpoint was tested first with the total alpha. If the primary endpoint reached statistical significance, a Bonferroni split was used, where 0.96α was allocated to testing time to CV death, and 0.04α was allocated to testing change from baseline to week 24 in KCCQ TSS. Alpha from a statistically significant result for either of these 2 endpoints after the split propagated to the other endpoint (Bretz et al., 2009), with a small alpha (0.0001 x fraction of the α used in the statistically significant test) propagating to testing time to first HF hospitalisation. If statistical significance was achieved for both time to CV death and change from baseline in KCCQ TSS, time to first HF hospitalisation was tested at the full alpha. If time to first HF hospitalisation was statistically significant, time to all-cause death was tested with the same alpha as the time to first HF hospitalisation. The multiplicity testing propagation approach is illustrated in Error! Reference source not found.. Alpha was only propagated if the direction of the statistically significant effect favored OM. Exploratory endpoints were assessed using a nominal alpha level of 0.05 and did not have multiplicity adjustments.



PC=primary composite endpoint; CV + cardiovascular; CV DTH=time to CV death; KCCQ TSS=Kansas City Cardiomyopathy Questionnaire Total Symptom Score; HF=heart failure; HFH=time to first heart failure hospitalisation; AC DTH=time to all-cause death
Notes: Each circle represents a hypothesis test. The values in boxes on the arrows indicate the fraction of α propagated in the direction of the arrow to the next hypothesis test(s). ε=0.0001, a small value to complete the graph while prioritising the CV death and KCCQ TSS endpoints over the time to first HF hospitalisation and all-cause death endpoints. Dashed arrows used to emphasise this prioritisation. No multiplicity adjustment was made for exploratory, additional, or sensitivity analyses.

Figure 9. Multiplicity Testing Propagation Approach

Results

Participant flow

An overview of subject disposition is depicted in Figure 10, and a detailed summary is provided in Table 11. A total of 11 121 subjects were screened for the study, of whom 8256 subjects were enrolled and randomised to double-blind treatment.

Overall, 8211 (99.7%) subjects received at least 1 dose of the investigational product, 4933 (59.9%) completed the investigational product, 21 (0.3%) never received the investigational product, and 3299 (40.1%) discontinued the investigational product. The most common reasons for discontinuation from the investigational product were death (1537 [18.7%]), subject request (980 [11.9%]), and adverse event (753 [9.1%]). The proportions of subjects who discontinued for these reasons were similar in the OM and placebo treatment groups. Two (<0.1%) subjects discontinued the investigational product because of an OM plasma concentration >1000 ng/mL after week 8.

A total of 6036 (73.3%) subjects completed the study, 2105 (25.6%) died, and 91 (1.1%) discontinued the study due to reasons other than death. Of those who discontinued, 45 subjects withdrew consent (final vital status known for 30 subjects and unknown for 15 subjects), and 46 subjects were lost to follow-up (final vital status known for 45 subjects and unknown for 1 subject).

At study entry, 2101 (25.5%) subjects were currently hospitalised for HF and 6131 (74.5%) were recently and not currently hospitalised for HF. Twenty-nine (0.4%) subjects had an incorrect

randomisationisation setting stratification, ie, a mismatch between their randomisationisation setting versus their actual setting.

Treatment assignments were unblinded to the investigators and the sponsor for 2 subjects due to PK concentrations of OM >1000 ng/mL. Four subjects were unblinded to the investigators only (but not the sponsor), based on study centres' requests for clinical care of these subjects. Three subjects were unblinded to external agencies (but not unblinded to the investigator or sponsor) for insurance company/compensation requests.

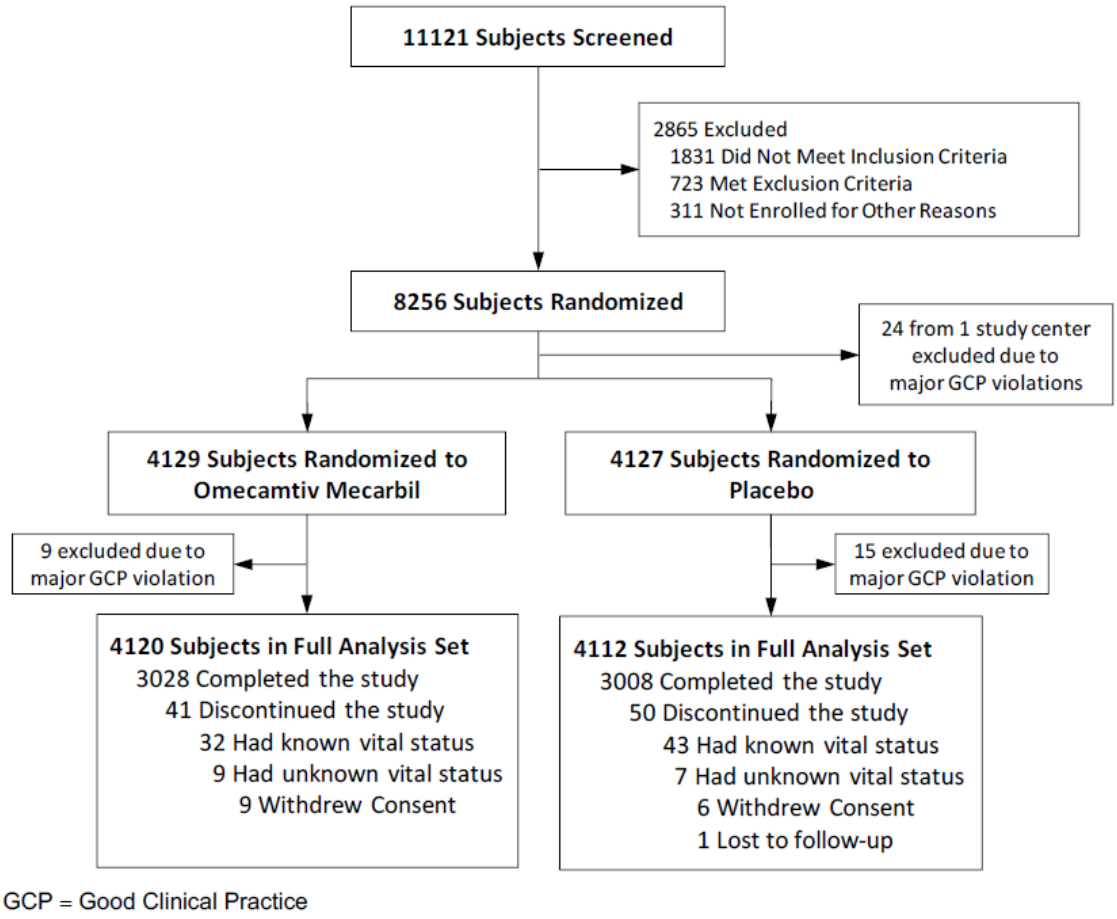


Figure 10. Participant Flow

Table 11. Subject Disposition With Discontinuation Reason Study 20110203 (Full Analysis Set)

	Recently and Not Currently Hospitalized for Heart Failure		Currently Hospitalized for Heart Failure		Overall		
	Placebo (N = 3072) n (%)	AMG 423 (N = 3076) n (%)	Placebo (N = 1040) n (%)	AMG 423 (N = 1044) n (%)	Placebo (N = 4112) n (%)	AMG 423 (N = 4120) n (%)	Total (N = 8232) n (%)
Investigational product accounting							
Subjects who never received investigational product	5 (0.2)	6 (0.2)	6 (0.6)	4 (0.4)	11 (0.3)	10 (0.2)	21 (0.3)
Subjects who received investigational product	3067 (99.8)	3070 (99.8)	1034 (99.4)	1040 (99.6)	4101 (99.7)	4110 (99.8)	8211 (99.7)
Subjects who completed investigational product	1872 (60.9)	1875 (61.0)	568 (54.6)	618 (59.2)	2440 (59.3)	2493 (60.5)	4933 (59.9)
Subjects who discontinued investigational product	1200 (39.1)	1201 (39.0)	472 (45.4)	426 (40.8)	1672 (40.7)	1627 (39.5)	3299 (40.1)
Adverse event	304 (9.9)	272 (8.8)	78 (7.5)	99 (9.5)	382 (9.3)	371 (9.0)	753 (9.1)
COVID-19 event	0 (0.0)	3 (<0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	4 (<0.1)	4 (<0.1)
Subject request	356 (11.6)	353 (11.5)	154 (14.8)	117 (11.2)	510 (12.4)	470 (11.4)	980 (11.9)
COVID-19 related[a]	24 (0.8)	18 (0.6)	9 (0.9)	9 (0.9)	33 (0.8)	27 (0.7)	60 (0.7)
COVID-19 control measures[a]	15 (0.5)	9 (0.3)	2 (0.2)	2 (0.2)	17 (0.4)	11 (0.3)	28 (0.3)
Decision by sponsor	3 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)	0 (0.0)	3 (<0.1)
Lost to follow-up	5 (0.2)	8 (0.3)	5 (0.5)	2 (0.2)	10 (0.2)	10 (0.2)	20 (0.2)
COVID-19 related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	530 (17.3)	565 (18.4)	235 (22.6)	207 (19.8)	765 (18.6)	772 (18.7)	1537 (18.7)
COVID-19 event	1 (<0.1)	3 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)	4 (<0.1)	6 (<0.1)
Protocol-specified criteria[b]	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	2 (<0.1)
Pregnancy	2 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	2 (<0.1)	2 (<0.1)	4 (<0.1)

	Recently and not currently hospitalized for heart failure		Currently hospitalized for heart failure		Overall		
	Placebo (N = 3072) n (%)	AMG 423 (N = 3076) n (%)	Placebo (N = 1040) n (%)	AMG 423 (N = 1044) n (%)	Placebo (N = 4112) n (%)	AMG 423 (N = 4120) n (%)	Total (N = 8232) n (%)
Study completion accounting							
Subjects who completed study	2311 (75.2)	2288 (74.4)	697 (67.0)	740 (70.9)	3008 (73.2)	3028 (73.5)	6036 (73.3)
Subjects who discontinued study	761 (24.8)	788 (25.6)	343 (33.0)	304 (29.1)	1104 (26.8)	1092 (26.5)	2196 (26.7)
Withdrawal of consent from study: final vital status available	14 (0.5)	8 (0.3)	4 (0.4)	4 (0.4)	18 (0.4)	12 (0.3)	30 (0.4)
COVID-19 related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal of consent from study: final vital status not available	5 (0.2)	6 (0.2)	1 (<0.1)	3 (0.3)	6 (0.1)	9 (0.2)	15 (0.2)
COVID-19 related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decision by sponsor: final vital status available	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decision by sponsor: final vital status not available	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up: final vital status available	17 (0.6)	17 (0.6)	8 (0.8)	3 (0.3)	25 (0.6)	20 (0.5)	45 (0.5)
COVID-19 related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up: final vital status not available	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
COVID-19 related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	724 (23.6)	757 (24.6)	330 (31.7)	294 (28.2)	1054 (25.6)	1051 (25.5)	2105 (25.6)
COVID-19 event	1 (<0.1)	5 (0.2)	1 (<0.1)	2 (0.2)	2 (<0.1)	7 (0.2)	9 (0.1)

AMG 423=omecamtiv mecarbil; COVID-19=coronavirus disease 2019; Notes: N=Number of subjects randomised excluding study centre 29002. Percentages are based on N. Number of subjects screened: 11 121. First subject enrolled: 22 December 2016.

a COVID-19 related and COVID-19 control measures overlap for 5 subjects.

b Omecamtiv mecarbil concentration >1000 ng/mL after week 8.

Disposition of Participants Following Pharmacokinetic-Guided Dosing

A PK-guided dosing strategy was used in Study 20110203 as a means to maximise participant exposure to omecamtiv mecarbil in a target concentration range (300-750 ng/mL), while minimising the frequency of excessive exposure (>1,000 ng/mL).

A summary of participants by dose group at Week 4 (dose selection determined by the Week 2 concentrations of omecamtiv mecarbil), at Week 8 (dose selection determined by the Week 6 concentrations of omecamtiv mecarbil), and the final dose at Week 12, is provided in Table 12. A flow diagram of dose titrations from Week 2 to Week 4 and Week 8 is summarised in Figure 11. Overall, the

proportions of participants receiving each omecamtiv mecarbil dose remained generally consistent over time.

Table 12. Summary of Dose Groups (Study 20110203)

	Overall		
	Placebo (N=4,112)	Omecamtiv Mecarbil (N=4,120)	Total (N=8,232)
Dose at Week 4, n (%)			
25 mg BID	0 (0.0)	993 (24.1)	993 (12.1)
37.5 mg BID	0 (0.0)	635 (15.4)	635 (7.7)
50 mg BID	0 (0.0)	2,173 (52.7)	2,173 (26.4)
Discontinued IP	164 (4.0)	132 (3.2)	296 (3.6)
No IP box dispensed	47 (1.1)	50 (1.2)	97 (1.2)
Placebo	3,766 (91.6)	0 (0.0)	3,766 (45.7)
Visit did not occur	135 (3.3)	137 (3.3)	272 (3.3)
Dose at Week 8, n (%)			
25 mg BID	0 (0.0)	1,180 (28.6)	1,180 (14.3)
37.5 mg BID	0 (0.0)	577 (14.0)	577 (7.0)
50 mg BID	0 (0.0)	2,002 (48.6)	2,002 (24.3)
Discontinued IP	265 (6.4)	257 (6.2)	522 (6.3)
No IP box dispensed	44 (1.1)	44 (1.1)	88 (1.1)
Placebo	3,724 (90.6)	0 (0.0)	3,724 (45.2)
Visit did not occur	79 (1.9)	60 (1.5)	139 (1.7)
Final Dose at Week 12, n (%)			
25 mg BID	0 (0.0)	1,192 (28.9)	1,192 (14.5)
37.5 mg BID	0 (0.0)	559 (13.6)	559 (6.8)
50 mg BID	0 (0.0)	1,961 (47.6)	1,961 (23.8)
Discontinued IP	366 (8.9)	347 (8.4)	713 (8.7)
No IP box dispensed	26 (0.6)	18 (0.4)	44 (0.5)
Placebo	3,668 (89.2)	0 (0.0)	3,668 (44.6)
Visit did not occur	52 (1.3)	43 (1.0)	95 (1.2)

	Overall		
	Placebo (N=4,112)	Omecamtiv Mecarbil (N=4,120)	Total (N=8,232)
BID=twice a day; IP=investigational product. Notes: N=number of participants randomised excluding study centre 29002. N=number of participants with observed data. Percentages are based on N. For “Discontinued IP”, the discontinuation occurred before the visit. For “No IP box dispensed”, the discontinuation occurred after the visit.			

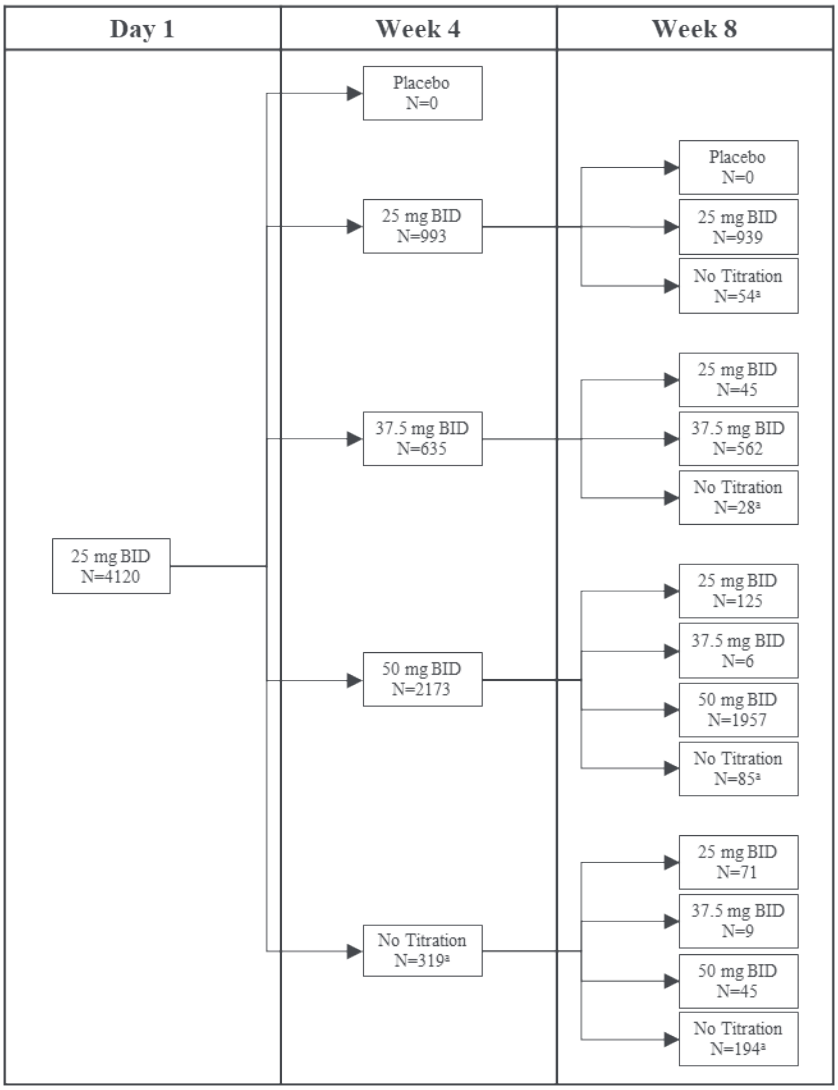


Figure 11. Overview of Dose Changes During the Titration Phase (Study 20110203)

Recruitment

Overall, 8256 subjects were enrolled and randomised to double-blind treatment at 944 study centres in 35 countries worldwide in the regions of Eastern Europe and Russia (32.6%); Western Europe, South Africa, and Australasia (23.3%); Latin America (19.1%); the United States/Canada (16.8%); and Asia (8.1%). A total of 1587 subjects were recruited from Western Europe.

Conduct of the study

A major GCP violation associated with questionable laboratory values and potential underreporting of events led to 24 subjects at study centre 29002 in Hungary being excluded from the analysis. Following investigations, including a sponsor-initiated audit, the sponsor, the Executive Committee, and DMC decided to exclude subjects from this study centre from analysis due to data irregularities and lack of source documentation necessary to verify the legitimacy of the questionable findings. Data summaries for study centre 29002 and subject narratives are provided separately. The study sponsor concluded that the protocol violations did not affect the integrity of the data or the study.

Baseline data

Baseline demographics are summarised in Table 13 and were similar between the OM and placebo groups. The study population majority were men (78.8%). The mean (SD) age of subjects was 64.5 (11.4) years, and 54.5% of subjects were ≥65 years of age. The majority of subjects were White (77.7%), 8.6% were Asian, 6.8% were Black or African American, 3.4% were other, 2.4% were multiple, and the remaining race categories (American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander) were represented by <1% of subjects. 1587 subjects were from Western Europe (19%).

Table 13. Baselin Characteristics

	Recently and Not Currently Hospitalized for Heart Failure		Currently Hospitalized for Heart Failure		Overall		
	Placebo (N = 3072)	AMG 423 (N = 3076)	Placebo (N = 1040)	AMG 423 (N = 1044)	Placebo (N = 4112)	AMG 423 (N = 4120)	Total (N = 8232)
Sex - n (%)							
Male	2396 (78.0)	2414 (78.5)	842 (81.0)	831 (79.6)	3238 (78.7)	3245 (78.8)	6483 (78.8)
Female	676 (22.0)	662 (21.5)	198 (19.0)	213 (20.4)	874 (21.3)	875 (21.2)	1749 (21.2)
Ethnicity - n (%)							
Hispanic/Latino	707 (23.0)	709 (23.0)	178 (17.1)	177 (17.0)	885 (21.5)	886 (21.5)	1771 (21.5)
Not Hispanic/Latino	2365 (77.0)	2367 (77.0)	862 (82.9)	867 (83.0)	3227 (78.5)	3234 (78.5)	6461 (78.5)
Race - n (%)							
American Indian or Alaska Native	33 (1.1)	26 (0.8)	5 (0.5)	9 (0.9)	38 (0.9)	35 (0.8)	73 (0.9)
Asian	262 (8.5)	264 (8.6)	93 (8.9)	91 (8.7)	355 (8.6)	355 (8.6)	710 (8.6)
Black or African American	226 (7.4)	231 (7.5)	51 (4.9)	54 (5.2)	277 (6.7)	285 (6.9)	562 (6.8)
Multiple	79 (2.6)	93 (3.0)	17 (1.6)	6 (0.6)	96 (2.3)	99 (2.4)	195 (2.4)
Native Hawaiian or Other Pacific Islander	4 (0.1)	4 (0.1)	2 (0.2)	3 (0.3)	6 (0.1)	7 (0.2)	13 (0.2)
White	2352 (76.6)	2339 (76.0)	849 (81.6)	857 (82.1)	3201 (77.8)	3196 (77.6)	6397 (77.7)
Other	116 (3.8)	119 (3.9)	23 (2.2)	24 (2.3)	139 (3.4)	143 (3.5)	282 (3.4)
Age - years							
n	3072	3076	1040	1044	4112	4120	8232
Mean	64.4	64.3	65.0	65.1	64.5	64.5	64.5
SD	11.4	11.4	11.4	11.2	11.4	11.3	11.4
Median	66.0	66.0	67.0	66.0	66.0	66.0	66.0
Q1, Q3	57.0, 73.0	57.5, 73.0	59.0, 73.0	58.0, 73.0	58.0, 73.0	58.0, 73.0	58.0, 73.0
Min, Max	20, 85	18, 89	24, 85	23, 88	20, 85	18, 89	18, 89
Age group - n (%)							
Age < 65 years	1418 (46.2)	1421 (46.2)	455 (43.8)	453 (43.4)	1873 (45.5)	1874 (45.5)	3747 (45.5)
Age ≥ 65 years	1654 (53.8)	1655 (53.8)	585 (56.3)	591 (56.6)	2239 (54.5)	2246 (54.5)	4485 (54.5)
Age ≥ 75 years	592 (19.3)	588 (19.1)	209 (20.1)	215 (20.6)	801 (19.5)	803 (19.5)	1604 (19.5)

Physical characteristics of subjects at baseline were similar between the OM and placebo groups and between the outpatient and inpatient subjects. For the overall study population, mean (SD) height was 169.9 (9.7) cm, body weight was 82.6 (20.6) kg, and body mass index (BMI) was 28.5 (6.2) kg/m2.

Vital sign parameters at baseline were similar between the OM and placebo groups. Mean (SD) systolic blood pressure was 116.5 (15.3) mm Hg, diastolic blood pressure was 71.5 (10.3) mm Hg, and heart rate was 72.4 (12.1) bpm. Both systolic and diastolic blood pressures were slightly lower among the inpatient subjects compared with the outpatient subjects. Mean (SD) systolic blood pressure was 114.1 (14.5) and 113.6 (14.2) mm Hg among inpatient subjects in the OM and placebo groups, respectively, compared with 117.0 (15.6) and 117.7 (15.5) mm Hg among outpatient subjects in each group, respectively. Mean (SD) diastolic blood pressure was 70.7 (9.9) and 70.9 (10.1) mm Hg among inpatient subjects in the OM and placebo groups, respectively, compared with 71.6 (10.4) and 71.9 (10.3) mm Hg among outpatient subjects, respectively.

Laboratory parameters at baseline were generally balanced between the OM and placebo groups. Median (Q1, Q3) NT-proBNP was 1998.0 (993.0, 4079.0) pg/mL, CK-MB was 1.80 (1.20, 2.80) ng/mL, troponin I was 0.0270 (0.0140, 0.0510) ng/mL, and eGFR was 58.76 (44.10, 74.09) mL/min/1.73m2. Both NT-proBNP and troponin levels were higher among inpatient subjects when compared with outpatient subjects, while eGFR was lower among inpatient subjects.

Overall, 62.3% of subjects had a history of coronary artery disease: 41.7% had an MI (mean [SD] time since MI was 114.1 [104.0] months), 7.5% had unstable angina, 29.6% had PCI, 16.0% had

CABG, and 14.5% had stable. A total of 70.3% of subjects had hypertension, and 55.0% had cardiac arrhythmias (42.2% with history of atrial fibrillation or flutter, 27.3% with atrial fibrillation or flutter present at screening, 23.7% with ventricular arrhythmias). A total of 38.4% had cardiac devices. Hypercholesterolemia was reported for 55.2% of subjects, diabetes mellitus for 41.0%, valvular heart disease for 33.1%, respiratory illness for 20.1%, cerebrovascular disease for 11.1%, and peripheral artery disease for 10.3%. A total of 36.4% of subjects had a medical history of chronic kidney disease. At baseline, 38.4% of subjects had an eGFR of 60 to 89 mL/min/1.73m2, 46.1% had an eGFR of 30 to 59 mL/min/1.73m2, and 6.3% had an eGFR of 15 to 29 mL/min/1.73m2.

These medical history characteristics were well balanced between the OM and placebo treatment groups, with incidences similar to those of the overall study population. Cardiac arrhythmias, chronic kidney disease, diabetes mellitus, cerebrovascular disease, and hypertension (OM group only) were more common among inpatient subjects compared with outpatient subjects, while the reverse was observed for cardiac devices and hypercholesterolemia. Most other medical history characteristics were balanced between the inpatient and outpatient subjects. The primary cause of HF for slightly more than half of subjects overall was ischaemic heart disease (53.6% vs 46.4% nonischaemic heart disease), and most subjects were NYHA Class II (53.1%) or Class III (43.9%). The median (Q1, Q3) LVEF was 28.0% (22.0%, 32.0%), and the mean (SD).

Among outpatient subjects, the median (Q1, Q3) time since the last known HF hospitalisation or urgent ER/ED visit was 3.2 (1.6, 6.3) months in the OM group and 3.1 (1.6, 6.2) months in the placebo group. These baseline disease characteristics were well balanced between the OM and placebo treatment groups, with incidences similar to those of the overall population. As expected, more subjects with NYHA Class II HF were outpatients while more subjects with Class III were inpatients. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC HF) risk score was 23.4 (6.4).

Nearly all (8229 of 8232 subjects) reported use of at least 1 medication of interest at baseline, as was expected given all subjects were to have been treated with SoC upon study entry. The most frequently used medications of interest at baseline were beta blockers (94%), diuretics other than MRAs (90%), ACEi, ARB, or ARNi (87%), and MRAs (78%), and their use was balanced between the OM and placebo groups. In both treatment groups, the use of beta blockers and ACEi, ARB, or ARNi was more common among outpatient subjects, while the use of diuretics other than MRAs and MRAs were more common among inpatient subjects. Overall, baseline target HF medication use was balanced in both the OM and placebo treatment groups.

At baseline, use of an ACEi, ARB, or ARNi was reported for 87% of subjects overall and in both treatment groups. Overall, 27% of subjects were receiving an ACEi, ARB, or ARNi at the recommended maximum dose or higher, 61% were receiving a dose below the maximum recommended dose, and 13% were not receiving an ACEi, ARB, or ARNi. Use of an MRA was reported for 78% of subjects overall and in both treatment groups. Overall, 60% were receiving an MRA at the recommended maximum dose or higher, 18% were receiving a dose below the maximum recommended dose, and 22% were not receiving an MRA. Use of a beta blocker was reported for 94% of subjects overall and inboth treatment groups. Overall, 22% were receiving a beta blocker at the recommended maximum dose or higher, 72%were receiving a dose below the maximum recommended dose, and 6% were not receiving a beta blocker. In both treatment groups, each of these medication classes were used among a greater proportion of outpatient subjects, except for MRAs which were used among a greater proportion of inpatient subjects. In addition to the above, the majority of subjects were receiving antihypertensives (99%), antithrombotics (84%), and lipid-lowering drugs (63%). A total of 2.6% were receiving a sodium glucose transport protein 2 (SGLT2) inhibitor.

Numbers analysed

The full analyses set consisted of 8232 subjects, 4112 in the placebo group and 4120 in the omecamtiv group. The efficacy analysis was performed on the full analysis set, which included all participants who had undergone randomisationisation except for 24 participants from a single site who were excluded on the basis of GCP violations. This was an intention to treat analysis set. No specific per protocol analysis sets were defined by the applicant.

There were 8211 (99.5%) subjects in the safety analysis set and 1200 (14.5%) subjects in the ECG analysis set, and the proportions of placebo-treated and OM-treated subjects in each of these analysis sets was similar. The PK analysis set included 4040 (97.8%) of the 4129 subjects in the OM group; 89 (2.2%) subjects were excluded.

Outcomes and estimation

Primary endpoint

The primary endpoint was the composite of time to CV death or first HF event, whichever occurred first. Overall, 37.0% of subjects in the OM group had a positively adjudicated primary composite endpoint event, compared with 39.1% in the placebo group, with CV death as the first event for 8.4% of subjects in the OM group and 9.0% in the placebo group, and an HF event as the first event for 28.6% of subjects in the OM group and 30.1% in the placebo group, see Table 14. Among those in the inpatient setting, 44.9% of subjects in the OM group and 47.8% in the placebo group had a positively adjudicated primary composite endpoint event, with CV death as the first event for 7.2% of subjects in the OM group and 10.2% in the placebo group, and an HF event as the first event for 37.7% of subjects in the OM group and 37.6% in the placebo group. Among those in the outpatient setting, 34.3% of subjects in the OM group and 36.1% in the placebo group had a positively adjudicated primary composite endpoint event, with CV death as the first event for 8.8% of subjects in the OM group and 8.6% in the placebo group, and an HF event as the first event for 25.5% of subjects in the OM group and 27.5% in the placebo group.

The hazard ratio (95% CI) was 0.92 (0.86, 0.99) comparing OM to placebo for the primary composite endpoint of time to CV death or first HF event, whichever occurred first (p=0.0252). The hazard ratio (95% CI) was 0.94 (0.86, 1.02) for outpatient subjects and 0.89 (0.78, 1.01) for inpatient subjects. The Kaplan-Meier curves are provided in Figure 12 for the overall population.

The planned tipping point sensitivity analysis had a HR of 0.93 (0.87, 1.00) for the primary endpoint (p=0.05) while the HR for imputation was 5.12 for participants who discontinued the study early. The tipping point analysis indicates that the treatment effect was insensitive to missing data, and the primary analysis result was robust.

Table 14. Subject Incidence of Positively Adjudicated Primary Endpoint (CV Death or HF Event)

	Recently and Not Currently Hospitalized for Heart Failure		Currently Hospitalized for Heart Failure		Overall	
	Placebo (N = 3072) n (%)	AMG 423 (N = 3076) n (%)	Placebo (N = 1040) n (%)	AMG 423 (N = 1044) n (%)	Placebo (N = 4112) n (%)	AMG 423 (N = 4120) n (%)
Number of subjects reporting positively adjudicated primary composite endpoint	1110 (36.1)	1054 (34.3)	497 (47.8)	469 (44.9)	1607 (39.1)	1523 (37.0)
Heart failure events as first event	845 (27.5)	783 (25.5)	391 (37.6)	394 (37.7)	1236 (30.1)	1177 (28.6)
Hospitalization for heart failure	771 (25.1)	733 (23.8)	362 (34.8)	374 (35.8)	1133 (27.6)	1107 (26.9)
Urgent heart failure ER/ED visit	51 (1.7)	32 (1.0)	23 (2.2)	13 (1.2)	74 (1.8)	45 (1.1)
Urgent heart failure office/practice visit	23 (0.7)	18 (0.6)	6 (0.6)	7 (0.7)	29 (0.7)	25 (0.6)
Cardiovascular death as first event	265 (8.6)	271 (8.8)	106 (10.2)	75 (7.2)	371 (9.0)	346 (8.4)
Cardiovascular death	194 (6.3)	185 (6.0)	83 (8.0)	54 (5.2)	277 (6.7)	239 (5.8)
Presumed cardiovascular death	45 (1.5)	57 (1.9)	9 (0.9)	14 (1.3)	54 (1.3)	71 (1.7)
Presumed sudden death	26 (0.8)	29 (0.9)	14 (1.3)	7 (0.7)	40 (1.0)	36 (0.9)
Number of subjects reporting positively adjudicated cardiovascular death endpoint	546 (17.8)	578 (18.8)	252 (24.2)	230 (22.0)	798 (19.4)	808 (19.6)

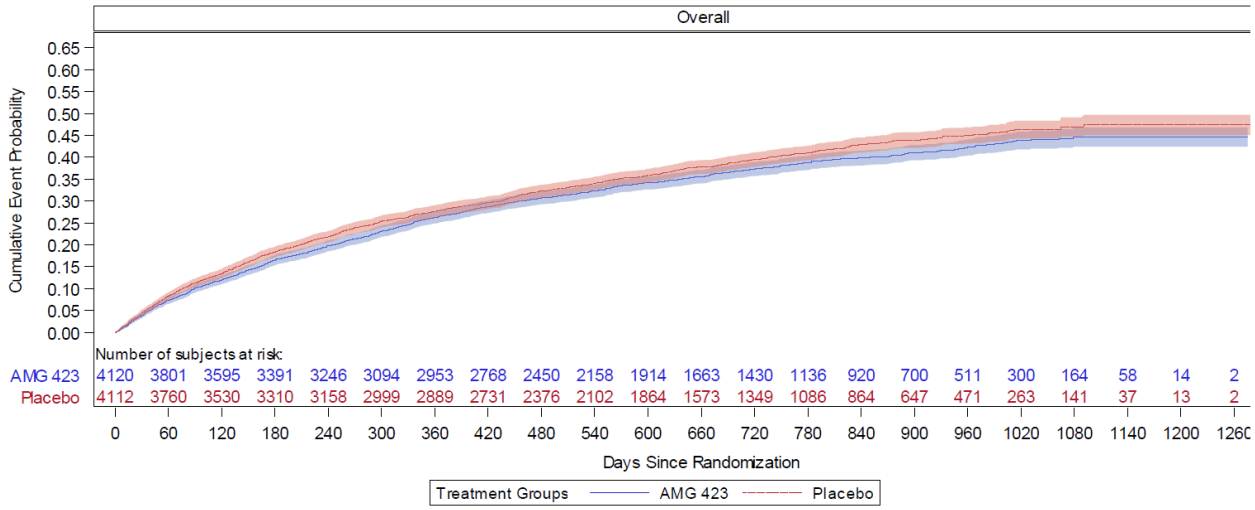


Figure 12. Cumulative Incidence Estimates for Primary Endpoint (CV Death or HF Event)

Subgroup Analyses of the Primary Composite Endpoint

Hazard ratio (95% CI) estimates for the treatment difference between groups in the primary composite endpoint for all subgroups are depicted in Figure 13.

Subgroup analyses of the primary composite endpoint generally demonstrated treatment effects for most subgroups consistent with those observed in the overall study population. In addition, nominally statistically significant interaction effects ($p < 0.05$ with no adjustment for multiplicity) were observed between OM and placebo for the following subgroups: median LVEF at baseline (p=0.0034), presence of atrial fibrillation/flutter at screening (p=0.0120), and baseline eGFR above or below 60 mL/min/1.73m2 (p=0.0434).

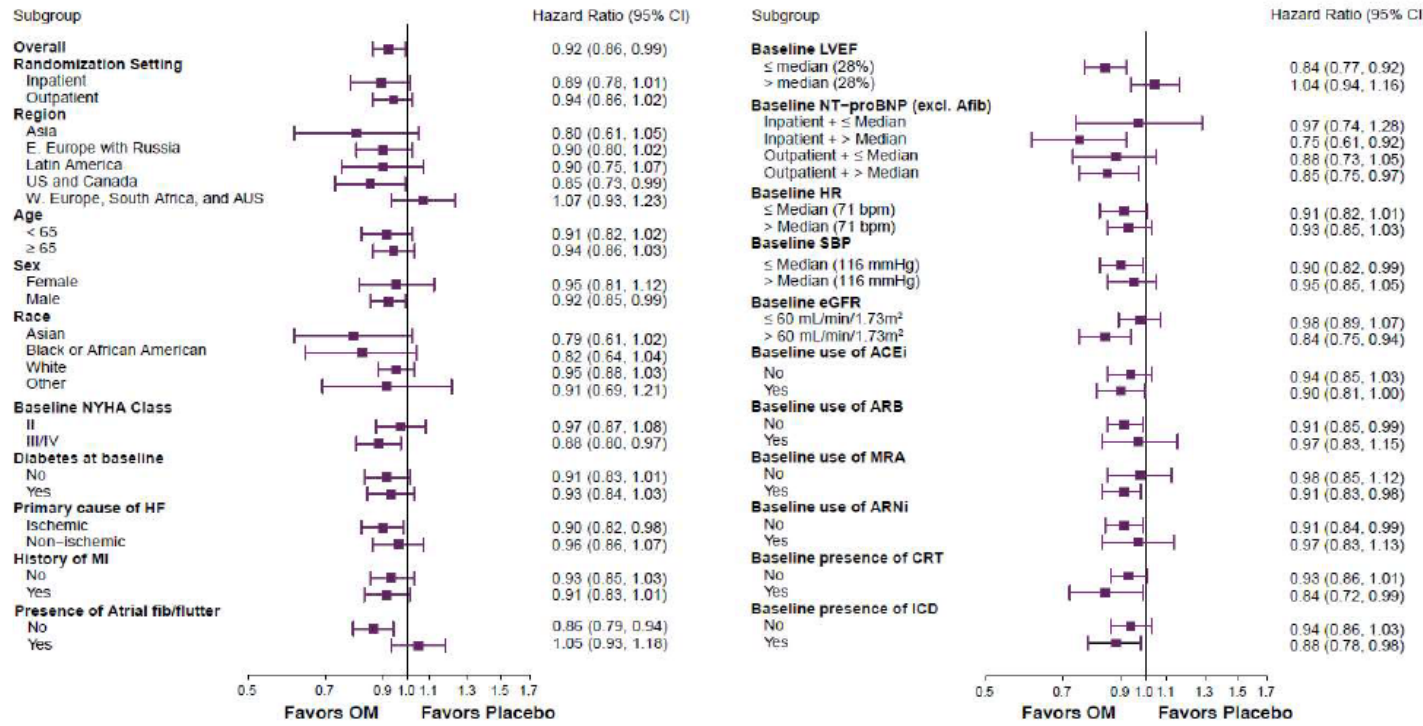


Figure 13. Forest Plot of the Subgroup Analysis for the Primary Composite Endpoint (Study 20110203, Full Analysis Set)

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; ARNi=angiotensin receptor blocker/ neprilysin inhibitor; AUS=Australia; CRT=cardiac resynchronisation therapy; eGFR=estimated glomerular filtration rate; HF=heart failure; HR=heart rate; ICD=implantable cardioverter defibrillator; LVEF=left ventricular ejection fraction; MI=myocardial infarction; MRA=mineralocorticoid receptor antagonist; NT proBNP=N terminal prohormone B type natriuretic peptide; NYHA=New York Heart Association; OM=omecamtiv mecarbil; SBP=systolic blood pressure; US=United States.

Secondary endpoints

An overview of the secondary endpoints is shown in Table 15.

Table 15. Summary of Secondary Efficacy Endpoints

Secondary Efficacy Endpoints	Placebo (N = 4112) n (%)	AMG 423 (N = 4120) n (%)	Hazard Ratio[a] / Mean Difference[b] (95% CI)	P-value[a] / Significance
Time to CV death	798 (19.4)	808 (19.6)	1.01 (0.92, 1.11)	0.8555 (non-sig)
KCCQ TSS change from baseline to week 24, LS mean[c]				0.0278 (non-sig)
Outpatient subjects			-0.46 (-1.40, 0.48)	
Inpatient subjects			2.50 (0.54, 4.46)	
Time to first HF hospitalization	1179 (28.7)	1142 (27.7)	0.95 (0.87, 1.03)	0.1902 (non-sig)
Time to all-cause death	1065 (25.9)	1067 (25.9)	1.00 (0.92, 1.09)	0.9633 (non-sig)

AMG 423 = omecamtiv mecarbil; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; KCCQ TSS = Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LS = least squares; N = number of subjects in the analysis set; n = number of subjects with observed data; non-sig = not significant

[a] Based on a stratified Cox model with treatment group and baseline eGFR as the independent variables and stratified by randomization setting and region.

[b] For KCCQ, within each randomization setting subgroup, LS mean is from the mixed model, 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.

[c] Positive changes represent improvements in symptoms.

Time to CV death

Overall, 19.6% of subjects in the OM group and 19.4% in the placebo group died due to a positively adjudicated CV death. The hazard ratio (95% CI) was 1.01 (0.92, 1.11), comparing OM to placebo for time to CV death. The hazard ratio (95% CI) was 1.07 (0.96, 1.21) for outpatient subjects and 0.87 (0.73, 1.05) for inpatient subjects. Hazard ratio (95% CI) estimates for the treatment difference between groups in the time to CV death for all subgroups are depicted in Figure 14 and Figure 15. Subgroup analyses of time to CV death generally demonstrated that treatment effects were broadly consistent with those observed in the overall study population. Nominally statistically significant interaction effects (p=0.05 with no adjustment for multiplicity) were observed between OM and placebo for the following subgroups: the presence of atrial fibrillation/flutter at screening (p=0.0014), baseline use of ARB (excluding ARNi) (p=0.0091), and median LVEF at baseline (p=0.0308).

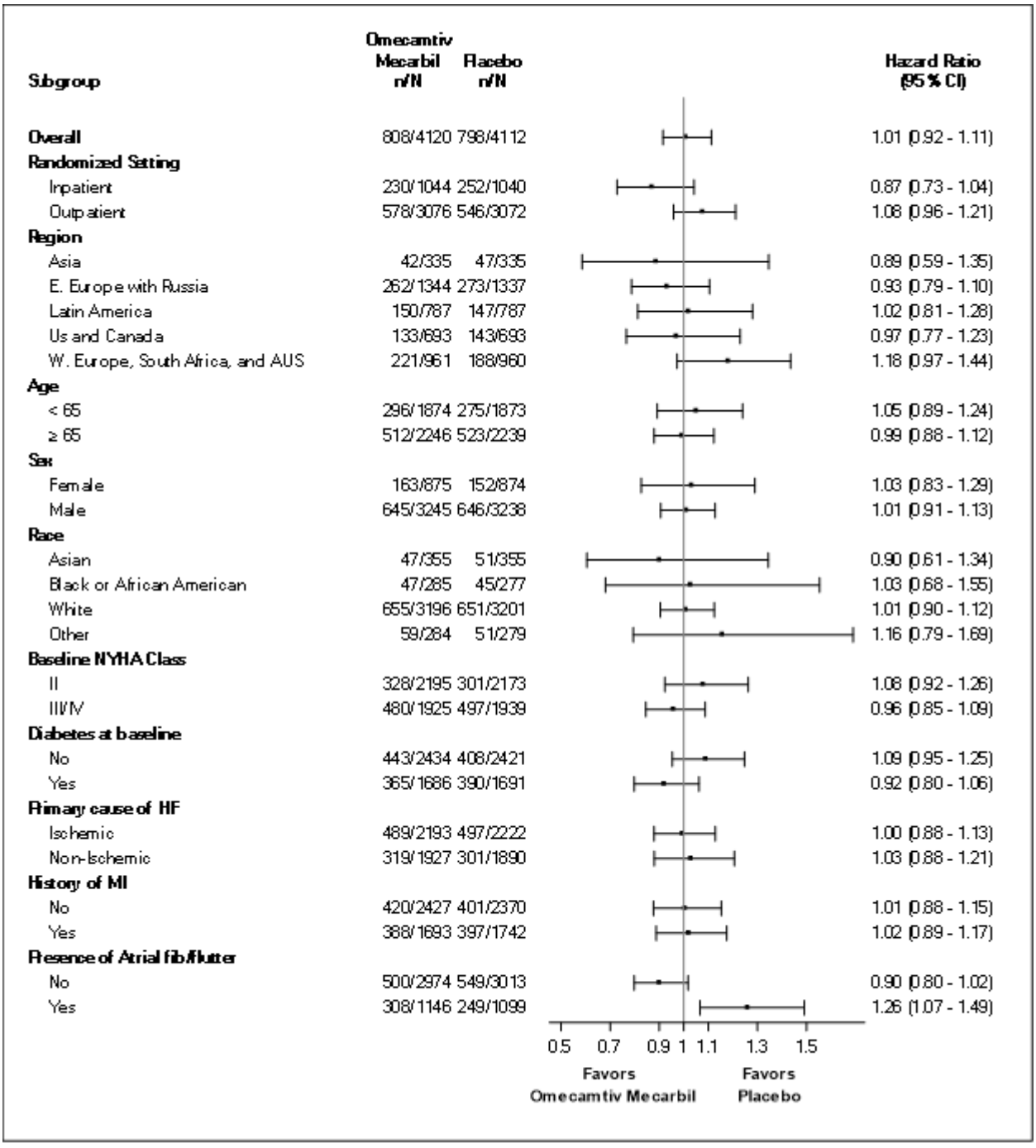


Figure 14. Forest Plot of the Subgroup Analysis for Time to CV Death

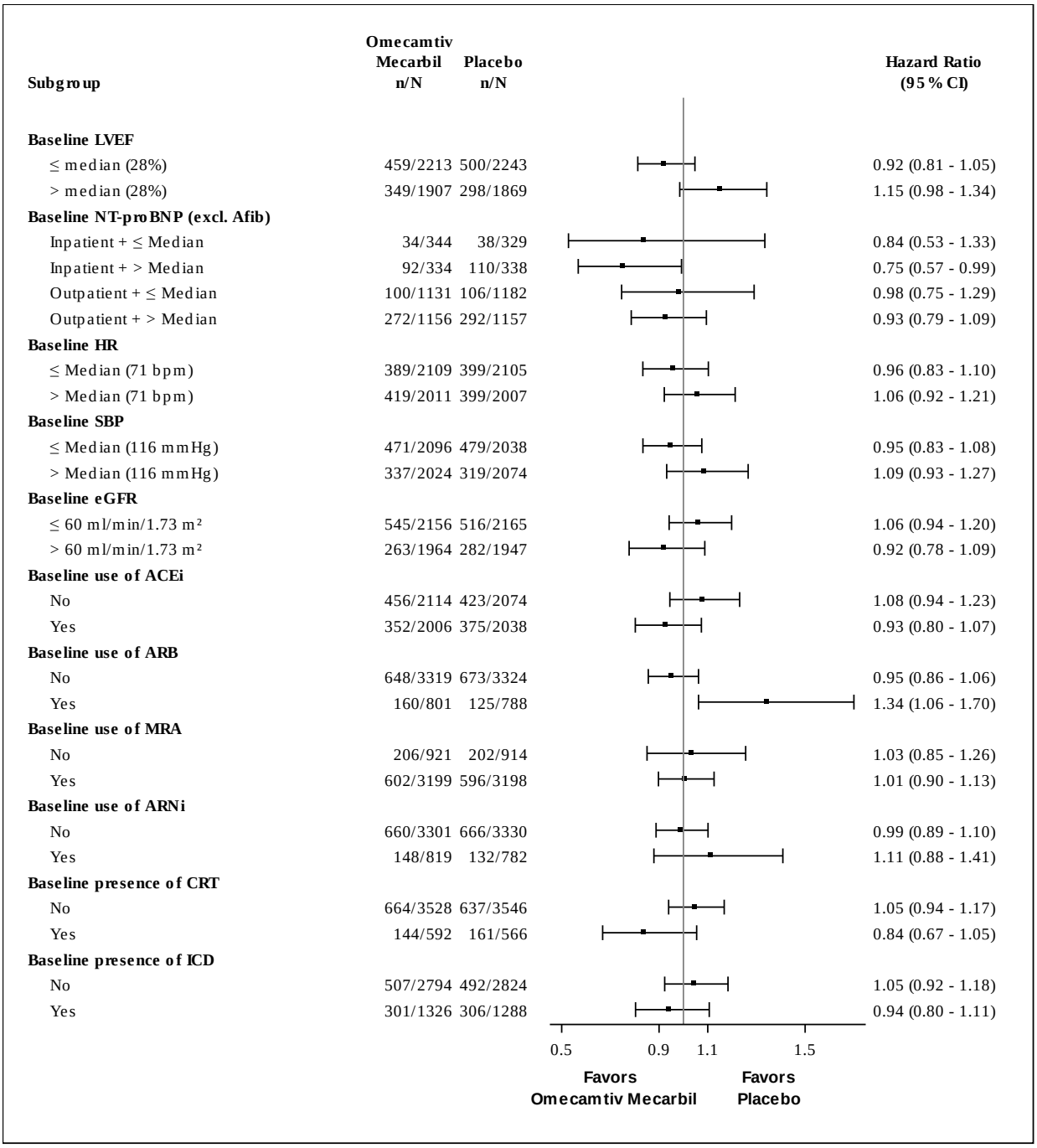


Figure 15. Forest Plot of the Subgroup Analysis for Time to CV Death (part 2)

Change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) from baseline to Week 24

At baseline, KCCQ TSS mean scores were notably higher among outpatient subjects when compared with inpatient subjects in both the OM and placebo treatment groups (Table 16). The least squares (LS) mean (SE) changes from baseline to week 24 in KCCQ TSS in the OM and placebo groups, respectively, were 23.65 (0.70) and 21.15 (0.71) among inpatient subjects and 5.83 (0.34) and 6.29 (0.34) among outpatient subjects. A nominally statistically significant jointly tested difference ($p < 0.05$ without multiplicity adjustment) was observed at week 24 with OM compared with placebo, driven by inpatient subjects (inpatient LS mean [SE]=2.50 [1.00] and outpatient LS mean [SE] -0.46 [0.48];

p=0.0278), but the hypothesis test was not statistically significant adjusting for multiplicity (alpha level: 0.002).

Table 16. Analysis of Change From Baseline in KCCQ TSS to Week 24

	Recently and Not Currently Hospitalized for Heart Failure		Currently Hospitalized for Heart Failure		Overall	
	Placebo (N = 3072)	AMG 423 (N = 3076)	Placebo (N = 1040)	AMG 423 (N = 1044)	Placebo (N = 4112)	AMG 423 (N = 4120)
Baseline						
n	3047	3053	1031	1034	4078	4087
Mean	71.4	70.7	51.5	53.8	66.4	66.4
SD	23.1	23.4	25.4	25.5	25.2	25.1
Median	75.0	74.0	52.1	54.2	68.8	68.8
Q1, Q3	56.3, 91.7	54.2, 90.6	31.3, 69.8	34.4, 72.9	49.0, 87.5	49.0, 87.5
Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0	0.0, 100.0	0.0, 100.0	0.0, 100.0
Change from baseline to week 24						
n	2704	2715	835	868	3539	3583
Mean	5.9	5.8	21.6	22.7	9.6	9.9
SD	20.9	21.1	28.6	29.1	23.9	24.3
Median	3.1	3.1	18.7	19.8	6.2	6.3
Q1, Q3	-4.2, 16.7	-4.2, 16.7	2.1, 40.6	2.1, 42.7	-3.1, 21.9	-3.1, 22.9
Min, Max	-86.5, 91.7	-92.7, 91.7	-75.0, 100.0	-77.1, 100.0	-86.5, 100.0	-92.7, 100.0
Change from baseline to week 24 Adjusted Analysis[a]						
LS Mean	6.29	5.83	21.15	23.65		
SE	0.34	0.34	0.71	0.70		
95% CI	(5.63, 6.95)	(5.17, 6.50)	(19.76, 22.55)	(22.28, 25.03)		
Treatment difference[b]						
LS Mean		-0.46		2.50		
SE		0.48		1.00		
95% CI		(-1.40, 0.48)		(0.54, 4.46)		
p-value[c]		0.3396		0.0124		0.0278
Pooled treatment difference[d]						
Mean						0.75
95% CI						(-2.55, 4.51)

AMG 423=omecamtiv mecarbil; eGFR=estimated glomerular filtration rate; KCCQ TSS=Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LS=least squares Notes: N=Number of subjects randomised excluding study centre 29002. N=Number of subjects with Total Symptom Scores. Total Symptom Score is the mean of the available summary scores of Symptom Frequency Score and Symptom Burden Score.
a Within each randomisationisation setting subgroup least squares mean is from the mixed model, which includes baseline Total Symptom Score value, region, baseline eGFR, scheduled visit, treatment group and interaction of treatment with scheduled visit as covariates. Only scheduled visits at weeks 12 and 24 are included.
B Treatment difference using placebo as the reference.
C Overall p-value computed using Omnibus F-test.
D Overall pooled estimate using random effects meta-analysis approach.

Time to First HF Hospitalisation

Overall, 1142 (27.7%) participants in the omecamtiv mecarbil group and 1,179 (28.7%) in the placebo group had a first HF hospitalisation. The HR (95% CI) was 0.95 (0.87, 1.03) comparing omecamtiv mecarbil to placebo for the time to first HF hospitalisation (p=0.1902). The HR for participants randomised in the hospital setting was 0.97 (0.84, 1.12) and for participants randomised outside the hospital setting was 0.93 (0.85, 1.03).

Time to All-cause Death

Overall, a positively adjudicated all-cause death was reported for 1,067 (25.9% participants in the omecamtiv mecarbil group and 1,065 (25.9%) in the placebo group. The HR (95% CI) was 1.00 (0.92, 1.09), comparing omecamtiv mecarbil to placebo for time to all-cause death (p=0.9633). The HR (95% CI) for participants randomised in the hospital setting was 0.85 (0.73, 1.00) and for participants randomised outside the hospital setting was 1.07 (0.96, 1.18)

Selected Exploratory Efficacy Endpoints

Incidence of HF events within the first 30 days and the first 60 days after index hospitalisation in subjects randomised during HF hospitalisation

The total numbers of subjects for these analyses were 1044 in the OM group and 1040 in the placebo group. A total of 50 (4.8%) developed HF events with the first 30 days after discharge, versus 62 (6.0%) in the placebo group. A total of 94 (9.0%) developed HF events within the first 60 days after discharge, versus 108 (10.4%) in the placebo group.

Incidence of HF hospitalisations within the first 30 days and the first 60 days after index hospitalisation in subjects randomised during HF hospitalisation

The total numbers of subjects for these analyses were 1044 in the OM group and 1040 in the placebo group. A total of 49 (4.7%) developed HF hospitalisation within the first 30 days after discharge versus 56 (5.4%) in the placebo group. A total of 90 (8.6%) developed HF hospitalisation within the first 60 days after discharge versus 96 (9.2%) in the placebo group.

Change in NT-proBNP from baseline to each assessment

Statistically, significantly greater reductions in NT-proBNP were observed at week 24 in the OM group when compared with placebo (p <0.0001). Overall, mean (SD) changes from baseline to week 24 in NT-proBNP were -614.3 (4957.3) in the OM group and -80.4 (4291.4) pg/mL in the placebo group. Among outpatient subjects, the mean (SD) changes from baseline to week 24 were -583.2 (3668.5) pg/mL in the OM group and -128.0 (3771.7) pg/mL in the placebo group, and among inpatient subjects, these values were -713.5 (7755.3) pg/mL in the OM group and 77.6 (5685.4) pg/mL in the placebo group (p <0.001 for difference). Overall, median (Q1, Q3) changes from baseline to week 24 in NT-proBNP were -251.0 (-1180.0, 295.0) and -180.0 (-915.0, 441.0) pg/mL in the OM and placebo groups, respectively. Among outpatient subjects, the median (Q1, Q3) changes from baseline to week 24 were -260.5 (-1103.5, 229.5) in the OM group and -187.0 (-825.0, 373.0) in the placebo group, and among inpatient subjects, these values were -215.0 (-1466.0, 574.0) in the OM group and -134.0 (-1264.0, 942.5) in the placebo group. The treatment difference for OM compared with placebo was statistically significant among inpatient subjects (mean [SD]=-791.1 [6822.4] pg/mL; 95% CI: [-1449.6, -132.7]; p= 0.019) and among outpatient subjects (-455.2 [3720.2] pg/mL; 95% CI: [-654.1, -256.4]; p=0.0001).

Change in resting heart rate from baseline to each assessment

Median (Q1, Q3) change from baseline to week 48 in heart rate was -1.3 (-8.6, 3.0) bpm in the OM group (N=604) vs -0.3 (-7.6, 5.7) bpm in the placebo group (N=596).

Time to first HF event

Overall, 1,177 (28.6%) participants in the omecamtiv mecarbil group and 1,236 (30.1%) in the placebo group had a first HF event. The HR (95% CI) was 0.93 (0.86, 1.00) comparing omecamtiv mecarbil to placebo for the time to first HF event (p=0.0631). The HR (95% CI) for participants randomised in the hospital setting was 0.95 (0.83, 1.09), and for participants randomised outside the hospital setting was 0.91 (0.83, 1.01).

Times to recurrent HF events

Treatment difference: negative binomial model rate ratio (95% CI)=0.97 (0.88, 1.07), in favour of OM vs placebo, but not significant.

Times to recurrent HF hospitalisations

Treatment difference: negative binomial model rate ratio (95% CI)=0.98 (0.88, 1.08), in favour of OM vs placebo, but not significant.

Composite of time to CV death or first HF hospitalisation, whichever occurs first

Overall, 36.3% of subjects in the OM group and 38.0% in the placebo group had a positively adjudicated CV death or first HF hospitalisation. The hazard ratio (95% CI) was 0.94 (0.87, 1.01), comparing OM to placebo for the composite of time to CV death or first HF hospitalisation. The hazard ratio (95% CI) was 0.95 (0.87, 1.03) for outpatient subjects and 0.91 (0.80, 1.03) for inpatient subjects.

Composite of time to all-cause death or first HF hospitalisation, whichever occurred first

Overall, 1664 (40.4%) subjects in the OM group and 1734 (42.2%) in the placebo group had a positively adjudicated endpoint of all-cause death or first HF hospitalisation. The hazard ratio (95% CI) was 0.94 (0.88, 1.00)(p=0.06), comparing OM to placebo for the composite of time to all-cause death or first HF hospitalisation.

Changes in KCCQ scores from baseline to each assessment

The number of patients experiencing clinically relevant changes of 5 or 10 points in KCCQ scores from baseline to week 24 were 1880 (52.5%) and 1538 (42.9%) for the OM group vs 1825 (51.6%) and 1484 (41.9%) for the placebo group, indicating that the number of subjects experiencing clinically relevant changes in KCCQ score is in favour of the OM group, albeit not significant (P=0.5 and 0.4 for 5 or 10 points, respectively).

OM concentration at Week 2 and Week 6

The OM concentrations at week 2, week 6 and weeks 12, 24 and 48 are shown in Table 17.

Table 17. Distribution of Plasma OM Concentration (ng/mL) Ranges Following BID Administration of 25, 37.5, or 50 mg OM

Time Point	OM Concentration (ng/mL)	Number of Subjects in Each Concentration Bin	Percentage of Subjects in Each Concentration Bin
Week 2 (N = 3921)	BQL[a]	468	11.9
	BQL - 199	2389	60.9
	200 - 299	817	20.8
	300 - 749	246	6.27
	750 - 999	1	0.0255
	>1000	0	0.00
Week 6 (N = 3790)	BQL[a]	287	7.57
	BQL - 199	824	21.7
	200 - 299	1045	27.6
	300 - 749	1625	42.9
	750 - 999	8	0.211
	>1000	1	0.0264
Week 12[b] (N = 2613)	BQL[a]	249	9.53
	BQL - 199	555	21.2
	200 - 299	703	26.9
	300 - 749	1098	42.0
	750 - 999	8	0.306
	>1000	0	0.00
Week 24[b] (N = 1124)	BQL[a]	181	16.1
	BQL - 199	313	27.8
	200 - 299	272	24.2
	300 - 749	351	31.2
	750 - 999	6	0.534
	>1000	1	0.0890
Week 48 (N = 3025)	BQL[a]	477	15.8
	BQL - 199	632	20.9
	200 - 299	669	22.1
	300 - 749	1227	40.6
	750 - 999	20	0.661
	>1000	0	0.00

Composite of time to CV death, HF event, myocardial infarction, hospitalisation for unstable angina, coronary revascularisation, and stroke, whichever occurs first

Overall, 39.8% of subjects in the OM group and 42.2% in the placebo group had a positively adjudicated first event in the composite endpoint of CV death, HF event, MI, hospitalisation for unstable angina, coronary revascularisation, or stroke. The hazard ratio (95% CI) was 0.92 (0.86, 0.98) comparing OM to placebo for this composite endpoint. The hazard ratio (95% CI) was 0.92 (0.85, 1.00) for outpatient subjects and 0.91 (0.80, 1.02) for inpatient subjects.

Ancillary analyses

Dose Response analyses in GALACTIC-HF FAS

Although the study design and individualised PK-guided dose titration in the active treatment arm precludes the establishment of a dose-response relationship on the basis of randomisation, a dose-response relationship was examined based on observed achieved doses of omecamtiv mecarbil (titration dose).

In analysing a potential dose-response relationship, a small group of participants (N=394) were excluded as they did not have a dose assigned on or prior to Week 12. This group of participants (215 on placebo and 179 on omecamtiv mecarbil) had a short median (interquartile range [IQR]) treatment duration of 0.5 (0.2-0.9) and 0.6 (0.3-1.0) months, respectively, and most had no plasma concentrations of omecamtiv mecarbil, median (IQR) was 0 (0-173) ng/mL in the active treatment group. In addition, some of these participants remained in the study for over a year (median duration of 14.6 months on placebo and 11.4 months on omecamtiv mecarbil). There were no significant differences in the primary and secondary outcomes between omecamtiv mecarbil and placebo in participants without a dose titration attempt.

Participants with a titrated dose formed the majority of randomised participants (3897 on placebo, 1269 on 25 mg, 602 on 37.5 mg, and 2070 on 50 mg), with participants on placebo and each of the omecamtiv mecarbil doses showing similar treatment duration. The last plasma concentration (median) measured on or before Week 12 was 173, 339, and 298 ng/mL for participants on 25, 37.5, and 50 mg BID, respectively, with participants on the 25 mg dose having lower than targeted concentrations of omecamtiv mecarbil likely as a result of failing to appropriately up-titrate all participants according to the dosing algorithm.

The primary composite endpoint and the time to CV death were analyzed using unadjusted and adjusted Cox models by titrated dose group (Table 18). When the analysis was adjusted for significant pre-specified baseline covariates by dose group, both the 37.5 mg BID and the 50 mg BID dose groups experienced a similar reduction in the risk of the primary composite endpoint compared to patients receiving placebo. The result in the 50 mg BID dose group was nominally statistically significant while the result in the 37.5 mg BID dose group was not; however, given that the HRs in the 2 groups were almost identical, the likely explanation for this is that there were substantially fewer participants and associated outcomes events in the 37.5 mg BID (N=602) dose group than in the 50 mg BID (N=2070) dose group. In contrast, risk reduction for the primary endpoint was attenuated in the 25 mg group. This observation may be explained by the large proportion of participants who remained within the 25 mg group rather than undergoing the expected dose titration due to plasma concentration results failing to be available in time for the titration visit or participant compliance failing to be confirmed, which effectively “diluted” the 25 mg group with participants whose drug plasma concentrations were below target (Table 18).

Table 18. Primary Composite Endpoint and CV Death by Titrated Dose Group Using Primary Analysis Cox Model or Adjusting for Significant Pre-specified Baseline Covariates (Study 20110203)

Dose Group [Mean Omecamtiv Mecarbil, (SD)] ng/mL	Treatment Groups (n/N)	Hazard Ratio	95% Confidence Interval	p-value
Primary Endpoint				
Planned Primary Analysis Cox Model				
25 mg BID [184, (121)]	Omecamtiv mecarbil (516/1,269) vs Placebo (1,477/3,897)	1.00	0.90, 1.10	0.98
37.5 mg BID [345, (134)]	Omecamtiv mecarbil (225/602) vs Placebo (1,477/3,897)	0.93	0.81, 1.08	0.35
50 mg BID [297, (138)]	Omecamtiv mecarbil (677/2,070) vs Placebo (1,477/3,897)	0.87	0.80, 0.96	0.003
Cox Model Adjusting for Significant Baseline Covariates				
25 mg BID [184, (121)]	Omecamtiv mecarbil (516/1,269) vs Placebo (1,477/3,897)	0.93	0.84, 1.03	0.19
37.5 mg BID [345, (134)]	Omecamtiv mecarbil (225/602) vs Placebo (1,477/3,897)	0.90	0.78, 1.03	0.13
50 mg BID [297, (138)]	Omecamtiv mecarbil (677/2,070) vs Placebo (1,477/3,897)	0.89	0.81, 0.97	0.009
CV Death				
Planned Primary Analysis Cox Model				
25 mg BID [184, (121)]	Omecamtiv mecarbil (284/1,269) vs Placebo (707/3,897)	1.18	1.02, 1.35	0.02
37.5 mg BID [345, (134)]	Omecamtiv mecarbil (110/602) vs Placebo (707/3,897)	1.00	0.81, 1.22	0.97
50 mg BID [297, (138)]	Omecamtiv mecarbil (333/2,070) vs Placebo (707/3,897)	0.91	0.80, 1.04	0.15
Cox Model Adjusting for Significant Baseline Covariates				
25 mg BID [184, (121)]	Omecamtiv mecarbil (284/1,269) vs Placebo (707/3,897)	1.11	0.97, 1.28	0.13
37.5 mg BID [345, (134)]	Omecamtiv mecarbil (110/602) vs Placebo (707/3,897)	0.94	0.77, 1.16	0.58
50 mg BID [297, (138)]	Omecamtiv mecarbil (333/2,070) vs Placebo (707/3,897)	0.98	0.86, 1.12	0.79

BID=twice a day; CV=cardiovascular; [omecamtiv mecarbil]=plasma concentration of omecamtiv mecarbil; n=Number of participants with observed data; N=Number of participants; SD=standard deviation.

Concentration Response in FAS

The risk reduction for the primary endpoint was observed in the 4 highest omecamtiv mecarbil concentration quintiles, but not in the lowest quintile. A similar pattern was observed for the secondary endpoints (Table 19).

Similar results were observed when the results were analysed using quintile bins for the highest omecamtiv mecarbil concentration observed at any time in the study, with an additional bin for highest concentrations >750 ng/mL (Table 20). This alternative approach for concentration-response analyses allows more specific investigation of the small subset of participants who had concentrations of omecamtiv mecarbil above the upper limit of the target concentration range. Notably, in the bin for omecamtiv mecarbil concentration >750 by ng/mL there was no clear evidence of increased risk for CV outcomes in the overall population (n=61).

Trends of higher risk in the lowest quintile are likely related to the fact that a large proportion of participants in the lowest quintile had an event early in the study, did not undergo dose appropriate titration on or prior to Week 12, and probably represent a sicker subset of those randomised to omecamtiv mecarbil (compared with the overall placebo population). This group of participants had a short median treatment duration, and approximately half (405 of 811 participants) had plasma concentrations below the limit of quantification (85 ng/mL) of omecamtiv mecarbil.

Table 19. Primary and Secondary Cardiovascular Outcomes by Quintiles of the Last Measured Concentration up to Week 12 (Adjusting for Significant Baseline Covariates) (Study 20110203; FAS)

		Last Concentration of OM up to Week 12									
		≤144 ng/mL		>144 to **≤225** ng/mL		>225 to **≤300** ng/mL		>300 to **≤377** ng/mL		>377 ng/mL	
	Placebo n/N (%)	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value
Primary Outcome	1607/4112 (39.1)	329/811 (40.6)	1.15 (1.02, 1.30); p=0.02	284/811 (35.0)	0.85 (0.75, 0.97); p=0.01	268/805 (33.3)	0.83 (0.73, 0.95); p=0.006	280/809 (34.6)	0.77 (0.68, 0.87); p <0.001	319/804 (39.7)	0.91 (0.80, 1.02); p=0.11
CV Death	798/4112 (19.4)	179/811 (22.1)	1.34 (1.14, 1.58); p <0.001	162/811 (20.0)	1.06 (0.90, 1.26); p=0.47	121/805 (15.0)	0.79 (0.65, 0.95); p=0.01	141/809 (17.4)	0.83 (0.69, 0.99); p=0.04	172/804 (21.4)	1.02 (0.86, 1.20); p=0.83
Heart Failure Hospitalisation	1179/4112 (28.7)	248/811 (30.6)	1.19 (1.03, 1.36); p=0.02	200/811 (24.7)	0.83 (0.71, 0.96); p=0.01	198/805 (24.6)	0.85 (0.73, 0.99); p=0.04	228/809 (28.2)	0.85 (0.74, 0.98); p=0.03	246/804 (30.6)	0.94 (0.82, 1.08); p=0.38
All-cause Death	1065/4112 (25.9)	222/811 (27.4)	1.22 (1.05, 1.41); p=0.009	210/811 (25.9)	1.02 (0.88, 1.19); p=0.78	175/805 (21.7)	0.84 (0.72, 0.99); p=0.03	189/809 (23.4)	0.83 (0.71, 0.97); p=0.02	225/804 (28.0)	1.02 (0.88, 1.17); p=0.83
First HF event	1236/4112 (30.1)	255/811 (31.4)	1.15 (1.01, 1.32); p=0.04	204/811 (25.2)	0.80 (0.69, 0.93); p=0.004	207/805 (25.7)	0.84 (0.73, 0.97); p=0.02	235/809 (29.0)	0.83 (0.72, 0.95); p=0.008	254/804 (31.6)	0.93 (0.81, 1.06); p=0.27

CI=confidence interval; CV=cardiovascular; FAS=full analysis set; HF=heart failure; HR=hazard ratio; OM=omecamtiv mecarbil.

Table 20. Primary and Secondary Cardiovascular Outcomes by Quintiles of the Highest Concentration During the Study Up to 750 ng/mL and a Bin >750 mg/mL (Adjusting for Significant Baseline Covariates) (Study 20110203; FAS)

		Highest Concentration of OM											
		≤199 ng/mL		>199 to **≤291** ng/mL		>291 to **≤366** ng/mL		>366 to **≤454** ng/mL		>454 to **≤750** ng/mL		>750 ng/mL	
	Placebo n/N (%)	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value
Primary Outcome	1607/4112 (39.1)	322/803 (40.1)	1.12 (0.99, 1.27) p=0.06	277/794 (34.9)	0.92 (0.81, 1.04) p=0.18	283/794 (35.6)	0.84 (0.74, 0.96) p=0.008	262/798 (32.8)	0.73 (0.64, 0.84) p<0.001	310/792 (39.1)	0.88 (0.78, 1.00) p=0.04	27/61 (44.3)	0.99 (0.68, 1.46) p=0.97
CV Death	798/4112 (19.4)	203/803 (25.3)	1.55 (1.33, 1.82) p<0.001	145/794 (18.3)	1.08 (0.91, 1.29) p=0.39	138/794 (17.4)	0.87 (0.73, 1.05) p=0.14	120/798 (15.0)	0.72 (0.60, 0.88) p<0.001	155/792 (19.6)	0.88 (0.74, 1.05) p=0.16	14/61 (23.0)	1.00 (0.58, 1.70) p=0.99
Heart Failure Hospitalisation	1179/4112 (28.7)	222/803 (27.6)	1.07 (0.93, 1.24) p=0.34	201/794 (25.3)	0.91 (0.78, 1.06) p=0.22	223/794 (28.1)	0.91 (0.79, 1.05) p=0.20	198/798 (24.8)	0.75 (0.65, 0.88) p<0.001	252/792 (31.8)	0.97 (0.85, 1.12) p=0.69	25/61 (41.0)	1.24 (0.83, 1.85) p=0.29
All-cause Death	1065/4112 (25.9)	244/803 (30.4)	1.36 (1.18, 1.56) p<0.001	219/794 (27.6)	1.20 (1.04, 1.39) p=0.01	182/794 (22.9)	0.86 (0.74, 1.01) p=0.06	163/798 (20.4)	0.74 (0.62, 0.87) p<0.001	196/792 (24.7)	0.84 (0.72, 0.98) p=0.03	17/61 (27.9)	0.92 (0.57, 1.49) p=0.73
First HF event	1236/4112 (30.1)	226/803 (28.1)	1.03 (0.89, 1.19) p=0.68	205/794 (25.8)	0.88 (0.76, 1.02) p=0.09	231/794 (29.1)	0.89 (0.77, 1.03) p=0.11	210/798 (26.3)	0.77 (0.66, 0.89) p<0.001	259/792 (32.7)	0.95 (0.83, 1.09) p=0.44	25/61 (41.0)	1.16 (0.78, 1.73) p=0.46

CI=confidence interval; CV=cardiovascular; FAS=full analysis set; HF=heart failure; HR=hazard ratio; OM=omecamtiv mecarbi

Treatment Effect According to Baseline LVEF as a Continuous Variable

The relationship between LVEF evaluated as a continuous variable and risk for the primary composite endpoint was further examined. As baseline LVEF decreased, the incidence of the primary composite endpoint increased in both the omecamtiv mecarbil and placebo groups, as expected; however, the incidence rate increased to a lesser extent in the omecamtiv mecarbil group, resulting in increasingly greater absolute risk reductions (Figure 16). Similarly, treatment with omecamtiv mecarbil was associated with increasingly greater risk reductions with decreasing baseline LVEF (Figure 17). Thus, there were greater absolute and relative risk reductions with omecamtiv mecarbil treatment vs. placebo associated with lower LVEF at baseline. This finding has biological plausibility in those patients with a worse left ventricular function who might be expected to benefit more from omecamtiv mecarbil because it increases cardiac contractility and stroke volume.

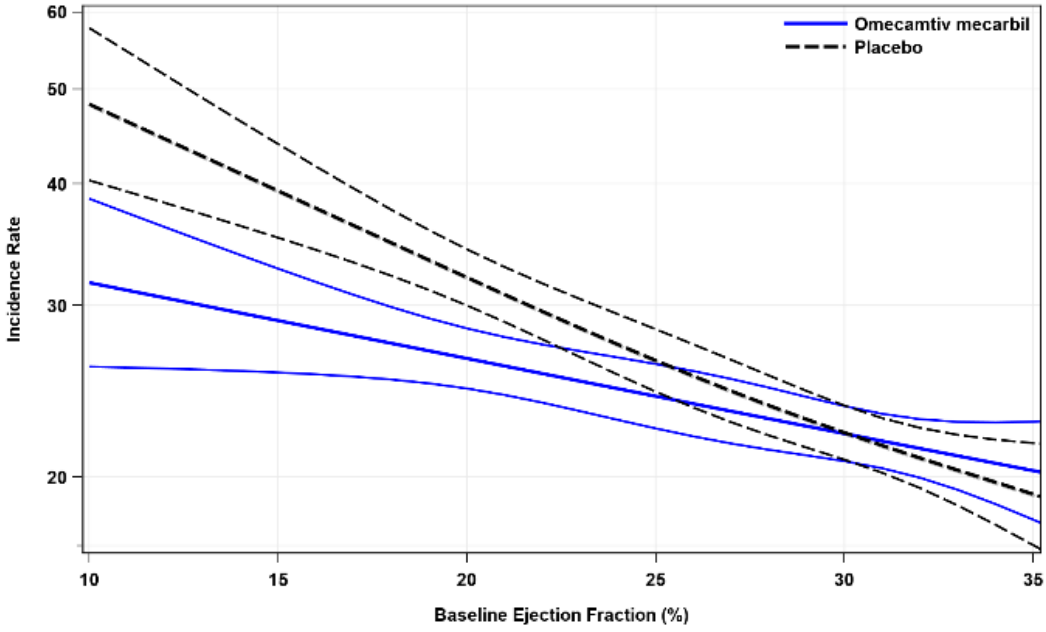


Figure 16. Incidence Rate for the Primary Endpoint as a Function of Left Ventricular Ejection Fraction

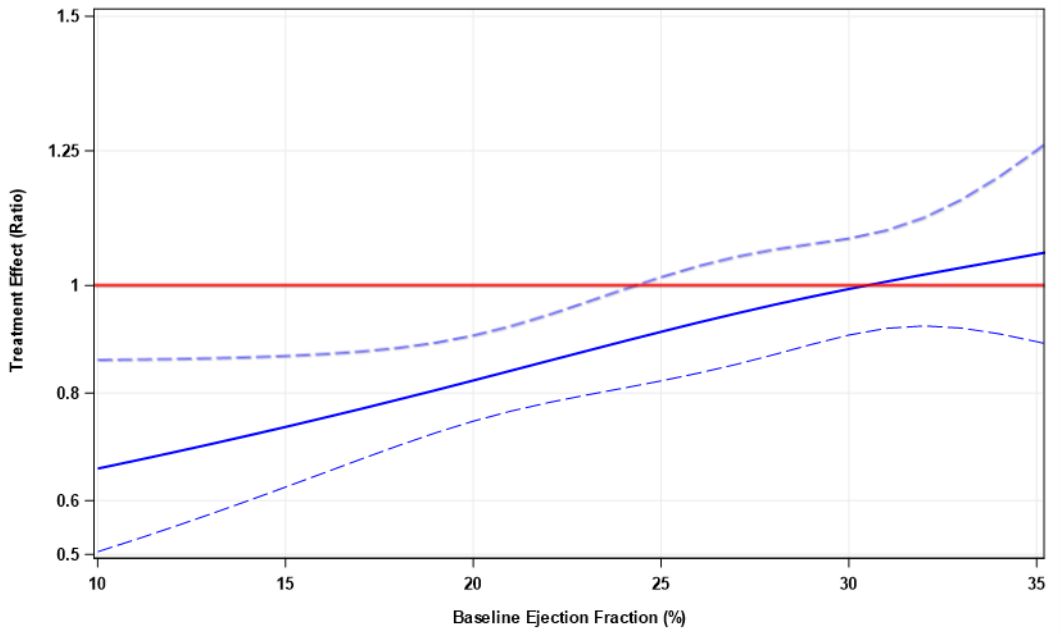


Figure 17. Treatment Effect for the Primary Endpoint as a Function of Left Ventricular Ejection Fraction

Characterisation of Cohort of Participants with Baseline LVEF <30% (Proposed Target Population)

Based on the results of the prespecified LVEF subgroup analyses and the supportive analysis that greater treatment benefit is a function of lower baseline ejection fraction, the sponsor is proposing an indication in adult patients with symptomatic chronic heart failure and reduced ejection fraction <30%, which is the upper limit for severely abnormal ejection fraction (Lang 2015). Overall, the LVEF <30% cohort (n=4704; 57.1%), which includes 248 patients more than the LVEF ≤28% cohort, closely approximates the pre-specified subgroup of LVEF ≤28% (n=4456; 54.1%) and is a more clinically practical and recognizable threshold. Therefore, the subgroup of participants with LVEF <30% was further evaluated and is proposed as the target population for the treatment indication to maximise the benefit-risk profile of omecamtiv mecarbil.

Disposition, Demographics and Baseline Characteristics of Participants with Baseline LVEF <30%

Among the 1,969 participants (41.9%) in the LVEF <30% cohort who discontinued investigational product, there was no meaningful difference in the overall frequency of IP discontinuation between omecamtiv mecarbil and placebo (40.2% vs. 43.5%, respectively), nor in the most common reasons for IP discontinuation (death, 19.1% vs. 20.2%; participant request, 11.3% vs. 12.3%; adverse event, 9.4% vs. 10.7%). A total of 3,355 participants (71.3%) completed the study, and 1,349 participants (28.7%) discontinued the study, of whom 1,294 (27.5%) discontinued the study due to death.

At Week 4, the dose (BID) of omecamtiv mecarbil was 25 mg for 581 (24.8%) participants, 37.5 mg for 372 (15.9%) participants, 50 mg for 1,192 (50.9%) participants, and placebo for 2,146 (90.8%) participants. Overall, the proportions of participants receiving each of the 3 omecamtiv mecarbil doses remained generally consistent over time.

Baseline characteristics for LVEF <30% and ⩾30% subgroups indicated that within each subgroup, there were no meaningful differences between the placebo and omecamtiv mecarbil groups, as was observed in the overall study population. Compared to the overall population, participants with LVEF <30% had higher NT-proBNP, lower SBP, higher cardiac troponin I, higher use of implantable

cardioverter defibrillator, and were less commonly from Eastern Europe and Russia. As expected, the baseline characteristics of the LVEF <30% subgroup were similar to those of the LVEF ⩽28% subgroup.

Table 21. Baseline Characteristics of LVEF <30% Subgroup and the Overall Population

	Baseline LVEF <30%		Overall	
	Placebo (n=2,363)	Omecamtiv Mecarbil (n=2,341)	Placebo (n=4,112)	Omecamtiv Mecarbil (n=4,120)
Demographics				
Age – yr (Mean ± SD)	63.5 ± 11.68	63.3 ± 11.70	64.5 ± 11.4	64.5 ± 11.3
Sex, Female, n (%)	480 (20.3)	455 (19.4)	874 (21.3)	875 (21.2)
Race, n (%)				
White	1750 (74.1)	1727 (73.8)	3,201 (77.8)	3,196 (77.6)
Asian	206 (8.7)	226 (9.7)	355 (8.6)	355 (8.6)
Black	211 (8.9)	201 (8.6)	277 (6.7)	285 (6.9)
Other	196 (8.3)	187 (8.0)	139 (3.4)	143 (3.5)
Geographic Region, n (%)				
Asia	191 (8.1)	212 (9.1)	335 (8.1)	335 (8.1)
Eastern Europe/Russia	597 (25.3)	575 (24.6)	1,337 (32.5)	1,344 (32.6)
Latin and South America	504 (21.3)	492 (21.0)	787 (19.1)[a]	787 (19.1)[a]
US And Canada	474 (20.1)	467 (19.9)	693 (16.9)	693 (16.8)
Western Europe/South Africa/Australasia	597 (25.3)	595 (25.4)	960 (23.3)	961 (23.3)
Randomisation Setting, n (%)				
Inpatient	618 (26.2)	583 (24.9)	1050 (25.5)	1051 (25.5)
Clinical Characteristics				
Atrial fibrillation or flutter at screening, n (%)	597 (25.3)	589 (25.2)	1099 (26.7)	1146 (27.8)
Type 2 diabetes mellitus, n (%)	948 (40.1)	901 (38.5)	1,691 (41.1)	1,686 (40.9)
History of stroke, n (%)	218 (9.2)	219 (9.4)	377 (9.2)	377 (9.2)
Ischaemic heart failure, n (%)	1184 (50.1)	1127 (48.1)	2222 (54.0)	2193 (53.2)
History of myocardial infarction, n (%)	959 (40.6)	861 (36.8)	1742 (42.4)	1693 (41.1)
History of coronary artery bypass surgery, n (%)	384 (16.3)	333 (14.2)	678 (16.5)	639 (15.5)
History of percutaneous coronary revascularisation, n (%)	675 (28.6)	645 (27.6)	1206 (29.3)	1232 (29.9)
LVEF – (%) (Mean ± SD)	22.2 ± 4.61	22.2 ± 4.55	26.5 ± 6.3	26.6 ± 6.3
NYHA Classification, n (%)				
Class II	1229 (52.0)	1226 (52.4)	2,173 (52.8)	2,195 (53.3)
Class III	1053 (44.6)	1033 (44.1)	1,815 (44.1)	1,801 (43.7)
Class IV	81 (3.4)	82 (3.5)	124 (3.0)	124 (3.0)
Median KCCQ Total Symptom Score (IQR)	66.7 (49.0 -87.5)	65.9 (47.9 -87.5)	68.8 (49.0, 87.5)	68.8 (49.0, 87.5)
Outpatient	72.1 (56.3 -91.7)	70.6 (54.2 -91.7)	75.0 (56.3, 91.7)	74.0 (54.2, 90.6)

	Baseline LVEF <30%		Overall	
	Placebo (n=2,363)	Omecamtiv Mecarbil (n=2,341)	Placebo (n=4,112)	Omecamtiv Mecarbil (n=4,120)
Inpatient	51.5 (30.2 -70.8)	51.8 (33.3 -70.8)	52.1 (31.3, 69.8)	54.2 (34.4, 72.9)
SBP, mmHg (Mean ± SD)	113.9 ± 15.17	113.7 ± 15.24	116.6 ± 15.3	116.3 ± 15.4
Heart rate, beats/min (Mean ± SD)	72.9 ± 12.17	72.8 ± 12.26	72.3 ± 12.1	72.4 ± 12.2
Mean NT-proBNP (IQR), pg/mL	3957.1 (1106.0 – 4625.0)	4073.4 (1168.0 – 4706.0)	3609.6 (1000.0 – 4105.0)	3644.7 (980.0 – 4061.0)
Mean cardiac troponin I (IQR), ng/L	0.1 (0.0 -0.1)	0.1 (0.0 -0.1)	0.0608 (0.0140 – 0.0510)	0.0605 (0.0140 – 0.0510)
eGFR (mean, IQR), mL/min/1.73m^2	60.6 (44.1 -74.1)	60.5 (44.2 -74.2)	60.28 (43.84 – 73.72)	60.36 (44.34 – 74.25)
Heart Failure Therapy, n (%)				
ACEi, ARB or ARNi	2048 (86.7)	2013 (86.0)	3,576 (87.0)	3,583 (87.0)
ARNi	511 (21.6)	540 (23.1)	782 (19.0)	819 (19.9)
BB	2229 (94.3)	2193 (93.7)	3,883 (94.4)	3,881 (94.2)
MRA	1864 (78.9)	1855 (79.2)	3,198 (77.8)	3,199 (77.6)
SGLT2 inhibitors	71 (3.0)	66 (2.8)	114 (2.8)	104 (2.5)
Digitalis glycosides	442 (18.7)	438 (18.7)	698 (17.0)	687 (16.7)
Cardiac resynchronisation therapy	397 (16.8)	410 (17.5)	566 (13.8)	592 (14.4)
Implantable cardioverter defibrillator	872 (36.9)	903 (38.6)	826 (20.1)	843 (20.5)

ACEi=angiotensin converting enzyme inhibitor; 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.

Efficacy in Participants with Baseline LVEF <30%

Efficacy analyses indicated that participants in the LVEF <30% subgroup experienced greater treatment benefit than those in the overall study population (Table 22). Nominally significant risk reductions were observed for the primary composite endpoint, time to first HF hospitalisation, and time to first HF event for omecamtiv mecarbil vs. placebo.

Table 22. Clinical Outcomes in the Baseline LVEF <30% Subgroup and Overall Study Population (Study 20110203)

	Placebo		Omecamtiv mecarbil				
Outcome	n/N (%)	Rate (per 100 pt-yrs)	n/N (%)	Rate (per 100 pt-yrs)	HR (95% CI)	p-value	ARR (per 100 pt-yrs)
LVEF <30%							
Primary outcome	1,014/2,363 (42.9)	30.6	889/2,341 (38.0)	25.7	0.85 (0.77, 0.93)	<0.001	4.9
CV death as first primary endpoint	225/2,363 (9.5)	-	204/2,341 (8.7)	-	-	-	-
HF hospitalisation as first primary event	723/2,363 (30.6)	-	642/2,341 (27.4)	-	-	-	-

Outcome	Placebo		Omecamtiv mecarbil		HR (95% CI)	p-value	ARR (per 100 pt-yrs)
	n/N (%)	Rate (per 100 pt-yrs)	n/N (%)	Rate (per 100 pt-yrs)			
Urgent outpatient visit as first primary event	66/2,363 (2.8)	-	43/2,341 (1.8)	-	-	-	-
CV death	522/2,363 (22.1)	12.7	476/2,341 (20.3)	11.6	0.92 (0.81, 1.04)	0.18	1.1
HF hospitalisation	754/2,363 (31.9)	22.4	664/2,341 (28.4)	19.1	0.86 (0.77, 0.95)	0.003	3.4
All-cause death	679/2,363 (28.7)	16.6	633/2,341 (27.0)	15.5	0.94 (0.84, 1.05)	0.26	1.1
First HF event	789/2,363 (33.4)	23.8	685/2,341 (29.3)	19.8	0.84 (0.76, 0.93)	<0.001	4.0
Overall Study Population							
Primary outcome	1,607 (39.1)	26.3	1,523 (37.0)	24.2	0.92 (0.86, 0.99)	0.0252	2.1
CV death as first primary endpoint	371 (9.0)	-	346 (8.4)	-	-	-	-
HF hospitalisation as first primary event	1,133 (27.6)	-	1,107 (26.9)	-	-	-	-
Urgent outpatient visit as first primary event	103 (2.5)	-	70 (1.7)	-	-	-	-
CV death	798 (19.4)	10.8	808 (19.6)	10.9	1.01 (0.92, 1.11)	0.8555	-0.1
HF hospitalisation	1,179 (28.7)	19.1	1,142 (27.7)	18.0	0.95 (0.87, 1.03)	0.1902	1.1
All-cause death	1,065 (25.9)	14.4	1,067 (25.9)	14.4	1.00 (0.92, 1.09)	0.9633	0.0
First HF event	1,236 (30.1)	20.3	1,177 (28.6)	18.7	0.93 (0.86, 1.00)	0.0631	1.5

Primary endpoint

A total of 889 (38.0%) participants in the omecamtiv mecarbil group and 1,014 (42.9%) in the placebo group had a primary outcome. The HR (95% CI) was 0.85 (0.77, 0.93) and the ARR was 4.9 per 100 patient years comparing omecamtiv mecarbil to placebo for the primary endpoint (CV death or HF event) as compared to in the overall population a HR of 0.92 (0.86, 0.99) and ARR 2.1%, indicating that participants with LVEF <30% treated with omecamtiv mecarbil had a significant risk reduction in time to first event in the primary composite endpoint (CV death or HF event). The Kaplan Meier curve for the participants with LVEF <30% is presented in Figure 18. The Kaplan Meier curves begin to separate at approximately 2 months in favor of the omecamtiv mecarbil group.

Subgroup analyses of the primary composite endpoint in the LVEF <30% group demonstrated treatment effects for the prespecified subgroups that were generally consistent with those observed in the overall LVEF <30% group. All point estimates for the primary endpoint were less than unity favoring omecamtiv mecarbil compared with placebo. Hazard ratio (95% CI) estimates for the treatment difference between groups in the primary composite endpoint for all subgroups are depicted in Figure 19 and Figure 20. An additional analysis in the LVEF <30% group showed that the primary composite endpoint results in the subgroup of participants from EU countries favored omecamtiv mecarbil (HR [95% CI]=0.86 [0.74, 1.01]; ARR=4.0 per 100 patient years), similar to the total LVEF <30% cohort, see Figure 22.

When the LVEF <30% cohort was analyzed in combination with other high risk factors for adverse HF outcomes such as high NT-proBNP (>2000 pg/mL), low SBP (<110 mm Hg), current or recent hospitalisation or New York Heart Association (NYHA) Class III/IV, substantial and incrementally greater relative risk reductions (RRRs) and ARRs were observed with omecamtiv mecarbil treatment versus placebo for the primary composite endpoint, with ARRs ranging from 6.2 per 100 patient years to 10.1 per 100 patient years (Figure 21).

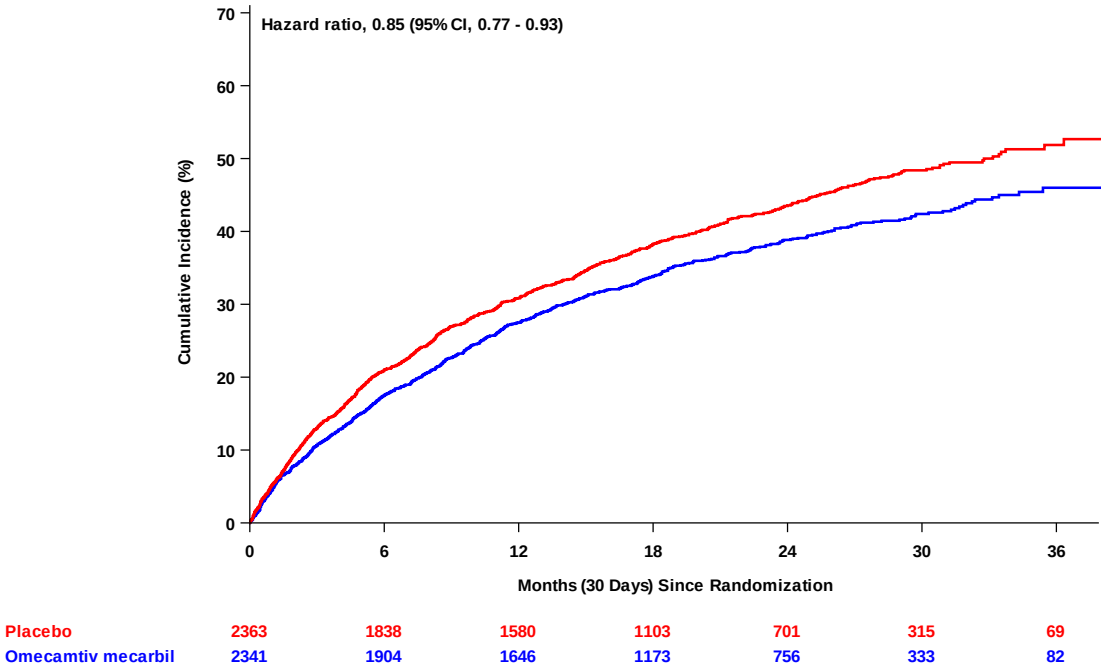


Figure 18. Cumulative Incidence Estimates for Primary Endpoint (Cardiovascular Death or Heart Failure Event) in the Baseline LVEF <30% Subgroup (Study 20110203)

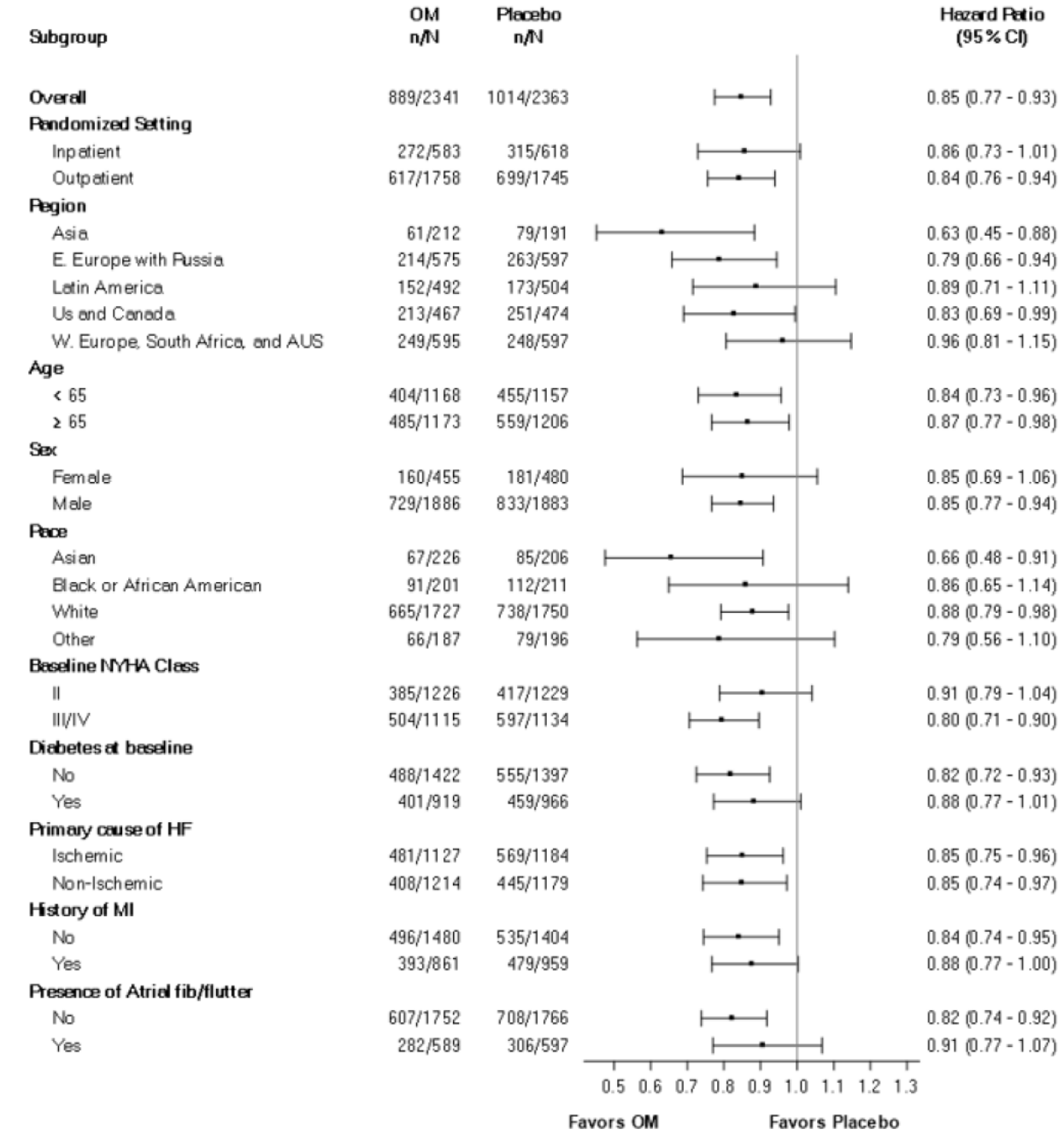


Figure 19. Study 20110203 Forest Plot of the Subgroup Analysis for Primary Composite Endpoint by Baseline LVEF <30% (part 1)

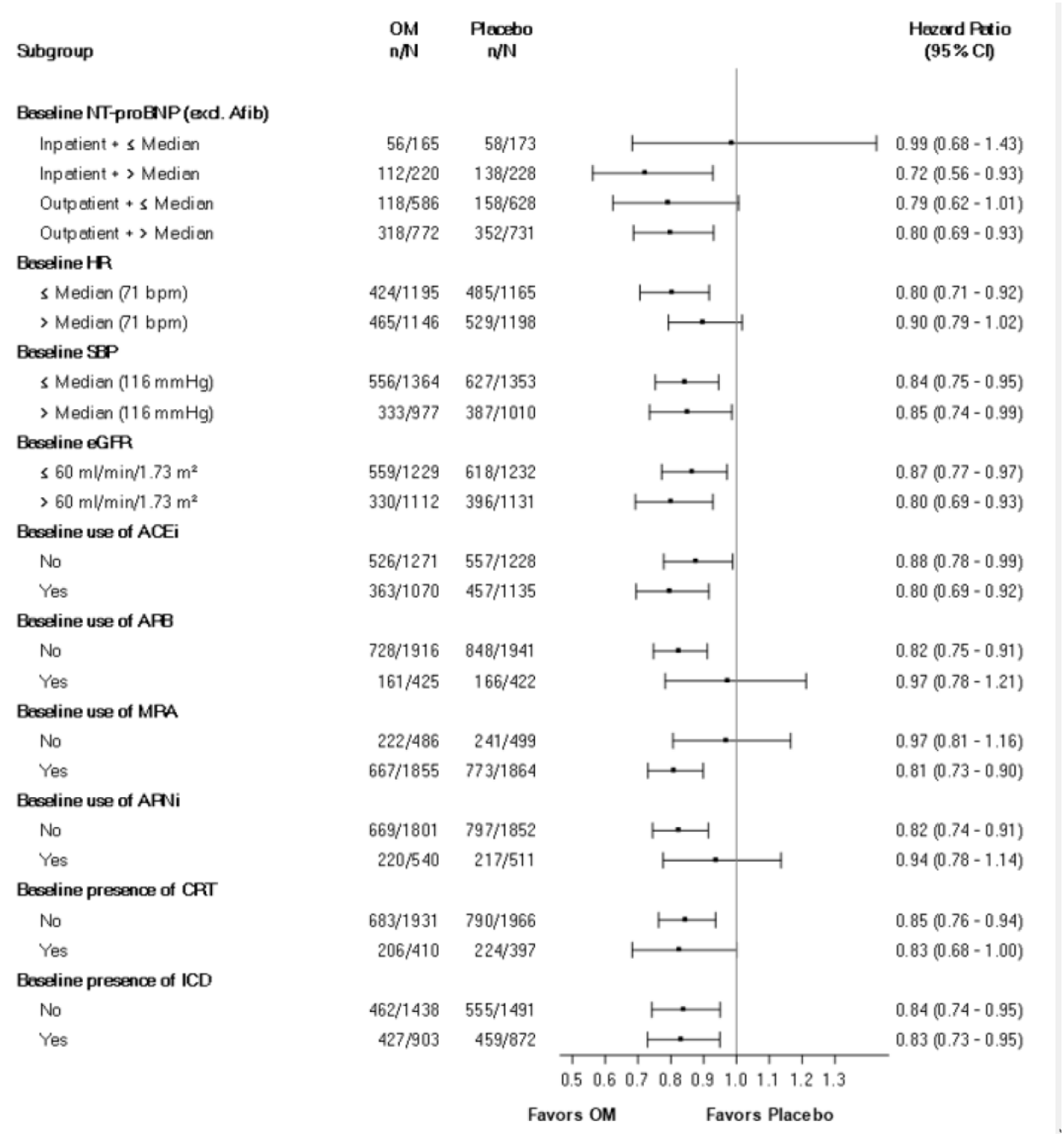


Figure 20. Study 20110203 Forest Plot of the Subgroup Analysis for Primary Composite Endpoint by Baseline LVEF <30% (part 2)

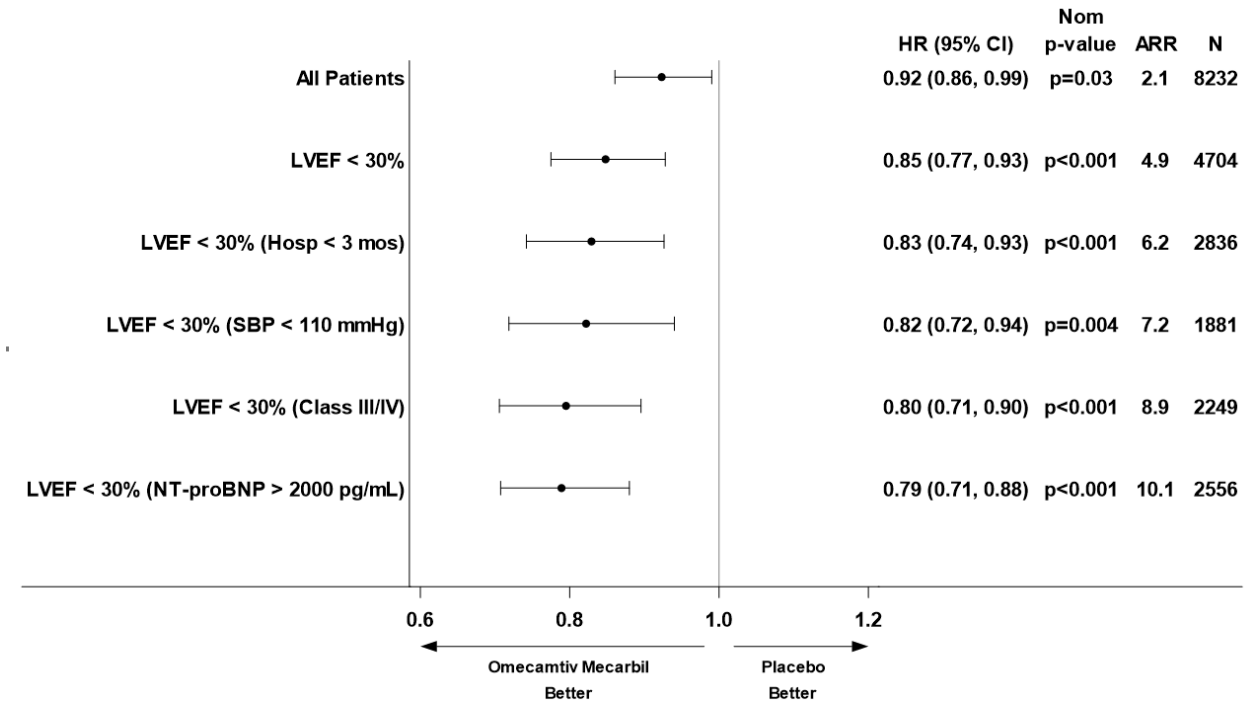


Figure 21. Forest Plot of Primary Composite Endpoint with Additional High Risk Factors of Hospitalisation Less Than 3 Months, NYHA Class III/IV, NT proBNP >2000 pg/mL, SBP <110 mmHg in the Baseline LVEF <30% (Study 20110203)

	Omecamtiv mecarbil		Placebo			
Outcome	n/N	Rate (per 100 pt yrs)	n/N	Rate (per 100 pt yrs)	HR (95% CI), p value	ARR (per 100 pt yrs)
Primary Outcome	297/798 (37.2)	23.7	328/799 (41.1)	27.7	0.86 (0.74, 1.01); p=0.07	4.0
CV Death as 1st Primary Event	54/798 (6.8)		55/799 (6.9)			
HF Hosp as 1st Primary Event	229/798 (28.7)		253/799 (31.7)			
Urgent Outpatient Visit as 1st Primary Event	14/798 (1.8)		20/799 (2.5)			
CV Death	156/798 (19.5)	10.5	169/799 (21.2)	11.5	0.92 (0.74, 1.14); p=0.43	1.0
Heart Failure Hospitalization	238/798 (29.8)	18.9	261/799 (32.7)	21.7	0.88 (0.74, 1.05); p=0.15	2.8
All-cause Death	218/798 (27.3)	14.7	235/799 (29.4)	16.0	0.92 (0.77, 1.11); p=0.38	1.3
First HF event	243/798 (30.5)	19.4	273/799 (34.2)	23.0	0.85 (0.72, 1.01); p=0.07	3.7

Figure 22. Subgroup Primary and Secondary Cardiovascular Outcomes in EU Countries by Baseline LVEF <30%.

Cardiovascular death

A total of 476 (20.3%) participants in the omecamtiv mecarbil group and 522 (22.1%) in the placebo group had an outcome of CV death. The HR (95% CI) was 0.92 (0.81, 1.04) in the LVEF <30% group versus 1.01 (0.92, 1.11) in the overall population (Table 22). The Kaplan Meier curve for the participants with LVEF <30% is presented in Figure 23. An additional analysis in the LVEF <30% group showed that the primary composite endpoint results in the subgroup of EU countries also favoured omecamtiv mecarbil and was consistent with the total LVEF <30% cohort (HR [95% CI]=0.86 [0.74, 1.01]; ARR=4.0 per 100 patient-years).

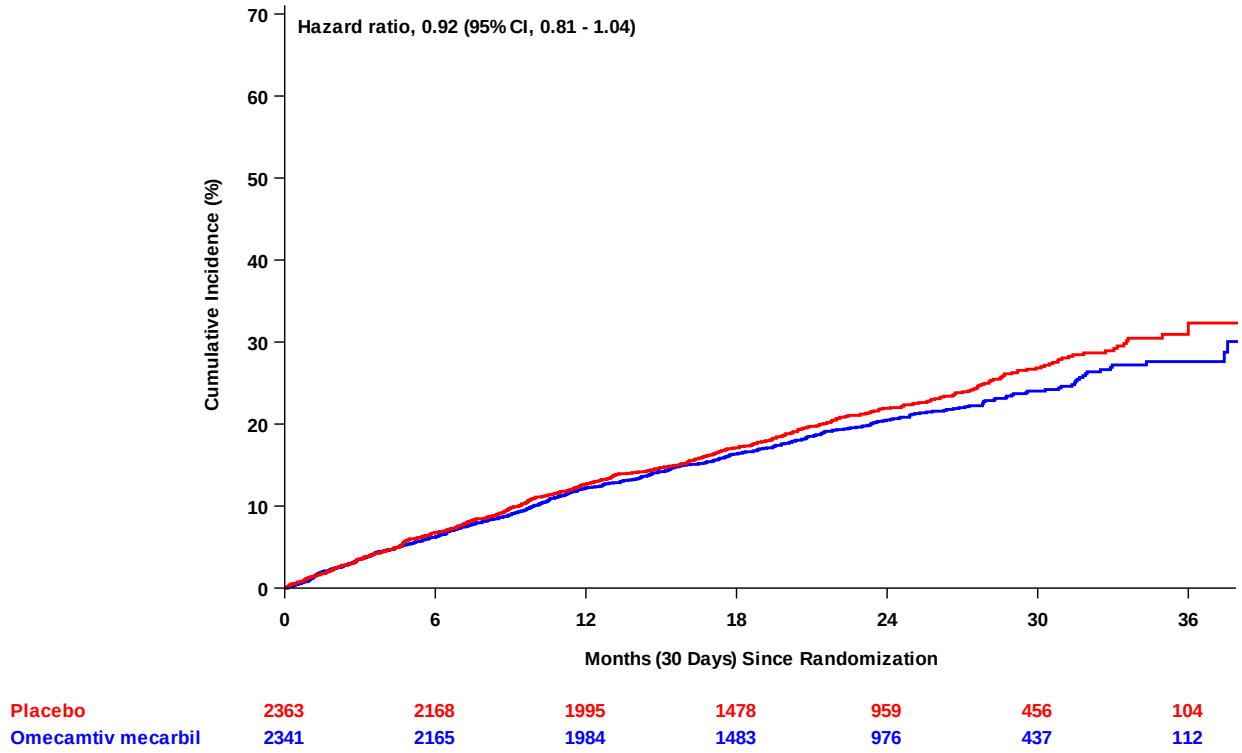


Figure 23. Cumulative Incidence Estimates for Cardiovascular Death in the Baseline LVEF <30% Subgroup (Study 20110203)

KCCQ-TSS change

At baseline, KCCQ-TSS mean scores were notably higher as expected among outpatient participants compared with inpatient participants in both the omecamtiv mecarbil and placebo treatment groups, and this was similar across both the LVEF <30% and ≥30% subgroups. The mean (SD) changes from baseline to Week 24 in KCCQ-TSS in the omecamtiv mecarbil and placebo groups, respectively, in the LVEF <30% subgroup were 24.6 (29.0) and 21.6 (31.1) among inpatient participants and 6.6 (21.7) and 5.6 (21.5) among outpatient participants, and this was similar to the change from baseline to Week 24 in participants with LVEF ≥30%.

Heart Failure Hospitalisation

Overall, 664 (28.4%) participants in the omecamtiv mecarbil group and 754 (31.9%) in the placebo group had an outcome of HF hospitalisation. The HR (95% CI) was 0.86 (0.77, 0.95) comparing omecamtiv mecarbil to placebo in participants with LVEF <30% and 0.95 (0.87, 1.03) in the overall population, indicating that participants with LVEF <30% and treated with omecamtiv mecarbil had a nominally statistically significant risk reduction in time to first HF hospitalisation. The Kaplan-Meier curve for the participants with LVEF <30% is presented in Figure 24. The Kaplan Meier curves begin to separate at approximately 2 months in favour of the omecamtiv mecarbil group.

The results for time to first heart failure hospitalisation were consistent with those for time to first heart failure event, for which participants in the omecamtiv mecarbil group experienced significantly lower risk compared with the placebo group (HR [95% CI]=0.84 (0.76, 0.93); p <0.001; ARR=4.0 per 100 patient-years).

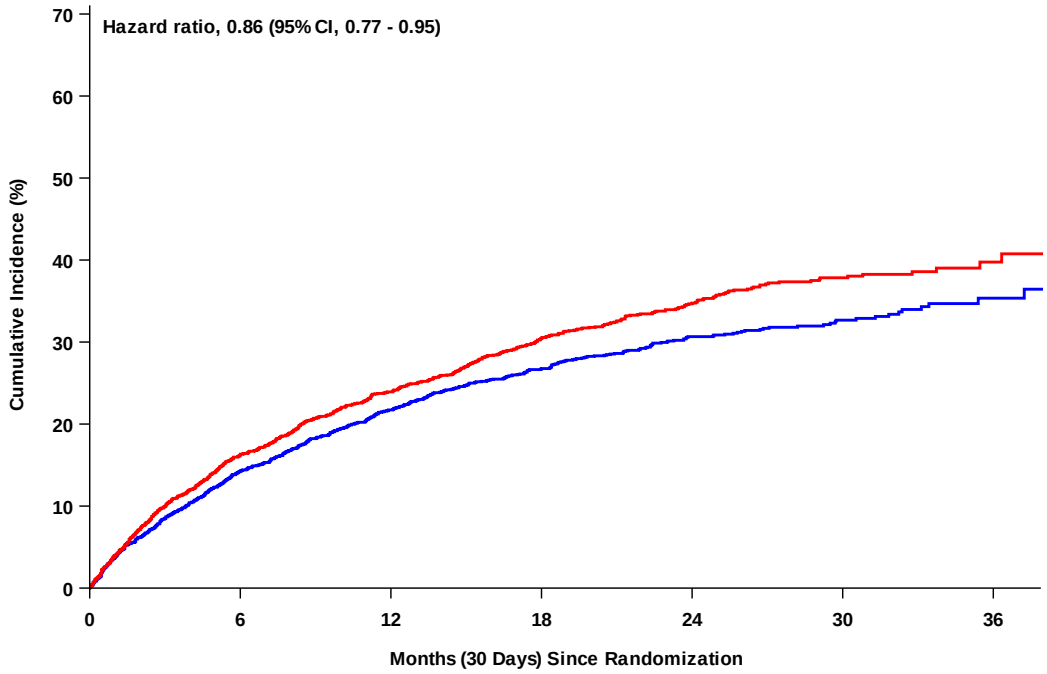


Figure 24. Cumulative Incidence Estimates for Heart Failure Hospitalisation in the Baseline LVEF <30% Subgroup (Study 20110203)

Time to all-cause death

A total of 476 (20.3%) participants in the omecamtiv mecarbil group and 679 (28.7%) in the placebo group had an outcome of all-cause death. A trend of relative risk reductions was observed with omecamtiv mecarbil versus placebo for all-cause death (HR=0.94; 95% CI 0.84, 1.05).

Selected exploratory outcomes

First HF Event

Analyses of time to first HF event indicated that participants in the LVEF <30% subgroup experienced greater treatment benefit than those in the LVEF ≥30% subgroup. In the LVEF <30% subgroup,a significant relative risk reduction was observed with omecamtiv mecarbil versus placebo for HF event (HR=0.84; 95% CI 0.76, 0.93). In the LVEF ≥30% subgroup, analysis of HF hospitalisation did not indicate a treatment benefit. These results are similar to those for the prespecified subgroups by median LVEF.

Recurrent hospitalisations

Analyses of times to recurrent event of HF hospitalisation showed that participants in the LVEF <30% subgroup experienced greater treatment benefit than those in the LVEF ≥30% subgroup. In the LVEF <30% subgroup, significant rate ratio reductions were observed with omecamtiv mecarbil versus placebo for times to recurrent event of HF hospitalisation (RR: 0.86, 95% CI 0.75, 0.98) based on a negative binomial model. This was consistent with the estimated hazard ratio of 0.84 (95% CI 0.74, 0.94) by a joint frailty model. In the LVEF ≥30% subgroup, these analyses did not indicate an overall treatment benefit.

NT-proBNP change

Analysis of change from baseline in NT-proBNP indicated that participants in the LVEF <30% subgroup experienced greater treatment benefit than those in the LVEF ≥30% subgroup. A significantly larger decrease from baseline at Week 24 of median NT-proBNP was observed in the omecamtiv mecarbil treatment group, compared to placebo, in the LVEF <30% subgroup (RR=0.84; 95% CI 0.80, 0.89) compared to that in the LVEF ≥30% subgroup (RR=0.98; 95% CI 0.92, 1.04).

Concentration response in LVEF <30%

In participants with LVEF <30%, risk reduction for the primary endpoint was observed in the 4 highest omecamtiv mecarbil concentration quintiles, but not in the lowest quintile. A similar pattern was observed for the secondary endpoint; A risk reduction was observed for all secondary endpoints in the 4 highest quintiles (Table 23). These results indicate a therapeutic effect for omecamtiv mecarbil concentrations is in the range of 200 – 750 ng/mL.

Similar results were observed when the results were analysed using quintile bins for the highest omecamtiv mecarbil concentration observed at any time in the study, with an additional bin for highest concentrations >750 ng/mL (Table 24). This alternative approach for concentration-response analyses allows more specific investigation of the small subset of participants who had concentrations of omecamtiv mecarbil above the upper limit of the target concentration range. Notably, in the bin for omecamtiv mecarbil concentration >750 by ng/mL there was no clear evidence of increased risk for CV outcomes in the overall population (n=61), and there were trends for decreased risk in participants with LVEF <30% (n=33).

Table 23. Primary and Secondary Cardiovascular Outcomes by Quintiles of the Last Measured Concentration up to Week 12 (Adjusting for Significant Baseline Covariates) in Participants with LVEF <30% (Study 20110203; FAS)

		Last Concentration of OM up to Week 12									
		≤144 ng/mL		>144 to **≤225** ng/mL		>225 to **≤300** ng/mL		>300 to **≤377** ng/mL		>377 ng/mL	
	Placebo n/N (%)	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value
Primary Outcome	1014/2363 (42.9)	189/457 (41.4)	1.06 (0.90, 1.24); p=0.49	153/451 (33.9)	0.71 (0.60, 0.85); p<0.001	171/459 (37.3)	0.82 (0.69, 0.96); p=0.01	158/458 (34.5)	0.67 (0.56, 0.79); p<0.001	188/469 (40.1)	0.82 (0.70, 0.96); p=0.01
CV Death	522/2363 (22.1)	105/457 (23.0)	1.26 (1.02, 1.56); p=0.04	85/451 (18.8)	0.88 (0.70, 1.11); p=0.28	80/459 (17.4)	0.79 (0.63, 1.00); p=0.05	88/458 (19.2)	0.77 (0.61, 0.97); p=0.02	97/469 (20.7)	0.87 (0.70, 1.08); p=0.21
Heart Failure Hospitalisation	754/2363 (31.9)	144/457 (31.5)	1.10 (0.92, 1.32); p=0.29	104/451 (23.1)	0.66 (0.54, 0.81); p<0.001	125/459 (27.2)	0.81 (0.67, 0.98); p=0.03	127/458 (27.7)	0.72 (0.59, 0.87); p<0.001	148/469 (31.6)	0.85 (0.71, 1.02); p=0.07
All-cause Death	679/2363 (28.7)	135/457 (29.5)	1.21 (1.00, 1.46); p=0.05	117/451 (25.9)	0.92 (0.76, 1.12); p=0.42	110/459 (24.0)	0.81 (0.66, 0.99); p=0.04	113/458 (24.7)	0.76 (0.62, 0.93); p=0.008	128/469 (27.3)	0.89 (0.74, 1.08); p=0.25
First HF event	789/2363 (33.4)	147/457 (32.2)	1.05 (0.88, 1.26); p=0.57	106/451 (23.5)	0.64 (0.52, 0.78); p<0.001	133/459 (29.0)	0.81 (0.68, 0.98); p=0.03	130/458 (28.4)	0.69 (0.58, 0.84); p<0.001	153/469 (32.6)	0.85 (0.71, 1.01); p=0.06

CI=confidence interval; CV=cardiovascular; FAS=full analysis set; HF=heart failure; HR=hazard ratio; LVEF=left ventricular ejection fraction; OM=omecamtiv mecarbil.

Table 24. Primary and Secondary Cardiovascular Outcomes by Quintiles of the Highest Concentration During the Study Up to 750 ng/mL and a Bin >750 ng/mL (Adjusting for Significant Baseline Covariates) in Participants with LVEF <30% (Study 20110203; FAS)

		Highest Concentration of OM									
		≤199 ng/mL		>199 to **≤291** ng/mL		>291 to **≤366** ng/mL		>366 to **≤454** ng/mL		>454 to **≤750** ng/mL	
	Placebo n/N (%)	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value	OM n/N (%)	HR (95% CI); p value
Primary Outcome	1014/2363 (42.9)	183/453 (40.4)	1.02 (0.87, 1.20) p=0.77	156/446 (35.0)	0.81 (0.69, 0.96) p=0.02	162/437 (37.1)	0.76 (0.65, 0.90) p=0.001	168/450 (37.3)	0.74 (0.63, 0.87) p<0.001	177/476 (37.2)	0.73 (0.62, 0.86) p<0.001
CV Death	522/2363 (22.1)	117/453 (25.8)	1.43 (1.16, 1.75) p<0.001	79/446 (17.7)	0.92 (0.73, 1.17) p=0.52	83/437 (19.0)	0.82 (0.65, 1.03) p=0.09	78/450 (17.3)	0.73 (0.57, 0.92) p=0.009	91/476 (19.1)	0.75 (0.60, 0.94) p=0.01
Heart Failure Hospitalisation	754/2363 (31.9)	125/453 (27.6)	0.95 (0.79, 1.16) p=0.64	110/446 (24.7)	0.78 (0.63, 0.95) p=0.01	128/437 (29.3)	0.81 (0.67, 0.98) p=0.03	126/450 (28.0)	0.75 (0.62, 0.90) p=0.003	146/476 (30.7)	0.81 (0.67, 0.96) p=0.02
All-cause Death	679/2363 (28.7)	148/453 (32.7)	1.35 (1.13, 1.62) p=0.001	120/446 (26.9)	1.05 (0.86, 1.28) p=0.63	105/437 (24.0)	0.79 (0.64, 0.97) p=0.03	104/450 (23.1)	0.74 (0.60, 0.91) p=0.004	117/476 (24.6)	0.74 (0.61, 0.90) p=0.003
First HF event	789/2363 (33.4)	128/453 (28.3)	0.91 (0.76, 1.11) p=0.36	113/446 (25.3)	0.75 (0.62, 0.92) p=0.005	133/437 (30.4)	0.80 (0.67, 0.96) p=0.02	132/450 (29.3)	0.75 (0.62, 0.90) p=0.002	150/476 (31.5)	0.79 (0.66, 0.94) p=0.008

CI=confidence interval; CV=cardiovascular; FAS=full analysis set; HF=heart failure; HR=hazard ratio; LVEF=left ventricular ejection fraction; OM=omecamtiv mecarbil

Modification of Treatment Effect According to Presence or Absence of Atrial Fibrillation/Flutter at Baseline

In the prespecified subgroup analyses in 20110203, atrial fibrillation/flutter at baseline was observed to have one of the strongest univariate treatment-covariate interactions for the primary composite endpoint (p=0.012). Consistent with the univariate treatment-covariate interaction analysis, the baseline atrial fibrillation/flutter-by-treatment interaction remained the second most significant covariate (p=0.006). Further analyses were conducted sequentially in order to better characterise and understand this observation.

Baseline characteristics indicated that participants with atrial fibrillation/flutter were older, had a higher incidence of inpatient status at randomisation, were more likely to be NYHA Class III/IV, had more frequent digoxin and anticoagulant use, had higher NT-proBNP, and had lower eGFR.

Analyses of time to first event for the primary composite endpoint, HF event, CV death, and all cause death indicated that the subgroup of participants without atrial fibrillation/flutter at baseline experienced nominally significant risk reductions with omecamtiv mecarbil compared with placebo for the primary composite endpoint, time to first HF event, time to first HF hospitalisation, and time to all-cause death (Table 25). In contrast, in the participants with atrial fibrillation/flutter at baseline, nominally significant increases of risk were observed with omecamtiv mecarbil for CV death and all cause death.

Table 25. Clinical Outcomes for Participants With Atrial Fibrillation/Flutter and Without Atrial Fibrillation/Flutter at Baseline (Study 20110203)

	Placebo		Omecamtiv mecarbil			
Outcome	n/N (%)	Rate (per 100 pt-yrs)	n/N (%)	Rate (per 100 pt-yrs)	HR (95% CI)	p-value
No Atrial Fibrillation/Flutter						
Primary outcome	1,103/3,013 (36.6)	24.2	981/2,974 (33.0)	20.7	0.86 (0.79, 0.94)	<0.001
CV death	549/3,013 (18.2)	10.2	500/2,974 (16.8)	9.2	0.90 (0.80, 1.02)	0.09
HF hospitalisation	796/3,013 (26.4)	17.3	715/2,974 (24.0)	15.0	0.87 (0.79, 0.97)	0.009
All-cause death	739/3,013 (24.5)	13.7	672/2,974 (22.6)	12.3	0.90 (0.81, 0.99)	0.04
First HF event	835/3,013 (27.7)	18.3	739/2,974 (24.8)	15.6	0.86 (0.78, 0.95)	0.003
Atrial Fibrillation/Flutter at Baseline						
Primary outcome	504/1,099 (45.9)	32.7	542/1,146 (47.3)	34.8	1.05 (0.93, 1.18)	0.47
CV death	249/1,099 (22.7)	12.5	308/1,146 (26.9)	15.7	1.26 (1.07, 1.49)	0.007
HF hospitalisation	383/1,099 (34.8)	24.4	427/1,146 (37.3)	27.1	1.09 (0.95, 1.25)	0.23
All-cause death	326/1,099 (29.7)	16.4	395/1,146 (34.5)	20.1	1.25 (1.08, 1.45)	0.003
First HF event	401/1,099 (36.5)	26.0	438/1,146 (38.2)	28.1	1.06 (0.92, 1.21)	0.41

CV=cardiovascular; HF=heart failure; HR=hazard ratio; n=Number of participants with observed data; N=Number of participants; NT proBNP=N terminal prohormone B type natriuretic peptide; pt-yrs=patient-years.

As expected, digoxin use was higher in the participants with baseline atrial fibrillation/flutter compared with participants without baseline atrial fibrillation/flutter (30.8% vs. 11.6%) and likely represents the use of digoxin for ventricular rate control. Analysis of digoxin use as an added covariate to the other prespecified parameters in the multivariable treatment-covariate model of the total cohort did not show a strong interaction between treatment and digoxin use (p=0.08). However, an analysis of atrial fibrillation/flutter with and without digoxin use in the multivariable treatment-covariate model revealed a statistically significant treatment-covariate interaction (p=0.003) that was primarily driven by co-administration of digoxin in patients with baseline atrial fibrillation/flutter. An additional multivariate treatment-covariate model was analyzed in participants with baseline atrial fibrillation/flutter subgroup alone to evaluate the impact of other baseline covariates that are more common in this population, such as the use of amiodarone or anticoagulants; no significant interactions with treatment were observed with the use of amiodarone or anticoagulants.

Analyses of HF outcomes by presence or absence of baseline atrial fibrillation/flutter and by use of digoxin were consistent with the possibility that the increased risk observed in the subgroup of participants with atrial fibrillation/flutter with omecamtiv mecarbil treatment was concentrated in those participants also receiving digoxin (Table 26). For both the primary composite endpoint and CV death, an increased risk was observed in participants with baseline atrial fibrillation/flutter who were also receiving digoxin, while increased risk was not observed in participants with baseline atrial fibrillation/flutter who were not receiving digoxin. In contrast, participants without baseline atrial fibrillation/flutter had decreased risk for the primary composite endpoint or CV death with omecamtiv mecarbil regardless of digoxin co-administration.

Table 26. Study 20110203 Outcomes for Participants With Atrial Fibrillation/Flutter at Baseline With and Without Digoxin Use (Full Analysis Set)

Outcome	Omecamtiv Mecarbil		Placebo		HR (95% CI); p-value	ARR (per 100 pt yrs)
	n/N (%)	Rate (per 100 pt yrs)	n/N (%)	Rate (per 100 pt yrs)		
With Digoxin Use						
Primary Outcome	172/341 (50.4)	37.3	139/351 (39.6)	26.7	1.34 (1.07, 1.68); p = 0.01	-10.6
CV Death	102/341 (29.9)	17.8	70/351 (19.9)	10.9	1.64 (1.21, 2.23); p = 0.002	-6.9
HF hospitalization	135/341 (39.6)	29.0	101/351 (28.8)	19.0	1.47 (1.13, 1.91); p = 0.004	-10.0
All-cause Death	129/341 (37.8)	22.5	93/351 (26.5)	14.4	1.61 (1.23, 2.11); p < 0.001	-8.1
First HF event	138/341 (40.5)	29.9	105/351 (29.9)	20.2	1.43 (1.10, 1.84); p = 0.007	-9.7
Without Digoxin Use						
Primary Outcome	370/805 (46.0)	33.8	365/748 (48.8)	35.8	0.94 (0.81, 1.09); p = 0.39	2.0
CV Death	206/805 (25.6)	14.9	179/748 (23.9)	13.3	1.12 (0.92, 1.37); p = 0.27	-1.6
HF Hospitalization	292/805 (36.3)	26.4	282/748 (37.7)	27.1	0.96 (0.82, 1.13); p = 0.65	0.8
All-cause Death	266/805 (33.0)	19.2	233/748 (31.1)	17.3	1.11 (0.93, 1.33); p = 0.23	-1.9
First HF event	300/805 (37.3)	27.4	296/748 (39.6)	29.0	0.94 (0.80, 1.10); p = 0.42	1.6

ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; n = number of participants with observed data; N = number of participants randomized excluding site number 29002.
Source: Table BT-14.2.2.13.

Atrial Fibrillation/Flutter in the Baseline LVEF <30% Subgroup

Analyses of time to first event for the primary composite endpoint, HF event, CV death, and all-cause death indicated that the baseline LVEF <30% subgroup of participants without atrial fibrillation/flutter at baseline experienced nominally statistically significant risk reductions with omecamtiv mecarbil compared with placebo for the primary composite endpoint, time to CV death, time to first HF hospitalisation, time to first HF event, and time to all-cause death (Table 27). In participants with atrial fibrillation/flutter at baseline, in contrast to the overall study population, trends of risk reduction were observed for the primary endpoint and first HF event with omecamtiv mecarbil compared with placebo; however, these results were not statistically significant.

Analyses of major HF outcomes comparing participants with atrial fibrillation/flutter at baseline who were also receiving digoxin (N=179) versus all remaining participants in the study cohort (N=2,162) are shown in Table 28. In the participants without atrial fibrillation/flutter at baseline who were not receiving digoxin (i.e. all remaining participants) a nominally statistically significant decreased risk was

observed with omecamtiv mecarbil versus placebo for the primary endpoint, CV death, HF hospitalisation, and time to first HF event was observed. In contrast, in the participants with atrial fibrillation/flutter at baseline who received digoxin, increased risk trends were observed with omecamtiv mecarbil versus placebo for each of these endpoints.

Table 27. Clinical Outcomes for Participants with Atrial Fibrillation/Flutter and Without Atrial Fibrillation/Flutter at Baseline in the Baseline LVEF <30% Subgroup (Study 20110203)

	Placebo		Omecamtiv mecarbil			
Outcome	n/N (%)	Rate (per 100 pt-yrs)	n/N (%)	Rate (per 100 pt-yrs)	HR (95% CI)	p-value
No Atrial Fibrillation/Flutter						
Primary outcome	708/1,766 (40.1)	27.9	607/1,752 (34.6)	22.6	0.82 (0.74, 0.92)	<0.001
CV death	360/1,766 (20.4)	11.7	312/1,752 (17.8)	10.0	0.86 (0.74, 1.00)	0.05
HF hospitalisation	521/1,766 (29.5)	20.3	444/1,752 (25.3)	16.4	0.82 (0.72, 0.93)	0.002
All-cause death	475/1,766 (26.9)	15.5	422/1,752 (24.1)	13.5	0.88 (0.77, 1.00)	0.05
First HF event	546/1,766 (30.9)	21.5	461/1,752 (26.3)	17.2	0.81 (0.72, 0.92)	<0.001
Atrial Fibrillation/Flutter at Baseline						
Primary outcome	306/597 (51.3)	39.8	282/589 (47.9)	36.6	0.91 (0.77, 1.07)	0.24
CV death	162/597 (27.1)	15.8	164/589 (27.8)	16.9	1.06 (0.85, 1.32)	0.60
HF hospitalisation	233/597 (39.0)	29.5	220/589 (37.4)	28.2	0.94 (0.78, 1.13)	0.53
All-cause death	204/597 (34.2)	19.8	211/589 (35.8)	21.7	1.10 (0.91, 1.34)	0.32
First HF event	243/597 (40.7)	31.6	224/589 (38.0)	29.1	0.91 (0.76, 1.09)	0.30

CV=cardiovascular; HF=heart failure; HR=hazard ratio; n=Number of participants with observed data; N=Number of participants; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; pt-yrs=patient-years.

Table 28. Clinical Outcomes for Participants with and Without Baseline Atrial Fibrillation/Flutter and Digoxin Use in the Baseline LVEF <30% Subgroup (Study 20110203)

	Placebo		Omecamtiv mecarbil			
Outcome	n/N	Rate (per 100 pt-yrs)	n/N	Rate (per 100 pt-yrs)	HR (95% CI)	p-value
Without Atrial Fibrillation/Flutter and Without Digoxin Use at Baseline						
Primary outcome	920/2162 (42.6)	30.2	796/2162 (36.8)	24.6	0.82 (0.75, 0.90)	<0.001
CV death	470/2162 (21.7)	12.5	417/2162 (19.3)	11.0	0.88 (0.77, 1.00)	0.05
HF Hospitalisation	688/2162 (31.8)	22.3	595/2162 (27.5)	18.3	0.82 (0.74, 0.92)	<0.001
All-cause death	611/2162 (28.3)	16.3	560/2162 (25.9)	14.7	0.90 (0.81, 1.01)	0.08
First HF event	719/2162 (33.3)	23.6	614/2162 (28.4)	19.0	0.81 (0.73, 0.90)	<0.001
With Atrial Fibrillation/Flutter and Digoxin Use at Baseline						

Outcome	Placebo		Omecamtiv mecarbil		HR (95% CI)	p-value
	n/N	Rate (per 100 pt-yrs)	n/N	Rate (per 100 pt-yrs)		
Primary outcome	94/201 (46.8)	35.0	93/179 (52.0)	41.4	1.20 (0.90, 1.61)	0.22
CV death	52/201 (25.9)	15.1	59/179 (33.0)	20.7	1.45 (0.99, 2.12)	0.06
HF hospitalisation	66/201 (32.8)	23.7	69/179 (38.5)	30.3	1.31 (0.93, 1.85)	0.13
All-cause death	68/201 (33.8)	19.8	73/179 (40.8)	25.6	1.40 (1.00, 1.97)	0.05
First HF event	70/201 (34.8)	26.1	71/179 (39.7)	31.6	1.24 (0.88, 1.73)	0.22

CI=confidence interval; CV=cardiovascular; HF=heart failure; HR=hazard ratio; n=Number of participants with observed data; N=Number of participants; pt-yrs=patient-years.

3.3.4.3. Summary of main efficacy results

Table 29. A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects with Chronic Heart Failure with Reduced Ejection Fraction

Study Identifier	Protocol Number: 20110203 (GALACTIC-HF) EudraCT Number: 2016-002299-28 NCT Number: NCT02929329		
Study Design	Phase 3, double-blind, randomised, placebo-controlled, multicentre, cardiovascular outcomes study to assess the efficacy and safety of oral OM in participants with chronic HfrEF receiving SoC. The study was event driven and concluded when approximately 1,590 CV death events had occurred.		
	Duration of main phase:	Approximately 24 months, until the occurrence of 1,590 CV death events	
	Duration of Run-in phase:	Not applicable	
	Duration of Extension phase:	Not applicable. At the occurrence of 1,590 CV death events, all participants would complete an End of Study Visit.	
Study Population	Adults with chronic HfrEF, NYHA Class II-IV, and left ventricular systolic dysfunction (LVEF ≤35%) who were either currently hospitalised with the primary reason of HF or had 1 of the following events within 1 year of screening: hospitalisation or urgent visit to the emergency department with primary reason of HF		
Hypothesis	The primary hypothesis was that when added to SoC, OM is well tolerated and superior to placebo in reducing the risk of CV death or HF events in participants with chronic HfrEF. Secondary hypotheses were that OM reduces the individual risks of CV death, HF hospitalisation, and all-cause death and improves symptoms in participants with chronic HfrEF compared with placebo.		
Treatment Groups	A total of 8,256 participants were enrolled and randomised in a 1:1 ratio to OM or placebo (4,127 to placebo, 4,129 to OM). The starting dose of OM was 25 mg BID, and a PK-based dose selection strategy was used to determine escalation from the initial starting dose. Three dose levels (25, 37.5, and 50 mg BID) were used.		
Endpoints and Definitions	Primary endpoint	Composite of time to CV death or first HF event, whichever occurred first	A death was defined as a CV death endpoint if the death was positively adjudicated as a CV death, presumed CV death, or presumed sudden death (Hicks 2015). An HF event was defined as an urgent, unscheduled clinic/office/ED visit, or hospital admission, with a primary diagnosis of HF, where the participant exhibited new or worsening symptoms of HF on presentation, had objective evidence of new or worsening HF, and received initiation or intensification of treatment specifically for HF (Hicks 2015).
	Secondary endpoint	Time to CV death	CV deaths for this endpoint were defined using the parameters used for the primary endpoint.
	Secondary endpoint	Change in KCCQ TSS from baseline to Week 24	This endpoint was defined as the mean changes in KCCQ TSS from baseline to week 24.
	Secondary endpoint	Time to first HF hospitalisation	This endpoint was defined as the proportion of participants experiencing HF hospitalisation.
	Secondary endpoint	Time to all-cause death	This endpoint was defined as the proportion of participants who died.
Data Cutoff Date(s)	The data presented in the CSR are based on a database snapshot date of 02 October 2020.		
Results and Analysis			
Efficacy Analysis Population and Time Point Description	FAS (all randomised participants except those 24 participants at 1 study centre due to GCP violations): 8,232 participants (4,112 placebo; 4,120 OM). Endpoint analysis was conducted based on all study data (except the 24 participants excluded for GCP violations) unless otherwise stated.		

Key Efficacy Results

Efficacy Endpoints	Placebo N=4,112 n (%)	OM N=4,120 n (%)	Hazard Ratio[a]/Mean Difference[b] (95% CI)	P-value[c]/ Significance[d]
Primary Endpoint				
Composite of time to CV death or first HF event, whichever occurred first	1,607 (39.1)	1,523 (37.0)	0.92 (0.86, 0.99)	0.0252*
Secondary Endpoints				
Time to CV death	798 (19.4)	808 (19.6)	1.01 (0.92, 1.11)	0.8555
Change in KCCQ TSS from baseline to Week 24, LS Mean[c]				0.0278
Outpatient participants	6.3 (0.3)	5.8 (0.3)	-0.46 (-1.40, 0.48)	
Inpatient participants	21.2 (0.7)	23.7 (0.7)	2.50 (0.54, 4.46)	
Time to first HF hospitalisation	1,179 (28.7)	1,142 (27.7)	0.95 (0.87, 1.03)	0.1902
Time to all-cause death	1,065 (25.9)	1,067 (25.9)	1.00 (0.92, 1.09)	0.9633
Exploratory Endpoints				
Time to first HF event	1,236 (30.1)	1,177 (28.6)	0.93 (0.86, 1.00)	0.0631

Subgroup Analysis of the Primary Endpoint[e]

Subgroup	Number of Patients (%)	Hazard Ratio (95% CI)	OM	Placebo
Total	8232 (100.0)	0.92 (0.86, 0.99)	1523 (37.0)	1607 (39.1)
Randomisation Setting				
Currently hospitalised for HF	2084 (25.3)	0.89 (0.78, 1.01)	469 (44.9)	497 (47.8)
Recently and not currently hospitalised for HF	6148 (74.7)	0.94 (0.86, 1.02)	1054 (34.3)	1110 (36.1)
Region				
Asia	670 (8.1)	0.80 (0.61, 1.05)	100 (29.9)	120 (35.8)
EEU with Russia	2681 (32.6)	0.90 (0.80, 1.02)	488 (36.3)	517 (38.7)
Latin America	1574 (19.1)	0.90 (0.75, 1.07)	227 (28.8)	248 (31.5)
US and Canada	1386 (16.8)	0.85 (0.73, 0.99)	306 (44.2)	345 (49.8)
WEU SA and AUS	1921 (23.3)	1.07 (0.93, 1.23)	402 (41.8)	377 (39.3)
Age				
<65 Years	3747 (45.5)	0.91 (0.82, 1.02)	616 (32.9)	646 (34.5)
≥65 Years	4485 (54.5)	0.94 (0.86, 1.03)	907 (40.4)	961 (42.9)
Sex				
Female	1749 (21.2)	0.95 (0.81, 1.12)	306 (35.0)	307 (35.1)
Male	6483 (78.8)	0.92 (0.85, 0.99)	1217 (37.5)	1300 (40.1)
Baseline Weight (Quartiles)				
Q1: 0 kg <weight ≤68.4 kg	2059 (25.0)	0.88 (0.77, 1.02)	372 (36.2)	423 (41.0)
Q2: 68.4 kg <weight ≤80.0 kg	2061 (25.0)	0.99 (0.86, 1.15)	380 (36.9)	377 (36.6)
Q3: 80.0 kg <weight ≤93.9 kg	2051 (24.9)	0.85 (0.74, 0.99)	348 (34.2)	396 (38.3)
Q4: weight >93.9 kg	2057 (25.0)	0.98 (0.85, 1.12)	422 (40.5)	411 (40.5)
Race				
Asian	710 (8.6)	0.79 (0.61, 1.02)	107 (30.1)	129 (36.3)
Black or African American	562 (6.8)	0.82 (0.64, 1.04)	124 (43.5)	144 (52.0)
White	6397 (77.7)	0.95 (0.88, 1.03)	1196 (37.4)	1233 (38.5)

Other[f]	563 (6.8)	0.91 (0.69, 1.21)	96 (33.8)	101 (36.2)
Ethnicity				
Hispanic or Latino	1771 (21.5)	0.90 (0.76, 1.06)	264 (29.8)	290 (32.8)
Not Hispanic or Latino	6461 (78.5)	0.93 (0.86, 1.00)	1259 (38.9)	1317 (40.8)
Baseline NYHA Class				
II	4368 (53.1)	0.97 (0.87, 1.08)	676 (30.8)	679 (31.2)
III/IV	3864 (46.9)	0.88 (0.80, 0.97)	847 (44.0)	928 (47.9)
Diabetes Mellitus at Baseline				
No	4855 (59.0)	0.91 (0.83, 1.01)	805 (33.1)	858 (35.4)
Yes	3377 (41.0)	0.93 (0.84, 1.03)	718 (42.6)	749 (44.3)
Primary Cause of Heart Failure				
Ischaemic	4415 (53.6)	0.90 (0.82, 0.98)	877 (40.0)	961 (43.2)
Non-ischaemic	3817 (46.4)	0.96 (0.86, 1.07)	646 (33.5)	646 (34.2)
Medical History of Myocardial Infarction				
No	4797 (58.3)	0.93 (0.85, 1.03)	822 (33.9)	838 (35.4)
Yes	3435 (41.7)	0.91 (0.83, 1.01)	701 (41.4)	769 (44.1)
Presence of Atrial Fibrillation/Flutter				
No	5987 (72.7)	0.86 (0.79, 0.94)	981 (33.0)	1103 (36.6)
Yes	2245 (27.3)	1.05 (0.93, 1.18)	542 (47.3)	504 (45.9)
Baseline LVEF Relative to the Median				
≤28%	4456 (54.1)	0.84 (0.77, 0.92)	850 (38.4)	971 (43.3)
>28%	3776 (45.9)	1.04 (0.94, 1.16)	673 (35.3)	636 (34.0)
Baseline NT-proBNP Relative to the Median[g]				
Hospitalised & NT-proBNP ≤2065 pg/mL	673 (8.2)	0.97 (0.74, 1.28)	104 (30.2)	100 (30.4)
Hospitalised & NT-proBNP >2065 pg/mL	672 (8.2)	0.75 (0.61, 0.92)	175 (52.4)	201 (59.5)
Not Hospitalised & NT-proBNP ≤1580 pg/mL	2313 (28.1)	0.88 (0.73, 1.05)	223 (19.7)	260 (22.0)
Not Hospitalised & NT-proBNP >1580 pg/mL	2313 (28.1)	0.85 (0.75, 0.97)	476 (41.2)	539 (46.6)
Baseline Resting HR Relative to the Median				
≤71 bpm	4214 (51.2)	0.91 (0.82, 1.01)	723 (34.3)	767 (36.4)
>71 bpm	4018 (48.8)	0.93 (0.85, 1.03)	800 (39.8)	840 (41.9)
Baseline SBP Relative to the Median				
≤116 mmHg	4134 (50.2)	0.90 (0.82, 0.99)	848 (40.5)	889 (43.6)
>116 mmHg	4098 (49.8)	0.95 (0.85, 1.05)	675 (33.3)	718 (34.6)
Baseline SBP				
≥100 mmHg	7105 (86.3)	0.92 (0.86, 1.00)	1242 (35.2)	1325 (37.0)
<100 mmHg	1127 (13.7)	0.89 (0.76, 1.05)	281 (47.3)	282 (52.9)
Baseline eGFR				
≤60 mL/min/1.73m^2	4321 (52.5)	0.98 (0.89, 1.07)	973 (45.1)	984 (45.5)
>60 mL/min/1.73m^2	3911 (47.5)	0.84 (0.75, 0.94)	550 (28.0)	623 (32.0)
Baseline Use of ACEi				
No	4188 (50.9)	0.94 (0.85, 1.03)	848 (40.1)	871 (42.0)
Yes	4044 (49.1)	0.90 (0.81, 1.00)	675 (33.6)	736 (36.1)
Baseline Use of ARB (excluding ARNi)				
No	6643 (80.7)	0.91 (0.85, 0.99)	1240 (37.4)	1322 (39.8)
Yes	1589 (19.3)	0.97 (0.83, 1.15)	283 (35.3)	285 (36.2)
Baseline Use of Aldosterone Inhibitor				
No	1835 (22.3)	0.98 (0.85, 1.12)	386 (41.9)	400 (43.8)
Yes	6397 (77.7)	0.91 (0.83, 0.98)	1137 (35.5)	1207 (37.7)
Baseline Use of ARNi				
No	6631 (80.6)	0.91 (0.84, 0.99)	1196 (36.2)	1289 (38.7)
Yes	1601 (19.4)	0.97 (0.83, 1.13)	327 (39.9)	318 (40.7)
Baseline Presence of CRT				
No	7074 (85.9)	0.93 (0.86, 1.01)	1239 (35.1)	1305 (36.8)
Yes	1158 (14.1)	0.84 (0.72, 0.99)	284 (48.0)	302 (53.4)
Baseline Presence of ICD				
No	5618 (68.2)	0.94 (0.86, 1.03)	918 (32.9)	974 (34.5)
Yes	2614 (31.8)	0.88 (0.78, 0.98)	605 (45.6)	633 (49.1)

Efficacy Conclusions	When used with current standard of care treatments, OM when compared with placebo resulted in the following: Statistically significant risk reduction (8%) of the primary composite endpoint of CV death or HF events No effect on risk of CV death Quality of life improvements (measured by KCCQ TSS) that were similar to those observed with placebo, with a trend toward improvement in the inpatient cohort, but not statistically significant per multiplicity adjustment A trend in the reduction in risk of HF hospitalisations, but not statistically significant No effect on risk of all-cause death A trend towards reduction in risk of first HF events, but not statistically significant

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; ARNi=angiotensin receptor neprilysin inhibitor; AUS=Australasia; BID=twice a day; CRT=cardiac resynchronisation therapy; CSR=clinical study report; CV=cardiovascular; ED=emergency department; EEU=Eastern Europe; eGFR=estimated glomerular filtration rate; FAS=full analysis set; GALACTIC HF=Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; GCP=Good Clinical Practice; HF=heart failure; HfrEF=heart failure with reduced ejection fraction; HR=heart rate; ICD=implantable cardioverter defibrillator; KCCQ=Kansas City Cardiomyopathy Questionnaire ; LS=least squares; LVEF=left ventricular ejection fraction; N=number of participants in the analysis set; n=number of participants with observed data; NT-proBNP=N terminal prohormone B-type natriuretic peptide; NYHA Class II-IV=New York Heart Association class IIIV; OM=omecamtiv mecarbil; PK=pharmacokinetics; SA=South Africa; SBP=systolic blood pressure; SoC=standard of care; TSS=total symptom score; WEU=Western Europe.

a Based on a stratified Cox model with treatment group and baseline eGFR as the independent variables and stratified by randomisation setting and region.

b For KCCQ, within each randomisation setting subgroup, LS mean is from the mixed model, which includes baseline TSS value, region, baseline eGFR, scheduled visit, treatment group and interaction of treatment with scheduled visit as covariates. The LS mean treatment difference is using placebo as the reference.

c Positive changes represent improvements in symptoms.

d Significant results are denoted with an asterisk (*).

e Primary endpoint is the composite of time to cardiovascular death or first heart failure event, whichever occurs first.

f Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, or Other.

g Excluded subjects with atrial fibrillation/flutter.

3.3.4.4. Clinical studies in special populations

No relevant supporting study.

3.3.4.5. In vitro biomarker test for patient selection for efficacy

N/A

3.3.4.6. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

3.3.4.7. Supportive study(ies)

Study 20110151 (COSMIC-HF)

Methods

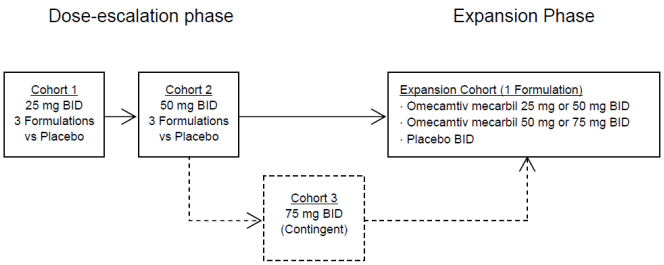
This study was a double-blind, randomised, placebo-controlled, multicentre, dose-escalation study to select and evaluate an oral modified release formulation of omecamtiv mecarbil in subjects with heart failure and left ventricular systolic dysfunction. This study was conducted at 105 centres in 13 countries in Europe, Australia, and North America; subjects were enrolled at 86 of these centres. The study period was from 29 January 2013 (first subject screened) to 19 August 2015 (last subject last follow-up visit).

Main inclusion criteria were heart failure with HfrEF (LVEF <40%), stable optimal pharmacological therapy for ≥4 weeks, including a beta blocker and either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, unless not tolerated.

The study consisted of a dose-escalation phase to select 1 of 3 OM oral formulations in up to 3 planned dose-escalation cohorts (2 dose cohorts were actually implemented), followed by an expansion phase to evaluate 20 weeks of administration of the selected OM formulation at 2 target dose levels, compared with placebo. In each of the dose-escalation cohorts, approximately 40 subjects were randomised to receive 1 of the 3 oral formulations of OM BID (25 mg BID cohort 1; 50 mg BID cohort 2), or placebo BID for 7 days. Pharmacokinetic and safety data were reviewed at a Dose Level Review Meeting (DLRM) before enrollment into the next cohort was initiated. In the expansion phase, approximately 450 subjects were randomised 1:1:1 into 1 of 3 treatment groups to receive the selected formulation of OM at 25 mg or 50 mg BID or placebo. Randomisation in all cohorts and both study phases was stratified by the presence or absence of atrial fibrillation/flutter. Subjects randomised to OM 50 mg BID target dose initiated administration at 25 mg BID until week 8. These subjects (PK-based titration group) started administration at 50 mg BID at the week 8 visit if eligible based on their week 2 predose OM plasma concentration. The expansion phase included transthoracic echocardiographic assessments. A graphical overview of the design is shown in Figure 25.

The oral formulation of OM was dihydrochloride hydrate drug substance formulated as a modified release oral solid dosage form at strengths of 25 mg and 50 mg of the free-base equivalent. Three formulations were evaluated: 1. Modified release matrix formulation F1 (M-F1); 2. Modified release matrix formulation F2 (M-F2); 3. Swellable core technology F2 (SCT-F2). The M-F1 formulation was evaluated further in the expansion phase. Placebo was presented in identical containers and stored/packaged the same as OM.

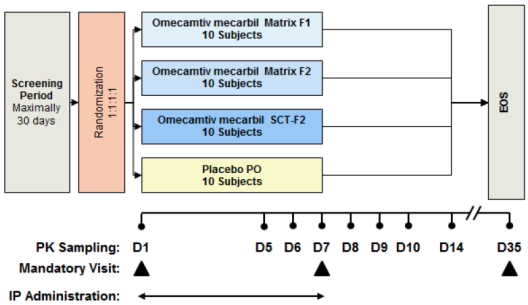
After signing the informed consent, subjects were randomised within 30 days. During the dose-escalation phase, subjects were treated with investigational product (IP) BID for 7 days with the end of study (EOS) visit at day 35 for a maximal duration of study participation of 65 days. For subjects enrolled into the expansion phase, treatment was for 20 weeks with the EOS visit at 24 weeks.

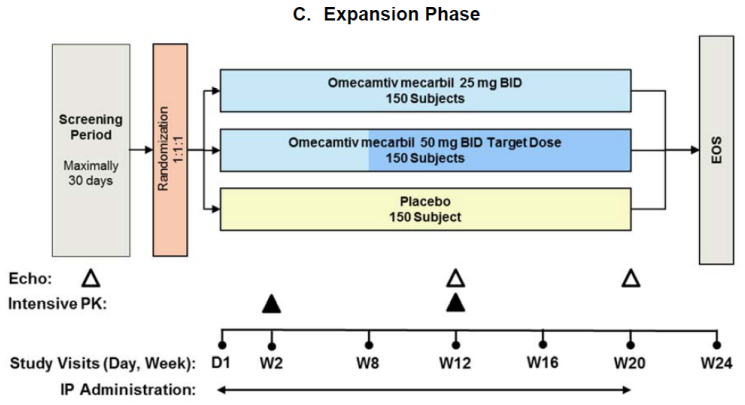


BID = twice daily.

Note: Cohort 3 was only to be enrolled if cohort 2 dosing did not achieve the expected target plasma concentration and if data from the prior cohorts indicated that plasma concentrations in individual subjects (> 1000 ng/mL) could be avoided at the higher dose. Cohort 3 was not enrolled as the expected targeted exposures were achieved from cohorts 1 and 2. Dose levels in the expansion phase did not exceed the highest dose level tested for the selected formulation during the dose-escalation phase.

B. Dose-escalation phase (Cohorts 1 – 3)





BID = twice daily; D = day; EOS = end of study; IP = investigational product; PK = pharmacokinetic; PO = oral; W = week

In the expansion phase, subjects in the PK-based titration group start at 25 mg and uptitrate to 50 mg BID at week 8 if the week 2 predose concentration is < 200 ng/mL. This regimen was called the 50 mg BID Target Dose in the schema.

Figure 25. Study Design and Treatment Schema

The primary endpoint during the dose escalation phase was the maximum observed drug concentration (Cmax), time at which Cmax is attained (Tmax), minimum observed drug concentration (Cmin), and area under the time vs concentration curve $(AUC)_{12h}$ of OM following dose on day 7. During the expansion phase this was the Cmax and/or concentration prior to IP administration (Cpredose) of OM at weeks 2, 8, 12, 16, and 20 with chronic oral BID dosing.

Secondary endpoints were applied to the expansion phase only and were the changes from baseline in systolic ejection time, stroke volume, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), and heart rate over 20 weeks of oral dosing with OM, and change from baseline in NT-proBNP at week 20.

Results

Dose-escalation Phase

A total of 2 cohorts were included in the dose-escalation phase. Cohorts 1 and 2 evaluated 25 mg and 50 mg BID OM, respectively. For cohort 1, 66 subjects were screened, of whom 49 were enrolled and randomly assigned to receive either placebo or 25 mg OM BID. A total of 48 subjects received treatment with IP, 11 subjects in the placebo group and 10, 14, and 13 subjects in the OM 25 mg M-F1, 25 mg M-F2, and 25 mg SCT-F2 groups (the three different formulations), respectively. For cohort 2, a total of 74 subjects were screened of whom 47 were enrolled and randomly assigned to receive either placebo or 50 mg OM BID. A total of 46 subjects received treatment, 10 subjects in the placebo group and 11, 11, and 14 subjects in the OM 50 mg M-F1, 50 mg M-F2, and 50 mg SCT-F2 groups, respectively. Sex: 76.2% men, 23.8% women in the pooled placebo group and 80.0% men and 20.0% women in pooled OM group. Age: The mean age was 64.4 years (range: 47 to 73) in the pooled placebo group and 65.4 years (range 40 to 82 years) in pooled OM group.

Following BID oral administration of OM with formulations M-F1, M-F2, and SCT-F2 at doses of 25 mg and 50 mg, OM plasma exposures of the 3 formulations were largely similar. The M-F1 formulation was selected for further evaluation in the expansion phase based on the low peak-to-trough variability in OM plasma concentration.

With the M-F1 formulation, mean Cmax and AUC12 values of OM increased proportionally from 25 mg to 50 mg. Mean Cmax and AUC12 values of OM on day 7 were 193 and 492 ng/mL, and 2030 and

5070 ng*hr/mL, respectively, for 25 and 50 mg BID doses. Median Tmax values on day 7 were 4 and 3 hours for 25 and 50 mg BID regimen, respectively. One subject in the 50 mg M-F1 group achieved an OM concentration (day 7 Cmax 1320 ng/mL) substantially outside the range of all the other subjects dosed (N=9, Cmax range: 349 to 654 ng/mL) and experienced a positively adjudicated myocardial infarction. This informed the implementation of PK-based titration in the expansion phase, which used the Cpredose at the 25 mg BID dose to guide dose escalation to 50 mg BID OM.

Expansion Phase

A total of 758 subjects were screened, of whom 448 were enrolled and randomly assigned 1:1:1 to the placebo group, 25 mg BID OM group, or the PK-based titration OM group. Three subjects, all of whom were assigned to receive OM, did not receive any IP. One subject withdrew consent before receiving any IP; the other 2 subjects who did not receive any IP were withdrawn because of a sponsor decision (one subject was hospitalised just after enrollment, and the other subject was randomised in error and did not meet eligibility requirements). Of the 445 subjects who received treatment, 149 were in the placebo group, 150 in the 25 mg BID group, and 146 in the PK-based titration group. All subjects assigned to treatment with OM initially received 25 mg BID. Of the 296 subjects who received OM, 150 were randomised to the 25 mg BID fixed-dose group and therefore received only 25 mg BID throughout the entire expansion phase. The 146 subjects assigned to the PK-based titration group had their dose escalated from 25 mg BID to 50 mg BID at the week 8 visit if the week 2 predose plasma concentration of OM was less than the predefined cutoff of 200 ng/mL. Of the 146 subjects who were randomised to the PK-based titration group and received treatment, 78 (53.4%) had their dose increased from 25 to 50 mg BID and 58 (39.7%) continued treatment with 25 mg BID OM.

Sex: 79.9% men, 20.1% women in the placebo group, 84.7% men and 15.3% women in the 25 mg BID group, and 83.9% men and 16.1% women in the PK-based titration group Age: The mean age was 63.7 years (range: 40 to 83) in the placebo group, 62.8 years (range 33 to 83) in the 25 mg BID group, and 62.7 years (range 32 to 84) in the PK-based titration group

Cardiovascular baseline characteristics: LVEF (29.3%, 29.3%, and 29.0% in the placebo, 25 mg BID, and PK-based titration groups, respectively); ischaemic heart disease as the primary cause of HF (59.7%, 64.7%, and 67.8% in the placebo, 25 mg BID, and PK-based titration groups, respectively).

In the 25 mg BID OM group, following oral administration of M-F1 OM formulation BID at 25 mg doses for 20 weeks, Cpredose values were stable over time and the mean (SD) Cpredose value was 149 (71.2) ng/mL at week 20. The estimated Cmax/Cpredose ratio at week 12, where more intensive PK was obtained, was 1.42. The observed highest Cmax in this cohort was 453 ng/mL. In the PK titration group, Cpredose values after dose titration were stable over time. The mean (SD) Cpredose value of the entire group was 239 (118) ng/mL at week 20. For subjects remaining on 25 mg BID (n=58) in the PK titration group, the mean (SD) Cpredose was 206 (74.4) ng/mL at week 20. For subjects that escalated to 50 mg BID (n=78), the mean (SD) Cpredose was 262 (138) ng/mL at week 20. The estimated Cmax/Cpredose ratio at week 12 was 1.27. The highest observed Cmax in this cohort was 831 ng/mL.

Changes from baseline to week 20 in SET, stroke volume, LVESD, LVEDD, heart rate measured by ECG, and NT-proBNP are summarised tabulated overview of these results is shown in Table 30.

Compared with placebo, treatment with OM resulted in a SET prolongation and stroke volume increase from baseline to week 20 for both the 25 mg BID group (11.2 msec [p=0.0007] and 4.58 mL [p=0.0036], respectively) and the PK-based titration group (25.0 msec [p <0.0001] and 3.63 mL [p=0.0217], respectively) compared with placebo. In addition, the PK-based titration group demonstrated a reduction in the mean change from baseline to week 20 in LVESD (-179 mm

[p=0.0027]), LVEDD (-129 mm [p=0.0128]), and heart rate (-2.97 bpm [p=0.0070]) when compared with placebo.

At week 20, there was a notable difference in the mean change from baseline for NT-proBNP between the 25 mg BID group and the placebo group (-822 pg/mL [p=0.0205]) and PK-based titration group and the placebo group (-970 pg/mL [p=0.0069]) in the FAS.

Table 30. Changes From Baseline to Week 20 in Secondary Endpoints (SET, Stroke Volume, LVESD, LVEDD, heart rate, and NT-proBNP; Full Analysis Set, Expansion Phase

			PK-guided Dose Titration (Randomized)		
	Placebo (N = 149)	**25 mg (Randomized) (N = 150)**	**25 mg (Not up-titrated to 50 mg) (N = 58)**	**25 mg (Up-titrated to 50 mg) (N = 78)**	**Overall (N = 146)**
SET (msec)					
LS Mean[a]	0.0	11.2	22.4	29.6	25.0
Treatment difference[b]		11.2	21.1	28.3	25.0
(95% CI)		(4.7, 17.6)	(12.3, 29.9)	(20.6, 36.0)	(18.4, 31.5)
p-value		0.0007			< 0.0001
Stroke Volume (mL)					
LS Mean[a]	-1.05	3.53	2.15	4.58	2.58
Treatment difference[b]		4.58	2.51	4.94	3.63
(95% CI)		(1.50, 7.65)	(-1.57, 6.59)	(1.38, 8.51)	(0.53, 6.72)
p-value		0.004			0.022
LVESD (cm)					
LS Mean[a]	-0.242	-0.322	-0.356	-0.520	-0.421
Treatment difference[b]		-0.079	-0.090	-0.254	-0.179
(95% CI)		(-0.194, 0.035)	(-0.239, 0.058)	(-0.388, -0.120)	(-0.295, -0.062)
p-value		0.173			0.003
LVEDD (cm)					
LS Mean[a]	0.089	0.023	-0.032	-0.093	-0.040
Treatment difference[b]		-0.067	-0.101	-0.161	-0.129
(95% CI)		(-0.166, 0.033)	(-0.230, 0.029)	(-0.278, -0.044)	(-0.231, -0.028)
p-value		0.190			0.013
HR (bpm)					
LS Mean[a]	0.57	-0.77	-1.38	-3.52	-2.40
Treatment difference[b]		-1.34	-1.83	-3.97	-2.97
(95% CI)		(-3.47, 0.79)	(-4.63, 0.97)	(-6.53, -1.41)	(-5.12, -0.81)
p-value		0.218			0.007
NT-proBNP (pg/mL)					
LS Mean[a]	502	-319	-550	-413	-468
Treatment difference[b]		-822	-927	-790	-970
(95% CI)		(-1,516, -127)	(-1,727, -127)	(-1,538, -41)	(-1,672, -268)
p-value		0.021			0.007

HR=heart rate; LS=least squares; LVEDD=left ventricular end diastolic diameter; LVESD=left ventricular end systolic diameter; NT proBNP=n-terminal prohormone B-type natriuretic peptide; PK=pharmacokinetic; SET=systolic ejection time.

A Least squares mean is from the repeated measures model, which includes treatment group, stratification factor (from IVRS), scheduled visit, interaction of treatment with scheduled visit, and baseline value as covariates.

B Treatment difference using placebo as a reference.

Additional exploratory endpoints included the change from baseline in LVEF and fractional shortening, which both increased in the PK titration group as well as left ventricular end-systolic volume and end-diastolic volume, which both decreased in the PK titration group compared to placebo in each case (see Table 31.

Table 31. Changes From Baseline to Week 20 in Exploratory Echocardiogram Endpoints (LVEF, LVFS, LVESV, LVEDV, and LV Cardiac Output); Full Analysis Set, Expansion Phase

			PK-based Titration		
	Placebo (N = 149)	25 mg (Randomized) (N = 150)	25 mg (not uptitrated to 50 mg) (N = 58)	25 mg (uptitrated to 50 mg (N = 78)	Overall (N = 146)
LVEF (%)					
LS Mean (SE)[a]	2.04 (0.62)	3.93 (0.62)	2.52 (0.94)	5.21 (0.83)	3.63 (0.65)
(95% CI)	(0.82, 3.26)	(2.70, 5.15)	(0.68, 4.37)	(3.58, 6.84)	(2.36, 4.90)
Treatment difference[b]					
LS Mean (SE)[a]		1.88 (0.84)	0.26 (1.08)	2.95 (0.96)	1.59 (0.85)
(95% CI)		(0.24, 3.53)	(-1.86, 2.38)	(1.05, 4.84)	(-0.09, 3.27)
p-value		0.0250			0.0630
LVFS (%)					
LS Mean (SE)[a]	0.85 (0.46)	2.33 (0.46)	1.75 (0.70)	3.34 (0.64)	2.44 (0.48)
(95% CI)	(-0.06, 1.75)	(1.42, 3.24)	(0.37, 3.14)	(2.08, 4.59)	(1.49, 3.39)
Treatment difference[b]					
LS Mean (SE)[a]		1.49 (0.62)	0.77 (0.81)	2.35 (0.74)	1.59 (0.63)
(95% CI)		(0.27, 2.71)	(-0.82, 2.37)	(0.90, 3.81)	(0.34, 2.84)
p-value		0.0171			0.0125
LVESV (mL)					
LS Mean (SE)[a]	-0.43 (2.87)	-9.54 (2.89)	-6.72 (4.72)	-18.41 (4.19)	-11.58 (3.00)
(95% CI)	(-6.07, 5.22)	(-15.23, -3.86)	(-16.02, 2.58)	(-26.65, -10.17)	(-17.47, -5.70)
Treatment difference[b]					
LS Mean (SE)[a]		-9.12 (3.86)	-5.14 (5.40)	-16.83 (4.84)	-11.16 (3.92)
(95% CI)		(-16.70, -1.53)	(-15.77, 5.49)	(-26.36, -7.30)	(-18.87, -3.44)
p-value		0.0186			0.0047

			PK-based Titration		
	Placebo (N = 149)	25 mg (Randomized) (N = 150)	25 mg (not uptitrated to 50 mg) (N = 58)	25 mg (uptitrated to 50 mg (N = 78)	Overall (N = 146)
LVEDV (mL)					
LS Mean (SE)[a]	4.47 (3.38)	-4.05 (3.41)	-2.36 (5.60)	-11.91 (4.95)	-6.27 (3.53)
(95% CI)	(-2.18, 11.11)	(-10.75, 2.65)	(-13.39, 8.67)	(-21.64, -2.17)	(-13.20, 0.66)
Treatment difference[b]					
LS Mean (SE)[a]		-8.51 (4.55)	-5.70 (6.40)	-15.25 (5.74)	-10.74 (4.63)
(95% CI)		(-17.47, 0.44)	(-18.31, 6.91)	(-26.55, -3.95)	(-19.84, -1.63)
p-value		0.0623			0.0209
LV Cardiac Output (L/min)					
LS Mean (SE)[a]	0.311 (0.111)	0.252 (0.111)	0.162 (0.180)	0.356 (0.159)	0.264 (0.115)
(95% CI)	(0.094, 0.529)	(0.035, 0.470)	(-0.193, 0.516)	(0.043, 0.669)	(0.039, 0.489)
Treatment difference[b]					
LS Mean (SE)[a]		-0.059 (0.149)	-0.144 (0.207)	0.051 (0.186)	-0.047 (0.152)
(95% CI)		(-0.352, 0.234)	(-0.551, 0.264)	(-0.316, 0.417)	(-0.345, 0.251)
p-value		0.6927			0.7547

Study 20120227

Methods

This was a phase 2 double-blind, randomised, placebo-controlled, multicentre study to evaluate the safety, pharmacokinetics, and efficacy of omecamtiv mecarbil in Japanese subjects with Heart Failure With reduced ejection fraction. The study was performed from 14th of April 2016 to 8th of May 2017 in 31 centre in Japan.

Eligible subjects were Japanese men or women ≥20 and ≤85 years of age at the time of written informed consent, who had a history of chronic stable heart failure with reduced ejection fraction (EF ≤40%), were treated for heart failure with stable optimal pharmacological therapy.

Omecamtiv mecarbil modified-release Matrix F1 tablets were dosed orally at 25, 37.5, and 50 mg BID. Matching placebo tablets also were dosed BID orally. Patients were to be randomised 1:1:1:1 to receive omecamtiv mecarbil 25 mg BID fixed dose (n=20), 25 to 37.5 mg BID PK-based titration (n=20), 25 to 50 mg BID PK-based titration (n=20), or placebo (n=20) on an outpatient basis.

Subjects were uptitrated at the week 4 or week 8 visits only if the week 2 Cpredose was <200 ng/mL. Subjects with a week 2 Cpredose ⩾ 200 ng/mL (or not available at week 8) continued at 25 mg BID for the remainder of the study. Subjects randomised to the placebo group or to the 25 mg BID fixed-dose group received the assigned investigational product throughout the study.

Maximal duration of study participation was approximately 24 weeks, which included a maximum 30-day screening period, a 16-week treatment period, followed by an end-of-study visit at week 20.

The primary PK endpoint was concentrations prior to administration (Cpredose) of omecamtiv mecarbil at weeks 2, 4, 12, and 16, and area under the curve (AUC) at week 8. The secondary outcome was the change from baseline in SET by echocardiography at week 16.

Results

A total of 81 participants were randomised and received treatment as follows: 21 participants to the placebo group, 21 to the omecamtiv mecarbil 25 mg BID fixed-dose group, 19 to the omecamtiv mecarbil 25 to 37.5 mg BID PK guided dose selection group, and 20 to the omecamtiv mecarbil 25 to 50 mg BID PK guided dose selection group. Of the 81 participants, 77 participants (95.1%) completed their investigational product, and 80 (98.8%) participants completed the study.

The majority of participants were men (84.0%) with a mean (SD) age of 65.4 (11.1) years, and 100% were Japanese. The baseline characteristics of the participants represented a moderate-risk population with chronic HfrEF: median LVEF was 32%, incidence of atrial fibrillation/flutter at baseline was 18.5%, NYHA Class II/III was 59.3%/12.3%, and median NT-proBNP was 809 and 812 pg/mL (omecamtiv mecarbil and placebo, respectively).

Higher Cpredose concentrations of omecamtiv mecarbil were achieved in the PK-guided titration groups than in the 25 mg BID fixed dose group (see Table 32).

Table 32. Predose Concentrations of Omecamtiv Mecarbil During the Study

	Omecamtiv Mecarbil		
	25 mg BID (n=17-20)	25 to 37.5 mg BID PK-guided Dose Titration (n=17 – 18)	25 to 50 mg BID PK-guided Dose Titration (n=19 – 20)
Mean (SD) $C_{predose}$, ng/mL			
Week 2	239 (106)	179 (77.1)	208 (61.6)
Week 4	222 (63.5)	196 (44.0)	209 (61.9)
Week 8	227 (84.5)	248 (58.6)	246 (108)
Week 12	217 (66.1)	228 (56.9)	282 (120)
Week 16	206 (84.5)	244 (67.7)	292 (118)

Compared with placebo, treatment with omecamtiv mecarbil increased SET from baseline up to Week 16. The LS mean (SE) differences compared with placebo at Week 16 were 22.1 (6.3) (p=0.0008), 29.3 (6.5) (p <0.0001), and 25.5 (6.5) (p=0.0002) milliseconds in the omecamtiv mecarbil 25 mg BID fixed-dose, 25 to 37.5 mg BID PK guided dose selection, and 25 to 50 mg BID PK guided dose selection groups, respectively (see Table 33).

Table 33. Systolic Ejection Time Change from Baseline (msec) to Week 16

			25 to 37.5 mg BID PK-guided Dose Titration (Randomised)			25 to 50 mg BID PK-guided Dose Titration (Randomised)		
	Placebo (N=21)	25 mg BID (N=25)	25 mg (Not up-titrated to 37.5 mg) (N=9)	25 mg Up-titrated to 37.5 mg (N=9)	Overall (N=19)	25 mg (Not up-titrated to 50 mg) (N=9)	25 mg Up-titrated to 50 mg (N=11)	Overall (N=20)
Change from baseline to Day 112 (Week 16)								
n	20	19	9	8	17	9	8	17
Mean	-0.4	23.1	32.4	31.2	31.9	23.5	27.9	25.6
SE	2.6	6.2	8.9	9.2	6.2	6.1	3.4	3.5
95% CI (mean)	(-5.9, 5.0)	(10.0, 36.1)	(12.0, 52.8)	(9.5, 53.0)	(18.7, 45.0)	(9.5, 37.6)	(19.8, 36.0)	(18.1, 33.1)
Median	0.0	23.3	26.7	26.7	26.7	16.7	28.3	26.7
Q1, Q3	-10.0, 6.7	3.3, 46.7	10.0, 60.0	20.0, 33.3	10.0, 50.0	10.0, 41.7	22.5, 30.8	13.3, 31.7
Min, Max	-22, 23	-23, 83	0, 63	0, 90	0, 90	-3, 47	13, 47	-3, 47
Change from baseline to Day 112 (Week 16)								
Adjusted analysis[a]								
LS Mean	-1.7	20.5	28.6	27.5	27.6	22.4	25.4	23.8
SE	4.7	4.9	6.4	7.2	5.4	6.7	6.4	5.2
95% CI	(-11.1, 7.8)	(10.7, 30.2)	(15.7, 41.5)	(13.0, 42.0)	(16.8, 38.5)	(8.8, 36.0)	(12.4, 38.3)	(13.5, 34.1)
Treatment difference[b]								
LS Mean		22.1	30.3	29.2	29.3	24.1	27.1	25.5

			25 to 37.5 mg BID PK-guided Dose Titration (Randomised)			25 to 50 mg BID PK-guided Dose Titration (Randomised)		
	Placebo (N=21)	25 mg BID (N=25)	25 mg (Not up-titrated to 37.5 mg) (N=9)	25 mg Up-titrated to 37.5 mg (N=9)	Overall (N=19)	25 mg (Not up-titrated to 50 mg) (N=9)	25 mg Up-titrated to 50 mg (N=11)	Overall (N=20)
SE		6.3	7.2	7.6	6.5	7.2	7.5	6.5
95% CI		(9.6, 34.7)	(15.9, 44.7)	(14.0, 44.3)	(16.3, 42.3)	(9.5, 38.7)	(12.0, 42.2)	(12.6, 38.4)
p-value		0.0008			<0.0001			0.0002

BID=twice daily; CI=confidence interval; LS=least squares; Max=maximum, Min=minimum; PK=pharmacokinetics; Q1=quartile 1, Q3=quartile 3; SE=standard error; N=number of participants; n=number of participants with observed data.

Notes: 25 mg (not up-titrated to 37.5 mg), 25 mg (up-titrated to 37.5 mg), 25 mg (not up-titrated to 50 mg), and 25 mg (up-titrated to 50 mg) include only those participants who had a minimum investigational product exposure period of 25 days. These 4 actual treatment groups should only be compared to each other.

A LS mean was from the repeated measures model, which included treatment group, stratification factor (from IVRS), scheduled visit, baseline value, and the interaction of treatment group with scheduled visit as covariates.

B Treatment difference using placebo as the reference.

3.3.5. Discussion on clinical efficacy

The efficacy is primarily based on the pivotal phase 3 study 20110203 (GALACTIC-HF), a double-blind, randomised, placebo-controlled, multicentre study to assess the efficacy and safety of omecamtiv mecarbil (OM) on mortality and morbidity in subjects with chronic heart failure with reduced ejection fraction (HfrEF). The study is also known by the name GALACTIC-HF: Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure.

Dose finding

Early dose escalation studies using intravenous formulations demonstrated linear relationships between the plasma concentrations of omecamtiv mecarbil and various echocardiographic PD markers (including SET, LVEF, LVFS) in both healthy adults and chronic heart failure patients, with changes evident at plasma concentrations ⩾200 to 300 ng/mL (depending on the PD marker).

The risk of cardiac ischaemia limited the maximal tolerable dose. In the early dose-finding studies, myocardial ischaemia or infarction events were observed in 6 of 16 participants with excessive plasma concentrations of omecamtiv mecarbil >1,200 ng/mL. These events likely result from an exaggerated pharmacological effect of omecamtiv mecarbil that prolongs systolic ejection time.

Given the rapid absorption of omecamtiv mecarbil and the desire to avoid excessive plasma concentrations of omecamtiv mecarbil, a BID dosing regimen and formulation that controlled the release of omecamtiv mecarbil to blunt Cmax to minimise peak to-trough fluctuations were considered optimal for continued development. To address these issues, several modified-release formulations were developed. Study 20110151 tested several oral formulations and found that formulation M-F1 had the lowest peak-to-trough variability in OM plasma concentration and was used for the subsequent phase. Furthermore, the expanded phase of study 20110151 compared 25mg BID omecamtiv mecarbil fixed dose with a PK-guided dosing strategy (which increased the dose to 50mg BID at week 8 if the plasma concentration at week 2 was <200ng/mL) and found that the prespecified PK-guided dose

selection strategy successfully achieved higher exposures of omecamtiv mecarbil compared with 25 mg BID fixed dose. For the GALACTIC-HF study, a similar PK-guided dosing strategy was employed, aiming at a OM target range of 300 to 750 ng/mL (Cpredose), which was informed by concentration-response and dose-response analyses in studies CY 1111, CY 1121, and 20110151. The details of the PK-guided dosing strategy for GALACTIC-HF are discussed in detail in the following section. The overall dose-finding strategy for GALACTIC-HF appears reasonable and acceptable. For the real world, the applicant proposes PK-guided dosing which is nearly identical to that used in the pivotal GALACTIC-HF study; while GALACTIC-HF uses a "single-step" dose titration algorithm, a sequential dosing regimen is proposed in the SmPC. In the sequential dosing regimen, patients can only be titrated to a dose nearest to the current dose, thus not from 25 mg BID to 50 mg BID, but only first to the intermediate strength 37.5 mg BID. This is simpler to understand and therefore more conventional to clinical practice. In support of the proposed simplified dosing algorithm, the applicant has conducted PK simulation analyses, which showed that in the proposed titration scenario, at Week 12, the majority of participants in the overall population had Cmin and Cmax in the therapeutic concentration range of ≥200 to <750 ng/mL (94.8% and 97.7%, respectively). No participants exceeded a Cmax ≥1,000 ng/mL at Week 12. At week 12, 60.9% received a dose of 50 mg BID and 31.9% a dose of 37.5mg BID. For the HF population with LVEF <30% similar simulation findings were found. Comparison of the proposed PK-guide dose titration simulation model to simulations of single-step titration and observed data from the GALACTIC-HF study showed nearly identical profiles. Therefore, the simplified PK-guide dosing algorithm is considered acceptable.

Since the PK-guided dosing is considered essential in titration of patients towards the therapeutic concentration range, and to prevent excessive drug concentrations and, consequently possible cardiotoxicity, it can be considered an integral part of the benefit risk assessment of omecamtiv mecarbil. Therefore the applicant discussed how validity and quality control of the proposed assay will be ensured in the clinical application of the assay, throughout the EU.

Design and conduct of clinical studies

The key inclusion criteria of GALACTIC-HF were an age of 18 – 85 years, HfrEF with an LVEF ≤35%, NYHA class II-IV, standard of care treatment (beta blocker and RAAS inhibitor), a BNP level ≥125 pg/mL or an NT-proBNP level ≥400 pg/mL (375 or 1200 respectively, in the presence of atrial fibrillation/flutter). Furthermore, patients had to be admitted to the hospital or have a history of hospitalisation or urgent emergency department visit related to HF in the last year. Key exclusion criteria were acute coronary syndromes, uncorrected valvular heart disease, hypertrophic or infiltrative cardiomyopathy, active myocarditis, constrictive pericarditis, symptomatic bradycardia without a pacemaker, usage of inotropes <7 days prior to randomisation, IV diuretics or vasodilators <12h prior to randomisation and chronic antiarrhythmic therapy (not counting digoxin, amiodarone, beta blockers and calcium channel blockers). Overall, the key inclusion and exclusion criteria may lead to an enriched population with a higher risk of HF-related hospitalisations, especially the inclusion criteria of recent hospitalisation or urgent ED visit. A study by Mefford et al. 2022 compared GALACTIC-HF eligible and ineligible HfrEF patients. Although that study has multiple limitations (including lack of appropriateness of dosing, titration, or adherence to guideline directed drug therapy, lack of data on comorbidities, residual confounding), the study appeared to indicate that a large proportion of the HfrEF population met the inclusion criteria of GALACTIC-HF, and that the GALACTIC-HF RCT population is representative of a real-world HfrEF (with EF ≤35%) population and that despite being on guideline-directed medical therapy, had hospitalisation rates similar to those not taking guideline-directed medical therapy. It should however be noted that using up to a year old echocardiographic readouts is considered a long a timeframe, which is a limitation given the fact that within a year echocardiographic parameters can substantially change.

The investigational products used in this study were omecamtiv mecarbil, administered in doses of 25, 37.5, and 50 mg BID, and matching placebo. Patients were randomised 1:1 to either omecamtiv mecarbil or placebo. Patients starting with omecamtiv mecarbil started on a dose of 25 mg BID. At week 2 and 6 predose OM levels were determined to guide dose titration at week 4 and 8, respectively. The applicant sought to maintain pharmacodynamically active omecamtiv mecarbil predose plasma concentrations (e.g., >300 ng/mL), but with the understanding that excessive omecamtiv mecarbil plasma concentrations (e.g., >1,200 ng/mL) lead to exaggerated pharmacology potentially resulting in cardiac ischaemia presumably due to reduced coronary perfusion during diastole. Subjects randomised to placebo will receive placebo throughout the study but will undergo identical PK and resupply procedures. Using a rule of thumb of 5 time the half-life (<24h for OM) to reach steady state, the period of two weeks will be sufficient to have reached steady state. This PK-guided titration previously demonstrated that it led to higher omecamtiv mecarbil exposure while limiting excessive omecamtiv mecarbil plasma concentrations. This dosing strategy is considered reasonable and acceptable.

The primary outcome of the GALACTIC-HF study was the composite of time to CV death or first HF event (defined as HF hospitalisation or urgent HF clinic/office/ED visit), whichever occurred first. Secondary outcomes included the time to CV death, time to HF hospitalisation, time to all-cause death and the change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) from baseline to week 24. One of the main therapeutic goals in the treatment of CHF is to reduce mortality. Thus, mortality is to be considered as the primary endpoint, either alone or as a component of a composite endpoint in combination with endpoint(s) related to the worsening of heart failure. Even though cardiovascular death is an adequate clinical outcome to reflect the disease process targeted by treatments for heart failure, all-cause mortality may be the preferred choice in many cases. The use of all-cause mortality as an endpoint (or as a component of a composite endpoint) simplifies statistical analysis since all deaths are treated as events rather than non-cardiovascular deaths needing to be handled through a statistical model with associated assumptions and risks of bias. On the other hand, in recent trials in HfrEF, the proportion of deaths from CV causes has decreased (possibly due to increasing standard of care), and there has been a corresponding increase in the proportion of non-CV deaths. A consensus report by the European Society of Cardiology (Zannad et al. 2013) states that cardiovascular death is preferred as the mortality-outcome. However, the consensus report does mention that additional analyses should be performed for situations where cardiovascular mortality is reduced, but total mortality is not to determine if non-cardiovascular mortality is increased. The use of CV mortality is in the primary endpoint is considered acceptable, given the fact that all-cause mortality is included as a secondary analyses. For a positive benefit-risk an adverse effect on all-cause mortality has to be reasonably ruled out, and a trend to benefit in all-cause mortality should be observed. With regards to HF events, the applicant used the definition defined by the “2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials” (Hicks et al. 2015), which includes hospitalisation, urgent ER/ED Visit and urgent office/practice visit. The CHMP recommended excluding such events from the primary endpoint definition. This advice has not been incorporated by the applicant. Instead, the applicant has argued that care for worsening HF will increasingly be provided in the outpatient setting (Zannad et al. 2013) and that data from the MADIT-CRT and PARADIGM-HF studies (Skali et al. 2014 & Okumura et al. 2016) demonstrated that CV mortality risk following outpatient HF events is similar to following inpatient HF events. Furthermore, the applicant refers to the DAPA-HF study, which also used this endpoint and was granted marketing authorisation in the EU for symptomatic HfrEF. Provided that a consistent magnitude of effect should be demonstrated for HF hospitalisation events and the ED/urgent care events, and provided that the ED/urgent care events do not drive the success of the overall trial, this endpoint can be considered acceptable. With regards to the secondary endpoints (components of the composite), the endpoint time to the first HF hospitalisation was not supported by the Scientific Advice Working Party (SAWP) (EMEA/H/SA/3243/1/2016/III). The informative censoring of patients who die before hospitalisation

creates the potential for this analysis to be misleading. The information about time to first hospitalisation is considered to be already adequately captured by the primary composite (if CV death is thought of as being a severe HF hospitalisation). The other secondary outcomes, time to CV death and time all-cause mortality, are acceptable. Furthermore, the chosen PRO, the KCCQ, is a well-defined PRO instrument for measuring the experience of HF patients. It has been validated in patients with HF since its initial development in the mid-1990s. The chosen exploratory outcomes are reasonable and acceptable. In alignment with the SA of the GALACTIC-HF trial, time to recurrent hospitalisations has also been included as an exploratory outcome. Recurrent hospitalisations are distressing for patients and a marker of disease progression with adverse prognostic implications. Even more, the conventional analysis of composite endpoints treats all contributory outcomes as of equal importance and only incorporates the first outcome.

The sample size calculation is based on the CV mortality component of the primary composite endpoint. The overall sample size calculation, planned interim analyses for futility and/or superiority and accompanying stopping rules are reasonable and acceptable. Randomisation and blinding strategies are also reasonable and acceptable.

Post-hoc, the applicant provided an estimand description that the study targeted. The estimand descriptions are considered acceptable.

Two interim analyses were performed for futility and one for efficacy. The efficacy interim used an alpha of 0.001 according to the Haybittle-Peto approach, which is acceptable. Multiplicity for the primary and key secondary endpoints was handled by a mixture of alpha-splitting and sequential testing, according to Bretz et al. This is an acceptable method to protect the overall type I error rate. The analysis of the primary endpoint uses Cox regression, which is considered standard and acceptable. The model contains the randomisation strata and baseline eGFR. Baseline eGFR is an additional covariate, while usually the most simple model, containing only randomisation strata, is expected. As it was accompanied by a sensitivity analysis without eGFR showing it did not influence the point estimate, this can be acceptable. Of note, baseline ejection fraction, according to which a more successful subgroup was chosen, was apparently not to have a large enough influence to be included in the primary analysis model. The primary analysis was accompanied by sensitivity analyses testing the influence of eGFR as a covariate and of the analysis cut-off date, and a tipping point analysis was conducted. These will allow for assessing the robustness of the primary model, and the sensitivity analyses are acceptable. Secondary time-to-event endpoints were analysed using the same model, which is considered acceptable. However, censoring subjects at the time of death attributable to noncardiovascular causes may be problematic. First, it may violate the assumption of noninformative censoring: it may be unreasonable to assume that subjects who died of noncardiovascular causes (and were thus treated as censored) can be represented by those subjects who remained alive and had not yet died of any cause. Second, even when the competing events are independent, censoring subjects at the time of a competing event may lead to incorrect conclusions because the event probability being estimated is interpreted as occurring in a setting where the censoring (eg, the competing events) does not occur. The cardiovascular example described above corresponds to a setting where death from noncardiovascular causes is not possible. However, post-hoc competing risk analyses were provided for both the primary endpoint and for secondary endpoints of time to CV death or first HF hospitalisation and non-CV death and competing events had a negligible influence on the outcomes. Change from baseline in KCCQ TSS was analysed using a mixed model, which is considered adequate for this type of endpoint. Time to recurrent HF events or hospitalisations was analyzed using a joint frailty model (Liu 2004), a negative binomial regression and mean cumulative rate function estimates (Ghosh and Lin 2000). As these methods cover different assumptions, these should allow for assessing the effect on recurrent events.

Efficacy data and additional analyses

The study ran from 22 December 2016 (the first subject enrolled) to 27 august 2020 (the last subject follow-up assessment). A total of 11121 subjects were screened for the study, of whom 8256 subjects were enrolled and randomised to double-blind treatment. Twenty-four subjects were excluded due to major GCP violations at one site in Hungary. At study entry, 2101 (25.5%) subjects were hospitalised for HF and 6131 (74.5%) were recently and not hospitalised for HF. A total of 8232 subjects were included in the full analysis set.

Overall, 8211 (99.7%) subjects received at least 1 dose of the investigational product, 4933 (59.9%) completed the investigational product, 21 (0.3%) never received the investigational product, and 3299 (40.1%) discontinued the investigational product. The most common reasons for discontinuation from the investigational product were death (1537 [18.7%]), subject request (980 [11.9%]), and adverse event (753 [9.1%]). The proportions of subjects discontinued for these reasons were similar in the OM and placebo treatment groups (41 vs 40%). A total of 6036 (73.3%) subjects completed the study, 2105 (25.6%) died, and 91 (1.1%) discontinued the study due to reasons other than death. Of those who discontinued, 45 subjects withdrew consent (final vital status known for 30 subjects and unknown for 15 subjects), and 46 subjects were lost to follow-up. Two patients (<0.1%) with an OM concentration >1000 ng/mL after the titration phase were discontinued investigational product because of an OM plasma concentration >1000 ng/mL after week 8.

Disposition of subjects following PK-guided dosing targeting OM predose concentrations of 300-700 ng/ml demonstrated that at week 12, roughly 47.6% were at the dose of 50mg BID, while 42.5% were at lower doses.

The study population consisted primarily of males (79%) with a mean age of 65 years and a BMI of 28.5 kg/m2. Patients from Western Europe were well represented in the study (roughly 20% of the participants). Median [IQR] NT-proBNP, troponin and eGFR were 1998.0 (993.0, 4079.0) pg/mL, 0.0270 (0.0140, 0.0510) ng/mL, and 58.76 (44.10, 74.09) mL/min/1.73m2, respectively. A total of 62% of subjects had a history of coronary artery disease, and 27% had atrial fibrillation or flutter present at screening. The primary cause of HF for slightly more than half of the subjects overall was ischaemic heart disease (53.6%), and most subjects were NYHA Class II (53.1%) or Class III (43.9%). The median (IQR) LVEF was 28.0% (22.0%, 32.0%). The most frequently used medications of interest at baseline were beta-blockers (94%), diuretics other than MRAs (90%), ACEi, ARB, or ARNi (87%), and MRAs (78%). The majority of subjects were receiving antihypertensives (99%), antithrombotics (84%), and lipid-lowering drugs (63%). Of note, only 2.5% of the patients were taking asodium–glucose cotransporter 2 (SGLT2) inhibitor, which had not been widely used in HfrEF when participants were enrolled. Overall, the demographics, vital signs, laboratory parameters, medical history, HF history and medication usage are well balanced between the omecamtiv mecarbil and placebo groups.

The study was able to demonstrate the superiority of OM over placebo with regards to the primary composite endpoint of time to CV death or first HF event with a hazard ratio (95% CI) of 0.92 (0.86, 0.99)(P=0.025). However, the beneficial effect is considered modest and the individual components did not reach significance in the FAS. Overall, 37.0% of subjects in the OM group had a positively adjudicated primary composite endpoint event, compared with 39.1% in the placebo group, with CV death as the first event for 8.4% of subjects in the OM group and 9.0% in the placebo group, and an HF event as the first event for 28.6% of subjects in the OM group and 30.1% in the placebo group. The HF events were largely driven by HF hospitalisations (94% and 92% in OM and placebo groups, respectively). For non-hospitalisation HF events, these events contributed for approximately 30% for the event difference between treatment arms, despite that the overall rate was relatively small in both treatment arms.

Subgroup analyses of the primary endpoint demonstrated significant effect modification according to LVEF at baseline (p=0.0034) and the presence of atrial fibrillation/flutter at screening (p=0.0120). In patients with a LVEF below median (28%) at baseline, the hazard ratio was 0.84 (0.77, 0.92), as compared to a hazard ratio of 1.04 (0.94, 1.16) in subjects with LVEF at baseline above the median. In patients without atrial fibrillation/flutter at baseline, the hazard ratio was 0.86 (0.79, 0.94), as compared to a hazard ratio of 1.05 (0.93, 1.18) in subjects with atrial fibrillation/flutter at baseline (see below for further discussion).

None of the secondary analyses reached statistical significance after adjusting for multiple testing and appear not to be supportive for the primary endpoint. For the time to CV death, the hazard ratio of OM over placebo was 1.01 (0.92, 1.11), with 1.07 (0.96, 1.21) for outpatient subjects and 0.87 (0.73, 1.05) for inpatient subjects. Overall, these analyses could suggest that the primary endpoint was largely driven by the effect of HF events, as there was neutral effect on CV death with OM treatment, with apparently increased risk in outpatient subjects. The least squares (LS) mean (SE) changes from baseline to week 24 in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) (higher score represents better functioning) in the OM and placebo groups, respectively, were 23.65 (0.70) and 21.15 (0.71) among inpatient subjects and 5.83 (0.34) and 6.29 (0.34) among outpatient subjects. A nominally statistically significant (p=0.0278) jointly tested difference was observed at week 24 with OM compared with placebo, driven by inpatient subjects, but the hypothesis test was not statistically significant, adjusting for multiplicity (alpha level: 0.002). The effect on KCCQ TSS thus is only very modest and cannot be regarded as supportive for a treatment effect, although infrequent evaluation and only a timeframe of 24 weeks could have limited sensitivity.

Considering that the hierarchical testing already stopped at the first secondary endpoint of CV death, only numerical evaluation was possible for the other endpoints. For the time to first HF hospitalisation, the HR (95% CI) was 0.95 (0.87, 1.03), comparing omecamtiv mecarbil to placebo (p=0.1902). Only a neutral effect appears for overall death. A positively adjudicated all-cause death was reported for 1,067 (25.9% participants in the omecamtiv mecarbil group and 1,065 (25.9%) in the placebo group (HR (95% CI): 1.00 (0.92, 1.09)). Exploratory analyses demonstrated that omecamtiv mecarbil significantly reduced NT-proBNP compared to the placebo.

Efficacy in the LVEF<30% subgroup

The applicant further investigated the relationship between LVEF as a continuous variable and the treatment effect on the the primary endpoint. With decreasing baseline LVEF, the incidence of the primary composite increased in the omecamtiv mecarbil group and the placebo group; however, the incidence rate increased to a lesser extent in the omecamtiv mecarbil group, resulting in increasingly greater absolute risk reductions. A possible explanation is that patients with worse left ventricular function might be expected to benefit more from omecamtiv mecarbil because of its effect on increasing cardiac contractility and stroke volume. However, such an assumptions seems somewhat to fail, as for LVEF >30% (to LVEF 35%), there is a suggestion for harm (HR 1.04 ((0.94-1.16)). Moreover, it is not entirely understood that improving contractility would more improve benefit with very low LVEF and not with somewhat higher LEVF in which HF effects/symptoms can also occur (MO). Based on the results of the prespecified LVEF subgroup analyses and the supportive analysis that greater treatment benefit is a function of lower baseline ejection fraction, the sponsor is proposing an indication in adult patients with symptomatic chronic heart failure and reduced ejection fraction <30%, which is aligned with the upper limit for 'severely abnormal ejection fraction' as defined in Lang et al. 2015. Overall, the LVEF <30% cohort (n=4704; 57%), with the addition of 248 participants, closely approximates the pre-specified subgroup of LVEF ≤28% (n=4456; 54%) but is a more clinically practical and recognizable threshold. Therefore, the applicant proposed to limit the indication to subjects with LVEF <30%. However, to consider this subgroup as credible, a variety of criteria have to

be met, as detailed in the guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013) Scenario 2, of which biological plausibility and the ability to find replication are key elements to evaluate the credibility of a subgroup finding. As first criterium, external evidence should exist that the subgroup of interest is a well-defined and clinically relevant entity. Usually it would be expected that the respective subgroup has been considered when planning the trial (e.g., stratified randomisation or that it has been mentioned amongst the key subgroups) with an argument provided as to why it is a clinically relevant entity. However, the strong interaction with LVEF was most likely not anticipated by the applicant, as there is no mentioning of this in the protocol of GALACTIC-HF. Although LVEF is mentioned in the subgroup analyses of the protocol, the total list of subgroups includes more than 20 covariates. Furthermore, there was no stratification according to LVEF in the GALACTIC-HF trial, although it is agreed that any stratification is not essentially needed, considering the large sample size. This does not exclude that the proposed subgroup selection is data-driven. Nevertheless, the absence of pre-specification cannot be taken as a direct argument that results in particular lack of credibility, according to the EMA subgroup guideline. However, the biological plausibility may be questioned based on the provided explanation of the mechanistic point of view in relation to the observed efficacy results (see discussion above). Further, the fourth criterium is the following: “Replication of subgroup findings from other relevant trials (internal to the MAA or external trials that are relevant). A particular challenge exists in applications based on a single pivotal study since replication is a key component of credibility. In this instance the biological plausibility and the clinical trial data from the subgroup would have to be exceptionally strong.” The company has only presented and discussed replication of findings based on PD effects (NT-proBNP) between the COSMIC-HF study and GALACTIC-HF study. Despite that the company has discussed current understanding of the prognostic and predictive value of NT-proBNP, this PD marker is not formally considered to be a surrogate for clinical treatment effects in HF. Overall, such a replication can be considered questionable and of too limited value. Any replication based on clinical outcome data is not available. For other HF therapies including ARB, ARNi, MRA and digitalis a comparable relationship between LVEF and treatment HR exists, although the level at which the HR reaches unity is much higher than with OM (based on current study) of at least LVEF 65%, as based on an editorial in the EHJ 2022 of Kondo et al. Of further notice is that the mechanism of action of these products is substantially different form current product (except digoxin). Overall, this cannot be considered to be exceptionally compelling, especially in the context of a single clinical trial. Therefore, the credibility of the subgroup is still insufficient (MO).

As the company is proposing the LVEF <30%, this cohort is further discussed in detail. The LVEF <30% cohort included 4,704 (57.1%) participants from the total study population (FAS). There were no meaningful differences in the overall frequency of IP discontinuation between omecamtiv mecarbil and placebo (40.2% vs 43.5%), nor in the most common reasons for IP discontinuation (death, 19.1% vs 20.2%; participant request, 11.3% vs 12.3%; adverse event, 9.4% vs 10.7%). Compared to the overall population, participants with LVEF <30% had higher NT-proBNP, lower SBP, higher cardiac troponin I, and higher use of implantable cardioverter defibrillator, which all reflect that this is a population at higher risk of adverse outcomes.

Efficacy analyses indicated that participants in the LVEF <30% subgroup experienced greater treatment benefit than those in the overall study population. Within the LVEF <30% subgroup, a total of 889 (38.0%) participants in the omecamtiv mecarbil group and 1,014 (42.9%) in the placebo group had a primary outcome (HR (95% CI): 0.85 (0.77, 0.93) as compared to an HR (95%CI): 0.92 (0.86, 0.99) in the overall population). Subgroup analyses of the primary composite endpoint in the LVEF <30% group demonstrated treatment effects for the prespecified subgroups that were generally consistent with those observed in the overall LVEF <30% group. All point estimates for the primary endpoint were less than unity favouring omecamtiv mecarbil compared with placebo.

Contrary to the full population, a modest reduction in risk for CV death has been observed in the omecamtiv mecarbil group compared with placebo (n=476 (20.3%) vs. n=522 (22.1%), respectively HR (95% CI): 0.92 (0.81, 1.04) as compared with HR (95%CI): 1.01 (0.92, 1.11) in the overall population). Overall, these data further support the notion that OM is more efficacious in patients with a more impaired heart function, as (CV) mortality was found to be neutral in the full analysis set. Similarly, as observed with CV mortality, a modest reduction in risk for all-cause mortality has been observed in the OM group compared with placebo (n=633 (27.0%) vs. n= 679 (28.7%), respectively; HR (95% CI): 0.94 (0.84, 1.05) as compared with HR (95%CI): 1.00 (0.92, 1.09) in the overall population).

Overall, 664 (28.4%) participants in the omecamtiv mecarbil group and 754 (31.9%) in the placebo group had an outcome of HF hospitalisation. The HR (95% CI) was 0.86 (0.77, 0.95) comparing omecamtiv mecarbil to placebo in participants with LVEF <30% and 0.95 (0.87, 1.03) in the overall population, indicating that participants with LVEF <30% and treated with omecamtiv mecarbil had a nominally statistically significant risk reduction in time to first HF hospitalisation.

OM treatment resulted in modest changes in KCCQ TSS from baseline to Week 24 compared to placebo in both randomisation setting subgroups ((24.6 (29.0) and 21.6 (31.1) among inpatient participants and 6.6 (21.7) and 5.6 (21.5) among outpatient participants, respectively). Similar to the FAS, a somewhat larger difference was found for inpatient patients than outpatient patients.

Efficacy in patients with atrial fibrillation/flutter at baseline

In the prespecified subgroup analyses in 20110203 in the overall population, atrial fibrillation/flutter at baseline was observed to have one of the strongest univariate treatment covariate interactions for the primary composite endpoint (p=0.012). Notably, in participants with atrial fibrillation/flutter at baseline, an apparently increased risk was observed with OM for the primary endpoint (HR (95%CI):1.05 (0.93;1.18); P=0.47) and the secondary endpoint of CV death (HR (95% CI): 1.26 (1.07; 1.49); P=0.007).

From the protocol, it is unclear how atrial fibrillation/flutter was diagnosed, presumably using an ECG at screening and not using a holter. To further investigate the relationship between atrial fibrillation and increased risk of HF outcomes in the OM group, analyses of the primary and secondary outcomes based on a history of atrial fibrillation (persistent vs paroxysmal), have also been presented, not showing any increase risk for this small subgroup. Similar analyses and findings have been shown for patients who developed atrial fibrillation during the study versus those who did not.

Alhough drawing conclusions on further subgroup differentiation analyses should be taken with caution, these analyses indicated that risk was mostly concentrated in a small subgroup of participants receiving digoxin at baseline. In the FAS (and to a lesser extent in the LVEF <30% subgroup), patients receiving digoxin and having atrial fibrillation/flutter at baseline had a higher risk of the primary endpoint (HR (95% CI): 1.34 (1.07; 1.69)) and CV death (HR (95% CI): 1.64 (1.21; 2.23)) not seen for those without digoxin. A PK interaction between omecamtiv mecarbil and digoxin or any other plausible mechanism could not explain the potential risk associated with atrial fibrillation/flutter and digoxin use. In the FAS, digoxin usage was 11.6% (693/5987) in the group without atrial flutter/fibrillation at baseline and 30.8% (692/2245) in the group with atrial flutter/fibrillation at baseline. In the FAS, participants without baseline AF/F had decreased risk for the primary composite endpoint (HR (95% CI): 0.86 (0.79; 0.94)) and a trend toward a decrease in CV death (HR (95% CI): 0.90 (0.80; 1.02)) with omecamtiv mecarbil regardless of digoxin co-administration. It could also be speculated that the combination of two positive inotropes, i.e. digoxin and OM, could be detrimental to the heart and lead to an increased risk of HF outcomes. Based on these data, a warning is included in

the proposed SmPC, which is acceptable, but does not entirely exclude any other possible reasons for the observed treatment effect according to AF status at baseline.

Concentration response

Concentration-response analyses for the primary and secondary efficacy endpoints based on the last observed OM concentrations up to Week 12 has been provided. Such post-hoc analyses may provide some trend suggestions, but caution should be exercised in drawing firm conclusions on such data. Nevertheless, in the overall population, the lowest quintile (OM ≤144 ng/ml) showed no benefit (HR: 1.15 (95% CI: 1.02, 1.30); p= 0.02), which according to the applicant can be explained by the fact that a large proportion of participants in this quintile had an event early in the study, did not undergo dose appropriate titration on or prior to Week 12, and probably represent a sicker subset of those randomised to OM, which is acknowledged. Subjects in the quantiles >144 to ≤225 ng/ml, >225 to ≤300 ng/ml and, >300 to ≤377 ng/ml appear to have benefit from OM when compared with placebo with HR of 0.85 (0.75, 0.97), 0.83 (0.73, 0.95), 0.77 (0.68, 0.87), respectively, and an apparently slightly less obvious benefit in the >377 ng/ml quiintile (HR 0.91 (95% CI: 0.80, 1.02)). However, this issue will not be pursued given the subgroup limitations to such analyses.

The applicant also provided concentration-response analyses based on the highest concentration during the study, since according to the applicant this allows more specific investigation of the small subset of subjects who had concentrations of OM above the upper limit of the target concentration range. It is agreed that this analyses can be informative, but considering that in the GALACTIC-HF study at week 8 dose down-titration occurred when the OM concentrations were ≥750 - <1000 ng/ml, the results, particularly in the >750 ng/ml quintile, are difficult to interpret.

3.3.6. Conclusions on clinical efficacy

The GALACTIC-HF demonstrated superiority of OM over placebo regarding the primary endpoint of time to first HF event or CV mortality, although the risk reduction was modest, and not supported by the secondary endpoint (with hierarchical testing failure).

Based on the modest beneficial effect on the primary composite endpoint observed in the full population of patients with LVEF<35%, the applicant proposes to narrow the indication to patients with a LVEF <30%, as efficacy analyses in this subgroup demonstrate a larger risk reduction for the primary endpoint. However, to identify this population for treatment, seems not credibly as several criteria as specified in the guideline on subgroups Scenario 2 cannot be met.

Further subgroup analyses in terms of atrial/fibrillation/flutter at baseline showed a trend toward an increased risk of the primary endpoint in the OM group for patients with atrial fibrillation/flutter at baseline, which appeared to be mostly concentrated in those patients also receiving digoxin, which is accordingly addressed in the SmPC.

3.3.7. Clinical safety

The safety profile of omecamtiv mecarbil in support of the proposed indication is primarily based on the pivotal Phase 3 cardiovascular (CV) outcomes study, 20110203 (GALACTIC-HF; N=8211) in patients with HFrEF receiving optimised HF standard of care therapies. Where applicable, supportive safety data are presented from the moderate duration Phase 2b studies (20110151 Expansion Phase (COSMIC-HF; N=445) and 20120227 (N=81)), the Phase 2 Study 20100754 (ATOMIC-AHF) conducted in participants with acute HF receiving an IV dose regimen of OM (N=606), the short duration Phase 2a studies (N=311), Phase 1 studies (N=953), and Study CY 1031 (METEORIC-HF; N=276)).

Consequently, the (integrated) safety analysis sets are as followed:

- CV Outcome Study of Chronic HF (GALACTIC-HF): This is the pivotal Phase 3 Study 20110203 (N=8256). Safety data from this study are presented independently and also integrated with safety data from the "Moderate Duration Studies of Chronic Heart Failure" as noted below.
- Moderate Duration Studies of Chronic HF: Two Phase 2b Studies, 20120227 (N=81) and 20110151 Expansion Phase (N=448), in participants with chronic HFrEF were integrated based on the treatment duration (16 and 20 weeks, respectively). In most safety analyses, this group is also combined with the CV outcome study. Key safety topics of interest from 20110151 Escalation Phase, also in participants with chronic HFrEF, are also discussed.
- Study 20100754 (ATOMIC-AHF): This was a Phase 2b study, that assessed the safety and efficacy of IV omecamtiv mecarbil in participants with acute HF. Data from this study were not integrated and are presented independently as the study was of shorter duration (4 weeks) with only 48 hours of treatment and used a different formulation (IV) from the other studies conducted in participants with HF. The study is included in the ISS and described in this SCS because it provides important safety data in this acutely decompensated population.
- Phase 2a Short Duration Studies: This group consists of short-term (≤10 days) studies conducted in participants with HF and includes Studies CY 1021, CY 1121, CY 1124, CY 1221, and 20110151 Dose Escalation Phase.
- Phase 1 Studies: This group includes the following studies conducted in healthy participants or specific populations: CY 1111, CY 1011, CY 1013, CY 1015, CY 1016, 20090229, 20090727, 20080676, CY 1211 (20120255), 20150134, 20160159, 20090231, 20120259, 20130253, 20130254, 20140209, 20160160, 20180328, 20180339, 20180340, 20180341, 20180342, 20180432, 20180435.
- Study CY 1031 (METEORIC-HF): A second Phase 3 study in participants with HFrEF (N=276) and decreased exercise capacity, CY 1031 (METEORIC-HF), which was not designed to support the proposed indication in this marketing application, provides additional safety data that are presented separately since it was completed after the integrated summary of safety was produced. In study CY 1031 Omecamtiv mecarbil utilised an identical dosing scheme to 20110203.

3.3.7.1. Patient exposure

In the studies, 5,637 participants were exposed to any dose of omecamtiv mecarbil, with a median IP exposure of 14.49 months (Table 34). In the pivotal Phase 3 CV outcomes study (20110203; GALACTIC-HF), 4,110 participants were exposed to omecamtiv mecarbil (median IP exposure 19.6

months; maximum 41.2 months) (Table 35). In the 2,335 participants enrolled in the CV outcome study 20110203 with LVEF <30% and treated with omecamtiv mecarbil (the intended population for the proposed indication), exposure was similar to the overall population.

Table 34. Exposure to IP in Studies of Omecamtiv Mecarbil Included in the ISS (Safety Analysis Set)

	Placebo/Non-OM Study Product (N=4,890)	Any OM (N=5,637)
IP Exposure (months)		
Mean (SD)	16.01 (11.41)	14.28 (11.88)
Median (Min, Max)	16.59 (0.03, 42.05)	14.49 (0.03, 41.20)
Q1, Q3	4.60, 25.36	1.51, 24.38
Study Duration (months)		
Mean (SD)	18.30 (11.05)	16.27 (11.76)
Median (Min, Max)	19.40 (0.03, 42.05)	17.02 (0.07, 41.89)
Q1, Q3	9.00, 27.17	4.60, 25.86
Treatment-emergent Time (months)		
Mean (SD)	16.83 (11.51)	15.13 (11.93)
Median (Min, Max)	17.46 (0.03, 43.04)	15.31 (0.07, 42.19)
Q1, Q3	5.52, 26.28	2.37, 25.30

IP=investigational product; Max=maximum; Min=minimum; N=number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; OM=omecamtiv mecarbil; Q1=first quartile; Q3=third quartile; SD=standard deviation.
For studies with participants dosed in multiple periods, the IP exposure, study duration and treatment emergent time were computed by period and summed.
Exposure when OM is given concurrently to a non-OM study product contributes to the OM group only.
Participants with multiple dosing periods can be counted in both treatment groups.
All ISS studies: 20080676, 20090229, 20090231, 20090727, 20100754, 20110151 Escalation, 20110151 Expansion, 20110203, 20120227, 20120259, 20130253, 20130254, 20140209, 20150134, 20160159, 20160160, 20180339, 20180340, 20180341, 20180342, 20180432, 20180435, CY 1011, CY 1013, CY 1015, CY 1016, CY 1021, CY 1111, CY 1121, CY 1124, CY 1211, CY 1221. Note that Study CY 1031 is not included in the ISS.

Table 35. Summary of Exposure to Study and Investigational Product – Study 20110203

	Recently and Not Currently Hospitalised for Heart Failure		Currently Hospitalised for Heart Failure		Overall		
	Placebo (N = 3072)	AMG 423 (N = 3076)	Placebo (N = 1040)	AMG 423 (N = 1044)	Placebo (N = 4112)	AMG 423 (N = 4120)	Total (N = 8232)
Total study duration (months)							
n	3072	3076	1040	1044	4112	4120	8232
Mean	22.2	22.1	19.2	19.8	21.5	21.6	21.5
SD	9.0	9.3	8.8	8.8	9.1	9.2	9.1
Median	22.1	22.1	20.0	20.7	21.7	21.9	21.8
Q1, Q3	16.1, 29.5	15.7, 29.6	13.7, 26.0	14.3, 26.2	15.4, 28.6	15.3, 28.7	15.4, 28.6
Min, Max	0, 42	0, 42	0, 41	0, 41	0, 42	0, 42	0, 42
Total investigational product administration duration (months)							
n	3067	3070	1034	1040	4101	4110	8211
Mean	19.6	19.7	16.9	17.7	18.9	19.2	19.0

	Recently and Not Currently Hospitalised for Heart Failure		Currently Hospitalised for Heart Failure		Overall		
	Placebo (N = 3072)	AMG 423 (N = 3076)	Placebo (N = 1040)	AMG 423 (N = 1044)	Placebo (N = 4112)	AMG 423 (N = 4120)	Total (N = 8232)
SD	10.2	10.2	9.9	9.9	10.2	10.2	10.2
Median	19.9	20.0	17.8	18.5	19.4	19.6	19.5
Q1, Q3	13.4, 27.7	13.2, 28.0	8.6, 25.3	9.6, 25.6	12.0, 26.8	12.3, 27.1	12.1, 27.0
Min, Max	0, 42	0, 41	0, 39	0, 40	0, 42	0, 41	0, 42

Dose Titration

The titration algorithm used in the CV outcome study 20110203 successfully avoided excessive concentrations in all but 3 participants (0.07%): 1 participant prior to Week 12 and 2 additional participants following Week 12 had an observed plasma concentration >1,000 ng/mL; none had plasma concentrations >1,200 ng/mL. Importantly, no participants experienced AEs, including myocardial ischaemia or infarction, associated with omecamtiv mecarbil plasma concentration >1,000 ng/mL. To evaluate the necessity of a PK-guided dosing strategy and to possibly simplify the dosing scheme for real-world use, a strategy of scheduled ("forced") titration to the maximum dose of 50 mg BID was examined. Simulations were conducted in 4,500 virtual participants using a population PK model to estimate the number, and percentage of virtual patients predicted to achieve Cmin or Cmax concentrations in the therapeutic range (200 to <750 ng/mL) as well as those with concentrations >1,000 and >1,200 ng/mL in the setting of scheduled dose-titration. In these simulations, the virtual patients received 25 mg BID of omecamtiv mecarbil as their starting dose for the first 2 weeks of treatment. The dose of omecamtiv mecarbil was increased to 37.5 mg BID at Week 2 and to 50 mg BID at Week 4. This scheduled dosing algorithm is the same as that described in Section 4.2 Posology of the proposed SmPC. The Cmin and Cmax concentrations were evaluated for each participant at the end of Weeks 2, 4, and 6.

No participants were predicted to achieve maximum plasma concentrations (Cmax) of >1,200 ng/mL at the 25 mg BID dose (Table 36). At the 37.5 mg BID dose, approximately 0.2% of participants were predicted to reach >1,200 ng/mL, including participants with baseline LVEF <30%. At the 50 mg BID dose, 1.4% of all participants and 1.8% of participants with baseline LVEF <30% were predicted to achieve Cmax >1,200 ng/mL. Comparing the simulation scheduled titration data (Cmin) to the observed PK-guided dose titration data (Ctrough) in 20110203, a substantially higher proportion of participants achieved the therapeutic concentration range of 200 to <750 ng/mL with scheduled titration (84%) compared with PK-guided titration (65%) (Figure 26Error! Reference source not found.).

Table 36. Estimated Percentage of Patients Achieving Concentration Ranges of Omecamtiv Mecarbil in a Simulation of Scheduled Dose Titration (Study CYKI-CP-3529 [Modeling and Simulation Report])

Population	Estimated Number (%) of Patients							
	<200 (ng/mL)	200 to <300 (ng/mL)	200 to <750 (ng/mL)	300 to <750 (ng/mL)	750 to 1,000 (ng/mL)	>1,000 to 1,200 (ng/mL)	>1,000 (ng/mL)	>1,200 (ng/mL)
C_{max} (ng/mL)								
25 mg BID (1-2 weeks)								
All	1,036 (23.0%)	1,869 (41.5%)	3454 (76.8%)	1,585 (35.2%)	9 (0.2%)	1 (0.02%)	1 (0.02%)	0 (0%)
<30% LVEF	1,020 (22.7%)	1,910 (42.4%)	3469 (77.1%)	1,559 (34.6%)	10 (0.2%)	1 (0.02%)	1 (0.02%)	0 (0%)
37.5 mg BID (3-4 weeks)								
All	133 (3.0%)	865 (19.2%)	4186 (93.0%)	3,321 (73.8%)	154 (3.4%)	17 (0.4%)	27 (0.6%)	10 (0.2%)
<30% LVEF	139 (3.1%)	826 (18.4%)	4155 (92.3%)	3,329 (74.0%)	178 (4.0%)	17 (0.4%)	28 (0.6%)	11 (0.2%)
50 mg BID (5-6 weeks)								
All	15 (0.3%)	260 (5.8%)	3702 (82.3%)	3,442 (76.5%)	601 (13.4%)	121 (2.7%)	182 (4.0%)	61 (1.4%)
<30% LVEF	20 (0.4%)	246 (5.5%)	3698 (82.2%)	3,452 (76.7%)	565 (12.6%)	134 (3.0%)	217 (4.8%)	83 (1.8%)
C_{min} (ng/mL)								
25 mg BID (1-2 weeks)								
All	3,066 (68.1%)	1,057 (23.5%)	1434 (31.9%)	377 (8.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<30% LVEF	3,064 (68.1%)	1,067 (23.7%)	1434 (31.9%)	367 (8.2%)	2 (0.04%)	0 (0%)	0 (0%)	0 (0%)
37.5 mg BID (3-4 weeks)								
All	1,349 (30.0%)	1,642 (36.5%)	3131 (69.6%)	1,489 (33.1%)	18 (0.4%)	2 (0.04%)	2 (0.04%)	0 (0%)
<30% LVEF	1,375 (30.6%)	1,594 (35.4%)	3096 (68.8%)	1,502 (33.4%)	28 (0.6%)	1 (0.02%)	1 (0.02%)	0 (0%)

BID=twice daily; Cmax=maximum observed drug concentration during a dosing interval; Cmin=minimum observed drug concentration during a dosing interval; LVEF=lower ventricular ejection fraction.
Note: Results are presented as the number of participants in exposure bin (percentage of participants in the dose group at visit in each exposure bin during the last dosing interval).

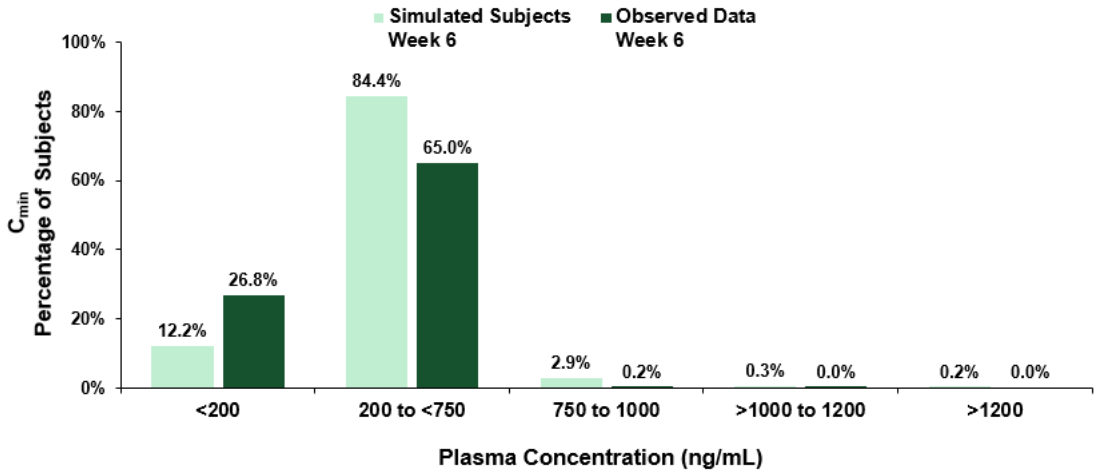


Figure 26. Comparison of Achieved Plasma Concentration Bins of Omecamtiv Mecarbil by Scheduled Titration (Simulated Subjects) vs. PK-guided Titration (Observed Data) in Study 20110203

3.3.7.2. Adverse events

General frequency of adverse events

CV outcome study of chronic HF (GALACTIC-HF)

In the CV outcome study GALACTIC-HF (study 20110203), the incidence of reported AEs (87.4% and 88.3%), SAEs (57.7% and 59.4%), AEs leading to IP discontinuation (10.5% and 10.9%), Grade ≥3 AEs (62.1% and 63.6%), and Grade ≥4 AEs (31.6% and 32.5%, respectively) were slightly lower in the omecamtiv mecarbil group compared with the placebo group (Table 37). Generally, similar results were observed in the subjects currently hospitalised for HF and Recently and subjects not currently hospitalised for heart failure.

Table 37. Summary of Subject Incidence of Treatment-emergent Adverse Events – Study 20110203 (Safety Analysis Set)

	Recently and Not Currently Hospitalized for Heart Failure		Currently Hospitalized for Heart Failure		Overall	
	Placebo (N = 3067) n (%)	AMG 423 (N = 3070) n (%)	Placebo (N = 1034) n (%)	AMG 423 (N = 1040) n (%)	Placebo (N = 4101) n (%)	AMG 423 (N = 4110) n (%)
All treatment-emergent adverse events	2720 (88.7)	2708 (88.2)	902 (87.2)	886 (85.2)	3622 (88.3)	3594 (87.4)
Grade ≥ 2	2480 (80.9)	2446 (79.7)	844 (81.6)	822 (79.0)	3324 (81.1)	3268 (79.5)
Grade ≥ 3	1905 (62.1)	1886 (61.4)	704 (68.1)	667 (64.1)	2609 (63.6)	2553 (62.1)
Grade ≥ 4	939 (30.6)	937 (30.5)	394 (38.1)	362 (34.8)	1333 (32.5)	1299 (31.6)
Serious adverse events	1756 (57.3)	1733 (56.4)	679 (65.7)	640 (61.5)	2435 (59.4)	2373 (57.7)
Leading to withdrawal of investigational product	350 (11.4)	315 (10.3)	97 (9.4)	117 (11.3)	447 (10.9)	432 (10.5)
Serious	261 (8.5)	236 (7.7)	76 (7.4)	96 (9.2)	337 (8.2)	332 (8.1)
Nonserious	90 (2.9)	88 (2.9)	22 (2.1)	22 (2.1)	112 (2.7)	110 (2.7)
Fatal adverse events	567 (18.5)	606 (19.7)	256 (24.8)	231 (22.2)	823 (20.1)	837 (20.4)

AMG 423 = omecamtiv mecarbil

Notes: N = Number of subjects randomized excluding study center 29002 and received at least 1 dose of investigational product. Percentages are based on N.

Moderate Duration Studies of Chronic HF

The incidence, nature, and severity of all AEs, SAEs, and AEs leading to discontinuation of IP were generally similar between the omecamtiv mecarbil groups and placebo group (Table 38).

Table 38. Participant Incidence of AEs in Moderate Duration Studies of Chronic HF (Safety Analysis Set)

	Moderate Duration Studies of Chronic HF		
	Oral Placebo (N=170) n (%)	Other Oral OM (N=171) n (%)	Oral OM PK-guided titration (N=185) n (%)
all AEs	105 (61.8)	102 (59.6)	117 (63.2)
Grade ≥2	72 (42.4)	66 (38.6)	74 (40.0)
Grade ≥3	37 (21.8)	32 (18.7)	34 (18.4)
Grade ≥4	5 (2.9)	9 (5.3)	11 (5.9)
SAEs	33 (19.4)	40 (23.4)	36 (19.5)
AEs leading to discontinuation of IP	12 (7.1)	10 (5.8)	13 (7.0)
Serious	6 (3.5)	6 (3.5)	8 (4.3)
Non-Serious	6 (3.5)	4 (2.3)	5 (2.7)
Fatal AEs	4 (2.4)	2 (1.2)	3 (1.6)

AE=adverse event; CV=cardiovascular; HF=heart failure; IP=investigational product; N=Number of participants who received at least one dose of IP post randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil; PK=pharmacokinetic; SAE=serious adverse event.

Percentages are based on N.

Moderate Duration Studies of Chronic HF: 20110151 Expansion, 20120227.

Study 20100754 (ATOMIC-AHF)

The incidence, nature, and severity of all AEs and SAEs were slightly lower in the omecamtiv mecarbil group compared with the placebo group (Table 39).

Table 39. Participant Incidence of AEs in Acute HF (Study 20100754, Safety Analysis Set)

	IV Placebo (N=303) n (%)	IV OM (N=303) n (%)
all AEs	191 (63.0)	177 (58.4)
Grade ≥2	135 (44.6)	120 (39.6)
Grade ≥3	73 (24.1)	59 (19.5)
Grade ≥4	26 (8.6)	20 (6.6)
SAEs	70 (23.1)	66 (21.8)
AEs leading to discontinuation of IP	15 (5.0)	15 (5.0)
Serious	6 (2.0)	7 (2.3)
Non-Serious	9 (3.0)	8 (2.6)
Fatal AEs	11 (3.6)	9 (3.0)

AE=adverse event; IV=intravenous; IP=investigational product; N=Number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil; SAE=serious adverse event.
Percentages are based on N.

Study CY 1031 (METEORIC-HF)

The incidence and severity of all AEs, SAEs, and AEs leading to discontinuation of the study drug were slightly higher in the omecamtiv mecarbil group compared with the placebo groups (Table 40). There were no notable patterns in the events reported in the omecamtiv mecarbil and placebo groups and their reported outcomes (Table 44 and Table 49). Fatal AEs had similar incidences and were reported in 1.6% and 1.1% of participants in the omecamtiv mecarbil and placebo groups, respectively.

Table 40. Overall Summary of AEs in HFrEF with Decreased Exercise Capacity (Study CY 1031, Safety Analysis Set)

	Placebo (N=91) n (%)	Omecamtiv Mecarbil (N=185) n (%)
Participants with at least 1 AE	58 (63.7)	126 (68.1)
Participants with at least 1 SAE	13 (14.3)	30 (16.2)
Participants with at least 1 AE leading to early treatment discontinuation	4 (4.4)	12 (6.5)
Participants with at least 1 related AE	9 (9.9)	25 (13.5)
Participants with maximum NCI-CTCAE Grade ≥3	13 (14.3)	33 (17.8)
Participants with fatal AEs	1 (1.1)	3 (1.6)

AE=adverse event; HFrEF=heart failure with reduced ejection fraction; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; SAE=serious adverse event.

Common TEAEs

CV outcome study of chronic HF (GALACTIC-HF)

The system organ classes (SOCs) with the highest reported incidence of AEs (>10% of participants in either treatment group) were Cardiac disorders (51.2% omecamtiv mecarbil group, 53.1% placebo group), Infections and infestations (35.1%, 36.2%), Metabolism and nutrition disorders (20.6%, 22.5%), Respiratory, thoracic and mediastinal disorders (20.6%, 21.2%), Gastrointestinal disorders (20.0%, 20.7%), General disorders and administration site conditions (18.8%, 19.2%), Nervous system disorders (18.1%, 18.9%), Renal and urinary disorders (17.5%, 17.4%), Vascular disorders (17.1%, 17.4%), Musculoskeletal and connective tissue disorders (14.0%, 15.3%), and Investigations (11.9%, 11.6%).

The most common AEs (by ≥ 5% in the omecamtiv mecarbil group) were cardiac failure (27.5% for omecamtive mercarbil vs 29.3% for placebo), hypotension (7.5%, 6.6%), dyspnea (6.6%, 6.8%), pneumonia (6.3%, 7.1%), dizziness (5.8%, 4.6%), atrial fibrillation (5.7%, 6.4%), acute kidney injury (5.6%, 5.5%), cardiac failure acute (5.4%, 6.4%), and hyperkalaemia (5.3%, 5.6%)(Table 41). The most common events were associated with the chronic HF condition, as expected in the study population, ie, cardiac failure events or known complications of chronic HFrEF.

Table 41. Treatment-emergent Adverse Events by Preferred Term Reported for **≥3%** of Subjects in Any Treatment Group – Study 20110203 (Safety Analysis Set)

	Recently and Not Currently Hospitalised for Heart Failure		Currently Hospitalised for Heart Failure		Overall	
Preferred Term	Placebo (N = 3067) n (%)	AMG 423 (N = 3070) n (%)	Placebo (N = 1034) n (%)	AMG 423 (N = 1040) n (%)	Placebo (N = 4101) n (%)	AMG 423 (N = 4110) n (%)
Number of subjects reporting treatment-emergent adverse events	2720 (88.7)	2708 (88.2)	902 (87.2)	886 (85.2)	3622 (88.3)	3594 (87.4)
Cardiac failure	828 (27.0)	762 (24.8)	375 (36.3)	370 (35.6)	1203 (29.3)	1132 (27.5)
Hypotension	211 (6.9)	249 (8.1)	60 (5.8)	60 (5.8)	271 (6.6)	309 (7.5)
Dyspnoea	219 (7.1)	207 (6.7)	58 (5.6)	66 (6.3)	277 (6.8)	273 (6.6)
Pneumonia	215 (7.0)	187 (6.1)	77 (7.4)	72 (6.9)	292 (7.1)	259 (6.3)
Dizziness	160 (5.2)	190 (6.2)	29 (2.8)	47 (4.5)	189 (4.6)	237 (5.8)
Atrial fibrillation	203 (6.6)	181 (5.9)	60 (5.8)	55 (5.3)	263 (6.4)	236 (5.7)
Acute kidney injury	176 (5.7)	184 (6.0)	49 (4.7)	46 (4.4)	225 (5.5)	230 (5.6)
Cardiac failure acute	198 (6.5)	169 (5.5)	65 (6.3)	52 (5.0)	263 (6.4)	221 (5.4)
Hyperkalaemia	172 (5.6)	156 (5.1)	58 (5.6)	60 (5.8)	230 (5.6)	216 (5.3)
Cardiac failure chronic	155 (5.1)	142 (4.6)	55 (5.3)	62 (6.0)	210 (5.1)	204 (5.0)
Hypertension	188 (6.1)	156 (5.1)	41 (4.0)	42 (4.0)	229 (5.6)	198 (4.8)
Nasopharyngitis	155 (5.1)	151 (4.9)	39 (3.8)	35 (3.4)	194 (4.7)	186 (4.5)
Upper respiratory tract infection	131 (4.3)	155 (5.0)	41 (4.0)	29 (2.8)	172 (4.2)	184 (4.5)
Renal impairment	119 (3.9)	143 (4.7)	57 (5.5)	40 (3.8)	176 (4.3)	183 (4.5)
Diarrhoea	140 (4.6)	138 (4.5)	52 (5.0)	40 (3.8)	192 (4.7)	178 (4.3)
Ventricular tachycardia	149 (4.9)	121 (3.9)	35 (3.4)	52 (5.0)	184 (4.5)	173 (4.2)
Cardiac failure congestive	143 (4.7)	131 (4.3)	41 (4.0)	32 (3.1)	184 (4.5)	163 (4.0)
Urinary tract infection	126 (4.1)	119 (3.9)	35 (3.4)	36 (3.5)	161 (3.9)	155 (3.8)
Oedema peripheral	128 (4.2)	120 (3.9)	40 (3.9)	32 (3.1)	168 (4.1)	152 (3.7)
Anaemia	121 (3.9)	119 (3.9)	43 (4.2)	32 (3.1)	164 (4.0)	151 (3.7)
Cough	131 (4.3)	123 (4.0)	38 (3.7)	27 (2.6)	169 (4.1)	150 (3.6)
Chronic kidney disease	108 (3.5)	106 (3.5)	35 (3.4)	40 (3.8)	143 (3.5)	146 (3.6)
Bronchitis	154 (5.0)	118 (3.8)	33 (3.2)	26 (2.5)	187 (4.6)	144 (3.5)
Gout	121 (3.9)	114 (3.7)	31 (3.0)	29 (2.8)	152 (3.7)	143 (3.5)
Back pain	97 (3.2)	101 (3.3)	24 (2.3)	30 (2.9)	121 (3.0)	131 (3.2)
Weight increased	91 (3.0)	89 (2.9)	26 (2.5)	37 (3.6)	117 (2.9)	126 (3.1)
Syncope	81 (2.6)	89 (2.9)	26 (2.5)	31 (3.0)	107 (2.6)	120 (2.9)
Diabetes mellitus	107 (3.5)	100 (3.3)	26 (2.5)	18 (1.7)	133 (3.2)	118 (2.9)
Angina pectoris	70 (2.3)	93 (3.0)	17 (1.6)	25 (2.4)	87 (2.1)	118 (2.9)
Headache	105 (3.4)	86 (2.8)	29 (2.8)	27 (2.6)	134 (3.3)	113 (2.7)
Hypokalaemia	94 (3.1)	78 (2.5)	31 (3.0)	30 (2.9)	125 (3.0)	108 (2.6)
Influenza	71 (2.3)	80 (2.6)	34 (3.3)	27 (2.6)	105 (2.6)	107 (2.6)
Fatigue	91 (3.0)	95 (3.1)	19 (1.8)	7 (0.7)	110 (2.7)	102 (2.5)

AMG 423 = omecamtiv mecarbil; MedDRA = Medical Dictionary for Regulatory Activities
Notes: N = Number of subjects randomised excluding study centre 29002 and received at least 1 dose of investigational product. Percentages are based on N. Adverse events were coded using MedDRA version 23.0.

Moderate Duration Studies of Chronic HF

In the moderate-duration studies of chronic HF, incidences of AEs by PT were generally similar between the omecamtiv mecarbil PK-guided titration, other omecamtiv mecarbil, and overall placebo groups (Table 42).

Table 42. AEs by Preferred Term Reported by **≥2%** of Participants in Any Treatment Group in Moderate Duration Studies of Chronic HF (Safety Analysis Set) (adjusted by assessor)

	Moderate Duration Studies of Chronic HF		
Preferred Term	Oral Placebo (N=170) n (%)	Other Oral OM (N=171) n (%)	Oral OM PK-guided titration (N=185) n (%)
Number of participants reporting AEs	105 (61.8)	102 (59.6)	117 (63.2)
Cardiac failure	14 (8.2)	7 (4.1)	9 (4.9)
Hypotension	3 (1.8)	1 (0.6)	7 (3.8)
Dyspnoea	8 (4.7)	11 (6.4)	13 (7.0)
Pneumonia	3 (1.8)	2 (1.2)	5 (2.7)
Dizziness	7 (4.1)	9 (5.3)	12 (6.5)
Atrial fibrillation	4 (2.4)	7 (4.1)	1 (0.5)
Acute kidney injury	0 (0.0)	2 (1.2)	1 (0.5)
Cardiac failure acute	1 (0.6)	3 (1.8)	3 (1.6)
Hyperkalaemia	1 (0.6)	3 (1.8)	1 (0.5)
Nasopharyngitis	9 (5.3)	9 (5.3)	13 (7.0)
Cardiac failure chronic	4 (2.4)	1 (0.6)	1 (0.5)
Hypertension	2 (1.2)	3 (1.8)	2 (1.1)
Upper respiratory tract infection	4 (2.4)	1 (0.6)	4 (2.2)
Renal impairment	2 (1.2)	2 (1.2)	2 (1.1)
Diarrhoea	6 (3.5)	5 (2.9)	4 (2.2)
Ventricular tachycardia	2 (1.2)	3 (1.8)	4 (2.2)
Cardiac failure congestive	3 (1.8)	6 (3.5)	5 (2.7)
Cough	2 (1.2)	4 (2.3)	8 (4.3)
Oedema peripheral	2 (1.2)	2 (1.2)	4 (2.2)
Urinary tract infection	1 (0.6)	2 (1.2)	1 (0.5)
Anaemia	2 (1.2)	0 (0.0)	1 (0.5)
Chronic kidney disease	1 (0.6)	4 (2.3)	1 (0.5)
Bronchitis	5 (2.9)	3 (1.8)	3 (1.6)
Gout	7 (4.1)	3 (1.8)	2 (1.1)
Back pain	3 (1.8)	3 (1.8)	3 (1.6)

Preferred Term	Moderate Duration Studies of Chronic HF		
	Oral Placebo (N=170) n (%)	Other Oral OM (N=171) n (%)	Oral OM PK-guided titration (N=185) n (%)
Weight increased	1 (0.6)	1 (0.6)	0 (0.0)
Angina pectoris	3 (1.8)	6 (3.5)	2 (1.1)
Fatigue	4 (2.4)	15 (8.8)	9 (4.9)
Headache	5 (2.9)	2 (1.2)	10 (5.4)
Syncope	2 (1.2)	1 (0.6)	2 (1.1)
Diabetes mellitus	4 (2.4)	2 (1.2)	2 (1.1)
Renal failure	1 (0.6)	3 (1.8)	3 (1.6)
Influenza	4 (2.4)	5 (2.9)	4 (2.2)
Chronic obstructive pulmonary disease	1 (0.6)	1 (0.6)	2 (1.1)
Hypokalaemia	2 (1.2)	3 (1.8)	2 (1.1)
Chest pain	1 (0.6)	3 (1.8)	2 (1.1)
Constipation	2 (1.2)	3 (1.8)	1 (0.5)
Arthralgia	1 (0.6)	1 (0.6)	3 (1.6)
Nausea	5 (2.9)	2 (1.2)	8 (4.3)
Non-cardiac chest pain	7 (4.1)	4 (2.3)	4 (2.2)
Vomiting	3 (1.8)	1 (0.6)	4 (2.2)
Fall	0 (0.0)	1 (0.6)	0 (0.0)
Respiratory tract infection	4 (2.4)	1 (0.6)	2 (1.1)
Decreased appetite	4 (2.4)	2 (1.2)	0 (0.0)

AE=adverse event; CV=cardiovascular; HF=chronic heart failure; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants who received at least one dose of IP post randomisation for studies with randomisation or post enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil; PK=pharmacokinetic.
Percentages are based on N.
AEs were coded using MedDRA version 23.0.
Moderate Duration Studies of Chronic HF: 20110151 Expansion, 20120227; CV Outcome Study of Chronic HF: 2011020

Study 20100754 (ATOMIC-AHF)

The incidences of the AEs by PT were slightly lower in the omecamtiv mecarbil group compared with the placebo groups (58.4% vs. 63.0%) (Table 43). The most common (≥5% of participants) AEs in either treatment group were cardiac failure (13.5%, 16.5%), hypotension (7.9%, 4.6%), and hypokalaemia (6.6%, 5.9%).

Table 43. AEs by Preferred Term Reported by **≥2%** of Participants in Any Treatment Group in Acute HF (Study 20100754, Safety Analysis Set)

Preferred Term	IV Placebo (N=303) n (%)	IV OM (N=303) n (%)
Number of participants reporting AEs	191 (63.0)	177 (58.4)
Cardiac failure	50 (16.5)	41 (13.5)
Hypotension	14 (4.6)	24 (7.9)
Dizziness	8 (2.6)	2 (0.7)
Atrial fibrillation	11 (3.6)	6 (2.0)
Acute kidney injury	8 (2.6)	8 (2.6)
Renal impairment	6 (2.0)	1 (0.3)
Diarrhoea	10 (3.3)	9 (3.0)
Ventricular tachycardia	11 (3.6)	13 (4.3)
Cardiac failure congestive	4 (1.3)	7 (2.3)
Anaemia	4 (1.3)	6 (2.0)
Gout	6 (2.0)	4 (1.3)
Headache	4 (1.3)	9 (3.0)
Hypokalaemia	18 (5.9)	20 (6.6)
Chest pain	6 (2.0)	5 (1.7)
Constipation	3 (1.0)	10 (3.3)
Nausea	8 (2.6)	8 (2.6)
Vomiting	6 (2.0)	6 (2.0)
Insomnia	5 (1.7)	7 (2.3)
Muscle spasms	6 (2.0)	0 (0.0)
Hypoglycaemia	6 (2.0)	3 (1.0)
Blood creatinine increased	5 (1.7)	6 (2.0)

AE=adverse event; HF=heart failure; IP=investigational product; IV=intravenous; MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants who received at least one dose of IP post randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil.
Percentages are based on N.

Study CY 1031 (METEORIC-HF)

The incidences of the AEs by PT were slightly higher in the omecamtiv mecarbil group compared with the placebo group (68.1% vs 63.7%) (Table 44). The most frequently reported AEs by PT (≥4% of participants in either treatment group) included cardiac failure (5.9% omecamtiv mecarbil, 3.3% placebo), dizziness (4.9%, 5.5%), fatigue (4.9%, 4.4%), ventricular tachycardia (4.3%, 2.2%),

diarrhea (3.8%, 4.4%), AF (3.2%, 4.4%), dyspnea (2.7%, 8.8%), back pain (2.7%, 4.4%), gout (2.2%, 4.4%), and rash (0%, 4.4%).

Table 44. AEs by Preferred Term Reported for **≥3%** of Participants in Either Treatment Group in HFrEF with Decreased Exercise Capacity (Study CY 1031, Safety Analysis Set)

Preferred Term	Placebo (N=91) n (%)	Omecamtiv Mecarbil (N=185) n (%)
Patients with at least 1 AE	58 (63.7)	126 (68.1)
Cardiac failure	3 (3.3)	11 (5.9)
Dizziness	5 (5.5)	9 (4.9)
Fatigue	4 (4.4)	9 (4.9)
Ventricular tachycardia	2 (2.2)	8 (4.3)
Diarrhoea	4 (4.4)	7 (3.8)
Fall	1 (1.1)	7 (3.8)
Atrial fibrillation	4 (4.4)	6 (3.2)
Hypotension	1 (1.1)	6 (3.2)
Arthralgia	0	6 (3.2)
Dyspnoea	8 (8.8)	5 (2.7)
Back pain	4 (4.4)	5 (2.7)
Gout	4 (4.4)	4 (2.2)
Angina pectoris	3 (3.3)	4 (2.2)
Headache	3 (3.3)	4 (2.2)
Non-cardiac chest pain	3 (3.3)	4 (2.2)
Hypertension	3 (3.3)	3 (1.6)
Nausea	3 (3.3)	3 (1.6)
Cardiac failure acute	3 (3.3)	2 (1.1)
Urinary tract infection	3 (3.3)	1 (0.5)
Rash	4 (4.4)	0

AE=Adverse event; N=Number of participants; n=number of participants with observed data; HFrEF=heart failure with reduced ejection fraction; OM=omecamtiv mecarbil.

Adverse drug reactions

A thorough evaluation of all adverse events from the safety population (defined as any participant who received at least one dose of study drug, either OM or placebo) from the CV outcome study of chronic HF (Study 20110203) was performed to determine whether there was a reasonable possibility of a causal relationship between omecamtiv mecarbil and an adverse event, which were then identified as Adverse Drug Reactions (Table 45). The analysis focused on several factors, including comparative incidence in clinical trials, investigator causality assessment from individual case reports, the biological plausibility of the drug leading to the adverse event, the seriousness of the adverse event, and concomitant illnesses and medications from individual case narrative review. Changes in vital signs and laboratory values were also considered in assessing potential adverse drug reactions (ADRs). In addition, low-frequency AEs were reviewed for any serious and/or severe events that might be indicative of typical drug-related ADRs.

Additional medical review of all reported AEs in Phase 2b studies of moderate duration (20120227 and 20110151 Expansion Phase), Phase 2a studies of short duration (20100754), Phase 1 studies (CY 1111, CY 1011, CY 1013, CY 1015, CY 1016, 20090229, 20090727, 20080676, CY 1211 (20120255), 20150134, 20160159, 20090231, 20120259, 20130253, 20130254, 20140209, 20160160, 20180328, 20180339, 20180340, 20180341, 20180342, 20180432, 20180435), and Phase 3 study (CY 1031 [METEORIC-HF]) in participants with chronic heart failure with reduced

ejection fraction (HFrEF) and decreased exercise capacity was also performed and did not identify additional ADRs that should be included.

Three potential ADRs were identified for omecamtiv mecarbil. The 3 associated PTs with their frequencies in the baseline LVEF <30% population (the intended population) are as follows: dizziness (5.8% in omecamtiv mecarbil, 4.6% in placebo; common), myocardial infarction (includes acute myocardial infarction; 3.0% in omecamtiv mecarbil, 3.3% in placebo; common), and angina pectoris (includes angina unstable, myocardial ischaemia; 4.6% in omecamtiv mecarbil, 3.3% in placebo), which are tabulated in the proposed SmPC.

In Phase 1 and 2 dose-finding studies, it was observed that excessively high plasma concentrations of omecamtiv mecarbil (>1,200 ng/mL) may be associated with the development of myocardial ischaemia or infarction. In Study 20110203, the incidence of adjudicated major cardiac ischaemic events was similar between omecamtiv mecarbil and placebo.

Additional medical review of all reported AEs in Phase 2b studies of moderate duration, Phase 2a studies of short duration, Phase 1 studies, and a Phase 3 study in participants with HFrEF and decreased exercise capacity did not identify additional ADRs that should be included.

Table 45. Potential Adverse Drug Reactions

Adverse Drug Reaction (Preferred Term)	Omecamtiv Mecarbil[a] (N=4,110) n (%)	Placebo (N=4,101) n (%)	Frequency Category
Dizziness	237 (5.8)	189 (4.6)	Common
Myocardial Infarction (includes Acute Myocardial Infarction)	122 (3.0)	134 (3.3)	Common
Angina Pectoris (includes Angina Unstable, Myocardial Ischaemia)	189 (4.6)	137 (3.3)	Common

N=Number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with valid observations.
a Incidence of preferred terms is provided from the safety population of Study 20110203.

3.3.7.3. Serious adverse events, deaths, and other significant events

Serious adverse events

CV outcome study of chronic HF (GALACTIC-HF)

The overall incidence of SAEs was slightly lower in the omecamtiv mecarbil (57.7%) compared with the placebo (59.4%) groups (Table 46). As anticipated in this study population, the most common SAEs by PT occurring in ≥5% of participants in either treatment group (omecamtiv mecarbil, placebo) were cardiac failure (24.0%, 25.5%) and cardiac failure acute (5.2%, 6.1%).

Table 46. Treatment-emergent Serious Adverse Events by Preferred Term Reported for ≥ 1% of Subjects in Any Treatment Group
Study 20110203 (Safety Analysis Set)

	Recently and Not Currently Hospitalised for Heart Failure		Currently Hospitalised for Heart Failure		Overall	
Preferred Term	Placebo (N = 3067) n (%)	AMG 423 (N = 3070) n (%)	Placebo (N = 1034) n (%)	AMG 423 (N = 1040) n (%)	Placebo (N = 4101) n (%)	AMG 423 (N = 4110) n (%)
Number of subjects reporting treatment-emergent serious adverse events	1756 (57.3)	1733 (56.4)	679 (65.7)	640 (61.5)	2435 (59.4)	2373 (57.7)
Cardiac failure	702 (22.9)	654 (21.3)	343 (33.2)	334 (32.1)	1045 (25.5)	988 (24.0)
Cardiac failure acute	190 (6.2)	161 (5.2)	61 (5.9)	51 (4.9)	251 (6.1)	212 (5.2)
Pneumonia	128 (4.2)	121 (3.9)	51 (4.9)	50 (4.8)	179 (4.4)	171 (4.2)
Cardiac failure chronic	124 (4.0)	107 (3.5)	46 (4.4)	49 (4.7)	170 (4.1)	156 (3.8)
Cardiac failure congestive	120 (3.9)	118 (3.8)	34 (3.3)	29 (2.8)	154 (3.8)	147 (3.6)
Acute kidney injury	103 (3.4)	103 (3.4)	35 (3.4)	26 (2.5)	138 (3.4)	129 (3.1)
Ventricular tachycardia	106 (3.5)	71 (2.3)	23 (2.2)	35 (3.4)	129 (3.1)	106 (2.6)
Atrial fibrillation	88 (2.9)	76 (2.5)	25 (2.4)	18 (1.7)	113 (2.8)	94 (2.3)
Cardiogenic shock	57 (1.9)	50 (1.6)	11 (1.1)	25 (2.4)	68 (1.7)	75 (1.8)
Acute myocardial infarction	51 (1.7)	54 (1.8)	13 (1.3)	17 (1.6)	64 (1.6)	71 (1.7)
Death	36 (1.2)	53 (1.7)	13 (1.3)	12 (1.2)	49 (1.2)	65 (1.6)
Angina unstable	43 (1.4)	54 (1.8)	6 (0.6)	9 (0.9)	49 (1.2)	63 (1.5)
Chronic obstructive pulmonary disease	32 (1.0)	51 (1.7)	6 (0.6)	12 (1.2)	38 (0.9)	63 (1.5)
Sudden death	32 (1.0)	43 (1.4)	26 (2.5)	9 (0.9)	58 (1.4)	52 (1.3)
Sepsis	46 (1.5)	37 (1.2)	14 (1.4)	14 (1.3)	60 (1.5)	51 (1.2)
Cardiac arrest	43 (1.4)	38 (1.2)	21 (2.0)	12 (1.2)	64 (1.6)	50 (1.2)
Hypotension	26 (0.8)	39 (1.3)	11 (1.1)	10 (1.0)	37 (0.9)	49 (1.2)
Syncope	34 (1.1)	26 (0.8)	12 (1.2)	16 (1.5)	46 (1.1)	42 (1.0)
Angina pectoris	33 (1.1)	32 (1.0)	7 (0.7)	9 (0.9)	40 (1.0)	41 (1.0)
Septic shock	24 (0.8)	31 (1.0)	8 (0.8)	6 (0.6)	32 (0.8)	37 (0.9)
Myocardial infarction	43 (1.4)	27 (0.9)	11 (1.1)	9 (0.9)	54 (1.3)	36 (0.9)
Ischaemic stroke	25 (0.8)	27 (0.9)	13 (1.3)	9 (0.9)	38 (0.9)	36 (0.9)
Chronic kidney disease	25 (0.8)	24 (0.8)	11 (1.1)	12 (1.2)	36 (0.9)	36 (0.9)
Ventricular fibrillation	42 (1.4)	24 (0.8)	7 (0.7)	6 (0.6)	49 (1.2)	30 (0.7)
Sudden cardiac death	23 (0.7)	20 (0.7)	14 (1.4)	7 (0.7)	37 (0.9)	27 (0.7)
Renal failure	20 (0.7)	11 (0.4)	11 (1.1)	14 (1.3)	31 (0.8)	25 (0.6)
Renal impairment	17 (0.6)	18 (0.6)	12 (1.2)	7 (0.7)	29 (0.7)	25 (0.6)
Respiratory tract infection	13 (0.4)	11 (0.4)	11 (1.1)	4 (0.4)	24 (0.6)	15 (0.4)

AMG 423=omecamtiv mecarbil; MedDRA ☐ Medical Dictionary for Regulatory Activities
Notes: N= Number of subjects randomised excluding study centre 29002 and received at least 1 dose of investigational product. Percentages are based on N. Coded using MedDRA version 23.0.

Moderate Duration Studies of Chronic Heart Failure

The overall incidence of SAEs was similar between the omecamtiv mecarbil PK-guided titration (19.5%), other omecamtiv mecarbil (23.4%), and placebo (19.4%) groups (Table 47). No SAEs occurred in ≥5% of participants by PT; the most common SAE was cardiac failure (3.2%, 2.3%, 2.9%; omecamtiv mecarbil PK-guided titration, other omecamtiv mecarbil, placebo).

In addition, among the 36 participants in Cohort 2 of the Dose Escalation Phase of 20110151, two participants in the 50-mg group discontinued because of SAEs (one Participant for angina unstable and a second Participant for myocardial ischaemia). Both events were positively adjudicated; the first Participant was hospitalised with “acute myocardial infarction”, and the second Participant was hospitalised with “chest pain (not meeting the criteria for myocardial infarction or unstable angina).” In addition, one additional SAE was reported (pneumonia, Participant in the 50-mg group).

Table 47. SAEs by Preferred Term Reported in **≥1%** of Participants in Any Treatment Group in Moderate Duration Studies of Chronic HF (Safety Analysis Set)(adjusted by assessor)

	Moderate Duration Studies of Chronic HF		
Preferred Term	Oral Placebo (N=170) n (%)	Other Oral OM (N=171) n (%)	Oral OM PK-guided titration (N=185) n (%)
Number of participants reporting SAEs	33 (19.4)	40 (23.4)	36 (19.5)
Cardiac failure	5 (2.9)	4 (2.3)	6 (3.2)
Cardiac failure acute	1 (0.6)	3 (1.8)	3 (1.6)
Pneumonia	3 (1.8)	1 (0.6)	4 (2.2)
Cardiac failure chronic	3 (1.8)	1 (0.6)	1 (0.5)
Cardiac failure congestive	3 (1.8)	4 (2.3)	3 (1.6)
Acute kidney injury	0 (0.0)	1 (0.6)	0 (0.0)
Ventricular tachycardia	1 (0.6)	2 (1.2)	1 (0.5)
Atrial fibrillation	1 (0.6)	2 (1.2)	0 (0.0)
Cardiogenic shock	0 (0.0)	0 (0.0)	0 (0.0)
Acute myocardial infarction	1 (0.6)	0 (0.0)	1 (0.5)
Death	0 (0.0)	1 (0.6)	0 (0.0)
Angina unstable	0 (0.0)	1 (0.6)	1 (0.5)
Chronic obstructive pulmonary disease	1 (0.6)	0 (0.0)	1 (0.5)
Sudden death	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	1 (0.6)	0 (0.0)
Cardiac arrest	2 (1.2)	1 (0.6)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)
Angina pectoris	0 (0.0)	3 (1.8)	2 (1.1)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis	0 (0.0)	1 (0.6)	2 (1.1)
Myocardial infarction	2 (1.2)	0 (0.0)	0 (0.0)

Preferred Term	Moderate Duration Studies of Chronic HF		
	Oral Placebo (N=170) n (%)	Other Oral OM (N=171) n (%)	Oral OM PK-guided titration (N=185) n (%)
Non-cardiac chest pain	2 (1.2)	0 (0.0)	1 (0.5)
Ventricular fibrillation	0 (0.0)	2 (1.2)	0 (0.0)
Dyspnoea	1 (0.6)	2 (1.2)	0 (0.0)
Bronchitis	2 (1.2)	0 (0.0)	0 (0.0)
Troponin increased	0 (0.0)	2 (1.2)	2 (1.1)

CV=cardiovascular; HF=heart failure; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil; PK=pharmacokinetics; SAE=serious adverse event.
Percentages are based on N.
Coded using MedDRA version 23.0.
Moderate Duration Studies of Chronic Heart Failure: 20110151 Expansion, 20120227;

Study 20100754 (ATOMIC-AHF)

The overall incidence of SAEs was slightly lower in the omecamtiv mecarbil group (21.8%) compared with the placebo (23.1%) group (Table 48). The most common SAEs by PT occurring in ≥5% of participants in either treatment group was cardiac failure (6.6% omecamtiv mecarbil, 8.3% placebo).

Table 48. SAEs by Preferred Term Reported in **≥1%** of Participants in Any Treatment Group in Acute HF (Study 20100754, Safety Analysis Set)

Preferred Term	IV Placebo (N=303) n (%)	IV OM (N=303) n (%)
Number of participants reporting SAEs	70 (23.1)	66 (21.8)
Cardiac failure	25 (8.3)	20 (6.6)
Pneumonia	3 (1.0)	4 (1.3)
Cardiac failure congestive	4 (1.3)	6 (2.0)
Acute kidney injury	4 (1.3)	6 (2.0)
Atrial fibrillation	3 (1.0)	0 (0.0)
Hypotension	0 (0.0)	3 (1.0)

Study CY 1031 (METEORIC-HF)

The incidence of SAEs was slightly higher in the omecamtiv mecarbil group (16.2%) compared with the placebo group (14.3%) (Table 49).

The SOC with the highest reported incidence of SAEs was Cardiac disorders (10.8% omecamtiv mecarbil, 8.8% placebo); all other SOCs had incidences between 0% and 2.7%. The most common SAEs (≥2% of participants in either treatment group) by PT were cardiac failure (3.8%, 1.1%), ventricular tachycardia (2.7%, 2.2%), and cardiac failure acute (1.1%, 3.3%). No SAE occurred during cardiopulmonary exercise testing.

Table 49. SAEs Reported for ≥2 Participants in Either Treatment Group by System Organ Class and Preferred Term in HFrEF with Decreased Exercise Capacity (Study CY 1031, Safety Analysis Set)

System Organ Class Preferred Term	Placebo (N=91) n (%)	Omecamtiv Mecarbil (N=185) n (%)
Patients with at least one AE	13 (14.3)	30 (16.2)
Cardiac disorders	8 (8.8)	20 (10.8)
Cardiac failure	1 (1.1)	7 (3.8)
Cardiac failure acute	3 (3.3)	2 (1.1)
Cardiac failure congestive	0	2 (1.1)
Ventricular tachycardia	2 (2.2)	5 (2.7)
Cardiac arrest	0	2 (1.1)
Atrial fibrillation	1 (1.1)	2 (1.1)
Acute myocardial infarction	2 (2.2)	0
Vascular disorders	0	2 (1.1)
Hypotension	0	2 (1.1)

Deaths

CV outcome study of chronic HF (GALACTIC-HF)

Positively adjudicated all-cause death occurred in 25.9% (n=1,067) of the subjects in the omecamtiv mecarbil group and in 25.9% (n=1,065) of the subjects in the placebo group. The percentage of CV death was similar in the omecamtiv mecarbil and the placebo groups (19.6% (n=806) and 19.4% (n=797), respectively). The reasons for CV deaths were balanced between the omecamtiv mecarbil and placebo groups, with slightly higher CV deaths due to HF but fewer sudden cardiac CV deaths and fewer CV deaths due to stroke in the omecamtiv mecarbil group compared with placebo (Table 50). The proportions of adjudicated non-CV deaths (3.9% and 4.6% for OM and placebo, respectively) and undetermined/unknown deaths (2.4% and 1.8) were smaller than that of CV deaths (Table 51). The reasons for non-CV deaths were well-balanced across the groups.

Table 50. Participant Incidence of Positively Adjudicated CV Death (Study 20110203, Safety Analysis Set)

Event type Subtype	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF		Overall	
	Placebo (N=3,067) n (%)	OM (N=3,070) n (%)	Placebo (N=1,034) n (%)	OM (N=1,040) n (%)	Placebo (N=4,101) n (%)	OM (N=4,110) n (%)
CV death	545 (17.8)	577 (18.8)	252 (24.4)	229 (22.0)	797 (19.4)	806 (19.6)
Due to an acute MI	8 (0.3)	15 (0.5)	7 (0.7)	3 (0.3)	15 (0.4)	18 (0.4)
Due to CV haemorrhage	1 (<0.1)	3 (<0.1)	1 (<0.1)	2 (0.2)	2 (<0.1)	5 (0.1)
Due to CV procedure	6 (0.2)	4 (0.1)	1 (<0.1)	2 (0.2)	7 (0.2)	6 (0.1)

Event type Subtype	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF		Overall	
	Placebo (N=3,067) n (%)	OM (N=3,070) n (%)	Placebo (N=1,034) n (%)	OM (N=1,040) n (%)	Placebo (N=4,101) n (%)	OM (N=4,110) n (%)
Due to heart failure	260 (8.5)	269 (8.8)	129 (12.5)	144 (13.8)	389 (9.5)	413 (10.0)
Due to stroke	22 (0.7)	14 (0.5)	10 (1.0)	4 (0.4)	32 (0.8)	18 (0.4)
Presumed CV death	74 (2.7)	87 (2.8)	23 (2.2)	23 (2.2)	97 (2.4)	110 (2.7)
Presumed sudden death	32 (1.0)	42 (1.4)	22 (2.1)	13 (1.3)	54 (1.3)	55 (1.3)
Sudden cardiac	135 (4.4)	137 (4.5)	55 (5.3)	35 (3.4)	190 (4.6)	172 (4.2)
Due to other CV causes	7 (0.2)	6 (0.2)	4 (0.4)	3 (0.3)	11 (0.3)	9 (0.2)

CV=cardiovascular; HF=heart failure; MI=myocardial infarction; N=Number of participants randomised excluding Study Centre 29002 and received at least 1 dose of investigational product; n=Number of participants with events; OM=omecamtiv mecarbil.

Table 51. Participant Incidence of Positively Adjudicated Deaths **≥0.1%** in any Treatment Group (Study 20110203, Safety Analysis Set)

Event type Subtype	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF		Overall	
	Placebo (N=3,067) n (%)	OM (N=3,070) n (%)	Placebo (N=1,034) n (%)	OM (N=1,040) n (%)	Placebo (N=4,101) n (%)	OM (N=4,110) n (%)
Non-CV death	130 (4.2)	116 (3.8)	60 (5.8)	43 (4.1)	190 (4.6)	159 (3.9)
Gastrointestinal	8 (0.3)	4 (0.1)	2 (0.2)	2 (0.2)	10 (0.2)	6 (0.1)
Hepatobiliary	2 (<0.1)	4 (0.1)	1 (<0.1)	0 (0.0)	3 (<0.1)	4 (<0.1)
Infection; includes sepsis	65 (2.1)	59 (1.9)	32 (3.1)	22 (2.1)	97 (2.4)	81 (2.0)
Malignancy	27 (0.9)	20 (0.7)	11 (1.1)	9 (.9)	38 (0.9)	29 (0.7)
Non-CV Haemorrhage	6 (0.2)	3 (<0.1)	1 (<0.1)	1 (<0.1)	7 (0.2)	4 (<0.1)
Pulmonary	4 (0.1)	3 (<0.1)	3 (0.3)	1 (<0.1)	7 (0.2)	4 (<0.1)
Renal	4 (0.1)	3 (<0.1)	1 (<0.1)	1 (<0.1)	5 (0.1)	4 (<0.1)
Suicide	3 (<0.1)	1 (<0.1)	2 (0.2)	2 (0.2)	5 (0.1)	3 (<0.1)
Trauma	8 (0.3)	10 (0.3)	5 (0.5)	3 (0.3)	13 (0.3)	13 (0.3)
Undetermined/unknown death	55 (1.8)	74 (2.4)	20 (1.9)	24 (2.3)	75 (1.8)	98 (2.4)

CV=cardiovascular; HF=heart failure; N=Number of participants randomised excluding Study Centre 29002 and received at least 1 dose of investigational product; n=Number of participants with events; OM=omecamtiv mecarbil.

In other studies combined, treatment emergent all-cause death occurred in 1.1% (n=17) of participants in the omecamtiv mecarbil group and in 1.6% (n=13) of participants in the placebo group.

AEs of special interest

Cardiotoxicity

In Phase 1 and 2 dose-finding studies, it was observed that excessively high plasma concentrations of omecamtiv mecarbil (>1,200 ng/mL) can be associated with the development of myocardial ischaemia or infarction. In Phase 1 and 2 studies, 6 of 16 participants with plasma concentrations of omecamtiv mecarbil >1,200 ng/mL experienced a myocardial ischaemic event. These events likely occur as a result of the exaggerated pharmacological effect of prolonged SET at the expense of diastole (when the majority of coronary artery perfusion occurs). These reported events of cardiac ischaemia were self-limiting following discontinuation of omecamtiv mecarbil with no observed long-term sequelae or lasting impact on cardiac function.

Myocardial ischaemia due to an excessive concentration of omecamtiv mecarbil was first identified in 3 subjects in the first-in-human study CY 1111:

- Two subjects dosed at the 1.0 mg/kg/hr dose level were discontinued from the study due to AEs judged to be related to the study drug.
    - Participant experienced chest discomfort during study drug infusion, which was stopped early. The highest omecamtiv mecarbil plasma concentration measured in Participant was 1338 ng/mL, 3 hours after starting the infusion; cardiac enzymes remained normal.
    - Participant experienced chest discomfort and ECG ST segment depression during the study drug infusion, which was stopped early. In addition, increased troponin levels were also seen in this participant. The highest omecamtiv mecarbil plasma concentration measured in Participant was 1333 ng/mL, 3 hours after starting the infusion.
- Participant was discontinued from the study following an AE of ECG ST segment depression judged to be related to the study drug after dosing with omecamtiv mecarbil at 0.75 mg/kg/hr for 6 hours. The highest omecamtiv mecarbil plasma concentration measured in Participant 29 was 1212 ng/mL just prior to the end of the 6-hour infusion; cardiac enzymes remained normal.

Myocardial ischaemia due to an excessive concentration of omecamtiv mecarbil was also observed 2 subjects in the first Phase 2 clinical trial of omecamtiv mecarbil in participants with HFrEF, CY 1121:

- Due to a pharmacy error in preparing the infusion, a Participant received an inadvertent overdose of omecamtiv mecarbil at 2.2 mg/kg/hr for 45 minutes, after which the study drug infusion was discontinued because the patient developed symptoms and signs of clinical intolerance. The last measured plasma concentration 15 minutes prior to discontinuing the infusion was 1,456 ng/mL, and at the time the infusion was discontinued, the omecamtiv mecarbil plasma concentration was estimated to have been in excess of 1,700 ng/mL. The participant was withdrawn from the study. An SAE of non-ST elevation myocardial infarction (NSTEMI) was reported.
- Participant was treated with the intended doses of omecamtiv mecarbil (two 1 hour loading infusions followed by a 70-hour maintenance infusion). After approximately 63 total hours of infusion, the patient began to experience transient episodes of tachycardia associated with

chest heaviness, eventually meeting stopping criteria with a heart rate exceeding 120 bpm for greater than 5 minutes associated with moderate dizziness and severe chest discomfort. The infusion was terminated after 66 hours and 24 minutes. Subsequent to the termination of the infusion, the terminal portion of the ST-T segment became more clearly inverted and small biphasic T waves developed; however, 3 days later, the ST segments were all isoelectric, and the T waves were all upright. The maximum omecamtiv mecarbil plasma concentration was 1345 ng/mL at 60 hours, in association with an elevated troponin I of 0.32 ng/mL (normal <0.6). At 66 hours, the omecamtiv mecarbil plasma concentration was 1,236 mg/mL and the troponin I was 0.59 mg/mL. The maximum troponin I was 1.15 ng/mL at 78 hours.

Myocardial ischaemia due to an excessive concentration of omecamtiv mecarbil was also observed in the Dose Escalation Phase of 20110151 (COSMIC-HF), during which different modified release (MR) formulations of omecamtiv mecarbil at fixed doses of 25 mg BID and 50 mg BID were explored in patients with HF and reduced ejection fraction. On Day 7 of dosing with omecamtiv mecarbil 50 mg BID, a Participant was hospitalised for unstable angina. Laboratory tests that day revealed elevated levels of creatine phosphokinase MB and troponin I, consistent with MI. The first plasma concentration of omecamtiv mecarbil measured that day was 1130 mg/mL; 3 hours later, it peaked at 1,320 mg/mL

Based on the above, the omecamtiv mecarbil target exposure range was 300-750 ng/ml in the CV outcome study 20110203. Safety endpoints were evaluated according to any SAEs and safety events of special interest (ventricular tachyarrhythmias and adjudicated major cardiac ischaemic events [MI, hospitalisation for unstable angina, coronary revascularisation]) according to the titrated dose groups.

Major cardiac ischaemic events

Adjudicated Major Cardiac Ischaemic Events

In the CV outcome study 20110203, positively adjudicated major cardiac ischaemic events occurred with similar incidence in the omecamtiv mecarbil group and the placebo group (4.9% and 4.6%, respectively) (Table 52). The hazard ratio (HR; 95% CI) was 1.06 (0.87, 1.30), comparing omecamtiv mecarbil to placebo for time to first positively adjudicated major cardiac ischaemic event. Myocardial infarction (3.0% OM group, 2.9% placebo group) and coronary revascularisation (2.8%, 2.9%; mostly PCI, 2.4% in each group) occurred more often than hospitalisation for unstable angina (0.6%, 0.3%).

In both treatment groups, the incidences of these events were generally lower among currently hospitalised participants (4.5% omecamtiv mecarbil group, 2.7% placebo group, HR: [95% CI] 1.62 [1.01, 2.59]) when compared with not currently hospitalised participants (5.0% omecamtiv mecarbil group, 5.2% placebo group, HR: 0.96 [0.77, 1.20]). Among the currently hospitalised participants, the incidences of these events were higher in the omecamtiv mecarbil group when compared with the placebo group (4.5% vs. 2.7%). The hazard ratio (95% CI) was 0.96 (0.77, 1.20) for outpatient subjects and 1.62 (1.01, 2.59) for inpatient subjects.

Table 52. Participant Incidence of Positively Adjudicated Major Cardiac Ischaemic Events (Study 20110203, Safety Analysis Set)

Event type Subtype	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF		Overall	
	Placebo (N=3,067) n (%)	OM (N=3,070) n (%)	Placebo (N=1,034) n (%)	OM (N=1,040) n (%)	Placebo (N=4,101) n (%)	OM (N=4,110) n (%)
Number of participants with positively adjudicated major ischaemic events[a]	160 (5.2)	153 (5.0)	28 (2.7)	47 (4.5)	188 (4.6)	200 (4.9)
Myocardial infarction	97 (3.2)	90 (2.9)	21 (2.0)	32 (3.1)	118 (2.9)	122 (3.0)
Type 1: Spontaneous MI	68 (2.2)	67 (2.2)	18 (1.7)	20 (1.9)	86 (2.1)	87 (2.1)
Type 2: Secondary to an ischaemic imbalance	26 (0.8)	24 (0.8)	2 (0.2)	11 (1.1)	28 (0.7)	35 (0.9)
Type 3: Resulting in death when biomarker values are unavailable	2 (<0.1)	1 (<0.1)	1 (<0.1)	0 (0.0)	3 (<0.1)	1 (<0.1)
Type 4a: Related to PCI	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Type 4b: Related to stent thrombosis	1 (<0.1)	2 (<0.1)	1 (<0.1)	0 (0.0)	2 (<0.1)	2 (<0.1)
Type 4c: Related to stent restenosis	1 (<0.1)	1 (<0.1)	2 (0.2)	3 (0.3)	3 (<0.1)	4 (<0.1)
Hospitalisation for unstable angina	12 (0.4)	20 (0.7)	0 (0.0)	5 (0.5)	12 (0.3)	25 (0.6)
CK-MB collected only	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
ECG and CK-MB collected	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
ECG and troponin collected	5 (0.2)	6 (0.2)	0 (0.0)	1 (<0.1)	5 (0.1)	7 (0.2)
ECG collected only	2 (<0.1)	2 (<0.1)	0 (0.0)	1 (<0.1)	2 (<0.1)	3 (<0.1)
ECG, troponin, and CK-MB collected	1 (<0.1)	4 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	4 (<0.1)
Troponin and CK-MB collected	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Troponin collected only	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
No ECG, CK-MB, or troponin collected	2 (<0.1)	4 (0.1)	0 (0.0)	2 (0.2)	2 (<0.1)	6 (0.1)
Coronary revascularisation	99 (3.2)	90 (2.9)	18 (1.7)	25 (2.4)	117 (2.9)	115 (2.8)
CABG	17 (0.6)	16 (0.5)	1 (<0.1)	4 (0.4)	18 (0.4)	20 (0.5)

Event type Subtype	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF		Overall	
	Placebo (N=3,067) n (%)	OM (N=3,070) n (%)	Placebo (N=1,034) n (%)	OM (N=1,040) n (%)	Placebo (N=4,101) n (%)	OM (N=4,110) n (%)
PCI	82 (2.7)	77 (2.5)	17 (1.6)	22 (2.1)	99 (2.4)	99 (2.4)

CABG=coronary artery bypass graft; CK-MB=creatine kinase-MB; ECG=electrocardiogram; HF=heart failure; MI=myocardial infarction; N=Number of participants randomised excluding Study Centre 29002 and received at least 1 dose of investigational product; n=Number of participants with events; OM=omecamtiv mecarbil; PCI=percutaneous coronary intervention.

[a] Major cardiac ischaemic events were fatal and nonfatal myocardial infarction, unstable angina hospitalisation, and coronary revascularisation.

In study 20110151 (Moderate Duration Studies of Chronic HF), the percentage of participants with positively adjudicated events and event types were similar across the randomised treatment groups (2 in the placebo group (both with PT MI) and 1 in the PK-guided titration group (PT acute MI). In 20120227 (Moderate Duration Studies of Chronic HF), there were no notable imbalances in the types of hospitalisations between the treatment groups. One hospitalisation that was reported as being due to effort angina pectoris (PT: angina pectoris) was positively adjudicated as a MI for 1 participant in the 25 to 50 mg BID PK-titration group.

In study 20100754 (ATOMIC-AHF), results of the initial adjudication showed that the participant incidence of positively adjudicated clinical events of death, rehospitalisation, resuscitated sudden death, and stroke was generally balanced across the 2 treatment groups, with the exception of the adjudicated MIs. Ten cases of MI were positively adjudicated in the omecamtiv mecarbil treated groups compared with 2 events in the pooled placebo group. Four of the 10 adjudicated MI events (3 in the omecamtiv mecarbil group and 1 in the placebo group) occurred more than 7 days following the termination of the 48-hour drug infusion. One of the MI events in the omecamtiv mecarbil group occurred after the patient underwent percutaneous coronary intervention (PCI). A secondary adjudication process evaluating only post-randomisation events (this trial required enrollment within 24 hours of arrival to the hospital, and some events started during the screening phase) identified 7 MIs in the omecamtiv mecarbil treated groups compared with 3 in placebo groups (2.3% vs 1.0% respectively).

Major cardiac ischaemic events and ventricular tachyarrhythmias reported by investigator

Myocardial ischaemia and MI AEs, as reported by the investigators, were evaluated in 20110203 using MedDRA SMQ (narrow search) and are provided based on participants' randomisation setting (hospitalised/not currently hospitalised). The overall incidence of these events was similar in the omecamtiv mecarbil and placebo treatment groups (Table 53).

Overall, the participant incidence of AEs in the ischaemic heart disease (SMQ) was similar for omecamtiv mecarbil and placebo (9.0%, 8.0%). The incidence of AEs in the ischaemic heart disease (SMQ) in participants currently hospitalised was 7.7% and 5.6%, and in participants not currently hospitalised was 9.5% and 8.9%, for omecamtiv mecarbil and placebo, respectively.

In the overall narrow search, the participant incidence of AEs in the MI (SMQ) was similar in the omecamtiv mecarbil and placebo groups (4.9% and 4.7%). The incidence of AEs in the MI (SMQ) in participants currently hospitalised at the time of enrollment was 4.0% and 3.2%, and in participants not currently hospitalised was 5.2% and 5.2% for omecamtiv mecarbil and placebo, respectively.

The overall incidence of Torsades de pointes/QT prolongation AEs of interest was similar in the oral omecamtiv mecarbil (4.3%) and oral placebo (4.8%) groups (Table 53). The overall incidence of ventricular tachyarrhythmia cardiovascular AEs of interest was similar between the oral omecamtiv mecarbil (7.1%), and oral placebo (7.4%) groups. For both SMQs, the most common AE was ventricular tachycardia: omecamtiv mecarbil (4.2%) and oral placebo (4.5%). The incidence of SAEs of ventricular arrhythmias as reported by the investigators requiring new treatment or alteration of treatment, was similar between the omecamtiv mecarbil group (3.7%) and the placebo group (3.8%).

Table 53.Treatment-emergent Adverse EOIs by Preferred Term – Narrow Search- Study 20110203 (Safety Analysis Set)

	Recently and Not Currently Hospitalised for Heart Failure		Currently Hospitalised for Heart Failure		Overall	
EOI High Level Term Preferred Term	Placebo (N = 3067) n (%)	AMG 423 (N = 3070) n (%)	Placebo (N = 1034) n (%)	AMG 423 (N = 1040) n (%)	Placebo (N = 4101) n (%)	AMG 423 (N = 4110) n (%)
Number of subjects reporting adverse events of interest	494 (16.1)	488 (15.9)	123 (11.9)	148 (14.2)	617 (15.0)	636 (15.5)
Ischaemic heart disease (SMQ)	272 (8.9)	291 (9.5)	58 (5.6)	80 (7.7)	330 (8.0)	371 (9.0)
Ischaemic coronary artery disorders	221 (7.2)	239 (7.8)	49 (4.7)	67 (6.4)	270 (6.6)	306 (7.4)
Angina pectoris	70 (2.3)	93 (3.0)	17 (1.6)	25 (2.4)	87 (2.1)	118 (2.9)
Acute myocardial infarction	55 (1.8)	54 (1.8)	13 (1.3)	18 (1.7)	68 (1.7)	72 (1.8)
Angina unstable	45 (1.5)	59 (1.9)	7 (0.7)	9 (0.9)	52 (1.3)	68 (1.7)
Myocardial infarction	45 (1.5)	29 (0.9)	11 (1.1)	9 (0.9)	56 (1.4)	38 (0.9)
Myocardial ischaemia	14 (0.5)	12 (0.4)	1 (<0.1)	4 (0.4)	15 (0.4)	16 (0.4)
Acute coronary syndrome	10 (0.3)	10 (0.3)	2 (0.2)	4 (0.4)	12 (0.3)	14 (0.3)
Prinzmetal angina	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Postinfarction angina	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Coronary artery disorders NEC	42 (1.4)	38 (1.2)	6 (0.6)	8 (0.8)	48 (1.2)	46 (1.1)
Coronary artery disease	24 (0.8)	29 (0.9)	4 (0.4)	4 (0.4)	28 (0.7)	33 (0.8)
Coronary artery stenosis	9 (0.3)	6 (0.2)	1 (<0.1)	2 (0.2)	10 (0.2)	8 (0.2)
Arteriosclerosis coronary artery	7 (0.2)	2 (<0.1)	1 (<0.1)	1 (<0.1)	8 (0.2)	3 (<0.1)
Coronary artery occlusion	2 (<0.1)	1 (<0.1)	1 (<0.1)	0 (0.0)	3 (<0.1)	1 (<0.1)
Coronary ostial stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Coronary artery insufficiency	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Skeletal and cardiac muscle analyses	10 (0.3)	15 (0.5)	0 (0.0)	3 (0.3)	10 (0.2)	18 (0.4)
Troponin increased	7 (0.2)	7 (0.2)	0 (0.0)	2 (0.2)	7 (0.2)	9 (0.2)
Troponin I increased	1 (<0.1)	5 (0.2)	0 (0.0)	1 (<0.1)	1 (<0.1)	6 (0.1)
Troponin T increased	2 (<0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	2 (<0.1)	3 (<0.1)

EOI High level term Preferred Term	Recently and not currently hospitalised for heart failure Placebo (N = 3067) n (%)	 AMG 423 (N = 3070) n (%)	Currently hospitalised for heart failure Placebo (N = 1034) n (%)	 AMG 423 (N = 1040) n (%)	Overall Placebo (N = 4101) n (%)	 AMG 423 (N = 4110) n (%)
Cardiomyopathies	10 (0.3)	8 (0.3)	3 (0.3)	4 (0.4)	13 (0.3)	12 (0.3)
Ischaemic cardiomyopathy	10 (0.3)	8 (0.3)	3 (0.3)	4 (0.4)	13 (0.3)	12 (0.3)
Arterial therapeutic procedures (excl aortic)	5 (0.2)	4 (0.1)	2 (0.2)	1 (<0.1)	7 (0.2)	5 (0.1)
Coronary revascularisation	1 (<0.1)	2 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)	3 (<0.1)
Coronary angioplasty	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Coronary artery bypass	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Percutaneous coronary intervention	3 (<0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	4 (<0.1)	0 (0.0)
Myocardial infarction (SMQ)	161 (5.2)	159 (5.2)	33 (3.2)	42 (4.0)	194 (4.7)	201 (4.9)
Ischaemic coronary artery disorders	150 (4.9)	144 (4.7)	32 (3.1)	40 (3.8)	182 (4.4)	184 (4.5)
Acute myocardial infarction	55 (1.8)	54 (1.8)	13 (1.3)	18 (1.7)	68 (1.7)	72 (1.8)
Angina unstable	45 (1.5)	59 (1.9)	7 (0.7)	9 (0.9)	52 (1.3)	68 (1.7)
Myocardial infarction	45 (1.5)	29 (0.9)	11 (1.1)	9 (0.9)	56 (1.4)	38 (0.9)
Acute coronary syndrome	10 (0.3)	10 (0.3)	2 (0.2)	4 (0.4)	12 (0.3)	14 (0.3)
Postinfarction angina	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)
Skeletal and cardiac muscle analyses	10 (0.3)	15 (0.5)	0 (0.0)	3 (0.3)	10 (0.2)	18 (0.4)
Troponin increased	7 (0.2)	7 (0.2)	0 (0.0)	2 (0.2)	7 (0.2)	9 (0.2)
Troponin I increased	1 (<0.1)	5 (0.2)	0 (0.0)	1 (<0.1)	1 (<0.1)	6 (0.1)
Troponin T increased	2 (<0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	2 (<0.1)	3 (<0.1)
Coronary artery disorders NEC	2 (<0.1)	1 (<0.1)	1 (<0.1)	0 (0.0)	3 (<0.1)	1 (<0.1)
Coronary artery occlusion	2 (<0.1)	1 (<0.1)	1 (<0.1)	0 (0.0)	3 (<0.1)	1 (<0.1)
Torsade de pointes/QT prolongation (SMQ)	158 (5.2)	124 (4.0)	37 (3.6)	52 (5.0)	195 (4.8)	176 (4.3)
Ventricular arrhythmias and cardiac arrest	149 (4.9)	121 (3.9)	35 (3.4)	52 (5.0)	184 (4.5)	173 (4.2)
Ventricular tachycardia	149 (4.9)	121 (3.9)	35 (3.4)	52 (5.0)	184 (4.5)	173 (4.2)
ECG investigations	10 (0.3)	3 (<0.1)	2 (0.2)	1 (<0.1)	12 (0.3)	4 (<0.1)
Electrocardiogram QT prolonged	10 (0.3)	3 (<0.1)	2 (0.2)	1 (<0.1)	12 (0.3)	4 (<0.1)

	Recently and not currently hospitalised for heart failure		Currently hospitalised for heart failure		Overall	
EOI High level term Preferred Term	Placebo (N = 3067) n (%)	AMG 423 (N = 3070) n (%)	Placebo (N = 1034) n (%)	AMG 423 (N = 1040) n (%)	Placebo (N = 4101) n (%)	AMG 423 (N = 4110) n (%)
Ventricular tachyarrhythmias (SMQ)	237 (7.7)	217 (7.1)	67 (6.5)	73 (7.0)	304 (7.4)	290 (7.1)
Ventricular arrhythmias and cardiac arrest	237 (7.7)	217 (7.1)	67 (6.5)	73 (7.0)	304 (7.4)	290 (7.1)
Ventricular tachycardia	149 (4.9)	121 (3.9)	35 (3.4)	52 (5.0)	184 (4.5)	173 (4.2)
Ventricular extrasystoles	42 (1.4)	47 (1.5)	19 (1.8)	11 (1.1)	61 (1.5)	58 (1.4)
Ventricular arrhythmia	21 (0.7)	30 (1.0)	10 (1.0)	9 (0.9)	31 (0.8)	39 (0.9)
Ventricular fibrillation	44 (1.4)	31 (1.0)	8 (0.8)	6 (0.6)	52 (1.3)	37 (0.9)
Ventricular tachyarrhythmia	7 (0.2)	7 (0.2)	1 (<0.1)	2 (0.2)	8 (0.2)	9 (0.2)
Ventricular flutter	1 (<0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	3 (<0.1)
Ventricular parasystole	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

AMG 423=omecamtiv mecarbil;; EOI=event of interest; NEC=not elsewhere classified; SMQ=standardised MedDRA query

Notes: N=Number of subjects randomised excluding study centre 29002 and received at least 1 dose of investigational product. Percentages are based on N. Event categories are defined using preferred terms from MedDRA and either SMQs or internal groupings. Each event category is defined by a unique set of preferred terms, while one preferred term can be categorised into more than one event category. Adverse events were coded using MedDRA version 23.0.

In the Moderate Duration Studies of Chronic HF, in the overall narrow search, the incidence of AEs in the omecamtiv mecarbil PK-guided titration, other omecamtiv mecarbil, and placebo groups were similar for both MI (SMQ) (3.2%, 3.5%, and 2.4%) and ischaemic heart disease SMQ (4.9%, 6.4%, and 4.1%). Furthermore, the incidence of participants (omecamtiv mecarbil PK guided titration, other omecamtiv mecarbil, and placebo) was similar for ventricular arrhythmia AEs (using Torsade De Pointes/QT prolongation SMQ (4 [2.2%], 3 [1.8%], and 2 [1.2%], respectively,) and ventricular tachyarrhythmias SMQ (6 [3.2%], 6 [3.5%], and 2 [1.2%], respectively). The incidence of SAEs of ventricular arrhythmias as reported by the investigators requiring new treatment or alteration of treatment in the integrated moderate duration studies of chronic HF was similar between the PK-guided titration omecamtiv mecarbil (0.5%), other omecamtiv mecarbil (1.8%), and placebo groups (0.6%).

In study 20100754 (ATOMIC-AHF), in the overall narrow search, the incidence of events in the omecamtiv mecarbil group was higher than that in the placebo group for both MI (SMQ) (7 [2.3%], 1 [0.3%]) and ischaemic heart disease SMQ (3.0%, 1.3%).

In Study CY 1031 (METEORIC-HF), the most common ventricular arrhythmia was ventricular tachycardia, reported with a slightly higher incidence in the omecamtiv mecarbil group (4.3%) than the placebo group (2.2%).

Dose/exposure-safety analysis

Analysis by dose

Overall, the incidence of adverse events (AEs), serious adverse events (SAEs), and AEs leading to withdrawal in the omecamtiv mecarbil dose groups was similar to or lower than for the placebo group; there was no pattern of increasing incidence of AEs or SAEs with increasing omecamtiv mecarbil dose level (Table 54 and Table 55). Importantly, there was no pattern of increasing incidence of ventricular tachyarrhythmias or adjudicated major cardiac ischaemic events and stroke with increasing omecamtiv mecarbil dose level (Table 56 and Table 57).

Table 54. Study 20110203 Summary of Participant Incidence of Adverse Events by Dose Group (Safety Analysis Set)

	Placebo	Omecamtiv Mecarbil		
		25 mg BID	37.5 mg BID	50 mg BID
	(N=4101) n (%)	(N=1269) n (%)	(N=602) n (%)	(N=2070) n (%)
All treatment-emergent adverse events	3622 (88.3)	1113 (87.7)	536 (89.0)	1817 (87.8)
Grade ≥2	3324 (81.1)	1017 (80.1)	489 (81.2)	1641 (79.3)
Grade ≥3	2609 (63.6)	838 (66.0)	367 (61.0)	1253 (60.5)
Grade ≥4	1333 (32.5)	432 (34.0)	189 (31.4)	608 (29.4)
Serious adverse events	2435 (59.4)	774 (61.0)	345 (57.3)	1158 (55.9)
Adverse events leading to withdrawal of investigational product	447 (10.9)	134 (10.6)	61 (10.1)	193 (9.3)

	Placebo	Omecamtiv Mecarbil		
		25 mg BID	37.5 mg BID	50 mg BID
	(N=4101) n (%)	(N=1269) n (%)	(N=602) n (%)	(N=2070) n (%)
Serious	337 (8.2)	109 (8.6)	46 (7.6)	151 (7.3)
Nonserious	112 (2.7)	29 (2.3)	16 (2.7)	45 (2.2)

BID=twice daily; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data.

Note: Percentages are based on N

Table 55. Study 20110203 Summary of Adverse Events by Preferred Term Reported for **≥3%** Subjects in Any Treatment Group by Dose Group (Safety Analysis Set)

	Placebo	Omecamtiv Mecarbil		
		25 mg BID	37.5 mg BID	50 mg BID
	(N=4101) n (%)	(N=1269) n (%)	(N=602) n (%)	(N=2070) n (%)
Number of participants reporting AEs	3622 (88.3)	1113 (87.7)	536 (89.0)	1817 (87.8)
Cardiac failure	1203 (29.3)	372 (29.3)	169 (28.1)	563 (27.2)
Atrial fibrillation	263 (6.4)	85 (6.7)	35 (5.8)	112 (5.4)
Cardiac failure acute	263 (6.4)	80 (6.3)	35 (5.8)	95 (4.6)
Dyspnoea	277 (6.8)	80 (6.3)	48 (8.0)	136 (6.6)
Hypotension	271 (6.6)	77 (6.1)	64 (10.6)	164 (7.9)
Acute kidney injury	225 (5.5)	75 (5.9)	50 (8.3)	98 (4.7)
Hyperkalaemia	230 (5.6)	72 (5.7)	42 (7.0)	99 (4.8)
Pneumonia	292 (7.1)	72 (5.7)	43 (7.1)	136 (6.6)
Cardiac failure chronic	210 (5.1)	67 (5.3)	29 (4.8)	100 (4.8)
Dizziness	189 (4.6)	66 (5.2)	39 (6.5)	125 (6.0)
Ventricular tachycardia	184 (4.5)	65 (5.1)	35 (5.8)	70 (3.4)
Cardiac failure congestive	184 (4.5)	64 (5.0)	25 (4.2)	69 (3.3)
Urinary tract infection	161 (3.9)	60 (4.7)	32 (5.3)	60 (2.9)
Diarrhoea	192 (4.7)	57 (4.5)	29 (4.8)	90 (4.3)
Oedema peripheral	168 (4.1)	54 (4.3)	31 (5.1)	64 (3.1)
Renal impairment	176 (4.3)	54 (4.3)	31 (5.1)	96 (4.6)
Gout	152 (3.7)	53 (4.2)	19 (3.2)	68 (3.3)

	Placebo	Omecamtiv Mecarbil		
		25 mg BID	37.5 mg BID	50 mg BID
	(N=4101) n (%)	(N=1269) n (%)	(N=602) n (%)	(N=2070) n (%)
Nasopharyngitis	194 (4.7)	51 (4.0)	25 (4.2)	110 (5.3)
Hypertension	229 (5.6)	50 (3.9)	24 (4.0)	124 (6.0)
Upper respiratory tract infection	172 (4.2)	49 (3.9)	37 (6.1)	96 (4.6)
Anaemia	164 (4.0)	48 (3.8)	26 (4.3)	73 (3.5)
Bronchitis	187 (4.6)	43 (3.4)	20 (3.3)	81 (3.9)
Chronic kidney disease	143 (3.5)	43 (3.4)	24 (4.0)	73 (3.5)
Cough	169 (4.1)	41 (3.2)	29 (4.8)	78 (3.8)
Weight increased	117 (2.9)	41 (3.2)	16 (2.7)	69 (3.3)
Constipation	90 (2.2)	39 (3.1)	12 (2.0)	42 (2.0)
Fatigue	110 (2.7)	39 (3.1)	14 (2.3)	48 (2.3)
Headache	134 (3.3)	39 (3.1)	13 (2.2)	58 (2.8)
Renal failure	100 (2.4)	36 (2.8)	25 (4.2)	52 (2.5)
Syncope	107 (2.6)	35 (2.8)	22 (3.7)	62 (3.0)
Angina pectoris	87 (2.1)	34 (2.7)	16 (2.7)	67 (3.2)
Back pain	121 (3.0)	34 (2.7)	19 (3.2)	76 (3.7)
Chronic obstructive pulmonary disease	99 (2.4)	33 (2.6)	16 (2.7)	62 (3.0)
Diabetes mellitus	133 (3.2)	32 (2.5)	24 (4.0)	62 (3.0)
Hypokalaemia	125 (3.0)	29 (2.3)	25 (4.2)	53 (2.6)
Bradycardia	50 (1.2)	22 (1.7)	18 (3.0)	26 (1.3)

BID=twice daily; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data.

Note: Percentages are based on N.

Table 56. Study 20110203 Summary of Ventricular Tachyarrhythmias (SMQ) by Dose Group (Safety Analysis Set)

	Placebo	Omecamtiv Mecarbil		
		25 mg BID	37.5 mg BID	50 mg BID
	(N=4101) n (%)	(N=1269) n (%)	(N=602) n (%)	(N=2070) n (%)
Ventricular Tachyarrhythmias (SMQ)	304 (7.4)	108 (8.5)	51 (8.5)	127 (6.1)
Ventricular tachycardia	184 (4.5)	65 (5.1)	35 (5.8)	70 (3.4)
Ventricular extrasystoles	61 (1.5)	17 (1.3)	8 (1.3)	32 (1.5)
Ventricular fibrillation	52 (1.3)	16 (1.3)	6 (1.0)	14 (0.7)

	Placebo	Omecamtiv Mecarbil		
		25 mg BID	37.5 mg BID	50 mg BID
	(N=4101) n (%)	(N=1269) n (%)	(N=602) n (%)	(N=2070) n (%)
Ventricular arrhythmia	31 (0.8)	14 (1.1)	4 (0.7)	21 (1.0)
Ventricular tachyarrhythmia	8 (0.2)	6 (0.5)	0 (0.0)	3 (0.1)
Ventricular parasystole	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Ventricular flutter	1 (<0.1)	0 (0.0)	0 (0.0)	3 (0.1)

BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data; SMQ=Standardised MedDRA Query.
Note: Percentages are based on N.

Table 57. Study 20110203 Summary of Adjudicated Death, Major Cardiac Ischaemic Events, and Stroke by Dose Group (Safety Analysis Set)

	Placebo	Omecamtiv Mecarbil		
		25 mg BID	37.5 mg BID	50 mg BID
	(N=4101) n (%)	(N=1269) n (%)	(N=602) n (%)	(N=2070) n (%)
CV Death	797 (19.4)	284 (22.4)	110 (18.3)	333 (16.1)
Non-CV death	190 (4.6)	45 (3.5)	29 (4.8)	75 (3.6)
Undetermined/ unknown death	75 (1.8)	31 (2.4)	12 (2.0)	46 (2.2)
Adjudicated Major Cardiac Ischaemic Event	188 (4.6)	70 (5.5)	26 (4.3)	94 (4.5)
Myocardial Infarction	118 (2.9)	42 (3.3)	14 (2.3)	59 (2.9)
Hospitalisation for Unstable Angina	12 (0.3)	8 (0.6)	5 (0.8)	10 (0.5)
Coronary Revascularisation	117 (2.9)	43 (3.4)	17 (2.8)	51 (2.5)
Adjudicated Stroke	112 (2.7)	24 (1.9)	8 (1.3)	41 (2.0)

BID=twice daily; CV=cardiovascular; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data.
Note: Percentages are based on N.

Analysis by exposure bins

The incidence of AEs in the omecamtiv mecarbil exposure groups was similar to or lower than for the placebo group (Table 58). There was not a trend of higher incidences of individual AE PTs with

increasing concentration bins, with the exception of hypotension; however, there were no trend of increasing blood pressure by omecamtiv concentration bin compared with placebo (Table 59). There was no pattern of increasing incidence of ventricular tachyarrhythmias, adjudicated major cardiac ischaemic events, or adjudicated stroke with increasing omecamtiv mecarbil exposure bins (Table 60 and Table 61).

A summary of the AEs of special interest by exposure bin using the highest concentration at any time during the study has also been provided. Both of these approaches (exposure bins defined using last concentration prior to Week 12 and highest concentration during the study) show no relationship between the occurrence of AE of special interest and omecamtiv mecarbil exposure. Thus, the analyses by exposure bin do not indicate clinically meaningful increased risk of major cardiac ischaemic events and stroke outcomes at higher omecamtiv mecarbil concentrations.

Table 58. Study 20110203 Summary of Participant Incidence of Adverse Events by Exposure Quintiles of the Last Measured Concentration up to Week 12 (Safety Analysis Set)

	Placebo	Omecamtiv Mecarbil (ng/mL) Quintile Bins of Last Concentration up to Week 12				
		<145	145-<225	225-<301	301-<377	**≥377**
	(N=4101) n (%)	(N=810) n (%)	(N=803) n (%)	(N=813) n (%)	(N=795) n (%)	(N=818) n (%)
All treatment-emergent adverse events	3622 (88.3)	696 (85.9)	690 (85.9)	716 (88.1)	700 (88.1)	745 (91.1)
Grade ≥2	3324 (81.1)	636 (78.5)	624 (77.7)	646 (79.5)	635 (79.9)	681 (83.3)
Grade ≥3	2609 (63.6)	510 (63.0)	495 (61.6)	487 (59.9)	478 (60.1)	546 (66.7)
Grade ≥4	1333 (32.5)	260 (32.1)	256 (31.9)	243 (29.9)	238 (29.9)	270 (33.0)
Serious adverse events	2435 (59.4)	470 (58.0)	461 (57.4)	452 (55.6)	448 (56.4)	505 (61.7)
Adverse events leading to withdrawal of investigational product	447 (10.9)	106 (13.1)	71 (8.8)	60 (7.4)	95 (11.9)	88 (10.8)
Serious	337 (8.2)	66 (8.1)	56 (7.0)	49 (6.0)	79 (9.9)	74 (9.0)
Nonserious	112 (2.7)	41 (5.1)	16 (2.0)	13 (1.6)	22 (2.8)	14 (1.7)

N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data.

Note: Percentages are based on N.

Table 59. Study 20110203 Summary of Adverse Events by Preferred Term Reported for **≥3%** Subjects in Any Treatment Group by Exposure Quintiles of the Last Measured Concentration up to Week 12 (Safety Analysis Set)

	Placebo	Omecamtiv Mecarbil (ng/mL) Quintile Bins of Last Concentration up to Week 12				
		<145	145-<225	225-<301	301-<377	**≥377**
	(N=4101) n (%)	(N=810) n (%)	(N=803) n (%)	(N=813) n (%)	(N=795) n (%)	(N=818) n (%)
Number of participants reporting AEs	3622 (88.3)	696 (85.9)	690 (85.9)	716 (88.1)	700 (88.1)	745 (91.1)
Cardiac failure	1203 (29.3)	213 (26.3)	218 (27.1)	223 (27.4)	234 (29.4)	236 (28.9)
Atrial fibrillation	263 (6.4)	52 (6.4)	41 (5.1)	43 (5.3)	47 (5.9)	52 (6.4)
Cardiac failure acute	263 (6.4)	42 (5.2)	31 (3.9)	46 (5.7)	43 (5.4)	55 (6.7)
Dyspnoea	277 (6.8)	43 (5.3)	59 (7.3)	56 (6.9)	49 (6.2)	64 (7.8)
Hypotension	271 (6.6)	46 (5.7)	51 (6.4)	52 (6.4)	71 (8.9)	88 (10.8)
Acute kidney injury	225 (5.5)	35 (4.3)	46 (5.7)	39 (4.8)	49 (6.2)	58 (7.1)
Hyperkalaemia	230 (5.6)	32 (4.0)	43 (5.4)	45 (5.5)	48 (6.0)	48 (5.9)
Pneumonia	292 (7.1)	50 (6.2)	43 (5.4)	59 (7.3)	57 (7.2)	47 (5.7)
Cardiac failure chronic	210 (5.1)	26 (3.2)	49 (6.1)	37 (4.6)	37 (4.7)	51 (6.2)
Dizziness	189 (4.6)	37 (4.6)	49 (6.1)	53 (6.5)	52 (6.5)	45 (5.5)
Ventricular tachycardia	184 (4.5)	34 (4.2)	39 (4.9)	25 (3.1)	35 (4.4)	38 (4.6)
Cardiac failure congestive	184 (4.5)	48 (5.9)	21 (2.6)	26 (3.2)	31 (3.9)	36 (4.4)
Urinary tract infection	161 (3.9)	36 (4.4)	24 (3.0)	26 (3.2)	32 (4.0)	36 (4.4)
Diarrhoea	192 (4.7)	31 (3.8)	26 (3.2)	34 (4.2)	42 (5.3)	44 (5.4)
Oedema peripheral	168 (4.1)	19 (2.3)	33 (4.1)	22 (2.7)	27 (3.4)	50 (6.1)
Renal impairment	176 (4.3)	23 (2.8)	25 (3.1)	43 (5.3)	47 (5.9)	45 (5.5)
Gout	152 (3.7)	19 (2.3)	30 (3.7)	35 (4.3)	27 (3.4)	31 (3.8)
Nasopharyngitis	194 (4.7)	34 (4.2)	30 (3.7)	47 (5.8)	38 (4.8)	37 (4.5)
Hypertension	229 (5.6)	38 (4.7)	41 (5.1)	46 (5.7)	38 (4.8)	35 (4.3)
Upper respiratory tract infection	172 (4.2)	26 (3.2)	35 (4.4)	33 (4.1)	35 (4.4)	54 (6.6)
Anaemia	164 (4.0)	24 (3.0)	29 (3.6)	35 (4.3)	40 (5.0)	22 (2.7)
Bronchitis	187 (4.6)	27 (3.3)	23 (2.9)	36 (4.4)	28 (3.5)	29 (3.5)
Chronic kidney disease	143 (3.5)	14 (1.7)	26 (3.2)	28 (3.4)	29 (3.6)	47 (5.7)

	Placebo	Omecamtiv Mecarbil (ng/mL) Quintile Bins of Last Concentration up to Week 12				
		<145	145-<225	225-<301	301-<377	**≥377**
	(N=4101) n (%)	(N=810) n (%)	(N=803) n (%)	(N=813) n (%)	(N=795) n (%)	(N=818) n (%)
Cough	169 (4.1)	18 (2.2)	30 (3.7)	35 (4.3)	32 (4.0)	34 (4.2)
Weight increased	117 (2.9)	25 (3.1)	29 (3.6)	21 (2.6)	25 (3.1)	26 (3.2)
Constipation	90 (2.2)	11 (1.4)	18 (2.2)	17 (2.1)	21 (2.6)	26 (3.2)
Fatigue	110 (2.7)	20 (2.5)	18 (2.2)	17 (2.1)	22 (2.8)	25 (3.1)
Headache	134 (3.3)	34 (4.2)	15 (1.9)	28 (3.4)	18 (2.3)	18 (2.2)
Influenza	105 (2.6)	22 (2.7)	23 (2.9)	18 (2.2)	16 (2.0)	28 (3.4)
Renal failure	100 (2.4)	16 (2.0)	17 (2.1)	23 (2.8)	25 (3.1)	33 (4.0)
Syncope	107 (2.6)	23 (2.8)	25 (3.1)	29 (3.6)	21 (2.6)	22 (2.7)
Angina pectoris	87 (2.1)	30 (3.7)	17 (2.1)	23 (2.8)	31 (3.9)	17 (2.1)
Back pain	121 (3.0)	20 (2.5)	23 (2.9)	36 (4.4)	23 (2.9)	29 (3.5)
Chronic obstructive pulmonary disease	99 (2.4)	21 (2.6)	16 (2.0)	27 (3.3)	22 (2.8)	24 (2.9)
Diabetes mellitus	133 (3.2)	20 (2.5)	27 (3.4)	28 (3.4)	26 (3.3)	17 (2.1)
Hypokalaemia	125 (3.0)	21 (2.6)	12 (1.5)	13 (1.6)	24 (3.0)	36 (4.4)
Chest pain	88 (2.1)	16 (2.0)	19 (2.4)	26 (3.2)	24 (3.0)	18 (2.2)
Cardiogenic shock	69 (1.7)	9 (1.1)	18 (2.2)	13 (1.6)	10 (1.3)	25 (3.1)
Arthralgia	103 (2.5)	9 (1.1)	11 (1.4)	27 (3.3)	19 (2.4)	25 (3.1)

N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data.

Note: Percentages are based on N.

The evaluation of death is based on adjudicated events; therefore, the preferred term death is not presented in the above table

Table 60. Study 20110203 Summary of Ventricular Tachyarrhythmias (SMQ) by Exposure Quintiles of the Last Measured Concentration up to Week 12 (Safety Analysis Set)

	Placebo	Omecamtiv Mecarbil **(µg/L)** Quintile Bins of Last Concentration up to Week 12				
		<145	145-<225	225-<301	301-<377	**≥377**
	(N=4101) n (%)	(N=810) n (%)	(N=803) n (%)	(N=813) n (%)	(N=795) n (%)	(N=818) n (%)
Any AEs of Ventricular Tachyarrhythmias (SMQ)	304 (7.4)	50 (6.2)	75 (9.3)	48 (5.9)	58 (7.3)	57 (7.0)

	Placebo	Omecamtiv Mecarbil **(µg/L)** Quintile Bins of Last Concentration up to Week 12				
		<145	145-<225	225-<301	301-<377	**≥377**
	(N=4101) n (%)	(N=810) n (%)	(N=803) n (%)	(N=813) n (%)	(N=795) n (%)	(N=818) n (%)
Ventricular tachycardia	184 (4.5)	34 (4.2)	39 (4.9)	25 (3.1)	35 (4.4)	38 (4.6)
Ventricular extrasystoles	61 (1.5)	6 (0.7)	17 (2.1)	14 (1.7)	10 (1.3)	10 (1.2)
Ventricular fibrillation	52 (1.3)	9 (1.1)	13 (1.6)	5 (0.6)	6 (0.8)	4 (0.5)
Ventricular arrhythmia	31 (0.8)	4 (0.5)	10 (1.2)	8 (1.0)	11 (1.4)	6 (0.7)
Ventricular tachyarrhythmia	8 (0.2)	3 (0.4)	2 (0.2)	3 (0.4)	1 (0.1)	0 (0.0)
Ventricular parasystole	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Ventricular flutter	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)

MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data; SMQ=Standardised MedDRA Query.

Note: Percentages are based on N.

Table 61. Study 20110203 Summary of Adjudicated Death, Major Cardiac Ischaemic Events, and Stroke by Exposure Quintiles of the Last Measured Concentration up to Week 12 (Safety Analysis Set)

	Placebo	Omecamtiv Mecarbil **(µg/L)** Quintile Bins of Last Concentration up to Week 12				
		<145	145-<225	225-<301	301-<377	**≥377**
	(N=4101) n (%)	(N=810) n (%)	(N=803) n (%)	(N=813) n (%)	(N=795) n (%)	(N=818) n (%)
CV Death	797 (19.4)	179 (22.1)	160 (19.9)	123 (15.1)	141 (17.7)	172 (21.0)
Non-CV death	190 (4.6)	21 (2.6)	34 (4.2)	30 (3.7)	31 (3.9)	35 (4.3)
Undetermined/ unknown death	75 (1.8)	21 (2.6)	14 (1.7)	24 (3.0)	15 (1.9)	20 (2.4)
Adjudicated Major Cardiac Ischaemic Event	188 (4.6)	48 (5.9)	37 (4.6)	41 (5.0)	45 (5.7)	27 (3.3)
Myocardial Infarction	118 (2.9)	33 (4.1)	22 (2.7)	20 (2.5)	29 (3.6)	16 (2.0)
Hospitalisation for Unstable Angina	12 (0.3)	7 (0.9)	5 (0.6)	6 (0.7)	4 (0.5)	3 (0.4)

	Placebo	Omecamtiv Mecarbil **(µg/L)** Quintile Bins of Last Concentration up to Week 12				
		<145	145-<225	225-<301	301-<377	**≥377**
	(N=4101) n (%)	(N=810) n (%)	(N=803) n (%)	(N=813) n (%)	(N=795) n (%)	(N=818) n (%)
Coronary Re-vascularisation	117 (2.9)	29 (3.6)	20 (2.5)	23 (2.8)	27 (3.4)	16 (2.0)
Adjudicated Stroke	112 (2.7)	19 (2.3)	14 (1.7)	14 (1.7)	9 (1.1)	20 (2.4)

CV=cardiovascular; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data.

Note: Percentages are based on N.

Hepatobiliary disorders

CV outcome study of chronic HF (GALACTIC-HF)

No imbalance was observed in the Hepatobiliary disorders SOC as reported by the investigators in Study the CV outcome Study 20110203. The overall incidence of AEs in the hepatobiliary disorders SOC was 202 (4.9%) participants in the omecamtiv mecarbil group and 204 (5.0%) participants in the placebo group, and AE incidence by preferred term was similar across treatment groups (Table 62). Incidence of SAEs (2.0% each) and AEs leading to withdrawal of IP (0.3% each) in the hepatobiliary disorders SOC were also similar between treatment groups.

Table 62. AEs in the System Organ Class Hepatobiliary Disorders by High Level Term and Preferred Term in **≥0.5%** of Participants in CV Outcome Study of Chronic HF (Safety Analysis Set)

System Organ Class High Level Term Preferred Term	CV Outcome Study of Chronic HF	
	Oral Placebo (N=4,101) n (%)	Oral OM PK-guided titration (N=4,110) n (%)
Hepatobiliary disorders	204 (5.0)	202 (4.9)
Cholecystitis and cholelithiasis	73 (1.8)	62 (1.5)
Cholelithiasis	34 (0.8)	28 (0.7)
Cholecystitis	17 (0.4)	20 (0.5)
Cholecystitis acute	20 (0.5)	15 (0.4)
Hepatocellular damage and hepatitis NEC	50 (1.2)	47 (1.1)
Hepatic steatosis	20 (0.5)	17 (0.4)
Cholestasis and jaundice	19 (0.5)	23 (0.6)
Hyperbilirubinaemia	12 (0.3)	19 (0.5)
Hepatic enzymes and function abnormalities	19 (0.5)	12 (0.3)
Hepatic function abnormal	19 (0.5)	12 (0.3)

System Organ Class	CV Outcome Study of Chronic HF	
Hepatic vascular disorders	18 (0.4)	12 (0.3)
Congestive hepatopathy	11 (0.3)	11 (0.3)

AE=adverse event; CV=cardiovascular; HF=heart failure; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants who received at least one dose of IP post randomisation for studies with randomisation or post enrollment for studies without randomisation; n=number of participants with valid observations: NEC=not elsewhere classified; OM=omecamtiv mecarbil; PK=pharmacokinetic.
Percentages are based on N.
Coded using MedDRA version 23.0.

Renal and Urinary disorders

CV outcome study of chronic HF (GALACTIC-HF)

No imbalance was observed in the Renal and urinary disorders SOC, as reported by the investigators in Study 20110203. The overall incidence of AEs in the renal and urinary disorders SOC was 721 (17.5%) participants in the omecamtiv mecarbil group and 713 (17.4%) participants in the placebo group, and AE incidence by the preferred term was similar across treatment groups (Table 63). Incidence of SAEs (5.6% vs 6.2%) and AEs leading to IP discontinuation (0.9% vs 0.6%) in the Renal and urinary disorders SOC were also similar between treatment groups.

Table 63. AEs in the System Organ Class Renal and Urinary Disorders by High Level Term and Preferred Term in **≥0.5%** of Participants in the CV Outcome Study of Chronic HF (Safety Analysis Set)

	CV Outcome Study of Chronic HF	
System Organ Class High Level Term Preferred Term	Oral Placebo (N=4,101) n (%)	Oral OM PK-guided titration (N=4,110) n (%)
Renal and urinary disorders	713 (17.4)	721 (17.5)
Renal failure and impairment	596 (14.5)	612 (14.9)
Acute kidney injury	225 (5.5)	230 (5.6)
Renal impairment	176 (4.3)	183 (4.5)
Chronic kidney disease	143 (3.5)	146 (3.6)
Renal failure	100 (2.4)	114 (2.8)
Bladder and urethral symptoms	57 (1.4)	46 (1.1)
Urinary retention	24 (0.6)	20 (0.5)
Dysuria	19 (0.5)	11 (0.3)
Urinary abnormalities	50 (1.2)	38 (0.9)
Haematuria	41 (1.0)	30 (0.7)
Proteinuria	7 (0.2)	6 (0.1)
Renal neoplasms	18 (0.4)	23 (0.6)
Renal cyst	17 (0.4)	22 (0.5)

	CV Outcome Study of Chronic HF	
Urinary tract signs and symptoms NEC	8 (0.2)	11 (0.3)

AE=adverse event; CV=cardiovascular; HF=heart failure; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with valid observations; NEC=not elsewhere classified; OM=omecamtiv mecarbil; PK=pharmacokinetic.
Percentages are based on N.
Coded using MedDRA version 23.0.

Eye disorders

The incidence in eye disorders was slightly higher in the omecamtiv mecarbil group compared with the placebo group (3.4% vs. 3.0%)(Table 64).

Table 64. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (n **≥2)** – Study 20110203 (safety Analysis Set)

System Organ Class Preferred Term	Recently and not currently hospitalized for heart failure Placebo (N = 3067) n (%)	 AMG 423 (N = 3070) n (%)	Currently hospitalized for heart failure Placebo (N = 1034) n (%)	 AMG 423 (N = 1040) n (%)	Overall Placebo (N = 4101) n (%)	 AMG 423 (N = 4110) n (%)
Eye disorders	100 (3.3)	113 (3.7)	25 (2.4)	26 (2.5)	125 (3.0)	139 (3.4)
Cataract	29 (0.9)	45 (1.5)	12 (1.2)	13 (1.3)	41 (1.0)	58 (1.4)
Vision blurred	6 (0.2)	10 (0.3)	0 (0.0)	1 (<0.1)	6 (0.1)	11 (0.3)
Glaucoma	3 (<0.1)	7 (0.2)	1 (<0.1)	1 (<0.1)	4 (<0.1)	8 (0.2)
Diabetic retinopathy	6 (0.2)	4 (0.1)	4 (0.4)	2 (0.2)	10 (0.2)	6 (0.1)
Visual impairment	6 (0.2)	5 (0.2)	1 (<0.1)	1 (<0.1)	7 (0.2)	6 (0.1)
Conjunctival haemorrhage	7 (0.2)	4 (0.1)	1 (<0.1)	1 (<0.1)	8 (0.2)	5 (0.1)
Retinal haemorrhage	1 (<0.1)	4 (0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)	5 (0.1)
Vitreous haemorrhage	2 (<0.1)	3 (<0.1)	1 (<0.1)	1 (<0.1)	3 (<0.1)	4 (<0.1)
Dry eye	6 (0.2)	3 (<0.1)	2 (0.2)	0 (0.0)	8 (0.2)	3 (<0.1)
Eye haemorrhage	5 (0.2)	2 (<0.1)	0 (0.0)	1 (<0.1)	5 (0.1)	3 (<0.1)
Visual acuity reduced	4 (0.1)	2 (<0.1)	1 (<0.1)	1 (<0.1)	5 (0.1)	3 (<0.1)
Astigmatism	2 (<0.1)	3 (<0.1)	0 (0.0)	0 (0.0)	2 (<0.1)	3 (<0.1)
Pterygium	0 (0.0)	3 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	3 (<0.1)
Diplopia	4 (0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	4 (<0.1)	2 (<0.1)
Conjunctivitis allergic	3 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	3 (<0.1)	2 (<0.1)
Blepharitis	1 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)
Retinopathy hypertensive	0 (0.0)	2 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)	2 (<0.1)
Amaurosis	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Eye irritation	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Mydriasis	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Retinal detachment	0 (0.0)	1 (<0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	2 (<0.1)
Retinal vein occlusion	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)

Skin and subcutaneous tissue disorders

The incidence in skin disorders was slightly higher in the omecamtiv mecarbil group compared with the placebo group (3.4% vs. 3.0%)(Table 65).

Table 65. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (n **≥5)** – Study 20110203 (Safety Analysis Set)

System Organ Class Preferred Term	Recently and not currently hospitalized for heart failure Placebo (N = 3067) n (%)	 AMG 423 (N = 3070) n (%)	Currently hospitalized for heart failure Placebo (N = 1034) n (%)	 AMG 423 (N = 1040) n (%)	Overall Placebo (N = 4101) n (%)	 AMG 423 (N = 4110) n (%)

Skin and subcutaneous tissue disorders	234 (7.6)	263 (8.6)	77 (7.4)	76 (7.3)	311 (7.6)	339 (8.2)
Pruritus	44 (1.4)	52 (1.7)	16 (1.5)	20 (1.9)	60 (1.5)	72 (1.8)
Rash	29 (0.9)	37 (1.2)	12 (1.2)	5 (0.5)	41 (1.0)	42 (1.0)
Skin ulcer	24 (0.8)	34 (1.1)	6 (0.6)	7 (0.7)	30 (0.7)	41 (1.0)
Eczema	7 (0.2)	13 (0.4)	2 (0.2)	8 (0.8)	9 (0.2)	21 (0.5)
Hyperhidrosis	9 (0.3)	14 (0.5)	3 (0.3)	4 (0.4)	12 (0.3)	18 (0.4)
Urticaria	7 (0.2)	9 (0.3)	2 (0.2)	5 (0.5)	9 (0.2)	14 (0.3)
Diabetic foot	8 (0.3)	10 (0.3)	4 (0.4)	3 (0.3)	12 (0.3)	13 (0.3)
Dermatitis allergic	2 (<0.1)	6 (0.2)	6 (0.6)	5 (0.5)	8 (0.2)	11 (0.3)
Alopecia	4 (0.1)	9 (0.3)	1 (<0.1)	1 (<0.1)	5 (0.1)	10 (0.2)
Dry skin	8 (0.3)	7 (0.2)	1 (<0.1)	2 (0.2)	9 (0.2)	9 (0.2)
Erythema	7 (0.2)	7 (0.2)	0 (0.0)	2 (0.2)	7 (0.2)	9 (0.2)
Ecchymosis	5 (0.2)	8 (0.3)	1 (<0.1)	1 (<0.1)	6 (0.1)	9 (0.2)
Dermatitis	14 (0.5)	5 (0.2)	0 (0.0)	2 (0.2)	14 (0.3)	7 (0.2)
Dermatitis contact	1 (<0.1)	6 (0.2)	1 (<0.1)	1 (<0.1)	2 (<0.1)	7 (0.2)
Decubitus ulcer	7 (0.2)	4 (0.1)	5 (0.5)	1 (<0.1)	12 (0.3)	5 (0.1)
Stasis dermatitis	4 (0.1)	4 (0.1)	1 (<0.1)	1 (<0.1)	5 (0.1)	5 (0.1)

3.3.7.4. Laboratory findings

Clinical chemistry

CV outcome study of chronic HF (GALACTIC-HF)

No noteworthy changes from baseline in chemistry parameters, including creatinine, total bilirubin, direct bilirubin, ALP, ALT, AST, and potassium, were observed between the OM and placebo treatment groups or between the outpatient and inpatient randomisation settings for these laboratory parameters.

Liver function test

CV outcome study of chronic HF (GALACTIC-HF)

The incidence of subjects with any postbaseline abnormalities was low in both treatment groups (Table 66). Among subjects any postbaseline measurements, slight imbalances were observed between the OM and placebo groups, i.e. ALT or AST >3 × ULN at any post-baseline visit occurred in 2.3% of participants in the omecamtiv mecarbil group and 2.1% of participants in the placebo group; ALT or AST >5 × ULN at any post-baseline visit occurred in 1.0% of participants in the omecamtiv mecarbil group and 0.7% of participants in the placebo group; and ALT or AST >10 × ULN at any post-baseline visit occurred in 0.3% of participants in the omecamtiv mecarbil group and 0.1% of participants in the placebo group.

Table 66. Subject Incidence of Liver Function Test Abnormalities for all subjects Study 20110203 (Safety Analysis Set)

	Recently and Not Currently Hospitalized for Heart Failure		Currently Hospitalized for Heart Failure		Overall	
	Placebo (N = 3067) n (%)	AMG 423 (N = 3070) n (%)	Placebo (N = 1034) n (%)	AMG 423 (N = 1040) n (%)	Placebo (N = 4101) n (%)	AMG 423 (N = 4110) n (%)
Baseline						
Subjects with baseline ALT, AST, total bilirubin, or INR measurement - N1	3067	3069	1019	1027	4086	4096
ALT or AST > 3 x ULN	7 (0.2)	9 (0.3)	11 (1.1)	6 (0.6)	18 (0.4)	15 (0.4)
ALT or AST > 5 x ULN	2 (0.1)	2 (0.1)	3 (0.3)	1 (0.1)	5 (0.1)	3 (0.1)
ALT or AST > 10 x ULN	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
ALT or AST > 20 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total bilirubin > 2 x ULN	19 (0.6)	21 (0.7)	11 (1.1)	17 (1.7)	30 (0.7)	38 (0.9)
(ALT or AST > 3 x ULN) and (total bilirubin > 2 x ULN or INR[a] > 1.5)	1 (<0.1)	1 (<0.1)	1 (0.1)	0 (0.0)	2 (<0.1)	1 (<0.1)
(ALT or AST > 3 x ULN) and (total bilirubin > 2 x ULN or INR[a] > 1.5) and ALP < 2 x ULN	1 (<0.1)	1 (<0.1)	1 (0.1)	0 (0.0)	2 (<0.1)	1 (<0.1)
Any Postbaseline						
Subjects with any postbaseline ALT, AST, total bilirubin, or INR measurement - N1	2861	2863	910	937	3771	3800
ALT or AST > 3 x ULN	59 (2.1)	58 (2.0)	22 (2.4)	29 (3.1)	81 (2.1)	87 (2.3)
ALT or AST > 5 x ULN	21 (0.7)	22 (0.8)	6 (0.7)	16 (1.7)	27 (0.7)	38 (1.0)
ALT or AST > 10 x ULN	4 (0.1)	4 (0.1)	1 (0.1)	8 (0.9)	5 (0.1)	12 (0.3)
ALT or AST > 20 x ULN	3 (0.1)	1 (<0.1)	1 (0.1)	4 (0.4)	4 (0.1)	5 (0.1)
Total bilirubin > 2x ULN	61 (2.1)	48 (1.7)	31 (3.4)	30 (3.2)	92 (2.4)	78 (2.1)
(ALT or AST > 3 x ULN) and (total bilirubin > 2 x ULN or INR[a] > 1.5)	8 (0.3)	3 (0.1)	2 (0.2)	7 (0.7)	10 (0.3)	10 (0.3)
(ALT or AST > 3 x ULN) and (total bilirubin > 2 x ULN or INR[a] > 1.5) and ALP < 2 x ULN	4 (0.1)	1 (<0.1)	1 (0.1)	4 (0.4)	5 (0.1)	5 (0.1)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AMG 423 = omecamtiv mecarbil; AST = aspartate aminotransferase; INR = international normalized ratio; ULN = upper limit of normal

Notes: Based on measurements assessed by the central laboratory. N = Number of subjects randomized excluding study center 29002 and received at least 1 dose of investigational product. N1 = Number of subjects with at least 1 nonmissing measurement. n = Number of subjects meeting criterion. Percentages are based on N1.

[a] Not collected by the central laboratory.

Renal function test

CV outcome study of chronic HF (GALACTIC-HF)

No shifts or trends indicative of clinically important treatment related laboratory abnormalities were observed (Table 67).

Table 67. Summary of Change from Baseline to the Lowest Post-baseline in eGFR (mL/min/1.73 m2) CV Outcome Study of Chronic HF (Safety Analysis Set)

	CV Outcome Study of Chronic HF	
	Oral Placebo (N=4,101)	Oral OM PK-guided titration (N=4,110)
Baseline		
n	4,101	4,110
Mean (SD)	60.3 (21.8)	60.4 (21.8)
Median (Min, Max)	58.7 (13.6, 243.9)	58.9 (7.8, 204.8)
Q1, Q3	43.8, 73.7	44.3, 74.3
The lowest post-baseline		
n	3,770	3,799
Mean (SD)	50.9 (20.1)	51.1 (20.6)
Median (Min, Max)	49.5 (4.6, 177.5)	49.1 (3.7, 172.8)
Q1, Q3	35.9, 64.0	35.9, 64.3
Change from baseline to the lowest post-baseline		
n	3,770	3,799
Mean (SD)	-9.8 (13.5)	-9.8 (13.7)
Median (Min, Max)	-8.4 (-94.9, 60.5)	-8.7 (-119.4, 56.5)
Q1, Q3	-16.6, -1.6	-16.8, -1.8

CV=cardiovascular; HF=heart failure; eGFR=estimated glomerular filtration rate; IP=investigational product; Max=maximum; Min=minimum; N=Number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=Number of participants with observed data; OM=omecamtive mecarbil; PK=pharmacokinetic; Q1=first quartile; Q3=third quartile; SD=standard deviation.
Moderate Duration Studies of Chronic Heart Failure: 20110151 Expansion, 20120227; CV Outcome Study of Chronic Heart Failure: 20110203.

Troponin I

CV outcome study of chronic HF (GALACTIC-HF)

Small increases of troponin I were observed with omecamtiv mecarbil treatment compared with placebo starting at the first assessment. The overall median baseline value for troponin was 0.0270 ng/mL in the omecamtiv mecarbil group and 0.0270 ng/mL in the placebo group. The median changes from baseline in the omecamtiv mecarbil group were 0.0040 ng/mL at week 2, 0.0080 ng/mL at week 6, 0.0040 ng/mL at week 24, and 0.0020 ng/mL at weeks 48, 96, and 144, compared with no changes (0.000 ng/mL) in the placebo group at these timepoints. These observations were generally consistent in both randomisation settings, with no noteworthy differences between the outpatient and inpatient subjects in either treatment group. There was a poor correlation between omecamtiv mecarbil plasma concentrations and maximum change from baseline in troponin I (r2=0.00). Importantly, there was no imbalance in adjudicated MI by continuous or categorical analyses of maximal troponin excursion, indicating no clinically important adverse treatment effect related to threshold-defined troponin levels (Table 68 and Figure 27).

Shifts from baseline to the highest post-baseline troponin I (measurability and magnitude) by treatment group are provided in Table 69. The proportion of participants in the baseline category of

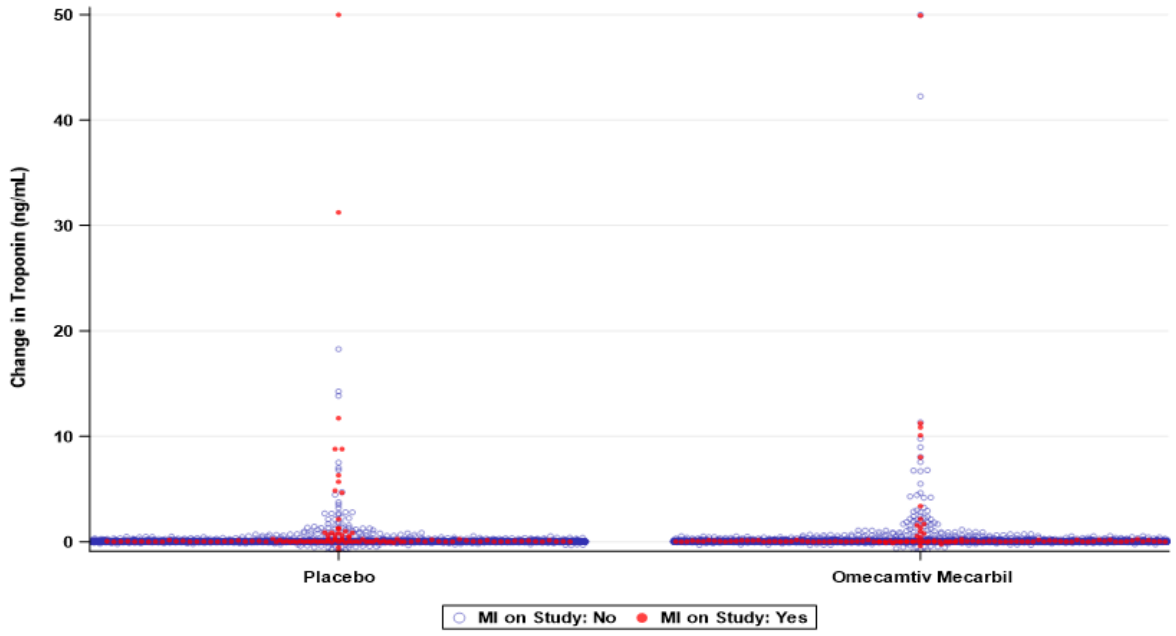
troponin >0.04 ng/mL was balanced between the treatment groups (30.6% omecamtiv mecarbil group, 30.7% placebo group). There was a moderately larger proportion of participants who shifted from the 0.016 to 0.04 ng/mL category to the >0.04 ng/mL category in the omecamtiv mecarbil group (21.7%) compared with the placebo group (14.9%) consistent with the small troponin I increase observed with omecamtiv mecarbil treatment.

Table 68. Positively Adjudicated Myocardial Infarction Diagnosis by Maximum Change from Post-baseline Troponin I (ng/mL) Category (Study 20110203)

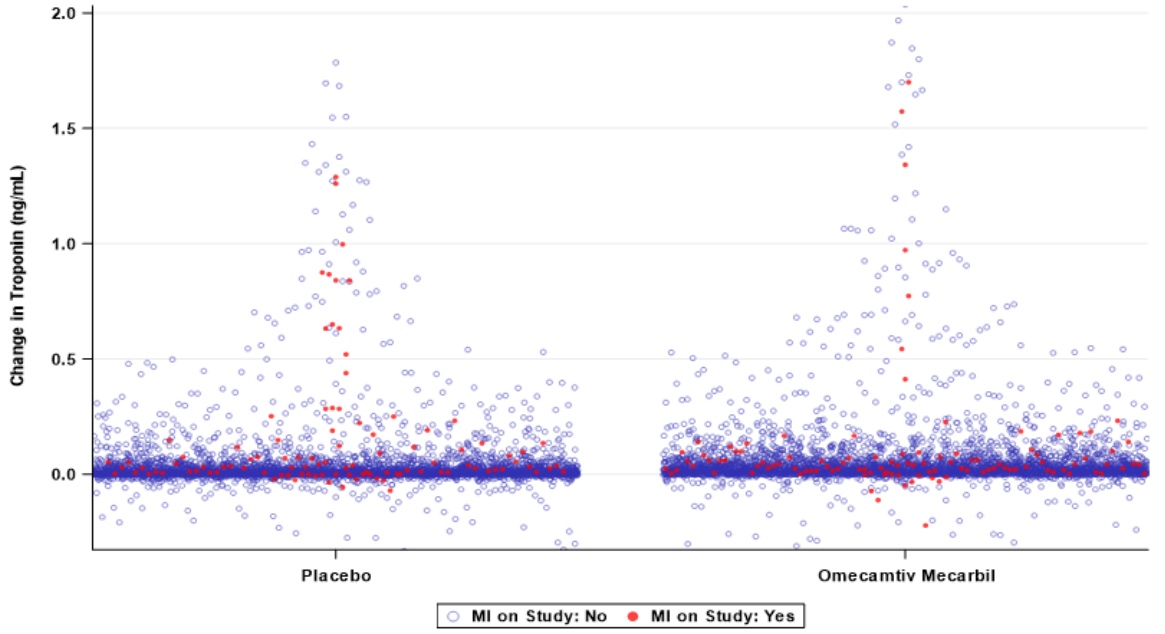
Maximum Troponin I Increase (ng/mL)	Placebo n/N (%)	Omecamtiv Mecarbil n/N (%)
<0	15/745 (2.0)	13/359 (3.6)
0- <0.04	43/2,387 (1.8)	45/2,285 (2.0)
≥0.04	56/847 (6.6)	61/1,355 (4.5)
≥2.0	10/31 (32.3)	7/36 (19.4)
≥10.0	3/6 (50.0)	4/7 (57.1)

IP=investigational product; N=number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data.

A 0-50 ng/mL



B 0-2.0 ng/mL



MI = myocardial infarction

Figure 27. Change from Baseline to the Highest Post-baseline Central Troponin by Treatment and Myocardial Infarction Status (Study 20110203, Safety Analysis Set)

Table 69. Shift Table From Study Baseline to the Worst (Highest) Postbaseline Troponin Category Study 20110203 (Safety Analysis Set)

	Highest Postbaseline Category				
Baseline Category	Missing n (%)	< 0.016 ng/mL n (%)	0–016 - 0.04 ng/mL n (%)	> 0.04 ng/mL n (%)	Total n (%)
Overall					
Placebo (N = 4101)					
Missing	4 (<0.1)	9 (0.2)	17 (0.4)	25 (0.6)	55 (1.3)
< 0.016 ng/mL	10 (0.2)	539 (13.1)	424 (10.3)	146 (3.6)	1119 (27.3)
0.016 - 0.04 ng/mL	20 (0.5)	81 (2.0)	784 (19.1)	686 (16.7)	1571 (38.3)
> 0.04 ng/mL	37 (0.9)	14 (0.3)	126 (3.1)	1179 (28.7)	1356 (33.1)
Total	71 (1.7)	643 (15.7)	1351 (32.9)	2036 (49.6)	4101 (100.0)
AMG 423 (N = 4110)					
Missing	1 (<0.1)	6 (0.1)	14 (0.3)	28 (0.7)	49 (1.2)
< 0.016 ng/mL	10 (0.2)	398 (9.7)	540 (13.1)	217 (5.3)	1165 (28.3)
0.016 - 0.04 ng/mL	17 (0.4)	34 (0.8)	469 (11.4)	1020 (24.8)	1540 (37.5)
> 0.04 ng/mL	35 (0.9)	7 (0.2)	47 (1.1)	1267 (30.8)	1356 (33.0)
Total	63 (1.5)	445 (10.8)	1070 (26.0)	2532 (61.6)	4110 (100.0)
Recently and not currently hospitalised for heart failure					
Placebo (N = 3067)					
Missing	0 (0.0)	6 (0.2)	7 (0.2)	12 (0.4)	25 (0.8)
< 0.016 ng/mL	7 (0.2)	450 (14.7)	352 (11.5)	115 (3.7)	924 (30.1)
0.016 - 0.04 ng/mL	8 (0.3)	50 (1.6)	628 (20.5)	533 (17.4)	1219 (39.7)
> 0.04 ng/mL	19 (0.6)	9 (0.3)	69 (2.2)	802 (26.1)	899 (29.3)
Total	34 (1.1)	515 (16.8)	1056 (34.4)	1462 (47.7)	3067 (100.0)
AMG 423 (N = 3070)					
Missing	0 (0.0)	4 (0.1)	5 (0.2)	10 (0.3)	19 (0.6)
< 0.016 ng/mL	9 (0.3)	337 (11.0)	442 (14.4)	183 (6.0)	971 (31.6)
0.016 - 0.04 ng/mL	10 (0.3)	30 (1.0)	370 (12.1)	772 (25.1)	1182 (38.5)
> 0.04 ng/mL	23 (0.7)	3 (<0.1)	24 (0.8)	848 (27.6)	898 (29.3)
Total	42 (1.4)	374 (12.2)	841 (27.4)	1813 (59.1)	3070 (100.0)
Currently hospitalised for heart failure					
Placebo (N = 1034)					
Missing	4 (0.4)	3 (0.3)	10 (1.0)	13 (1.3)	30 (2.9)
< 0.016 ng/mL	3 (0.3)	89 (8.6)	72 (7.0)	31 (3.0)	195 (18.9)
0.016 - 0.04 ng/mL	12 (1.2)	31 (3.0)	156 (15.1)	153 (14.8)	352 (34.0)
> 0.04 ng/mL	18 (1.7)	5 (0.5)	57 (5.5)	377 (36.5)	457 (44.2)
Total	37 (3.6)	128 (12.4)	295 (28.5)	574 (55.5)	1034 (100.0)
AMG 423 (N = 1040)					
Missing	1 (<0.1)	2 (0.2)	9 (0.9)	18 (1.7)	30 (2.9)
< 0.016 ng/mL	1 (<0.1)	61 (5.9)	98 (9.4)	34 (3.3)	194 (18.7)
0.016 - 0.04 ng/mL	7 (0.7)	4 (0.4)	99 (9.5)	248 (23.8)	358 (34.4)
> 0.04 ng/mL	12 (1.2)	4 (0.4)	23 (2.2)	419 (40.3)	458 (44.0)
Total	21 (2.0)	71 (6.8)	229 (22.0)	719 (69.1)	1040 (100.0)

Moderate Duration Studies of Chronic Heart Failure

The median baseline troponin value was 0.0190 ng/mL in the omecamtiv mecarbil PK-guided titration group, 0.0230 ng/mL in the other omecamtiv mecarbil group, and 0.0230 ng/mL in the placebo group. There was a larger median increase from baseline to the highest post-baseline value of troponin I in the omecamtiv mecarbil PK-guided titration group (0.018 ng/mL) and other omecamtiv mecarbil groups (0.016 ng/mL) compared with placebo (0.008 ng/mL). The proportion of participants in the baseline category of troponin >0.04 ng/mL was balanced between the treatment groups (24.9% omecamtiv mecarbil PK-guided titration group, 25.1% in the other omecamtiv mecarbil group, 24.1% placebo group). There was a moderately larger proportion of participants who shifted from the 0.016 to 0.04 ng/mL category to the >0.04 ng/mL category in the omecamtiv mecarbil PK guided titration group (28.6%) and other omecamtiv mecarbil groups (25.7%) compared with the placebo group (21.8%).

Creatine kinase - MB

CV outcome study of chronic HF (GALACTIC-HF)

The median baseline value for creatine kinase-MB (CK-MB) was 1.80 ng/mL in both treatment groups overall and lower among inpatient subjects compared with outpatient subjects. Small increases from baseline were observed in both treatment groups starting at the first assessment, and these increases were greater with OM compared with placebo. The median changes from baseline in the OM group were 0.40 ng/mL at week 2, 0.80 ng/mL at week 6, 0.70 ng/mL at week 24, 0.60 ng/mL at weeks 48 and 96, and 0.70 ng/mL at week 144, compared with increases that ranged from 0.10 to 0.40 ng/mL in the placebo group at these timepoints (Table 70). These increases in CK-MB were generally greater among inpatient subjects than outpatient subjects in both treatment groups.

Table 70. Summary of CK-MB (ng/mL) Change From Baseline to Week 24 Study 20110203 (Safety Analysis Set)

	Recently and Not Currently Hospitalized for Heart Failure		Currently Hospitalized for Heart Failure		Overall	
CK-MB, ng/mL	Placebo (N = 3067)	AMG 423 (N = 3070)	Placebo (N = 1034)	AMG 423 (N = 1040)	Placebo (N = 4101)	AMG 423 (N = 4110)
Baseline						
n	3044	3039	1001	1005	4045	4044
Mean	2.33	2.39	1.92	2.02	2.23	2.30
SD	2.19	2.04	1.49	3.06	2.05	2.34
Median	1.90	1.90	1.50	1.60	1.80	1.80
Q1, Q3	1.20, 2.80	1.20, 2.90	1.00, 2.40	1.00, 2.60	1.10, 2.70	1.20, 2.80
Min, Max	0.2, 60.9	0.2, 35.1	0.2, 13.3	0.2, 84.0	0.2, 60.9	0.2, 84.0
Change from baseline to week 24						
n	2653	2668	788	830	3441	3498
Mean	0.17	0.71	0.72	1.33	0.30	0.85
SD	1.69	1.81	2.12	3.35	1.81	2.29
Median	0.10	0.60	0.60	1.00	0.20	0.70
Q1, Q3	-0.40, 0.70	-0.10, 1.30	0.00, 1.20	0.30, 2.00	-0.30, 0.80	0.00, 1.50
Min, Max	-23.1, 31.0	-20.6, 15.0	-8.9, 35.4	-69.8, 24.6	-23.1, 35.4	-69.8, 24.6

AMG 423 = omecamtiv mecarbil; CK-MB = creatine kinase-MB
Notes: N = Number of subjects randomized excluding study center 29002 and received at least 1 dose of investigational product. n = Number of subjects with observed data.

Vital Signs

CV outcome study of chronic HF (GALACTIC-HF)

In 20110203, there were no notable differences between groups concerning blood pressure. The median baseline values were similar between the omecamtiv mecarbil and placebo groups for systolic (116.0 and 117.0 mm Hg, respectively) and diastolic (70.0 and 71.0 mm Hg) blood pressure. Overall, the changes from baseline in systolic and diastolic blood pressure were balanced between groups, and the absence of change was consistent over time.

A small decrease in heart rate was observed in the omecamtiv mecarbil group (1-2 bpm) compared with the placebo group (Table 71). The median changes from baseline in heart rate (pulse) across timepoints ranged from -2.0 to 0.0 bpm in the omecamtiv mecarbil group and from 0.0 to 2.0 bpm in the placebo group. These observations were generally consistent in both randomisation settings, with no noteworthy differences between the outpatient and inpatient participants in either treatment group.

Table 71. Summary of Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate Changes From Baseline to Week 24 (Study 20110203, Safety Analysis Set)

	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF		Overall	
	Placebo (N=3,067)	OM (N=3,070)	Placebo (N=1,034)	OM (N=1,040)	Placebo (N=4,101)	OM (N=4,110)
Systolic blood pressure, mm Hg						
Baseline						
n	3,067	3,070	1,034	1,040	4,101	4,110
Mean	117.7	117.0	113.6	114.1	116.6	116.3
SD	15.5	15.6	14.1	14.5	15.3	15.4
Median	118.0	117.0	114.0	115.0	117.0	116.0
Q1, Q3	106.0, 130.0	105.0, 130.0	103.0, 124.0	103.0, 125.0	105.0, 128.0	105.0, 128.0
Min, Max	75, 211	65, 187	82, 162	74, 159	75, 211	65, 187
Change from baseline to Week 24						
n	2,737	2,762	848	881	3,585	3,643
Mean	1.0	0.7	3.0	3.4	1.5	1.4
SD	15.1	15.1	16.9	15.8	15.6	15.3
Median	0.0	0.0	2.0	2.0	0.0	0.0
Q1, Q3	-9.0, 10.0	-9.0, 10.0	-8.0, 12.0	-7.0, 13.0	-8.0, 10.0	-8.0, 10.0
Min, Max	-65, 84	-67, 83	-72, 81	-47, 70	-72, 84	-67, 83
Diastolic blood pressure, mm Hg						
Baseline						
n	3,067	3,070	1,034	1,040	4,101	4,110
Mean	71.9	71.7	70.9	70.7	71.6	71.4
SD	10.3	10.4	10.0	9.9	10.3	10.3
Median	71.0	71.0	70.0	70.0	71.0	70.0

	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF		Overall	
	Placebo (N=3,067)	OM (N=3,070)	Placebo (N=1,034)	OM (N=1,040)	Placebo (N=4,101)	OM (N=4,110)
Q1, Q3	65.0, 80.0	64.0, 80.0	63.0, 80.0	63.0, 80.0	64.0, 80.0	64.0, 80.0
Min, Max	40, 114	33, 121	41, 102	40, 112	40, 114	33, 121
Change from baseline to Week 24						
n	2,736	2,762	848	880	3,584	3,642
Mean	0.3	0.1	0.4	1.5	0.3	0.5
SD	11.0	10.5	11.4	10.9	11.1	10.6
Median	0.0	0.0	0.0	1.0	0.0	0.0
Q1, Q3	-6.0, 7.0	-6.0, 7.0	-7.0, 8.0	-5.0, 9.0	-7.0, 7.0	-6.0, 7.0
Min, Max	-49, 61	-48, 43	-40, 57	-34, 43	-49, 61	-48, 43
Heart rate measured by pulse, beats/min						
Baseline						
n	3,067	3,070	1,034	1,040	4,101	4,110
Mean	72.1	72.2	73.1	73.2	72.3	72.4
SD	12.2	12.4	11.8	11.5	12.1	12.2
Median	70.0	70.0	72.0	72.0	71.0	71.0
Q1, Q3	63.0, 80.0	63.0, 80.0	64.0, 80.0	64.0, 80.0	64.0, 80.0	64.0, 80.0
Min, Max	40, 141	39, 150	45, 110	49, 118	40, 141	39, 150
Change from baseline to Week 24						
n	2,737	2,763	848	881	3,585	3,644
Mean	-0.6	-2.2	-0.4	-2.0	-0.5	-2.1
SD	12.4	12.3	13.8	13.3	12.8	12.6
Median	0.0	-2.0	0.0	-1.0	0.0	-2.0
Q1, Q3	-8.0, 6.0	-9.0, 4.0	-8.0, 8.0	-10.0, 6.0	-8.0, 6.0	-9.0. 5.0
Min, Max	-58, 65	-60, 60	-52, 102	-73, 42	-58, 102	-73, 60

HF=heart failure; Max=maximum; Min=minimum; N=number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil; PK=pharmacokinetic; Q1=first quartile; Q3=third quartile; SD=standard deviation.

QT prolongation

Consistent with results of the modified QT Study 20090231, there were no notable differences between treatment groups concerning ECG assessments in the overall population of 20110203, including no differences in corrected QT interval using Fredericia's formula (QTcF). In the analysis set of centrally read ECGs, the incidence of baseline and new post-baseline QTcF values (omecamtiv mecarbil, placebo) >450 msec (7.3%, 7.7%), >480 msec (2.8%, 3.1%) and >500 msec (1.2%, 1.4%) were

balanced between treatment groups. Maximum post baseline increases (omecamtiv mecarbil, placebo) in QTcF >30 msec (1.5%, 2.0%), and >60 msec (0.3%, 0.3%) were similar between the omecamtiv mecarbil and placebo groups. Note that the ECG analysis set of centrally read ECGs for these assessments was a small subset of the total participant population.

Participant incidences of baseline and new post-baseline ECG abnormalities in the omecamtiv mecarbil group were similar to those observed in the placebo group. Overall, small increases were observed in the PR interval in both the omecamtiv mecarbil and placebo groups, increases in the RR interval consistent with a decreased heart rate were observed in the omecamtiv mecarbil group compared with placebo, and small decreases in QRS duration were observed in the omecamtiv mecarbil group compared with increases in the placebo group.

In the absence of a signal in the overall population, analysis of ECG parameters was not conducted in the baseline LVEF <30% subgroup.

3.3.7.5. In vitro biomarker test for patient selection for safety

N/A

3.3.7.6. Safety in special populations

Subjects with LVEF<30%

Based on the results of the prespecified LVEF subgroup analyses and the supportive analysis of LVEF as a continuous variable indicating increasing treatment benefit with decreasing baseline ejection fraction, the proposed indication is the treatment of adult patients with symptomatic chronic heart failure and reduced ejection fraction <30%; this threshold is the upper limit for severely abnormal ejection fraction. Overall, the LVEF <30% cohort (4,704 participants; 57.1%), which includes 248 patients more than the LVEF ≤28% cohort, closely approximates the pre-specified subgroup of LVEF ≤28% (the median LVEF) (n=4,456; 54.1%) but is a more clinically practical and recognizable threshold. Compared with placebo, safety data (including frequency, severity, SAEs, and cardiac outcomes) were similar in the omecamtiv mecarbil group with baseline LVEF <30%.

Adverse events summary

The overall incidence of AEs was slightly lower in the omecamtiv mecarbil group compared with the placebo group in participants with baseline LVEF <30% (87.4% vs. 88.7%, respectively), including in the subgroups of participants who were recently and not currently hospitalised for heart failure (88.0% vs. 88.9%) as well as participants currently hospitalised for heart failure (85.5% vs 88.3%). In addition, the proportions of SAEs, fatal Aes, AEs Grade ≥3, and AEs leading to withdrawal were also slightly lower in the OM group than in the placebo group (Table 72).

Table 72. Summary of Subject Incidence of AEs in Participants with Baseline LVEF <30% (Study 20110203, Safety Analysis Set)

	Recently and Not Currently Hospitalised for Heart Failure		Currently Hospitalised for Heart Failure		Overall	
	Placebo (N=1,742) n (%)	OM (N=1,755) n (%)	Placebo (N=613) n (%)	OM (N=580) n (%)	Placebo (N=2,355) n (%)	OM (N=2,335) n (%)
All treatment-emergent adverse events	1,549 (88.9)	1,544 (88.0)	541 (88.3)	496 (85.5)	2,090 (88.7)	2,040 (87.4)
Grade ≥2	1,445 (83.0)	1,396 (79.5)	509 (83.0)	462 (79.7)	1,954 (83.0)	1,858 (79.6)
Grade ≥3	1,138 (65.3)	1,098 (62.6)	422 (68.8)	374 (64.5)	1,560 (66.2)	1,472 (63.0)
Grade ≥4	583 (33.5)	541 (30.8)	234 (38.2)	202 (34.8)	817 (34.7)	743 (31.8)
Serious adverse events	1,051 (60.3)	1,014 (57.8)	406 (66.2)	360 (62.1)	1,457 (61.9)	1,374 (58.8)
Leading to withdrawal of investigational product	230 (13.2)	177 (10.1)	66 (10.8)	74 (12.8)	296 (12.6)	251 (10.7)
Serious	182 (10.4)	137 (7.8)	50 (8.2)	60 (10.3)	232 (9.9)	197 (8.4)
Non-Serious	49 (2.8)	45 (2.6)	17 (2.8)	14 (2.4)	66 (2.8)	59 (2.5)
Fatal adverse events	367 (21.1)	358 (20.4)	155 (25.3)	133 (22.9)	522 (22.2)	491 (21.0)

AE=adverse event; LVEF=left ventricular ejection fraction; N=Number of subjects randomised excluding Site Number 29002 and received at least one dose of investigational product; n=number of participants with observed data; OM=omecamtiv mecarbil
Percentages are based on N.

Common adverse events

The most frequent AEs by preferred term were similar between participants in the omecamtiv mecarbil group and participants in the placebo group with baseline LVEF <30%, including in the subgroups of participants who were recently and not currently hospitalised for heart failure as well as participants currently hospitalised for heart failure. The most common AEs by preferred term in participants in the omecamtiv mecarbil group with baseline LVEF <30% were cardiac failure (27.8%), hypotension (8.2%), and dyspnoea (7.0%). In participants in the placebo group with baseline LVEF <30%, the most common AEs by preferred term were cardiac failure (31.0%), cardiac failure acute (7.6%), and dyspnoea (7.3%)(Table 73).

Table 73. Study 20110203 TEAEs by Preferred Term Reported by **≥5.0%** Participants in any treatment group by baseline LVEF <30% or **≥30%** (Safety Analysis Set)

Variable, n (%)	Omecamtiv Mecarbil N = 2,335	Placebo N = 2,355
LVEF < 30%		
Number of participants reporting TEAEs	2040 (87.4)	2090 (88.7)
Cardiac failure	649 (27.8)	730 (31.0)
Hypotension	192 (8.2)	167 (7.1)
Dyspnoea	163 (7.0)	172 (7.3)
Acute kidney injury	146 (6.3)	144 (6.1)
Pneumonia	145 (6.2)	166 (7.0)
Cardiac failure acute	142 (6.1)	179 (7.6)
Atrial fibrillation	142 (6.1)	146 (6.2)
Dizziness	136 (5.8)	108 (4.6)
Hyperkalaemia	124 (5.3)	132 (5.6)
Cardiac failure chronic	122 (5.2)	132 (5.6)
Upper respiratory tract infection	121 (5.2)	96 (4.1)
Ventricular tachycardia	115 (4.9)	127 (5.4)
Cardiac failure congestive	107 (4.6)	125 (5.3)
Hypertension	94 (4.0)	117 (5.0)
	Omecamtiv Mecarbil N = 1,775	**Placebo N = 1,746**
LVEF ≥ 30%		
Number of participants reporting TEAEs	1554 (87.5)	1532 (87.7)
Cardiac failure	483 (27.2)	473 (27.1)
Hypotension	117 (6.6)	104 (6.0)
Pneumonia	114 (6.4)	126 (7.2)
Dyspnoea	110 (6.2)	105 (6.0)
Hypertension	104 (5.9)	112 (6.4)
Dizziness	101 (5.7)	81 (4.6)
Atrial fibrillation	94 (5.3)	117 (6.7)
Hyperkalaemia	92 (5.2)	98 (5.6)
Diarrhoea	71 (4.0)	90 (5.2)

LVEF = left ventricular ejection fraction; N = number of participants; n = number of participants with observed data; SAE = serious adverse event; TEAE = treatment emergent adverse event.

Adverse events considered by investigators related to study drug

The participant incidence of AEs considered related to study drug was similar for the omecamtiv mecarbil group and the placebo group for the full population and for the population with LVEF <30% at baseline (Table 74).

Table 74. Study 20110203 Summary of Participant Incidence of Adverse Events Considered by Investigators to be Related to Omecamtiv Mecarbil

	Safety Analysis Set		LVEF <30%	
	Placebo (N=4,101) n (%)	Omecamtiv Mecarbil (N=4,110) n (%)	Placebo (N=2,355) n (%)	Omecamtiv Mecarbil (N=2,335) n (%)
All treatment-emergent adverse events	430 (10.5)	459 (11.2)	264 (11.2)	283 (12.1)
Grade ≥2	316 (7.7)	312 (7.6)	192 (8.2)	196 (8.4)
Grade ≥3	174 (4.2)	153 (3.7)	108 (4.6)	96 (4.1)
Grade ≥4	58 (1.4)	44 (1.1)	36 (1.5)	30 (1.3)
Serious adverse events	139 (3.4)	121 (2.9)	90 (3.8)	75 (3.2)
Adverse events leading to withdrawal of investigational product	99 (2.4)	99 (2.4)	58 (2.5)	57 (2.4)
Serious	41 (1.0)	42 (1.0)	26 (1.1)	28 (1.2)
Nonserious	58 (1.4)	58 (1.4)	32 (1.4)	30 (1.3)

Adverse drug reactions

The incidence of adverse drug reactions in subjects in Study 20110203 with baseline LVEF <30% were similar when compared to the overall population (Table 75).

Table 75. Potential Adverse Drug Reactions (Baseline LVEF <30%)

Adverse Drug Reaction (Preferred Term)	Omecamtiv Mecarbil[a] (N=2,335) n (%)	Placebo (N=2,355) n (%)	Frequency Category
Dizziness	136 (5.8)	108 (4.6)	Common
Myocardial Infarction (includes Acute Myocardial Infarction)	72 (3.1)	74 (3.1)	Common
Angina Pectoris (includes Angina Unstable, Myocardial Ischaemia)	105 (4.5)	68 (2.9)	Common

LVEF=left ventricular ejection fraction; N=Number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with valid observations.

[a] Incidence of preferred terms is provided from the safety population of Study 20110203.

Effects of dose and concentration on AEs

In participants with baseline LVEF <30%, there were no clinically meaningful differences in the safety events by any dose group compared with placebo (Table 76). As observed for the dose-response analyses, there were no clinically meaningful differences in these safety events by categories of omecamtiv mecarbil plasma concentration ranges compared with placebo (Table 77). Furthermore, exposure-safety analyses conducted in 2,238 participants with baseline LVEF <30% showed no exposure relationship with the major cardiac ischaemic event, myocardial infarction, coronary revascularisation, stroke, Torsade de Pointes/QT prolongation, ventricular arrhythmia, or ventricular arrhythmia leading to treatment.

Table 76. Safety Outcomes of Special Interest by Dose Group as Defined in SAP in Participants With Baseline LVEF <30% (Study 20110203, Safety Analysis Set)

Variable, n (%)	OM 25 mg BID (N=755) n (%)	OM 37.5 mg BID (N=346) n (%)	OM 50 mg BID (N=1,137) n (%)	OM Overall (N=2,238) n (%)	Placebo (N=2,221) n (%)
Any treatment-emergent serious adverse event	463 (61.3)	206 (59.5)	647 (56.9)	1,316 (58.8)	1,372 (61.8)
SMQ: Ventricular tachyarrhythmia	71 (9.4)	36 (10.4)	79 (6.9)	186 (8.3)	182 (8.2)
SMQ: Torsade de Pointes or QT prolongation[a]	45 (6.0)	23 (6.6)	49 (4.3)	117 (5.2)	130 (5.9)
Serious adverse ventricular arrhythmia leading to treatment	30 (4.0)	17 (4.9)	30 (2.6)	77 (3.4)	77 (3.5)
Adjudicated major cardiac ischaemic event	39 (5.2)	12 (3.5)	50 (4.4)	101 (4.5)	93 (4.2)
Myocardial infarction	25 (3.3)	8 (2.3)	32 (2.8)	65 (2.9)	62 (2.8)
Hospitalisation for unstable angina	3 (0.4)	2 (0.6)	2 (0.2)	7 (0.3)	4 (0.2)
Coronary revascularisation	25 (3.3)	7 (2.0)	27 (2.4)	59 (2.6)	56 (2.5)
Adjudicated stroke	13 (1.7)	4 (1.2)	20 (1.8)	37 (1.7)	62 (2.8)

IP=investigational product; LVEF=left ventricular ejection fraction; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil; PT=preferred term; SMQ=Standardised MedDRA Query.

[a] Although these events were included in this SMQ, no events with the PT of torsade de pointes were reported in the study.

Table 77. Safety Outcomes of Special Interest by Concentration Bin (<200, 200 - <750, **≥750)** in Subjects Having Titration Dose in Participants With Baseline LVEF <30% (Study 20110203, Safety Analysis Set)

Variable, n (%)	Omecamtiv Mecarbil			Placebo (N=2,221) n (%)
	PK Concentration <200 µg/L (N=712) n (%)	PK Concentration 200 - <750 µg/L (N=1,521) n (%)	PK Concentration **≥750** µg/L (N=5) n (%)	
Any treatment-emergent serious adverse event	423 (59.4)	890 (58.5)	3 (60.0)	1,372 (61.8)
SMQ: Ventricular tachyarrhythmia	61 (8.6)	125 (8.2)	0 (0.0)	182 (8.2)
SMQ: Torsade de Pointes or QT prolongation[a]	38 (5.3)	79 (5.2)	0 (0.0)	130 (5.9)
Serious adverse ventricular arrhythmia leading to treatment	24 (3.4)	53 (3.5)	0 (0.0)	77 (3.5)
Adjudicated major cardiac ischaemic event	37 (5.2)	64 (4.2)	0 (0.0)	93 (4.2)
Myocardial infarction	25 (3.5)	40 (2.6)	0 (0.0)	62 (2.8)
Hospitalisation for unstable angina	4 (0.6)	3 (0.2)	0 (0.0)	4 (0.2)
Coronary revascularisation	22 (3.1)	37 (2.4)	0 (0.0)	56 (2.5)
Adjudicated stroke	16 (2.2)	21 (1.4)	0 (0.0)	62 (2.8)

IP=investigational product; LVEF=left ventricular ejection fraction; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data; PK=pharmacokinetic; PT=preferred term; SMQ=Standardised MedDRA Query.

[a] Although these events were included in this SMQ, no events with the PT of torsade de pointes were reported in the study.

Serious Events

In participants with baseline LVEF <30%, the overall incidence of SAEs was similar between the omecamtiv mecarbil (58.8%) and placebo (61.9%) groups (Table 78). With regard to randomisation setting, in both treatment groups, fewer outpatient participants (56.4% omecamtiv mecarbil, 57.3% placebo) had SAEs compared with inpatient participants (61.5% omecamtiv mecarbil, 65.7% placebo). The most common SAEs by preferred term reported in the omecamtiv mecarbil and placebo groups were cardiac failure (24.2% omecamtiv mecarbil, 27.0% placebo), cardiac failure acute (5.8%, 7.3%), and cardiac failure congestive (4.1%, 4.4%).

Table 78. Study 20110203 Treatment-emergent SAEs by Preferred Term Reported by **≥2.0%** Participants in any Treatment Group by Baseline LVEF <30% or **≥30%** (Safety Analysis Set)

Variable, n (%)	Omecamtiv Mecarbil N = 2,335	Placebo N = 2,355
LVEF < 30%		
Number of participants reporting treatment-emergent SAEs	1374 (58.8)	1457 (61.9)
Cardiac failure	564 (24.2)	635 (27.0)
Cardiac failure acute	136 (5.8)	173 (7.3)
Cardiac failure congestive	95 (4.1)	104 (4.4)
Pneumonia	92 (3.9)	95 (4.0)
Cardiac failure chronic	89 (3.8)	106 (4.5)
Acute kidney injury	82 (3.5)	92 (3.9)
Ventricular tachycardia	69 (3.0)	90 (3.8)
Atrial fibrillation	59 (2.5)	67 (2.8)
Cardiogenic shock	47 (2.0)	46 (2.0)
	Omecamtiv Mecarbil N = 1,775	**Placebo N = 1,746**
LVEF ≥ 30%		
Number of participants reporting treatment-emergent SAEs	999 (56.3)	978 (56.0)
Cardiac failure	424 (23.9)	410 (23.5)
Pneumonia	79 (4.5)	84 (4.8)
Cardiac failure acute	76 (4.3)	78 (4.5)
Cardiac failure chronic	67 (3.8)	64 (3.7)
Cardiac failure congestive	52 (2.9)	50 (2.9)
Acute kidney injury	47 (2.6)	46 (2.6)
Ventricular tachycardia	37 (2.1)	39 (2.2)
Angina unstable	37 (2.1)	26 (1.5)
Atrial fibrillation	35 (2.0)	46 (2.6)

LVEF = left ventricular ejection fraction; N = number of participants; n = number of participants with observed data; SAE = serious adverse event.

Deaths

In the baseline LVEF <30% population, treatment-emergent all-cause death occurred in 27.0% (n=633) of the subjects in the omecamtiv mecarbil group and in 28.7% (n=679) of the subjects in the placebo group. Treatment-emergent CV death occurred in 20.3% (n=476) of the subjects in the omecamtiv mecarbil group and 22.1% (n=522) of the subjects in the placebo group (Table 79). Treatment-emergent fatal AEs occurred in fewer participants in the omecamtiv mecarbil group (491 [21.0%]) compared to participants in the placebo group (522 [22.2%]). The proportions of adjudicated non-CV deaths and undetermined/unknown deaths were smaller than that of CV deaths. Rates were similar with omecamtiv mecarbil and placebo for adjudicated non-CV deaths (3.8% omecamtiv mecarbil, 4.9% placebo) and undetermined/unknown deaths (2.8% omecamtiv mecarbil, 1.7% placebo).

Table 79. Participant Incidence of Positively Adjudicated CV Death in Participants With Baseline LVEF <30% (Study 20110203, Safety Analysis Set)

Event type Subtype	Placebo (N=2,355) n (%)	OM (N=2,335) n (%)
CV death	521 (22.1)	475 (20.3)
Due To An Acute MI	7 (0.3)	11 (0.5)
Due To CV Haemorrhage	2 (0.1)	3 (0.1)
Due To CV Procedure	7 (0.3)	4 (0.2)
Due To Heart Failure	274 (11.6)	252 (10.8)
Due To Stroke	20 (0.8)	8 (0.3)
Presumed CV Death	64 (2.7)	57 (2.4)
Presumed Sudden Death	27 (1.1)	40 (1.7)
Sudden Cardiac Death	114 (4.8)	94 (4.0)
Due To Other CV Causes	6 (0.3)	6 (0.3)

AEs of special interest

In the baseline LVEF <30% population, there was no meaningful difference between treatment groups in adjudicated MI or ventricular arrhythmias while there was a nominally significant reduction in adjudicated stroke with omecamtiv mecarbil (1.6%) compared to placebo (2.9%)(Table 80).

Table 80. Study 20110203 Safety Outcomes (Safety Analysis Set)

Variable N (%)	Baseline LVEF <30%		Overall Population	
	Omecamtiv Mecarbil (N=2,335)	Placebo (N=2,355)	Omecamtiv Mecarbil (N=3,941)	Placebo (N=3,896)
Any treatment-emergent serious adverse event	1374 (58.8)	1457 (61.9)	2,277 (57.8)	2,307 (59.2)
SMQ: Ventricular tachyarrhythmia[a]	187 (8.0)	188 (8.0)	286 (7.3)	296 (7.6)
SMQ: Torsade de Pointes or QT prolongation[bc]	118 (5.1)	133 (5.6)	286 (7.3)	190 (4.9)
Serious adverse ventricular arrhythmia leading to treatment	78 (3.3)	82 (3.5)	116 (2.9)	119 (3.1)

Variable N (%)	Baseline LVEF <30%		Overall Population	
	Omecamtiv Mecarbil (N=2,335)	Placebo (N=2,355)	Omecamtiv Mecarbil (N=3,941)	Placebo (N=3,896)
Adjudicated Major Cardiac Ischaemic Event	104 (4.5)	98 (4.2)	190 (4.8)	175 (4.5)
Myocardial Infarction	67 (2.9)	65 (2.8)	115 (2.9)	109 (2.8)
Hospitalisation for Unstable Angina	8 (0.3)	4 (0.2)	23 (0.6)	12 (0.3)
Coronary Revascularisation	60 (2.6)	60 (2.5)	111 (2.8)	108 (2.8)
Adjudicated Stroke	38 (1.6)	68 (2.9)	73 (1.9)	104 (2.7)

LVEF=left ventricular ejection fraction; N=number of participants who received at least one dose of investigational product post randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil; PT=preferred term; SMQ=Standardised MedDRA Query.

[a] Search was conducted using a broad SMQ.

[b] Search was conducted using a narrow SMQ.

[c] Although these events were included in this SMQ, no events with the PT of torsade de pointes were reported in the study.

AEs leading to withdrawal of investigational product

In participants with baseline LVEF <30%, the incidence of AEs that led to withdrawal of IP was slightly lower in the omecamtiv mecarbil group (10.7%) compared with the placebo group (12.6%). Most AEs leading to IP withdrawal occurred in the SOC Cardiac disorders for omecamtiv mecarbil (5.9%) and placebo (6.9%) treatment groups. The only AE leading to withdrawal of IP in ≥1% of participants in either treatment group was cardiac failure (2.7% omecamtiv mecarbil, 2.5% placebo).

Troponin I

In participants with baseline LVEF <30%, there was a small median increase from baseline to Week 24 in troponin I (0.004 ng/mL) in the omecamtiv mecarbil group compared with no change in the placebo group, but there was a poor correlation between omecamtiv mecarbil plasma concentrations and maximum change from baseline in troponin I (r2=0.00). Similar results were observed in the overall population.

Vital signs

In both the LVEF <30% and LVEF ≥30% subgroups, there were no notable differences in blood pressure, potassium, or creatine at Week 24 between treatment groups (Table 81), whereas a small increase in cardiac troponin I and a small decrease in heart rate (pulse) of approximately 1-2 bpm was observed in the omecamtiv mecarbil group compared with the placebo group.

Table 81. Study 20110203 Subgroup Vital Signs and Laboratory Parameters by Baseline LVEF <30% or **≥30%** (Safety Analysis Set)

Variable (Change from Baseline)	LVEF < 30%		LVEF ≥ 30%	
	Omecamtiv Mecarbil N = 2,335	Placebo N = 2,355	Omecamtiv Mecarbil N = 1,775	Placebo N = 1,746
Systolic Blook Pressure (mmHg)				
At Week 24	2.3 ± 15.5	1.9 ± 15.7	0.2 ± 15.0	1.0 ± 15.5
At Week 48	2.8 ± 16.2	2.2 ± 16.3	1.1 ± 15.8	1.5 ± 15.7
Heart Rate (bpm)				
At Week 24	-2.5 ± 13.0	-1.0 ± 12.9	-1.7 ± 12.0	0.1 ± 12.5
At Week 48	-2.6 ± 13.1	-0.6 ± 13.2	-1.1 ± 13.2	0.3 ± 13.2
Potassium (mmol/L)				
At Week 24	-0.01 ± 0.57	-0.02 ± 0.57	-0.01 ± 0.58	-0.00 ± 0.57
At Week 48	-0.04 ± 0.58	-0.03 ± 0.58	-0.01 ± 0.61	-0.01 ± 0.58
Creatinine (mg/dL)				
At Week 24	0.03 ± 0.33	0.02 ± 0.31	0.04 ± 0.34	0.03 ± 0.33
At Week 48	0.07 ± 0.44	0.05 ± 0.36	0.05 ± 0.32	0.05 ± 0.40
Median Cardiac Troponin I (IQR – ng/L)				
At Week 24	4 (-3 to 22)	0 (-10 to 9)	4 (-2 to 21)	0 (-9 to 7)
At Week 48	2 (-5 to 18)	0 (-10 to 9)	3 (-3 to 18)	0 (-8 to 8)

IQR = interquartile range; LVEF = left ventricular ejection fraction; N = number of participants; n = number of participants with observed data.

Subgroups of in- and outpatient subjects among subjects with LVEF <30%

General frequency of adverse events

For both the outpatients and inpatients with LVEF <30% at baseline, the omecamtiv mecarbil group had a trend of lower participant incidence of serious adverse events (SAEs) and Grade ≥4 AEs compared with the placebo group. In both treatment groups, the participant incidence of SAEs and Grade ≥4 AEs was approximately 5% higher in the inpatient versus outpatient participants with LVEF <30% at baseline (Table 82).

The overall incidence of AEs leading to discontinuation in the LVEF <30% population trended lower in the omecamtiv mecarbil group compared with placebo (n=251; 10.7% vs. n=296; 12.6%, respectively). AEs leading to discontinuation in the omecamtiv mecarbil group compared to placebo were numerically lower in outpatients and numerically higher in inpatients. Cardiac failure was the most common PT reported that led to discontinuation, reported at similar frequency for the omecamtiv mecarbil group and the placebo group with LVEF <30% (n=33; 1.9% and n=23, 1.3%, respectively). For both treatment groups, the incidence of cardiac failure was lower for inpatients than outpatients (2.1% and 4.3% for outpatients and inpatients, respectively, in the omecamtiv mecarbil group, and 2.3% and 2.9%, respectively in the placebo group). All other PTs leading to discontinuation were reported at an incidence <1%.

Table 82. Study 20110203 Summary of Participant Incidence of Adverse Events by Hospitalisation Status at Randomisation (Safety Analysis Set) in the Population with Baseline LVEF <30%

Number (%) of subjects with	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF	
	Placebo (N=1742) n (%)	Omecamtiv Mecarbil (N=1755) n (%)	Placebo (N=613) n (%)	Omecamtiv Mecarbil (N=580) n (%)
All treatment-emergent adverse events	1549 (88.9)	1544 (88.0)	541 (88.3)	496 (85.5)
Grade ≥2	1445 (83.0)	1396 (79.5)	509 (83.0)	462 (79.7)
Grade ≥3	1138 (65.3)	1098 (62.6)	422 (68.8)	374 (64.5)
Grade ≥4	583 (33.5)	541 (30.8)	234 (38.2)	202 (34.8)
Serious adverse events	1051 (60.3)	1014 (57.8)	406 (66.2)	360 (62.1)
Adverse events leading to withdrawal of investigational product	230 (13.2)	177 (10.1)	66 (10.8)	74 (12.8)
Serious	182 (10.4)	137 (7.8)	50 (8.2)	60 (10.3)
Nonserious	49 (2.8)	45 (2.6)	17 (2.8)	14 (2.4)

HF=heart failure; LVEF=left ventricular ejection fraction; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data.

Note: Percentages are based on N

Adverse events

No clinically relevant differences were noted between treatment groups by randomisation setting in the LVEF <30% population for the frequent or the less common AEs (Table 83). The most frequently reported AEs by PT (≥5% of participants in any treatment group) were generally similar between the treatments in the outpatient and inpatient subgroups in the LVEF <30% population. For both outpatients and inpatients, the most common events were associated with the chronic HF condition as expected in the study population, ie, cardiac failure events or known complications of chronic heart failure with reduced ejection fraction (HFrEF).

Table 83. Study 20110203 Summary of Adverse Events Reported by **≥5%** of Participants in Any Treatment Group by Preferred Term and by Hospitalisation Status at Randomisation (Safety Analysis Set) Population with Baseline LVEF <30%

Number (%) of subjects with	Recently and Not Currently Hospitalised for HF		Currently hospitalised for HF	
	Placebo (N=1742) n (%)	Omecamtiv Mecarbil (N=1755) n (%)	Placebo (N=613) n (%)	Omecamtiv Mecarbil (N=580) n (%)
Treatment-emergent adverse events	1549 (88.9)	1544 (88.0)	541 (88.3)	496 (85.5)
Cardiac failure	499 (28.6)	440 (25.1)	231 (37.7)	209 (36.0)
Hypotension	126 (7.2)	157 (8.9)	41 (6.7)	35 (6.0)
Dyspnoea	135 (7.7)	120 (6.8)	37 (6.0)	43 (7.4)
Acute kidney injury	110 (6.3)	113 (6.4)	34 (5.5)	33 (5.7)
Pneumonia	124 (7.1)	110 (6.3)	42 (6.9)	35 (6.0)
Cardiac failure acute	132 (7.6)	109 (6.2)	47 (7.7)	33 (5.7)
Atrial fibrillation	112 (6.4)	113 (6.4)	34 (5.5)	29 (5.0)
Dizziness	91 (5.2)	110 (6.3)	17 (2.8)	26 (4.5)
Hyperkalaemia	98 (5.6)	86 (4.9)	34 (5.5)	38 (6.6)
Cardiac failure chronic	100 (5.7)	86 (4.9)	32 (5.2)	36 (6.2)
Upper respiratory tract infection	74 (4.2)	101 (5.8)	22 (3.6)	20 (3.4)
Ventricular tachycardia	99 (5.7)	83 (4.7)	28 (4.6)	32 (5.5)
Cardiac failure congestive	100 (5.7)	83 (4.7)	25 (4.1)	24 (4.1)
Diarrhoea	67 (3.8)	85 (4.8)	35 (5.7)	22 (3.8)
Renal impairment	61 (3.5)	75 (4.3)	42 (6.9)	25 (4.3)
Hypertension	95 (5.5)	72 (4.1)	22 (3.6)	22 (3.8)
Bronchitis	92 (5.3)	69 (3.9)	17 (2.8)	15 (2.6)

HF=heart failure; LVEF=left ventricular ejection fraction; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data.
Note: Percentages are based on N.

Serious adverse events

The incidence of SAEs by PT was generally similar or lower between treatments in both the outpatient and inpatient subgroups in the LVEF <30% population. In both treatment groups with LVEF <30% at baseline, fewer outpatient participants had SAEs than inpatient participants (Table 84). As anticipated in this study population, the most common SAEs by PT occurring in ≥5% of participants in either treatment group were cardiac failure, cardiac failure acute, and cardiac failure congestive.

Table 84. Study 20110203 Summary of Serious Adverse Events Reported in **≥1%** of Participants in Any Treatment Group by Hospitalisation Status at Randomisation (Safety Analysis Set) Population with Baseline LVEF <30%

Number (%) of subjects with	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF	
	Placebo (N=1742) n (%)	Omecamtiv Mecarbil (N=1755) n (%)	Placebo (N=613) n (%)	Omecamtiv Mecarbil (N=580) n (%)
Treatment-emergent serious adverse events	1051 (60.3)	1014 (57.8)	406 (66.2)	360 (62.1)
Cardiac failure	428 (24.6)	376 (21.4)	207 (33.8)	188 (32.4)
Cardiac failure acute	128 (7.3)	104 (5.9)	45 (7.3)	32 (5.5)
Cardiac failure congestive	83 (4.8)	74 (4.2)	21 (3.4)	21 (3.6)
Pneumonia	69 (4.0)	68 (3.9)	26 (4.2)	24 (4.1)
Cardiac failure chronic	81 (4.6)	62 (3.5)	25 (4.1)	27 (4.7)
Acute kidney injury	68 (3.9)	66 (3.8)	24 (3.9)	16 (2.8)
Ventricular tachycardia	71 (4.1)	49 (2.8)	19 (3.1)	20 (3.4)
Atrial fibrillation	53 (3.0)	48 (2.7)	14 (2.3)	11 (1.9)
Cardiogenic shock	39 (2.2)	29 (1.7)	7 (1.1)	18 (3.1)
Acute myocardial infarction	28 (1.6)	32 (1.8)	6 (1.0)	8 (1.4)
Chronic obstructive pulmonary disease	23 (1.3)	32 (1.8)	6 (1.0)	2 (0.3)
Sepsis	30 (1.7)	21 (1.2)	9 (1.5)	10 (1.7)
Sudden death	20 (1.1)	25 (1.4)	17 (2.8)	6 (1.0)
Syncope	21 (1.2)	18 (1.0)	4 (0.7)	12 (2.1)
Cardiac arrest	27 (1.5)	23 (1.3)	13 (2.1)	6 (1.0)
Septic shock	18 (1.0)	24 (1.4)	5 (0.8)	4 (0.7)
Angina unstable	22 (1.3)	21 (1.2)	1 (0.2)	5 (0.9)
Hypotension	13 (0.7)	21 (1.2)	6 (1.0)	5 (0.9)
Myocardial infarction	25 (1.4)	18 (1.0)	4 (0.7)	6 (1.0)
Non-cardiac chest pain	12 (0.7)	17 (1.0)	7 (1.1)	5 (0.9)
Ventricular arrythmia	10 (0.6)	17 (1.0)	4 (0.7)	4 (0.7)
Angina pectoris	16 (0.9)	18 (1.0)	4 (0.7)	2 (0.3)
Chronic kidney disease	18 (1.0)	13 (0.7)	9 (1.5)	5 (0.9)
Renal impairment	11 (0.6)	13 (0.7)	9 (1.5)	5 (0.9)
Ventricular fibrillation	27 (1.5)	13 (0.7)	3 (0.5)	4 (0.7)
Ischaemic stroke	15 (0.9)	12 (0.7)	7 (1.1)	5 (0.9)
Cerebrovascular accident	14 (0.8)	12 (0.7)	6 (1.0)	1 (0.2)
Dyspnoea	11 (0.6)	9 (0.5)	8 (1.3)	8 (1.4)
Sudden cardiac death	15 (0.9)	14 (0.8)	9 (1.5)	2 (0.3)
Urinary tract infection	9 (0.5)	13 (0.7)	7 (1.1)	3 (0.5)
Renal failure	12 (0.7)	6 (0.3)	5 (0.8)	8 (1.4)

Number (%) of subjects with	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF	
	Placebo (N=1742) n (%)	Omecamtiv Mecarbil (N=1755) n (%)	Placebo (N=613) n (%)	Omecamtiv Mecarbil (N=580) n (%)
Respiratory tract infection	8 (0.5)	6 (0.3)	9 (1.5)	3 (0.5)

HF=heart failure; LVEF=left ventricular ejection fraction; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data.
Note: Percentages are based on N.
The evaluation of death is based on adjudicated events, therefore, the preferred term death is not presented in the above table

Deaths

The incidence of adjudicated all-cause and CV death was numerically lower in the omecamtiv mecarbil group compared with placebo in both the outpatient and inpatient subgroups in the LVEF <30% population (Table 85). There were no adjudicated individual causes of death for which there were clinically meaningful differences between treatments by randomisation setting. Time to CV death was directionally favourable for both the outpatient and inpatient subgroups in the LVEF <30% population: HR=0.86; [95% CI: 0.69, 1.08] and HR=0.94; [95% CI: 0.81, 1.10].

Table 85. Study 20110203 Summary of Adjudicated All Cause and Cardiovascular Deaths by Hospitalisation Status at Randomisation (Safety Analysis Set) Population with Baseline LVEF <30%

Number (%) of subjects with	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF	
	Placebo (N=1742) n (%)	Omecamtiv Mecarbil (N=1755) n (%)	Placebo (N=613) n (%)	Omecamtiv Mecarbil (N=580) n (%)
All-cause death	472 (27.1)	453 (25.8)	204 (33.3)	177 (30.5)
CV death	359 (20.6)	340 (19.4)	162 (26.4)	135 (23.3)
Due To An Acute MI	4 (0.2)	9 (0.5)	3 (0.5)	2 (0.3)
Due To CV Haemorrhage	1 (<0.1)	2 (0.1)	1 (0.2)	1 (0.2)
Due To CV Procedure	6 (0.3)	4 (0.2)	1 (0.2)	0 (0.0)
Due To Heart Failure	186 (10.7)	162 (9.2)	88 (14.4)	90 (15.5)
Due To Stroke	13 (0.7)	7 (0.4)	7 (1.1)	1 (0.2)
Presumed CV Death	46 (2.6)	44 (2.5)	18 (2.9)	13 (2.2)
Presumed Sudden Death	17 (1.0)	31 (1.8)	10 (1.6)	9 (1.6)
Sudden Cardiac	82 (4.7)	76 (4.3)	32 (5.2)	18 (3.1)
Due To Other CV Causes	4 (0.2)	5 (0.3)	2 (0.3)	1 (0.2)

CV=cardiovascular; HF=heart failure; LVEF=left ventricular ejection fraction; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data.

Note: Percentages are based on N

Ventriculara Tachyarrhythmias

In both treatment groups with LVEF <30% at baseline, more outpatient participants had ventricular tachyarrhythmias than inpatient participants (Table 86). There were no clinically meaningful differences in the incidence of ventricular tachyarrhythmias in the omecamtiv mecarbil group compared with the placebo group in either outpatients or inpatients.

Table 86. Study 20110203 Summary of Ventricular Tachyarrhythmias (SMQ) Narrow Search by Hospitalisation Status at Randomisation (Safety Analysis Set) Population with Baseline LVEF <30%

	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF	
Number (%) of subjects with	Placebo (N=1742) n (%)	Omecamtiv Mecarbil (N=1755) n (%)	Placebo (N=613) n (%)	Omecamtiv Mecarbil (N=580) n (%)
Ventricular tachyarrhythmias (SMQ)	145 (8.3)	145 (8.3)	43 (7.0)	42 (7.2)
Ventricular tachycardia	99 (5.7)	83 (4.7)	28 (4.6)	32 (5.5)
Ventricular arrhythmia	12 (0.7)	26 (1.5)	7 (1.1)	6 (1.0)
Ventricular extrasystoles	22 (1.3)	27 (1.5)	8 (1.3)	4 (0.7)
Ventricular fibrillation	29 (1.7)	18 (1.0)	4 (0.7)	4 (0.7)
Ventricular tachyarrhythmia	4 (0.2)	5 (0.3)	1 (0.2)	2 (0.3)
Ventricular flutter	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)
Ventricular parasystole	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)

HF=heart failure; LVEF=left ventricular ejection fraction; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants with observed data; SMQ=Standardised MedDRA Query.
Note: Percentages are based on N.

Major Ischaemic Events

In the LVEF <30% population, the overall incidence of adjudicated major cardiac ischaemic events (MCIE) was similar in the omecamtiv mecarbil group compared with placebo (n=104; 4.5% vs. n=98; 4.2%, respectively). These results are consistent with time to first MICIE (including death due to MI; HR=1.08; 95% CI: 0.82, 1,42]).

The number of MCIEs trended lower in the omecamtiv mecarbil group in outpatients while the number trended higher with omecamtiv mecarbil in inpatients, although the total number of events was relatively small in the inpatient subgroup (Table 87). These results are consistent with time to first MICIE (including death due to MI) in the outpatient and inpatient subgroups (HR=0.96 [95% CI: 0.71, 1.29]) and HR=1.93 [95% CI: 0.98, 3.79], respectively). The small number of MCIEs in the inpatient subgroup reduces the reliability of these results.

The incidence of adjudicated stroke trended lower with omecamtiv mecarbil compared with placebo in both outpatient and inpatient participants in the LVEF <30% population.

Table 87. Study 20110203 Summary of Adjudicated Major Cardiac Ischaemic Events and Stroke by Hospitalisation Status at Randomisation (Safety Analysis Set) Population with Baseline LVEF <30%

	Recently and Not Currently Hospitalised for HF		Currently Hospitalised for HF	
Number (%) of subjects with	Placebo (N=1742) n (%)	Omecamtiv Mecarbil (N=1755) n (%)	Placebo (N=613) n (%)	Omecamtiv Mecarbil (N=580) n (%)
Positively adjudicated major ischaemic events[a]	86 (4.9)	80 (4.6)	12 (2.0)	24 (4.1)
Myocardial infarction	56 (3.2)	49 (2.8)	9 (1.5)	18 (3.1)
Hospitalisation for unstable angina	4 (0.2)	6 (0.3)	0 (0.0)	2 (0.3)
Coronary revascularisation	52 (3.0)	50 (2.8)	8 (1.3)	10 (1.7)
Adjudicated stroke	50 (2.9)	31 (1.8)	18 (2.9)	7 (1.2)

HF=heart failure; LVEF=left ventricular ejection fraction; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; n=number of participants with observed data.
Note: Percentages are based on N.
[a] Major cardiac ischaemic events include fatal and nonfatal myocardial infarction, unstable angina hospitalisation, and coronary revascularisation.

Atrial fibrillation or flutter

In the prespecified subgroup analyses in 20110203 in the overall population, atrial fibrillation/flutter at baseline was observed to have one of the strongest univariate treatment covariate interactions for the primary composite endpoint (p=0.012), which remained significant in a multivariate model (p=0.006). In participants with atrial fibrillation/flutter compared to those without atrial fibrillation/flutter at baseline, a nominally significant increased risk of CV death was observed with omecamtiv mecarbil (HR=1.26; 95% CI 1.07, 1.49 vs. HR=0.90; 95% CI 0.80, 1.02, respectively).

Further analyses indicated that risk was mostly concentrated in a small subgroup of participants who were also receiving digoxin at baseline. Participants receiving digoxin but without atrial fibrillation/flutter at baseline did not experience increased risk. The potential risk associated with atrial fibrillation/flutter and digoxin use could not be explained by a PK interaction between omecamtiv mecarbil and digoxin or any other plausible mechanism.

Post hoc analyses did not suggest that the increased risk of CV death in the subgroup with baseline atrial fibrillation/flutter was related to myocardial ischaemia based on the observation that there was no increased incidence of MI, ventricular arrhythmias or sudden cardiac death with omecamtiv mecarbil versus placebo (Table 88). In contrast, there was a higher incidence of HF as an adjudicated cause of CV death in participants with atrial fibrillation/flutter who were treated with omecamtiv mecarbil compared with placebo. The incidence of stroke was decreased with omecamtiv mecarbil versus placebo in both participants with and without atrial fibrillation/flutter at baseline.

Table 88. Safety Outcomes of Special Interest for Participants with Atrial Fibrillation/Flutter and Patients without Atrial Fibrillation/Flutter at Baseline (Study 20110203)

	No Atrial Fibrillation/Flutter		Atrial Fibrillation/Flutter	
Variable, n (%)	OM (N=2,965)	Placebo (N=3,005)	OM (N=1,145)	Placebo (N=1,096)
Any treatment-emergent serious adverse event	1,621 (54.7)	1,733 (57.7)	752 (65.7)	702 (64.1)
SMQ: Ventricular tachyarrhythmia	199 (6.7)	217 (7.2)	91 (7.9)	87 (7.9)
SMQ: Torsade de Pointes or QT prolongation[a]	118 (4.0)	130 (4.3)	58 (5.1)	65 (5.9)
Serious adverse ventricular arrhythmia leading to treatment	78 (2.6)	88 (2.9)	41 (3.6)	39 (3.6)
Adjudicated Major Cardiac Ischaemic Event	169 (5.7)	153 (5.1)	31 (2.7)	35 (3.2)
Myocardial Infarction	104 (3.5)	99 (3.3)	18 (1.6)	19 (1.7)
Hospitalisation for Unstable Angina	20 (0.7)	9 (0.3)	5 (0.4)	3 (0.3)
Coronary Revascularisation	95 (3.2)	90 (3.0)	20 (1.7)	27 (2.5)
Adjudicated Stroke	54 (1.8)	71 (2.4)	22 (1.9)	41 (3.7)
Adjudicated CV Death	499 (16.8)	548 (18.2)	307 (26.8)	249 (22.7)
Acute Myocardial Infarction	14 (0.5)	13 (0.4)	4 (0.3)	2 (0.2)
Heart Failure	226 (7.6)	266 (8.9)	187 (16.3)	123 (11.2)
Sudden Cardiac	120 (4.0)	132 (4.4)	52 (4.5)	58 (5.3)

CV=cardiovascular; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil; SMQ=Standardised MedDRA Query.

[a] Although these events were included in this SMQ, no events with the PT of torsade de pointes were reported in the study

Additional analyses of HF outcomes by presence or absence of baseline atrial fibrillation/flutter and by use of digoxin were consistent with the possibility that the increased risk observed in the subgroup of patients with atrial fibrillation/flutter with omecamtiv mecarbil treatment was concentrated in those patients also receiving digoxin. There was no difference between groups in the incidences of ventricular arrhythmias or adjudicated major cardiac ischaemic events. The most notable difference was the higher incidence of adjudicated CV death due to HF in the subgroup of patients with atrial fibrillation/flutter at baseline who were receiving concomitant digoxin and omecamtiv mecarbil (versus placebo) compared with the rest of the study cohort (63 [18.5%]) vs. 29 [8.3%], respectively) (Table 89).

Table 89. Safety Outcomes of Special Interest for Participants with Atrial Fibrillation/Flutter Receiving Digoxin Versus the Rest of Participants (Study 20110203)

	Patients with Atrial Fibrillation/ Flutter also Receiving Digoxin (N=690)		Rest of Study Patients (N=7,521)	
Variable, n (%)	OM (N=341)	Placebo (N=349)	OM (N=3,769)	Placebo (N=3,752)
Any treatment-emergent SAE	230 (67.4)	204 (58.5)	2,143 (56.9)	2,231 (59.5)
SMQ: Ventricular tachyarrhythmia	28 (8.2)	24 (6.9)	262 (7.0)	280 (7.5)
SMQ: Torsade de pointes /or QT prolongation[a]	17 (5.0)	16 (4.6)	159 (4.2)	179 (4.8)
Ventricular tachyarrhythmia leading to treatment	14 (4.1)	5 (1.4)	105 (2.8)	122 (3.3)
Adjudicated Major Cardiac Ischaemic Event	11 (3.2)	11 (3.2)	189 (5.0)	177 (4.7)
Myocardial Infarction	8 (2.3)	7 (2.0)	114 (3.0)	111 (3.0)
Hospitalisation for Unstable Angina	1 (0.3)	0 (0)	24 (0.6)	12 (0.3)
Coronary Revascularisation	6 (1.8)	9 (2.6)	109 (2.9)	108 (2.9)
Adjudicated Stroke	7 (2.1)	9 (2.6)	69 (1.8)	103 (2.7)
Adjudicated CV Death	102 (29.9)	70 (20.1)	704 (18.7)	727 (19.4)
Acute myocardial infarction	2 (0.6)	1 (0.3)	16 (0.4)	14 (0.4)
Heart Failure Death	63 (18.5)	29 (8.3)	350 (9.3)	360 (9.6)
Sudden Cardiac Death	21 (6.2)	21 (6.0)	151 (4.0)	169 (4.5)

CV=cardiovascular; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil; SAE=serious adverse event; SMQ=Standardised MedDRA Query.

[a] Although these events were included in this SMQ, no events with the PT of torsade de pointes were reported in the study.

Similar to the overall population, in participants with baseline LVEF <30%, incidences of ventricular tachyarrhythmias and major cardiac ischaemic events were not different between omecamtiv mecarbil and placebo by baseline atrial fibrillation or flutter (AF/F) status. While the incidence of CV death was lower in participants without baseline AFF treated with omecamtiv mecarbil when compared with placebo, the incidence of CV death was similar in those with baseline AF/F (Table 90). Finally, the incidence of stroke was decreased in participants with and without atrial fibrillation/flutter who were treated with omecamtiv mecarbil compared with placebo.

Table 90. Safety Outcomes of Special Interest for Participants with without Atrial Fibrillation/Flutter at Baseline in Participants With Baseline LVEF <30% (Study 20110203, Safety Analysis Set)

	No Atrial Fibrillation/Flutter		Atrial Fibrillation/Flutter	
Variable, n (%)	OM (N=1,746)	Placebo (N=1,761)	OM (N=589)	Placebo (N=594)
Any treatment-emergent serious adverse event	970 (55.6)	1,050 (59.6)	404 (68.6)	407 (68.5)
SMQ: Ventricular tachyarrhythmia	131 (7.5)	136 (7.7)	56 (9.5)	52 (8.8)
SMQ: Torsade de Pointes or QT prolongation[a]	79 (4.5)	94 (5.3)	39 (6.6)	39 (6.6)
Serious adverse ventricular arrhythmia leading to treatment	50 (2.9)	55 (3.1)	28 (4.8)	27 (4.5)
Adjudicated Major Cardiac Ischaemic Event	85 (4.9)	81 (4.6)	19 (3.2)	17 (2.9)
Myocardial Infarction	54 (3.1)	56 (3.2)	13 (2.2)	9 (1.5)
Hospitalisation for Unstable Angina	7 (0.4)	4 (0.2)	1 (0.2)	0 (0.0)
Coronary Revascularisation	49 (2.8)	46 (2.6)	11 (1.9)	14 (2.4)
Adjudicated Stroke	32 (1.8)	45 (2.6)	6 (1.0)	23 (3.9)
Adjudicated CV Death	311 (17.8)	359 (20.4)	164 (27.8)	162 (27.3)

CV=cardiovascular; IP=investigational product; LVEF=left ventricular ejection fraction; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil; SMQ=Standardised MedDRA Query.

[a] Although these events were included in this SMQ, no events with the PT of torsade de pointes were reported in the study.

In participants with baseline LVEF <30%, as in the overall population, there was not an increase in the incidence of ventricular tachyarrhythmias and major cardiac ischaemic events between omecamtiv mecarbil and placebo by presence or absence of baseline atrial fibrillation/flutter and concomitant use of digoxin (Table 91). The incidence of CV death was higher in participants with baseline AF/F+digoxin status in the omecamtiv mecarbil group compared to placebo, although the difference was smaller than that of the AF/F+digoxin subgroup in the overall population. In the remaining participants in the LVEF <30% cohort (those without both baseline atrial fibrillation/flutter and concomitant use of digoxin – i.e., the rest of the cohort), the incidence of CV death was lower with omecamtiv mecarbil compared with placebo.

Table 91. Safety Outcomes of Special Interest for Participants with Atrial Fibrillation/Flutter Receiving Digoxin Versus the Rest of Participants in Participants With Baseline LVEF <30% (Study 20110203, Safety Analysis Set)

	Participants With Both Atrial Fibrillation/ Flutter and Digoxin Use (N=378)		Rest of Study Participants (N=4312)	
Variable, n (%)	OM (N=179)	Placebo (N=199)	OM (N=2,156)	Placebo (N=2,156)
Any treatment-emergent SAE	123 (68.7)	124 (62.3)	1,251 (58.0)	1,333 (61.8)
SMQ: Ventricular tachyarrhythmia	19 (10.6)	17 (8.5)	168 (7.8)	171 (7.9)
SMQ: Torsade de pointes or QT prolongation[a]	13 (7.3)	12 (6.0)	105 (4.9)	121 (5.6)

Variable, n (%)	Participants With Both Atrial Fibrillation/ Flutter and Digoxin Use (N=378)		Rest of Study Participants (N=4312)	
	OM (N=179)	Placebo (N=199)	OM (N=2,156)	Placebo (N=2,156)
Serious adverse ventricular tachyarrhythmia leading to treatment	12 (6.7)	5 (2.5)	66 (3.1)	77 (3.6)
Adjudicated Major Cardiac Ischaemic Event	7 (3.9)	9 (4.5)	97 (4.5)	89 (4.1)
Myocardial Infarction	6 (3.4)	6 (3.0)	61 (2.8)	59 (2.7)
Hospitalisation for Unstable Angina	0 (0.0)	0 (0.0)	8 (0.4)	4 (0.2)
Coronary Revascularisation	4 (2.2)	8 (4.0)	56 (2.6)	52 (2.4)
Adjudicated Stroke	0 (0.0)	5 (2.5)	38 (1.8)	63 (2.9)
Adjudicated CV Death	59 (33.0)	52 (26.1)	416 (19.3)	469 (21.8)

CV=cardiovascular; LVEF=left ventricular ejection fraction; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants who received at least one dose of IP post-randomisation for studies with randomisation or post-enrollment for studies without randomisation; n=number of participants with observed data; OM=omecamtiv mecarbil; SAE=serious adverse event; SMQ=Standardised MedDRA Query.

[a] Although these events were included in this SMQ, no events with the PT of torsade de pointes were reported in the study.

Based on these data, a warning is included in the proposed Summary of Product Characteristics (SmPC) regarding an increased risk of HF outcomes in patients with atrial fibrillation/flutter who are receiving concomitant omecamtiv mecarbil and digoxin. Further, the proposed SmPC advises that if treatment with omecamtiv mecarbil is considered and digoxin cannot be discontinued, patients with atrial fibrillation and concomitant use of digoxin should be closely monitored for signs and symptoms of worsening heart failure.

Elderly

Overall, there were no relevant differences between omecamtiv mecarbil and placebo in the overall incidence of adverse events (AEs), or in the types of AEs across the age groups <65 years, 65-74 years, and 75-84 years. Due to the small number of participants 85 years of age and older enrolled in Study 20110203, the data in this subgroup should be interpreted with caution and meaningful conclusions regarding outcomes in this age group cannot be drawn (Table 92 and Table 93).

In the participants with LVEF <30%, there was no pattern to suggest an increased incidence of AEs between omecamtiv mecarbil and placebo with increasing age group.

Table 92. Study 20110203 Overall Summary of Treatment-Emergent Adverse Events by Older Age Categories (Safety Analysis Set)

	Age <65 years		Age 65-74 years		Age 75-84 years		Age 85+ years	
	Placebo (N= 1865) N (%)	Omecamtiv Mecarbil (N= 1870) N (%)	Placebo (N= 1436) N (%)	Omecamtiv Mecarbil (N= 1440) N (%)	Placebo (N= 772) N (%)	Omecamtiv Mecarbil (N= 775) N (%)	Placebo (N= 28) N (%)	Omecamtiv Mecarbil (N= 25) N (%)
Total AEs	1619 (86.8)	1608 (86.0)	1278 (89.0)	1259 (87.4)	699 (90.5)	704 (90.8)	26 (92.9)	23 (92.0)
Serious AEs – Total	1015 (54.4)	1008 (53.9)	902 (62.8)	851 (59.1)	501 (64.9)	494 (63.7)	17 (60.7)	20 (80.0)
- Fatal	291 (15.6)	320 (17.1)	323 (22.5)	298 (20.7)	203 (26.3)	206 (26.6)	6 (21.4)	13 (52.0)
- Hospitalisation/ prolong existing hospitalisation	925 (49.6)	908 (48.6)	821 (57.2)	788 (54.7)	465 (60.2)	457 (59.0)	15 (53.6)	18 (72.0)
- Life-threatening	283 (15.2)	285 (15.2)	264 (18.4)	230 (16.0)	142 (18.4)	146 (18.8)	2 (7.1)	7 (28.0)
- Disability/ incapacity	96 (5.1)	100 (5.3)	105 (7.3)	83 (5.8)	55 (7.1)	43 (5.5)	0 (0.0)	0 (0.0)
- Other (medically significant)	206 (11.0)	190 (10.2)	178 (12.4)	153 (10.6)	116 (15.0)	84 (10.8)	2 (7.1)	0 (0.0)
AE leading to drop-out	189 (10.1)	187 (10.0)	157 (10.9)	149 (10.3)	98 (12.7)	94 (12.1)	3 (10.7)	2 (8.0)
Psychiatric disorders (SOC)	125 (6.7)	98 (5.2)	99 (6.9)	77 (5.3)	77 (10.0)	57 (7.4)	4 (14.3)	5 (20.0)
Nervous system disorders (SOC)	332 (17.8)	331 (17.7)	277 (19.3)	275 (19.1)	160 (20.7)	134 (17.3)	7 (25.0)	4 (16.0)
Accidents and injuries (SMQ) - broad search	125 (6.7)	121 (6.5)	126 (8.8)	139 (9.7)	86 (11.1)	98 (12.6)	5 (17.9)	4 (16.0)
Cardiac disorders (SOC)	948 (50.8)	908 (48.6)	792 (55.2)	755 (52.4)	425 (55.1)	424 (54.7)	12 (42.9)	18 (72.0)
Vascular disorders (SOC)	313 (16.8)	296 (15.8)	258 (18.0)	264 (18.3)	137 (17.7)	137 (17.7)	5 (17.9)	4 (16.0)
Cerebrovascular disorders (SMQ)[a]	79 (4.2)	59 (3.2)	67 (4.7)	63 (4.4)	36 (4.7)	26 (3.4)	0 (0.0)	1 (4.0)
Infections and infestations (SOC)	673 (36.1)	641 (34.3)	527 (36.7)	510 (35.4)	275 (35.6)	282 (36.4)	11 (39.3)	9 (36.0)
Anticholinergic syndrome (SMQ) - broad search	171 (9.2)	171 (9.1)	123 (8.6)	159 (11.0)	94 (12.2)	90 (11.6)	7 (25.0)	4 (16.0)

	Age <65 years		Age 65-74 years		Age 75-84 years		Age 85+ years	
	Placebo (N= 1865) N (%)	Omecamtiv Mecarbil (N= 1870) N (%)	Placebo (N= 1436) N (%)	Omecamtiv Mecarbil (N= 1440) N (%)	Placebo (N= 772) N (%)	Omecamtiv Mecarbil (N= 775) N (%)	Placebo (N= 28) N (%)	Omecamtiv Mecarbil (N= 25) N (%)
Quality of life decreased [b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	193 (10.3)	191 (10.2)	137 (9.5)	186 (12.9)	106 (13.7)	106 (13.7)	6 (21.4)	4 (16.0)
Other AE appearing more frequently in older patients[c]	1072 (57.5)	1026 (54.9)	917 (63.9)	904 (62.8)	518 (67.1)	550 (71.0)	21 (75.0)	17 (68.0)

AE=adverse event; N=Number of participants randomised excluding Study Centre 29002 and who received at least 1 dose of investigational product; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants with observed data; SMQ=Standardised MedDRA Query; SOC=system organ class

[a] Includes 4 narrow search SMQs - Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Ischaemic central nervous system vascular conditions (SMQ), and Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (SMQ).

[b] Includes two preferred terms - Impaired quality of life and Quality of life decreased.

[c] Includes all the adverse events that had higher incidence rate in any of older age groups compared to the group of Age <65 but not reported in any of the above groups.

Table 93. Study 20110203 Overall Summary of Treatment-Emergent Adverse Events by Older Age Categories (Safety Analysis Set) Subgroup with Baseline LVEF <30%

	Age <65 years		Age 65-74 years		Age 75-84 years		Age 85+ years	
	Placebo (N= 1151) N (%)	Omecamtiv Mecarbil (N= 1165) N (%)	Placebo (N= 804) N (%)	Omecamtiv Mecarbil (N= 784) N (%)	Placebo (N= 387) N (%)	Omecamtiv Mecarbil (N= 377) N (%)	Placebo (N= 13) N (%)	Omecamtiv Mecarbil (N= 9) N (%)
Total AEs	1007 (87.5)	1007 (86.4)	718 (89.3)	685 (87.4)	352 (91.0)	339 (89.9)	13 (100.0)	9 (100.0)
Serious AEs – Total	668 (58.0)	645 (55.4)	523 (65.0)	480 (61.2)	258 (66.7)	242 (64.2)	8 (61.5)	7 (77.8)
- Fatal	216 (18.8)	216 (18.5)	193 (24.0)	157 (20.0)	109 (28.2)	112 (29.7)	4 (30.8)	6 (66.7)

	Age <65 years		Age 65-74 years		Age 75-84 years		Age 85+ years	
	Placebo (N= 1151) N (%)	Omecamtiv Mecarbil (N= 1165) N (%)	Placebo (N= 804) N (%)	Omecamtiv Mecarbil (N= 784) N (%)	Placebo (N= 387) N (%)	Omecamtiv Mecarbil (N= 377) N (%)	Placebo (N= 13) N (%)	Omecamtiv Mecarbil (N= 9) N (%)
- Hospitalisation/ prolong existing hospitalisation	605 (52.6)	581 (49.9)	480 (59.7)	446 (56.9)	243 (62.8)	224 (59.4)	7 (53.8)	6 (66.7)
- Life-threatening	196 (17.0)	191 (16.4)	165 (20.5)	126 (16.1)	69 (17.8)	75 (19.9)	1 (7.7)	2 (22.2)
- Disability/ incapacity	63 (5.5)	79 (6.8)	65 (8.1)	46 (5.9)	26 (6.7)	18 (4.8)	0 (0.0)	0 (0.0)
- Other (medically significant)	141 (12.3)	132 (11.3)	105 (13.1)	93 (11.9)	65 (16.8)	42 (11.1)	2 (15.4)	0 (0.0)
AE leading to drop-out	140 (12.2)	118 (10.1)	94 (11.7)	88 (11.2)	60 (15.5)	44 (11.7)	2 (15.4)	1 (11.1)
Psychiatric disorders (SOC)	77 (6.7)	63 (5.4)	67 (8.3)	42 (5.4)	45 (11.6)	28 (7.4)	3 (23.1)	2 (22.2)
Nervous system disorders (SOC)	195 (16.9)	221 (19.0)	149 (18.5)	144 (18.4)	89 (23.0)	63 (16.7)	3 (23.1)	1 (11.1)
Accidents and injuries (SMQ) - Broad Search	78 (6.8)	88 (7.6)	70 (8.7)	82 (10.5)	32 (8.3)	53 (14.1)	4 (30.8)	1 (11.1)
Cardiac disorders (SOC)	621 (54.0)	590 (50.6)	459 (57.1)	424 (54.1)	231 (59.7)	199 (52.8)	8 (61.5)	6 (66.7)
Vascular disorders (SOC)	193 (16.8)	187 (16.1)	132 (16.4)	137 (17.5)	79 (20.4)	68 (18.0)	1 (7.7)	0 (0.0)
Cerebrovascular disorders (SMQ)[a]	52 (4.5)	40 (3.4)	37 (4.6)	28 (3.6)	18 (4.7)	9 (2.4)	0 (0.0)	0 (0.0)
Infections and infestations (SOC)	417 (36.2)	405 (34.8)	313 (38.9)	289 (36.9)	146 (37.7)	136 (36.1)	4 (30.8)	2 (22.2)
Anticholinergic syndrome (SMQ) - Broad Search	102 (8.9)	115 (9.9)	61 (7.6)	86 (11.0)	58 (15.0)	46 (12.2)	4 (30.8)	1 (11.1)
Quality of life decreased[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	123 (10.7)	137 (11.8)	78 (9.7)	103 (13.1)	61 (15.8)	58 (15.4)	3 (23.1)	1 (11.1)

	Age <65 years		Age 65-74 years		Age 75-84 years		Age 85+ years	
	Placebo (N= 1151) N (%)	Omecamtiv Mecarbil (N= 1165) N (%)	Placebo (N= 804) N (%)	Omecamtiv Mecarbil (N= 784) N (%)	Placebo (N= 387) N (%)	Omecamtiv Mecarbil (N= 377) N (%)	Placebo (N= 13) N (%)	Omecamtiv Mecarbil (N= 9) N (%)
Other AE appearing more frequently in older patients[c]	664 (57.7)	635 (54.5)	499 (62.1)	475 (60.6)	258 (66.7)	275 (72.9)	11 (84.6)	7 (77.8)

AE=adverse event; LVEF=left ventricular ejection fraction; N=Number of participants randomised excluding study centre 29002 and who received at least 1 dose of investigational product; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants with observed data; SMQ=Standardised MedDRA Query; SOC=system organ class

[a] Includes 4 narrow search SMQs - Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Ischaemic central nervous system vascular conditions (SMQ), and Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (SMQ).

[b] Includes two preferred terms - Impaired quality of life and Quality of life decreased.

[c] Includes all the adverse events that had higher incidence rate in any of older age groups compared to the group of Age <65 but not reported in any of the above groups.

Sex

There were no relevant differences in the overall incidence of AEs, or in the types of AEs between the sexes (Table 94 and Table 95).

Of note, there was a numerically lower frequency of AEs related to cardiac failure in the omecamtiv mecarbil group compared with the placebo group for both sexes. For some individual preferred terms of renal events (acute kidney injury, renal impairment, and chronic kidney disease), a numerically higher frequency was observed in females in the omecamtiv mecarbil group compared with the placebo group. Therefore, a summary of the high level term (HTL) Renal Failure and Impairment was generated and all of the preferred terms (PTs) within the HLT, which indicated a higher incidence of renal failure and impairment AEs in females randomised to omecamtiv mecarbil compared with placebo. In contrast, the frequency of renal failure and impairment AEs was lower in males in the omecamtiv mecarbil group compared to placebo.

The medical history of the SOC Renal and Urinary Disorders as well as changes of serum creatinine over time in study 20110203 in males and females, to understand the origin of possible imbalances in renal events (renal impairment, renal failure) described above, were also further assessed.

At baseline, a higher incidence of renal failure and impairment was present in females randomised to omecantiv mecarbil compared to placebo (41.6% and 35.8% respectively), a difference that could have contributed to the higher incidence of renal impairment and renal failure AEs in females in the omecamtiv mecarbil group compared to placebo. No other gender differences in events at baseline in this SOC were considered to have clinical relevance. The higher incidence of renal impairment and renal failure at baseline in females randomised to omecamtiv mecarbil compared with placebo is consistent with worse baseline renal function in females randomised to omecamtiv mecarbil compared

with placebo (mean serum creatinine: 1.17 vs. 1.13 mg/dL, respectively). Changes from baseline in serum creatinine were not meaningfully different between treatments and thus did not suggest worsening of renal function in females randomised to omecamtiv mecarbil compared to placebo.

Table 94. Study 20110203 Subgroup Summary of Subject Incidence of Treatment-Emergent Adverse Events by Sex (Safety Analysis Set)

	Male		Female	
	Placebo (N=3230) n (%)	Omecamtiv Mecarbil (N=3237) n (%)	Placebo (N=871) n (%)	Omecamtiv Mecarbil (N=873) n (%)
All treatment-emergent adverse events	2844 (88.0)	2809 (86.8)	778 (89.3)	785 (89.9)
Grade ≥2	2622 (81.2)	2551 (78.8)	702 (80.6)	717 (82.1)
Grade ≥3	2092 (64.8)	2023 (62.5)	517 (59.4)	530 (60.7)
Grade ≥4	1093 (33.8)	1047 (32.3)	240 (27.6)	252 (28.9)
Serious adverse events	1961 (60.7)	1888 (58.3)	474 (54.4)	485 (55.6)
Leading to withdrawal of investigational product	354 (11.0)	339 (10.5)	93 (10.7)	93 (10.7)
Serious	271 (8.4)	274 (8.5)	66 (7.6)	58 (6.6)
Non-Serious	85 (2.6)	73 (2.3)	27 (3.1)	37 (4.2)

Table 95. Study 20110203 Subgroup Summary of Adverse Events by Preferred Term Reported by >2% of Subjects in Any Treatment Group by Sex (Safety Analysis Set)

	Male		Female	
	Placebo (N=3230) n (%)	Omecamtiv Mecarbil (N=3237) n (%)	Placebo (N=871) n (%)	Omecamtiv Mecarbil (N=873) n (%)
Number of subjects reporting treatment-emergent adverse events	2844 (88.0)	2809 (86.8)	778 (89.3)	785 (89.9)
Cardiac failure	965 (29.9)	911 (28.1)	238 (27.3)	221 (25.3)
Hypotension	207 (6.4)	244 (7.5)	64 (7.3)	65 (7.4)
Pneumonia	240 (7.4)	217 (6.7)	52 (6.0)	42 (4.8)
Dyspnoea	230 (7.1)	211 (6.5)	47 (5.4)	62 (7.1)
Atrial fibrillation	212 (6.6)	190 (5.9)	51 (5.9)	46 (5.3)
Dizziness	137 (4.2)	181 (5.6)	52 (6.0)	56 (6.4)

	Male		Female	
	Placebo (N=3230) n (%)	Omecamtiv Mecarbil (N=3237) n (%)	Placebo (N=871) n (%)	Omecamtiv Mecarbil (N=873) n (%)
Cardiac failure acute	203 (6.3)	175 (5.4)	60 (6.9)	46 (5.3)
Acute kidney injury	193 (6.0)	174 (5.4)	32 (3.7)	56 (6.4)
Cardiac failure chronic	169 (5.2)	160 (4.9)	41 (4.7)	44 (5.0)
Hyperkalaemia	183 (5.7)	160 (4.9)	47 (5.4)	56 (6.4)
Nasopharyngitis	148 (4.6)	153 (4.7)	46 (5.3)	33 (3.8)
Ventricular tachycardia	165 (5.1)	153 (4.7)	19 (2.2)	20 (2.3)
Hypertension	173 (5.4)	150 (4.6)	56 (6.4)	48 (5.5)
Upper respiratory tract infection	137 (4.2)	139 (4.3)	35 (4.0)	45 (5.2)
Diarrhoea	150 (4.6)	132 (4.1)	42 (4.8)	46 (5.3)
Renal impairment	137 (4.2)	126 (3.9)	39 (4.5)	57 (6.5)
Oedema peripheral	135 (4.2)	120 (3.7)	33 (3.8)	32 (3.7)
Bronchitis	143 (4.4)	117 (3.6)	44 (5.1)	27 (3.1)
Cardiac failure congestive	147 (4.6)	117 (3.6)	37 (4.2)	46 (5.3)
Anaemia	124 (3.8)	116 (3.6)	40 (4.6)	35 (4.0)
Gout	129 (4.0)	113 (3.5)	23 (2.6)	30 (3.4)
Cough	125 (3.9)	111 (3.4)	44 (5.1)	39 (4.5)
Chronic kidney disease	116 (3.6)	104 (3.2)	27 (3.1)	42 (4.8)
Back pain	92 (2.8)	103 (3.2)	29 (3.3)	28 (3.2)
Syncope	90 (2.8)	102 (3.2)	17 (2.0)	18 (2.1)
Weight increased	91 (2.8)	102 (3.2)	26 (3.0)	24 (2.7)
Urinary tract infection	99 (3.1)	94 (2.9)	62 (7.1)	61 (7.0)
Chronic obstructive pulmonary disease	78 (2.4)	93 (2.9)	21 (2.4)	18 (2.1)
Diabetes mellitus	100 (3.1)	91 (2.8)	33 (3.8)	27 (3.1)
Angina pectoris	64 (2.0)	89 (2.7)	23 (2.6)	29 (3.3)
Renal failure	85 (2.6)	89 (2.7)	15 (1.7)	25 (2.9)
Hypokalaemia	103 (3.2)	85 (2.6)	22 (2.5)	23 (2.6)
Headache	90 (2.8)	79 (2.4)	44 (5.1)	34 (3.9)
Chest pain	67 (2.1)	77 (2.4)	21 (2.4)	26 (3.0)
Influenza	91 (2.8)	76 (2.3)	14 (1.6)	31 (3.6)
Constipation	77 (2.4)	74 (2.3)	13 (1.5)	19 (2.2)

	Male		Female	
	Placebo (N=3230) n (%)	Omecamtiv Mecarbil (N=3237) n (%)	Placebo (N=871) n (%)	Omecamtiv Mecarbil (N=873) n (%)
Fatigue	88 (2.7)	73 (2.3)	22 (2.5)	29 (3.3)
Arthralgia	72 (2.2)	71 (2.2)	31 (3.6)	20 (2.3)
Fall	42 (1.3)	64 (2.0)	25 (2.9)	17 (1.9)
Non-cardiac chest pain	65 (2.0)	61 (1.9)	22 (2.5)	21 (2.4)
Cardiogenic shock	57 (1.8)	56 (1.7)	12 (1.4)	19 (2.2)
Insomnia	68 (2.1)	56 (1.7)	25 (2.9)	15 (1.7)
Respiratory tract infection	75 (2.3)	55 (1.7)	18 (2.1)	20 (2.3)
Hyperuricaemia	58 (1.8)	47 (1.5)	18 (2.1)	13 (1.5)
Abdominal pain	58 (1.8)	36 (1.1)	19 (2.2)	13 (1.5)
Depression	-	-	28 (3.2)	23 (2.6)
Nausea	-	-	27 (3.1)	31 (3.6)
Vomiting	-	-	26 (3.0)	29 (3.3)
Palpitations	-	-	26 (3.0)	19 (2.2)
Pruritus	-	-	11 (1.3)	19 (2.2)
Asthenia	-	-	21 (2.4)	18 (2.1)
Abdominal pain upper	-	-	18 (2.1)	17 (1.9)
Gastroenteritis	-	-	25 (2.9)	15 (1.7)
Hypothyroidism	-	-	21 (2.4)	15 (1.7)
Pain in extremity	-	-	27 (3.1)	11 (1.3)

Renal impairment

There were no relevant differences in the overall incidence of AEs, or in the types of AEs by renal function (Table 96 and Table 97). The majority of participants had mild or moderate renal impairment. Worsening renal impairment was associated with higher incidence rates of all categories of AEs, however within each renal function group the rates for omecamtiv mecarbil were generally similar to those of placebo. While AEs of acute kidney injury (n=20; 7.4% vs. n=27; 10.7%) and renal impairment (n=22; 8.1% vs. n=26;10.3%) were numerically lower with omecamtiv mecarbil compared with placebo in the severe renal impairment subgroup, the AE of renal failure was numerically higher (n=21; 7.7% vs. n=12; 4.7%). There were no major differences between omecamtiv mecarbil and placebo in reported cardiovascular AEs by severity of renal impairment.

The proposed starting dose of omecamtiv mecarbil and subsequent dose selection based on omecamtiv mecarbil plasma level does not need to be modified in these patient populations.

Table 96. Study 20110203 Subgroup Summary of Incidence of Treatment-Emergent Adverse Events by Severity of Renal Impairment (Safety Analysis Set)

	Normal (eGFR ≥90 L/min/1.73 m²)		Mild (eGFR 60 to <90 L/min/1.73 m²)		Moderate (eGFR 30 to <60 L/min/1.73 m²)		Severe (eGFR<30 L/min/1.73m²)	
	Placebo (N=372) n (%)	Omecamtiv Mecarbil (N=370) n (%)	Placebo (N=1568) n (%)	Omecamtiv Mecarbil (N=1590) n (%)	Placebo (N=1908) n (%)	Omecamtiv Mecarbil (N=1878) n (%)	Placebo (N=253) n (%)	Omecamtiv Mecarbil (N=272) n (%)
All treatment-emergent adverse events	315 (84.7)	309 (83.5)	1349 (86.0)	1333 (83.8)	1714 (89.8)	1696 (90.3)	244 (96.4)	256 (94.1)
Grade ≥2	287 (77.2)	272 (73.5)	1213 (77.4)	1188 (74.7)	1593 (83.5)	1567 (83.4)	231 (91.3)	241 (88.6)
Grade ≥3	213 (57.3)	179 (48.4)	894 (57.0)	895 (56.3)	1295 (67.9)	1259 (67.0)	207 (81.8)	220 (80.9)
Grade ≥4	101 (27.2)	84 (22.7)	420 (26.8)	414 (26.0)	689 (36.1)	666 (35.5)	123 (48.6)	135 (49.6)
Serious adverse events	195 (52.4)	165 (44.6)	824 (52.6)	823 (51.8)	1216 (63.7)	1176 (62.6)	200 (79.1)	209 (76.8)
Leading to withdrawal of investigational product	31 (8.3)	22 (5.9)	142 (9.1)	143 (9.0)	233 (12.2)	213 (11.3)	41 (16.2)	54 (19.9)
Serious	20 (5.4)	15 (4.1)	102 (6.5)	107 (6.7)	181 (9.5)	168 (8.9)	34 (13.4)	42 (15.4)
Non-Serious	11 (3.0)	8 (2.2)	40 (2.6)	37 (2.3)	54 (2.8)	50 (2.7)	7 (2.8)	15 (5.5)

Table 97. Study 20110203 Subgroup Summary of Adverse Events by Preferred Term Reported by >2% of Subjects in Any Treatment Group by Severity of Renal Impairment (Safety Analysis Set)

	Normal (eGFR ≥90 L/min/1.73 m²)		Mild (eGFR 60 to <90 L/min/1.73 m²)		Moderate (eGFR 30 to <60 L/min/1.73 m²)		Severe (eGFR<30 L/min/1.73m²)	
	Placebo (N=372) n (%)	Omecamtiv Mecarbil (N=370) n (%)	Placebo (N=1568) n (%)	Omecamtiv Mecarbil (N=1590) n (%)	Placebo (N=1908) n (%)	Omecamtiv Mecarbil (N=1878) n (%)	Placebo (N=253) n (%)	Omecamtiv Mecarbil (N=272) n (%)
Cardiac failure	90 (24.2)	58 (15.7)	390 (24.9)	349 (21.9)	612 (32.1)	616 (32.8)	111 (43.9)	109 (40.1)
Hypotension	13 (3.5)	24 (6.5)	97 (6.2)	105 (6.6)	144 (7.5)	156 (8.3)	17 (6.7)	24 (8.8)
Atrial fibrillation	21 (5.6)	12 (3.2)	100 (6.4)	103 (6.5)	130 (6.8)	109 (5.8)	12 (4.7)	12 (4.4)
Dyspnoea	22 (5.9)	20 (5.4)	96 (6.1)	98 (6.2)	149 (7.8)	128 (6.8)	10 (4.0)	27 (9.9)
Dizziness	25 (6.7)	25 (6.8)	76 (4.8)	97 (6.1)	79 (4.1)	104 (5.5)	9 (3.6)	11 (4.0)
Pneumonia	23 (6.2)	21 (5.7)	97 (6.2)	93 (5.8)	148 (7.8)	123 (6.5)	24 (9.5)	22 (8.1)
Hypertension	32 (8.6)	13 (3.5)	89 (5.7)	88 (5.5)	97 (5.1)	85 (4.5)	11 (4.3)	12 (4.4)
Nasopharyngitis	18 (4.8)	19 (5.1)	77 (4.9)	80 (5.0)	91 (4.8)	82 (4.4)	8 (3.2)	5 (1.8)
Cardiac failure chronic	18 (4.8)	12 (3.2)	71 (4.5)	68 (4.3)	106 (5.6)	108 (5.8)	15 (5.9)	16 (5.9)
Upper respiratory tract infection	26 (7.0)	23 (6.2)	80 (5.1)	66 (4.2)	58 (3.0)	90 (4.8)	8 (3.2)	5 (1.8)
Cardiac failure acute	19 (5.1)	15 (4.1)	82 (5.2)	63 (4.0)	133 (7.0)	120 (6.4)	29 (11.5)	23 (8.5)
Hyperkalaemia	9 (2.4)	7 (1.9)	70 (4.5)	62 (3.9)	133 (7.0)	130 (6.9)	18 (7.1)	17 (6.3)
Cough	15 (4.0)	10 (2.7)	69 (4.4)	58 (3.6)	73 (3.8)	67 (3.6)	12 (4.7)	15 (5.5)
Diarrhoea	14 (3.8)	12 (3.2)	49 (3.1)	56 (3.5)	111 (5.8)	93 (5.0)	18 (7.1)	17 (6.3)

	Normal (eGFR **≥90** L/min/1.73 m²)		Mild (eGFR 60 to <90 L/min/1.73 m²)		Moderate (eGFR 30 to <60 L/min/1.73 m²)		Severe (eGFR<30 L/min/1.73m²)	
	Placebo (N=372) n (%)	Omecamtiv Mecarbil (N=370) n (%)	Placebo (N=1568) n (%)	Omecamtiv Mecarbil (N=1590) n (%)	Placebo (N=1908) n (%)	Omecamtiv Mecarbil (N=1878) n (%)	Placebo (N=253) n (%)	Omecamtiv Mecarbil (N=272) n (%)
Acute kidney injury	4 (1.1)	9 (2.4)	58 (3.7)	56 (3.5)	136 (7.1)	145 (7.7)	27 (10.7)	20 (7.4)
Ventricular tachycardia	11 (3.0)	10 (2.7)	63 (4.0)	54 (3.4)	100 (5.2)	98 (5.2)	10 (4.0)	11 (4.0)
Angina pectoris	10 (2.7)	10 (2.7)	35 (2.2)	53 (3.3)	38 (2.0)	50 (2.7)	4 (1.6)	5 (1.8)
Anaemia	12 (3.2)	6 (1.6)	41 (2.6)	53 (3.3)	95 (5.0)	78 (4.2)	16 (6.3)	14 (5.1)
Cardiac failure congestive	12 (3.2)	11 (3.0)	49 (3.1)	52 (3.3)	99 (5.2)	81 (4.3)	24 (9.5)	19 (7.0)
Headache	21 (5.6)	12 (3.2)	51 (3.3)	51 (3.2)	57 (3.0)	42 (2.2)	5 (2.0)	8 (2.9)
Bronchitis	18 (4.8)	12 (3.2)	75 (4.8)	50 (3.1)	84 (4.4)	71 (3.8)	10 (4.0)	11 (4.0)
Renal impairment	-	-	32 (2.0)	49 (3.1)	116 (6.1)	111 (5.9)	26 (10.3)	22 (8.1)
Back pain	12 (3.2)	8 (2.2)	54 (3.4)	47 (3.0)	50 (2.6)	68 (3.6)	5 (2.0)	8 (2.9)
Influenza	9 (2.4)	17 (4.6)	41 (2.6)	45 (2.8)	47 (2.5)	38 (2.0)	8 (3.2)	7 (2.6)
Chronic obstructive pulmonary disease	9 (2.4)	11 (3.0)	29 (1.8)	44 (2.8)	53 (2.8)	53 (2.8)	8 (3.2)	3 (1.1)
Weight increased	10 (2.7)	17 (4.6)	45 (2.9)	44 (2.8)	52 (2.7)	51 (2.7)	10 (4.0)	14 (5.1)
Oedema peripheral	11 (3.0)	14 (3.8)	53 (3.4)	43 (2.7)	91 (4.8)	81 (4.3)	13 (5.1)	14 (5.1)
Urinary tract infection	12 (3.2)	8 (2.2)	38 (2.4)	42 (2.6)	97 (5.1)	87 (4.6)	14 (5.5)	18 (6.6)
Syncope	14 (3.8)	9 (2.4)	41 (2.6)	41 (2.6)	44 (2.3)	59 (3.1)	8 (3.2)	11 (4.0)

	Normal (eGFR ≥90 L/min/1.73 m²)		Mild (eGFR 60 to <90 L/min/1.73 m²)		Moderate (eGFR 30 to <60 L/min/1.73 m²)		Severe (eGFR<30 L/min/1.73m²)	
	Placebo (N=372) n (%)	Omecamtiv Mecarbil (N=370) n (%)	Placebo (N=1568) n (%)	Omecamtiv Mecarbil (N=1590) n (%)	Placebo (N=1908) n (%)	Omecamtiv Mecarbil (N=1878) n (%)	Placebo (N=253) n (%)	Omecamtiv Mecarbil (N=272) n (%)
Diabetes mellitus	12 (3.2)	17 (4.6)	53 (3.4)	41 (2.6)	61 (3.2)	55 (2.9)	7 (2.8)	5 (1.8)
Chest pain	9 (2.4)	11 (3.0)	30 (1.9)	40 (2.5)	43 (2.3)	49 (2.6)	6 (2.4)	3 (1.1)
Gout	5 (1.3)	6 (1.6)	39 (2.5)	34 (2.1)	94 (4.9)	88 (4.7)	14 (5.5)	15 (5.5)
Non-cardiac chest pain	10 (2.7)	9 (2.4)	36 (2.3)	32 (2.0)	38 (2.0)	37 (2.0)	3 (1.2)	4 (1.5)
Arthralgia	7 (1.9)	6 (1.6)	32 (2.0)	31 (1.9)	55 (2.9)	46 (2.4)	9 (3.6)	8 (2.9)
Hypokalaemia	6 (1.6)	15 (4.1)	39 (2.5)	31 (1.9)	65 (3.4)	52 (2.8)	15 (5.9)	10 (3.7)
Respiratory tract infection	4 (1.1)	6 (1.6)	39 (2.5)	31 (1.9)	47 (2.5)	31 (1.7)	3 (1.2)	7 (2.6)
Fatigue	8 (2.2)	9 (2.4)	38 (2.4)	30 (1.9)	57 (3.0)	57 (3.0)	7 (2.8)	6 (2.2)
Chronic kidney disease	-	-	-	-	93 (4.9)	86 (4.6)	26 (10.3)	35 (12.9)
Renal failure	-	-	30 (1.9)	24 (1.5)	56 (2.9)	64 (3.4)	12 (4.7)	21 (7.7)
Constipation	6 (1.6)	7 (1.9)	-	-	53 (2.8)	51 (2.7)	5 (2.0)	5 (1.8)
Cardiogenic shock	4 (1.1)	4 (1.1)	20 (1.3)	19 (1.2)	39 (2.0)	47 (2.5)	6 (2.4)	5 (1.8)
Pruritus	-	-	-	-	36 (1.9)	44 (2.3)	8 (3.2)	7 (2.6)
Nausea	8 (2.2)	5 (1.4)	-	-	39 (2.0)	42 (2.2)	4 (1.6)	8 (2.9)
Fall	-	-	-	-	40 (2.1)	40 (2.1)	9 (3.6)	11 (4.0)
Hypothyroidism	-	-	-	-	24 (1.3)	38 (2.0)	10 (4.0)	4 (1.5)

	Normal (eGFR ≥90 L/min/1.73 m²)		Mild (eGFR 60 to <90 L/min/1.73 m²)		Moderate (eGFR 30 to <60 L/min/1.73 m²)		Severe (eGFR<30 L/min/1.73m²)	
	Placebo (N=372) n (%)	Omecamtiv Mecarbil (N=370) n (%)	Placebo (N=1568) n (%)	Omecamtiv Mecarbil (N=1590) n (%)	Placebo (N=1908) n (%)	Omecamtiv Mecarbil (N=1878) n (%)	Placebo (N=253) n (%)	Omecamtiv Mecarbil (N=272) n (%)
Vomiting	7 (1.9)	3 (0.8)	22 (1.4)	28 (1.8)	47 (2.5)	38 (2.0)	3 (1.2)	13 (4.8)
Insomnia	7 (1.9)	8 (2.2)	27 (1.7)	24 (1.5)	52 (2.7)	37 (2.0)	7 (2.8)	2 (0.7)
Acute myocardial infarction	-	-	-	-	39 (2.0)	33 (1.8)	4 (1.6)	6 (2.2)
Depression	7 (1.9)	4 (1.1)	28 (1.8)	29 (1.8)	39 (2.0)	29 (1.5)	6 (2.4)	5 (1.8)
Pain in extremity	7 (1.9)	7 (1.9)	-	-	43 (2.3)	27 (1.4)	7 (2.8)	8 (2.9)
Hyperuricaemia	-	-	-	-	38 (2.0)	26 (1.4)	3 (1.2)	8 (2.9)
Abdominal pain	5 (1.3)	6 (1.6)	29 (1.8)	17 (1.1)	38 (2.0)	25 (1.3)	5 (2.0)	1 (0.4)
Sudden death	8 (2.2)	3 (0.8)	23 (1.5)	18 (1.1)	25 (1.3)	23 (1.2)	2 (0.8)	8 (2.9)
Pleural effusion	-	-	-	-	--	-	6 (2.4)	7 (2.6)
Sepsis	-	-	-	-	36 (1.9)	31 (1.7)	7 (2.8)	7 (2.6)
Asthenia	-	-	28 (1.8)	19 (1.2)	35 (1.8)	30 (1.6)	5 (2.0)	6 (2.2)
Cardiac arrest	-	-	27 (1.7)	18 (1.1)	-	-	10 (4.0)	6 (2.2)
Lower respiratory tract infection	-	-	-	-	-	-	6 (2.4)	6 (2.2)
Vertigo	-	-	-	-	-	-	3 (1.2)	6 (2.2)
Epistaxis	-	-	-	-	-	-	5 (2.0)	5 (1.8)
Orthostatic hypotension	-	-	-	-	-	-	6 (2.4)	5 (1.8)
Hypoglycaemia	3 (0.8)	6 (1.6)	-	-	-	-	7 (2.8)	4 (1.5)

	Normal (eGFR ≥90 L/min/1.73 m²)		Mild (eGFR 60 to <90 L/min/1.73 m²)		Moderate (eGFR 30 to <60 L/min/1.73 m²)		Severe (eGFR<30 L/min/1.73m²)	
	Placebo (N=372) n (%)	Omecamtiv Mecarbil (N=370) n (%)	Placebo (N=1568) n (%)	Omecamtiv Mecarbil (N=1590) n (%)	Placebo (N=1908) n (%)	Omecamtiv Mecarbil (N=1878) n (%)	Placebo (N=253) n (%)	Omecamtiv Mecarbil (N=272) n (%)
Myocardial infarction	-	-	-	-	-	-	6 (2.4)	4 (1.5)
Muscle spasms	-	-	-	-	-	-	5 (2.0)	3 (1.1)
Urinary retention	-	-	-	-	-	-	6 (2.4)	3 (1.1)
Fluid overload	-	-	-	-	-	-	5 (2.0)	2 (0.7)
Rib fracture	-	-	-	-	-	-	6 (2.4)	2 (0.7)
Sciatica	-	-	-	-	-	-	5 (2.0)	2 (0.7)
Cellulitis	-	-	-	-	28 (1.5)	32 (1.7)	5 (2.0)	11 (4.0)
Dehydration	0 (0.0)	6 (1.6)	-	-	18 (0.9)	26 (1.4)	3 (1.2)	11 (4.0)
Iron deficiency	-	-	-	-	-	-	5 (2.0)	1 (0.4)
Urosepsis	-	-	-	-	-	-	5 (2.0)	1 (0.4)
Abdominal pain upper	9 (2.4)	8 (2.2)	-	-	-	-	-	-
Palpitations	13 (3.5)	7 (1.9)	-	-	-	-	-	-
Ventricular extrasystoles	9 (2.4)	7 (1.9)	27 (1.7)	30 (1.9)	-	-	-	-
Chest discomfort	9 (2.4)	5 (1.4)	-	-	-	-	4 (1.6)	1 (0.4)
Tachycardia	8 (2.2)	4 (1.1)	-	-	-	-	-	-
Gynaecomastia	8 (2.2)	2 (0.5)	-	-	-	-	1 (0.4)	3 (1.1)

eGFR=estimated glomerular filtration rate

- Denotes that the frequency did not meet the threshold for inclusion in the source table.

The evaluation of death is based on adjudicated events; therefore, the preferred term death is not presented in the above table.

Hepatic impairment

Subjects with hepatic impairment (total bilirubin ≥2 times the upper limit of normal, or alanine aminotransferase or aspartate aminotransferase ≥3 times upper limit of normal) were not eligible to participate in Study 20110203; therefore, an analysis of AEs by hepatic impairment is not possible based on this study.

Phase 1 study 20130253 was conducted in participants with mild and moderate hepatic impairment; there were no abnormal trends in mean clinical laboratory parameter values during the study for participants with normal hepatic function and for participants with mild or moderate hepatic impairment. Only 1 treatment-emergent AE (foot fracture) was reported during the study. No studies have been conducted in participants with severe hepatic impairment. The proposed starting dose of omecamtiv mecarbil and subsequent dose selection based on omecamtiv mecarbil plasma level does not need to be modified in these patient populations.

3.3.7.7. Immunological events

Because omecamtiv mecarbil is a small molecule and not an antimicrobial or antiviral drug, no immunogenicity or clinical microbial studies contributed to this clinical programme.

3.3.7.8. Safety related to drug-drug interactions and other interactions

See PD section.

3.3.7.9. Discontinuation due to adverse events

CV outcome study of chronic HF (GALATIC-HF)

Overall, the incidence of AEs leading to IP discontinuation was similar between the omecamtiv mecarbil (10.5%) and placebo (10.9%) treatment groups (Table 98). Most AEs leading to IP withdrawal occurred in the SOC Cardiac disorders for omecamtiv mecarbil (5.3%) and placebo (5.5%) treatment groups. AEs leading to IP discontinuation in ≥2% of participants in either treatment group included cardiac failure (2.3% omecamtiv mecarbil, 2.0% placebo). However, regarding hospital setting at randomisation (in/outpatient), a slightly higher percentage of subjects who discontinued the study drug due to AEs in the omecamtiv mecarbil group compared with placebo in the inpatients subgroup was observed (11.3% vs 9.4%, respectively), while a lower percentage in the omecamtiv mecarbil group compared with placebo was observed in the outpatient subgroup (10.3% vs 11.4%).

Table 98. Treatment-emergent Adverse Events Leading to Withdrawal of Investigational Product by Preferred Term Reported for **≥0.1%** of Subjects in Any Treatment Group Overall (Safety Analysis Set)

	Recently and Not Currently Hospitalised for Heart Failure		Currently Hospitalised for Heart Failure		Overall	
System Organ Class Preferred Term	Placebo (N = 3067) n (%)	AMG 423 (N = 3070) n (%)	Placebo (N = 1034) n (%)	AMG 423 (N = 1040) n (%)	Placebo (N = 4101) n (%)	AMG 423 (N = 4110) n (%)
Number of subjects reporting treatment-emergent adverse events	350 (11.4)	315 (10.3)	97 (9.4)	117 (11.3)	447 (10.9)	432 (10.5)
Cardiac disorders	177 (5.8)	148 (4.8)	49 (4.7)	68 (6.5)	226 (5.5)	216 (5.3)
Cardiac failure	56 (1.8)	63 (2.1)	25 (2.4)	32 (3.1)	81 (2.0)	95 (2.3)
Cardiac failure chronic	15 (0.5)	12 (0.4)	1 (<0.1)	4 (0.4)	16 (0.4)	16 (0.4)
Cardiac failure acute	17 (0.6)	12 (0.4)	4 (0.4)	3 (0.3)	21 (0.5)	15 (0.4)
Angina unstable	7 (0.2)	11 (0.4)	0 (0.0)	2 (0.2)	7 (0.2)	13 (0.3)
Cardiac failure congestive	15 (0.5)	7 (0.2)	2 (0.2)	4 (0.4)	17 (0.4)	11 (0.3)
Acute myocardial infarction	7 (0.2)	5 (0.2)	2 (0.2)	5 (0.5)	9 (0.2)	10 (0.2)
Angina pectoris	4 (0.1)	8 (0.3)	0 (0.0)	1 (<0.1)	4 (<0.1)	9 (0.2)
Cardiogenic shock	8 (0.3)	4 (0.1)	3 (0.3)	3 (0.3)	11 (0.3)	7 (0.2)
Ventricular tachycardia	10 (0.3)	3 (<0.1)	1 (<0.1)	4 (0.4)	11 (0.3)	7 (0.2)
Cardiac arrest	5 (0.2)	4 (0.1)	2 (0.2)	1 (<0.1)	7 (0.2)	5 (0.1)
Acute coronary syndrome	1 (<0.1)	3 (<0.1)	1 (<0.1)	2 (0.2)	2 (<0.1)	5 (0.1)
Ventricular fibrillation	5 (0.2)	3 (<0.1)	0 (0.0)	1 (<0.1)	5 (0.1)	4 (<0.1)
Myocardial infarction	8 (0.3)	0 (0.0)	1 (<0.1)	2 (0.2)	9 (0.2)	2 (<0.1)
Renal and urinary disorders	19 (0.6)	27 (0.9)	6 (0.6)	8 (0.8)	25 (0.6)	35 (0.9)
Acute kidney injury	10 (0.3)	10 (0.3)	2 (0.2)	3 (0.3)	12 (0.3)	13 (0.3)
Renal impairment	1 (<0.1)	5 (0.2)	3 (0.3)	2 (0.2)	4 (<0.1)	7 (0.2)
Chronic kidney disease	4 (0.1)	5 (0.2)	0 (0.0)	1 (<0.1)	4 (<0.1)	6 (0.1)
Renal failure	2 (<0.1)	4 (0.1)	1 (<0.1)	1 (<0.1)	3 (<0.1)	5 (0.1)
Nervous system disorders	31 (1.0)	25 (0.8)	7 (0.7)	4 (0.4)	38 (0.9)	29 (0.7)
Cerebrovascular accident	3 (<0.1)	6 (0.2)	1 (<0.1)	0 (0.0)	4 (<0.1)	6 (0.1)
Ischaemic stroke	3 (<0.1)	5 (0.2)	1 (<0.1)	1 (<0.1)	4 (<0.1)	6 (0.1)
Dizziness	11 (0.4)	5 (0.2)	0 (0.0)	0 (0.0)	11 (0.3)	5 (0.1)
Infections and infestations	13 (0.4)	25 (0.8)	8 (0.8)	2 (0.2)	21 (0.5)	27 (0.7)
Pneumonia	3 (<0.1)	7 (0.2)	3 (0.3)	1 (<0.1)	6 (0.1)	8 (0.2)
Sepsis	1 (<0.1)	7 (0.2)	3 (0.3)	0 (0.0)	4 (<0.1)	7 (0.2)
General disorders and administration site conditions	20 (0.7)	20 (0.7)	1 (<0.1)	4 (0.4)	21 (0.5)	24 (0.6)
Fatigue	1 (<0.1)	5 (0.2)	0 (0.0)	0 (0.0)	1 (<0.1)	5 (0.1)
Death	5 (0.2)	2 (<0.1)	0 (0.0)	2 (0.2)	5 (0.1)	4 (<0.1)
Respiratory, thoracic and mediastinal disorders	17 (0.6)	21 (0.7)	1 (<0.1)	3 (0.3)	18 (0.4)	24 (0.6)
Dyspnoea	6 (0.2)	5 (0.2)	0 (0.0)	1 (<0.1)	6 (0.1)	6 (0.1)
Gastrointestinal disorders	26 (0.8)	15 (0.5)	6 (0.6)	5 (0.5)	32 (0.8)	20 (0.5)
Vomiting	5 (0.2)	3 (<0.1)	0 (0.0)	0 (0.0)	5 (0.1)	3 (<0.1)
Skin and subcutaneous tissue disorders	7 (0.2)	10 (0.3)	2 (0.2)	3 (0.3)	9 (0.2)	13 (0.3)
Pruritus	1 (<0.1)	4 (0.1)	0 (0.0)	1 (<0.1)	1 (<0.1)	5 (0.1)
Vascular disorders	5 (0.2)	11 (0.4)	4 (0.4)	1 (<0.1)	9 (0.2)	12 (0.3)
Hypotension	0 (0.0)	7 (0.2)	3 (0.3)	1 (<0.1)	3 (<0.1)	8 (0.2)

AMG 423 = omecamtiv mecarbil; MedDRA = Medical Dictionary for Regulatory Activities

Notes: N = Number of subjects randomised excluding study centre 29002 and received at least 1 dose of investigational product. Percentages are based on N. Adverse events were coded using MedDRA version 23.0.

3.3.7.10. Post marketing experience

Omecamtiv mecarbil is not yet a marketed product in any region.

3.3.8. Discussion on clinical safety

Omecamtiv mecarbil (OM) is a first-in-class cardiac myosin activator, so there is no previous safety experience. In the current dossier, the safety is primarily based on the pivotal phase 3 cardiovascular (CV) outcome study 20110203 (GALACTIC-HF; n=8211), supplemented by safety data from the moderate duration Phase 2b studies (20110151 Expansion Phase (COSMIC-HF; N=445) and 20120227 (N=81)), the Phase 2 Study 20100754 conducted in participants with acute HF receiving an IV dose regimen of OM (N=606), the short duration Phase 2a (N=311), Phase 1 studies (N=953), and Study CY 1031 (METEORIC-HF; N=276) when applicable.

Patient exposure. Overall median exposure to any dose of OM across the clinical development programme was 14.49 months derived from 5637 subjects. In the CV outcome study 20110203 (GALACTIF-HF), a total of 4110 subjects with HFrEF has been exposed to OM with dosage levels of clinical use, with a mean IP exposure of 19.2 months, mean study duration of 21.6 months, and subject-years of exposure of 6567.3. According to the guideline ICH-E1 'Population Exposure: The Extent of Population Exposure to Assess Clinical Safety' 100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety database at dosage levels intended for clinical use. Currently, the number of subjects exposed and duration of exposure fulfil the requirements of ICH-E1 and are therefore supportive of a drug for intended chronic use.

Dose titration. The CV outcome GALACTIC-HF study used a PK-guided dosing strategy, aiming at a target range of 300-750 ng/mL. As already described in the "Clinical efficacy-Results" section, the disposition of subjects following this PK-guided dosing in the GALACTIC-HF study demonstrated that at week 12, roughly 47.6% were at the dose of 50 mg.

Adverse events. In the pivotal CV outcome study GALACTIC-HF, treatment-emergent adverse events (TEAEs) were frequently reported; however, the percentage was slightly lower in the OM group (87.4%) compared with the placebo group (88.3%). Similarly, slightly lower percentages of subjects with Grade ≥4 (31.6% vs 32.5%, respectively), serious adverse events (SAEs) (57.7% vs 59.4%) and AEs leading to discontinuation (10.5% vs 10.9%) were reported in the OM group compared with placebo, which is reassuring. Similar results were observed in the subjects currently hospitalised for HF (inpatient subjects) and subjects recently and not currently hospitalised for HF (outpatient subjects), except for a slightly higher percentage of subjects who discontinued the study drug due to AEs in the OM group compared with placebo in the inpatient subgroup (see also "Discontinuation due to adverse events"). The system organ classes mostly affected (>30% of participants in either treatment group) within the pivotal study were cardiac disorders (51.2% vs. 53.1% in the OM and placebo groups, respectively), infections and infestations (35.1% vs. 36.2%). The most frequent AEs (≥5% of subjects in the OM group) with a higher incidence in the OM group compared with the placebo group were hypotension (7.5% vs. 6.6%), dizziness (5.8% vs. 4.6%), and acute kidney injury (5.6% vs. 5.5%). Generally, similar results were observed in the in- and outpatient subjects. The most common events were associated with the chronic HF condition, as expected in the study population, i.e., cardiac failure events or known complications of chronic HFrEF.

The other safety analysis sets of “moderate duration studies of Chronic HF” and “study 20100754 (ATOMIC-AHF)” showed safety results consistent to those observed in the pivotal CV outcome study GALACTIC-HF. However, Study CY 1031 (METEORIC-HF) showed a higher percentage of subjects with TEAEs (68.1% vs. 63.7%, respectively), SAEs (16.2% vs. 14.3%), AEs leading to discontinuation of study drug (13.5% vs. 9.9%) and AE considered related to study drug (13.5% vs 9.9%) in the OM group compared with placebo. There were no notable patterns in the events reported in the OM and placebo groups, with the exception of a higher incidence of cardiac failure (5.9 % vs. 3.3% for TEAEs and 3.8% vs. 1.1% for SAEs) and ventricular tachycardia (4.3 % vs. 2.2 % for TEAEs and 2.7% vs. 2.2% for SAEs) in the OM group compared with the placebo group. In this respect, the applicant has adequately justified that cardiac failure and ventricular tachycardia should not be considered ADRs, since 1) there is a lack of supporting evidence for causal relationship 2) the risk of these events is not higher for OM treated patients compared with placebo in the larger pivotal GALACTIC-HF trial 3) only small numbers of patients were involved in METEORIC-HF making firm conclusions difficult. Moreover, the pivotal GALACTIC-HF trial enrolled a population of patients with a baseline LVEF ≤35% at significantly higher risk for adverse cardiovascular outcomes than those in METEORIC-HF, which makes GALACTIC-HF a much more reliable indicator of the safety and tolerability of OM.

Adverse drug reactions. Three adverse drug reactions have been identified, i.e. dizziness, myocardial infarction, and angina pectoris. The inclusion of dizziness as ADR of OM in section 4.8 of the SmPC is agreed upon due to the observed clear disbalances in the different safety analysis sets, including the CV outcome study GALACTIC-HF (5.8% vs 4.6% for OM and placebo, respectively). Myocardial infarction was identified as ADR based on the cardiac ischaemic events observed with excessive exposure of OM (≥1200 ng/ml) observed in phase I and II studies. However, in the pivotal study 20110203, the percentage of subjects with MI was similar between the OM and placebo groups (3.0% vs. 3.3%, respectively). Similarly, in the subgroup of LVEF <30%, the percentages were also comparable between both groups (3.1% in each group; see“Safety in special population”). Considering that PK-guided dosing with a therapeutic range of 300 – 750 ng/ml is proposed in section 4.2 of the SmPC, myocardial infarction is not included as an ADR in section 4.8, however, a warning in section 4.4 and information in section 4.8 under “description of selected adverse reactions” with a reference to section 4.9 has been included in the labeling, following the request of CHMP, which is acceptable. Regarding the ADR angina pectoris, considering that none of the patients in the pivotal study exceeded OM plasma levels of ≥1200 ng/ml, while there was an increased risk for angina pectoris observed (4.6% vs. 3.3%), implied that the cut-off for the increased risk for ischaemic events is lower than the anticipated OM plasma concentration of ≥1200 ng/ml. However, concentration-safety response analyses for adverse events of special interest showed no increased incidences of angina pectoris in the highest quintile both in the overall population and the subpopulation of subjects with LVEF <30%, although such analyses may be limited in drawing clear conclusions. Additionally, there were no patterns of increasing incidence ventricular tachyarrhythmias, adjudicated major cardiac ischaemic events, cardiogenic shock or adjudicated stroke with increasing OM exposure bins. Concentration-safety response analyses did not indicate a concentration-response relationship for AEIs, either in the overall population or in the subpopulation of subjects with LVEF <30%.

Furthermore, it was questioned whether hypotension should be included as an ADR in section 4.8 of the SmPC due to the observed disbalances in the different safety analysis sets, including the CV outcome study GALACTIC-HF (TEAEs: 7.5% vs. 6.6% for OM and placebo, respectively), moderate duration studies of chronic HF (TEAEs: 3.8%, 0.6% and 1.8% for OM PK-guided titration, other OM, and overall placebo groups, respectively), study 20100754 (TEAEs: 7.9% vs. 4.6% for OM and placebo, respectively), and Study CY 1031 (TEAEs: 3.2% vs. 1.1%). Moreover, treatment with OM was associated with a small decrease in heart rate (1-2 bpm). The applicant argued that in the large pivotal study GALACTIC-HF, the incidence of vascular hypotensive disorders AEs in both the full population and the subpopulation of patients with LVEF <30% was approximately similar between the OM and

placebo groups. Further, there were also no difference in incidence in vascular hypotensive disorders AEs considered related to study drug, which is reassuring. Although a higher frequency of AEs denoting hypotension were observed in smaller studies, the applicant highlighted that the number of events was low and that the incidence in SAEs and AEs leading to discontinuation were approximately similar. Moreover, there were no clinically relevant differences with respect to vital signs, including blood pressure in all clinical studies. Based on above, it is agreed that there is no supporting evidence to suspect a causal relationship between hypotension and administration of OM, and that hypotension should not be considered as an ADR in section 4.8 of the SmPC. Similarly, it was also questioned whether ventricular tachycardia should be included as an ADR in section 4.8 of the SmPC, considering the observed disbalances in the different safety analysis sets, including the subgroup of inpatients in the CV outcome study GALACTIC-HF (TEAEs: 5.0% vs. 3.4% and SAEs: 3.4% vs. 2.2% for OM and placebo, respectively), moderate duration studies of chronic HF (TEAEs: 2.2%, 1.8% and 1.2% for OM PK-guided titration, other OM, and overall placebo groups, respectively), Study 20100754 (TEAEs: 4.3% vs. 3.6% for OM and placebo, respectively), and Study CY 1031 (TEAEs: 4.3% vs. 2.2%) The applicant argued that the incidences of ventricular tachycardia AEs assessed as related to study drug by the investigator and events leading to discontinuation of study drug were similar between the OM and placebo groups for both the full population and the subpopulation of patients with LVEF <30%. Moreover, the incidence of SAEs of ventricular tachycardia was slightly lower for OM compared with placebo for both the full population and the subpopulation of patients with LVEF <30%. Based on above it is agreed that ventricular tachycardia should not be considered as an ADR in section 4.8 of the SmPC.

Serious AEs. In the pivotal CV outcome study GALACTIC-HF, the percentage of subjects experiencing SAEs was high, however, slightly lower in the OM group compared with the placebo group (57.7% vs. 59.4%), which is reassuring. The most frequently reported SAEs (incidence ≥5% for OM) were cardiac failure (24.0% vs. 25.5% for OM and placebo, respectively) and acute cardiac failure (5.2% vs. 6.1%). Overall, no patterns indicative for a safety signal for OM in the total population were observed. Similarly, in both the subgroups of inpatient subjects (61.5% vs. 65.7%) and outpatient subjects (56.4% vs. 57.3%), a slightly lower percentage of subjects in the OM group compared with the placebo group experienced SAEs, although the frequency of SAEs was lower in outpatient group compared with the inpatient group.

Deaths. Adjudicated all-cause death was a secondary efficacy endpoint of the GALACTIC-HF study (see also “Clinical efficacy” section). In this study, the incidence of all-cause death was similar between the OM and placebo groups (25.9% (n=1067) vs. 25.9% (n=1065]), respectively). This result is driven by CV death, a component of the composite primary endpoint and also analysed as a secondary endpoint (19.6% vs 19.4%, respectively), which is covered in the efficacy section. In other studies combined, treatment-emergent all-cause death occurred in 1.1% (n=17) of subjects in the OM group and 1.6% (n=13) in the placebo group. Furthermore, the incidences of non-CV deaths were generally similar between the OM and the placebo groups (3.9% and 4.6%), with well-balanced reasons for non-CV across the treatment groups.

AEs of special interest. *Major cardiac ischaemic events.* During several phase I and II studies, the risk of cardiac ischaemia at OM concentrations ≥1200 ng/ml due to exaggerated pharmacology has been identified. Six (n= 1 in study CY 1111, 2 in CY 1121 and 1 in study 20110151) out of a total of 16 subjects with OM plasma concentrations >1200 ng/ml experienced events of myocardial ischaemia or infarction (chest discomfort, ECG ST segment depression, non-ST elevation MI, and unstable angina). Based on this finding, the OM target predose exposure range was 300-750 ng/ml in the CV outcome study GALACTIC-HF. Moreover, adjudicated major cardiac ischaemic events (MI, hospitalisation for unstable angina, coronary revascularisation) and ventricular tachyarrhythmias were evaluated as safety events of special interest.

In the pivotal CV outcome study GALACTIC-HF, the percentage of subjects with positively adjudicated major cardiac ischaemic events was slightly higher the OM group compared with the placebo group (4.9% and 4.6%, respectively). This small imbalance was due to a higher incidence in these events in the randomisation setting subgroup of inpatient subjects (4.5% vs. 2.7%; HR (95%) of 1.62 (1.01, 2.59)), whereas the incidences of these events were similar between the treatment groups in the outpatient subjects (5.0 vs. 5.2%; HR (95%) of 0.96 (0.77, 1.20). This imbalance in the inpatient subject subgroup was observed in every type of major ischaemic event, including MI (3.1% vs 2.0%), and hospitalisation for unstable angina (0.5% vs 0.0%), coronary revascularisation (2.4% vs. 1.7%)(see below subgroups for further discussion).

Generally, the major cardiac ischaemic events reported by the investigator showed consistent results to the adjudicated major cardiac ischaemic results. The overall incidence was slightly higher in the OM compared in the placebo group in the overall population (15.5% and 15.0%, respectively), due to a higher incidence in the OM compared with the placebo group in the inpatient subject subgroup (14.2% vs. 11.9%, respectively). The overall incidence of ventricular tachyarrhythmia (SMQ) was similar between the OM and placebo groups (7.1% vs. 7.4%) and also generally similar among the outpatient subgroup, while among the inpatient subject group, a higher incidence in the OM compared with the placebo group was observed (7.0% vs. 6.5%, respectively), mainly due to an imbalance in ventricular tachycardia 5.0% vs. 3.4%), as already described above.

Dose/exposure-safety analysis. In the CV outcome study 20110203, dose-safety response analyses showed no differences in SAEs and AEs of interest (ventricular tachyarrhythmias and major cardiac ischaemic events [MI, deaths, hospitalisation for unstable angina, coronary revascularisation] and adjudicated first stroke) by any dose or exposure group. Regarding exposure-safety response analyses, a higher incidence of AEs and SAE was observed in the OM group in the highest concentration group compared to other OM concentration groups and placebo. There was no trend of higher incidences of individual AEs with increasing concentration, with the exception of hypotension and cardiogenic shock. Regarding hypotension, there was no trend of increasing blood pressure by increasing exposure to OM. Further as also indicated above, the incidence of vascular hypotensive disorders AEs in both the full population and the subpopulation of patients with LVEF <30% was approximately similar between the OM and placebo groups. There was also no difference in incidence in vascular hypotensive disorders AEs considered related to study drug, which is reassuring. Moreover, there were no clinically relevant differences with respect to vital signs, including blood pressure in all clinical studies.

Furthermore, there were no patterns of increasing incidence of ventricular tachyarrhythmias, adjudicated major cardiac ischaemic events, or adjudicated stroke with increasing OM exposure bins.

Hepatobiliary disorders. Based on the results of the CV outcome GALACTIC-HF, OM appears not to have a detrimental effect on the liver as no imbalance in the SOC ” Hepatobiliary disorders” SOC in terms of TEAEs (4.9% vs. 5.0%), SAEs (2.0% each), and AEs leading to discontinuation of study drug (0.3% each) in the OM group compared with the placebo group were observed. However, liver function laboratory evaluations showed small imbalances in the incidences of subjects with abnormalities for ALT or AST >3x ULN, ALT or AST >5x ULN, ALT or AST >10x ULN (2.3% vs 2.1%, 1.0% vs 0.7%, and 0.3% vs 0.1% for OM and placebo, respectively), which were only evident in the inpatient subgroup. The applicant has conducted a thorough review of individual cases in severe ALT/AST elevation categories which showed that often identified alternative aetiologies for the hepatic laboratory abnormalities, such as concurrent acute decompensated cardiac failure. Overall, it can be concluded that despite small differences in some categories of transaminase elevations, the totality of data in terms of hepatic laboratory assessments and individual case profiles does not indicate a signal of hepatotoxic risk with OM.

Renal disorders. Based on the results of the CV outcome GALACTIC-HF, OM appears not to have a detrimental effect on the kidneys as no imbalance in the SOC "Renal and urinary disorders" in terms of TEAEs (17.5% vs. 17.4%), SAEs (5.6% vs 6.2%), and AEs leading to discontinuation of study drug (0.9% vs 0.6%) in the OM group compared with the placebo group were observed. Also, renal function laboratory parameters were generally comparable between both treatment groups.

Non-clinical studies showed accumulations of OM in the eyes and skin (see non-clinical section 3.2). In the pivotal study, slightly higher incidences in the SOC "*eye disorders*" (3.4% vs. 3.0%) and "Skin and subcutaneous tissue disorders" (8.2% vs. 7.6%) were observed in the OM group compared with the placebo group. However, considering that the incidences of these events are low and the differences between OM and the placebo group are small, firm conclusions are difficult to made.

Laboratory findings. *Clinical chemistry.* No clinically relevant changes in terms of creatinine, total bilirubin, direct bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALA), aspartate aminotransferase (AST), and potassium were observed between the OM and placebo groups or between the outpatient and inpatient randomisation settings.

Troponin I. In the CV outcome GALACTIC-HF study, increased values of cardiac biomarkers, including troponin-I and creatine kinase-MB, in the OM groups were observed compared with the placebo groups. The peak increase for both biomarkers occurred at week 6 (0.0080 vs. 0.000 ng/ml for Troponin I and 0.80 vs. 0.10 to 0.40 ng/ml for creatine kinase-MB in the OM and placebo group, respectively), and the increases remained up to week 144; It has to be noted that the week 6 measurement was the last measure before subjects could potentially be down titrated at week 8 in the CV outcome study 20110203 (~13% of treated subjects at week 4 were down-titrated at week 8). The percentage of subjects meeting troponin-I abnormality criteria postbaseline (>0.04 ng/ml) was also higher in the OM group compared with the placebo group (61.1% vs 49.4%, respectively). Study 20110203 found a poor correlation between OM plasma levels and maximum change from baseline in troponin-I (r2=0.00). Additionally, there was no imbalance in adjudicated MI by continuous or categorical analyses of maximal troponin excursion, indicating no clinically important adverse treatment effect related to threshold-defined troponin levels. Nevertheless, the clinical relevance of the increased troponin-I and creatine-kinase MB values during OM treatment is unclear. The applicant has mentioned increased troponin-I and creatine kinase-MB levels as ADRs in section 4.8 of the SmPC (OC).

Vital sings. In the CV outcome GALACTIC-HF study, there were no clinically relevant differences with respect to blood pressure and ECG assessments, although treatment with OM was associated with a small decrease in heart rate (1-2 bpm), which is thought to be a direct pharmacodynamic effect of omecamtiv mecarbil due to a favourable increase in stroke volume and more efficient cardiac output .

Safety in special populations. *Subjects with LVEF <30%.* Given the modest effect on the primary composite endpoint observed in the total population of GALACTIC-HF, and the stronger risk reduction in patients with a lower LVEF, the applicant proposes to limit the indication for OM to patients with LVEF<30%. The applicant has conducted safety evaluations within subjects with the LVEF<30% population. Generally similar results as those in the full population were observed. In short, the LVEF<30% subgroup included 4704 subjects (57.1% of the full population). In subjects with LVEF <30%, the incidences of TEAs (87.4% vs. 88.7%), Grade ≥4 (31.8% vs. 34.7%), SAEs (58.8% vs. 61.9%) and AEs leading to discontinuation (10.7% vs. 12.6%) were slightly lower in the OM group compared with placebo. Similar to the full population, the most frequent AEs (by ≥5 % in the OM group) with a higher incidence in the OM group compared with the placebo group were hypotension (8.2% vs. 7.1%), acute kidney injury (6.3% vs. 6.1%) and dizziness (5.8% vs. 4.6%). The same ADR as in the full population were identified, i.e. dizziness (5.8% vs 4.6% for OM and placebo, respectively), myocardial infarction (3.1% vs. 3.1%), and angina pectoris (4.5% vs 2.9%). Also

concerning the randomised setting (in- outpatient), no differences in the summary of the incidence of AEs and the most frequent AEs between both treatment groups in the subgroup of LVEF<30% is observed. However, the incidence of SAE of cardiogenic shock was approximately similar between treatments in the outpatient subgroup (2.2% vs. 1.7% for OM and placebo, respectively) whereas this incidence was higher for OM compared with placebo in the inpatient subgroup (3.1% vs. 1.1% for OM and placebo, respectively), which makes it challenging to provide definite treatment related conclusions. The incidence of positively adjudicated major ischaemic events was approximately similar between treatments in the outpatient subgroup (4.6% vs. 4.9% for OM and placebo, respectively), whereas this incidence was higher for OM compared with placebo in the inpatient subgroup (4.1% vs. 2.0% for OM and placebo, respectively). These results are consistent with time to first positively adjudicated major ischaemic events (including death due to MI) in the outpatient and inpatient subgroups (HR=0.96 [95% CI: 0.71, 1.29]) and HR=1.93 [95% CI: 0.98, 3.79], respectively).

The percentage of subjects experiencing SAEs was high, however, slightly lower in the OM group compared with the placebo group (58.8% vs 61.9%), which is reassuring. The most frequently reported SAEs (incidence ≥4% for OM) were cardiac failure (24.2% vs. 27.0% for OM and placebo, respectively), acute cardiac failure (5.8% vs. 7.3%), and cardiac failure congestive (4.1% vs. 4.4%). While the incidence of all-cause death was similar between the OM and placebo groups in the full population (25.9% (n=1067) vs. 25.9% (n=1065]), respectively), the incidence of all-cause death in the subgroup of LVEF<30% was somewhat lower in the OM group compared with the placebo group (27.0% (n=633) vs. 28.7% (n=679), respectively). A lower incidence of CV death was observed in the OM group compared with the placebo group in the LVEF <30% population (20.3% (n=476) vs. 22.1% (n=522), respectively), whereas in the LVEF >30% CV death occurred more often in subjects in the OM group (18.7%) compared with the placebo group (15.8%) for which the underlying reasons remain unclear.

Regarding AEs of special interest, similarly as observed in the full population, the incidence of adjudicated major cardiac ischaemic events was slightly higher in the OM group compared with the placebo group (4.5% vs. 4.2% for OM and placebo, respectively). On the other hand, the overall incidence of ventricular tachyarrhythmia was similar between the OM and placebo groups (8.0% vs. 8.0%). Interestingly, the incidence of adjudicated stroke is lower in the OM group compared with the placebo group for both the LVEF<30% subgroup (1.6% and 2.9%) and the full population (1.9% vs. 2.7%). The applicant has provided a plausible hypothesis for the lower incidences in adjudicated stroke in the OM group compared with the placebo group. Decreased left atrial contractility is associated with thrombus formation in the chamber, which can embolise to cause strokes. It is hypothesised that since that OM improves atrial contractility as well as ventricular contractility, improved left atrial and ventricular contractility due to OM would be predicted to reduce left atrial and ventricular thrombus formation, and, in turn, reduce the occurrence of embolic strokes.

Atrial fibrillation/flutter. In the prespecified subgroup analyses in the CV outcome, study 20110203 in the overall population, atrial fibrillation/flutter (AF/flutter) at baseline was observed to have one of the strongest univariate treatment covariate interactions for the primary composite endpoint (p=0.012). In subjects with AF/flutter at baseline compared to those without AF/flutter, a significant increase in the risk of CV death was observed with OM (HR=1.26; 95% CI 1.07, 1.49 vs. HR=0.90; 95% CI 0.80, 1.02, respectively) (see also “Clinical efficacy” section), whereas there were no differences in ventricular arrhythmias or adjudicated major cardiac ischaemic events. This increased risk of CV death in subjects with AF/flutter was not related to MI or sudden cardiac death but to heart failure. Also, in the subgroup of subjects with LVEF <30%, the incidence of CV death was lower in subjects without baseline AF/flutter treated with OM compared with placebo (17.8% vs. 20.4%), while the incidence of CV death was similar in those with baseline AF/flutter between OM and placebo groups (27.8% vs. 27.3%).

Further analyses indicated that the risk was mostly concentrated in a small subgroup of subjects who were also receiving digoxin at baseline based on comparisons of the subgroups of subjects with AF/flutter + digoxin use vs. AF/flutter – digoxin use in both the total population and the subgroup of subjects with LVEF <30% (see also efficacy discussion). Based on these findings, a contra-indication for with atrial fibrillation/flutter with concomitant digoxin usage with reference to sections 4.5 and 5.1 is included in the SmPC which is considered appropriate.

Elderly. There were no relevant differences between OM and placebo in the overall incidence of AEs or in the types of AEs across the age groups <65 years, 65 74 years, and 75-84 years in the full population and the subgroup of patients with LVEF <30%. Regarding the category of patients ≥85 years of age, the results should be interpreted with caution and no firm conclusions can be made due to the limit number of patients and, consequently, the limited number of events in this subgroup.

Gender. There were no relevant differences between OM and placebo in the overall incidence of AEs or in the types of AEs between sexes. However, a numerically higher frequency of renal events was observed in females in the OM group compared with the placebo group (18.4% vs. 11.6% for any AEs and 6.0% vs 3.2 % for serious AE in the HLT of renal failure and impairment). In contrast, the frequency of renal failure and impairment AEs was lower in males in the OM group compared to placebo (13.9% vs. 15.3% for any AEs and 5.0% vs 6.3% for serious AE in the HLT of renal failure and impairment). Assessment of medical history of the SOC Renal and Urinary Disorders showed that a higher incidence of renal failure and impairment was present in females randomised to OM compared to placebo (41.6% and 35.8%, respectively), which could have contributed to the higher incidence of renal events in females in the OM group compared with placebo. Additionally, females randomised to OM had worse renal function at baseline as indicated by higher serum creatinine, which is consistent with the higher incidence of medical history of renal impairment. Based on above, it can be concluded that OM is not increasing the risk of renal impairment in either women or men.

Renal impairment. There were no relevant differences in the overall incidence of AEs, or in the types of AEs by renal function. Worsening renal impairment was associated with higher incidence rates of all categories of AEs, however within each renal function group the rates for OM were generally approximately similar to those of placebo.

Hepatic impairment. Regarding hepatic impairment, subjects with hepatic impairment (total bilirubin ≥2 times the upper limit of normal, or alanine aminotransferase or aspartate aminotransferase ≥3 times upper limit of normal) were not eligible to participate in the pivotal study GALACTIC-HF. Therefore, an analysis of AEs by hepatic impairment is not possible based on this study. Nevertheless, Phase 1 study 20130253 was conducted in participants with mild and moderate hepatic impairment. There were no abnormal trends in mean clinical laboratory parameter values during the study for participants with normal hepatic function and for participants with mild or moderate hepatic impairment. Patients with severe hepatic impairment is included as missing information in the RMP, which is considered appropriate.

Discontinuations due to AEs. In the pivotal CV outcome study GALACTIC-HF, the incidence of AEs leading to study discontinuation was slightly lower in the OM group (10.5%) than in the placebo group (10.9%). The most frequent AEs leading to discontinuations was cardiac failure (2.3% vs. 2.0%, respectively), while all other AES leading to discontinuation occurred in less than 0.5% of the study population. No pattern for increased risk of AE leading to discontinuation of study drug could be observed in the total population. However, regarding hospital setting at randomisation (in/outpatient), a slightly higher percentage of subjects who discontinued the study drug due to AEs in the OM group compared with placebo in the inpatients subgroup was observed (11.3% vs 9.4%, respectively), while a lower percentage in the OM group compared with placebo was observed in the outpatient subgroup

(10.3% vs 11.4%). This imbalance in the inpatient subgroup was mainly due to a higher incidence in SOC cardiac disorders (6.5% vs 4.7%).

3.3.9. Conclusions on clinical safety

Omecamtiv mecarbil is a first-in-class cardiac myosin activator, so there is no previous safety experience is indicated for the treatment of adult patients with symptomatic chronic heart failure. Generally, at the therapeutic predose target plasma concentration range of 300- 750 ng/ml omecamtiv mecarbil appears to be well tolerated, although there is a small increase in the risk for angina pectoris, which appeared not to be dose-dependent.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in patients with severe hepatic impairment
	Use in pregnancy and lactation

3.4.1.1. Discussion on safety specification

It is agreed not to include "*<18 years and >85 of age at signing of informed consent*", "*acute coronary syndrome*", and "*eGFR<20 ml/min/1.73m²*" as missing information in the RMP. Furthermore, it is agreed to include "use in patients with severe hepatic impairment" and "use in pregnancy and lactation" as missing information in the summary of safety concerns.

There was no difference in incidence of myocardial infarction between the OM and placebo groups both in the full population and in the subpopulation of patients with LVEF <30% and an approximately similar PK-guided dosing as in the pivotal trial is proposed for the labelling. Further, angina pectoris, of which the incidence appeared not to be exposure dependent, is included in the ADR table of section 4.8, and no additional Risk minimisation measures are required.

Since use in patients with atrial fibrillation/flutter (AFF) who are taking digoxin is currently contra-indicated, it is agreed not to include "*Increased risk of heart failure outcomes in patients with atrial fibrillation taking digoxin and omecamtiv mecarbil*" as a safety concern in the RMP.

3.4.1.2. Conclusions on the safety specification

This is considered acceptable.

3.4.2. Pharmacovigilance plan

3.4.2.1. Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reaction reporting and signal detection as specific targeted follow-up questionnaires or other forms of routine pharmacovigilance activities are proposed for Kinharto.

3.4.2.2. Summary of additional PhV activities

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

No additional pharmacovigilance activities have been proposed by the applicant.

Routine pharmacovigilance activities are considered sufficient to further characterise the proposed missing information on “use in patients with severe hepatic impairment” and “use in pregnancy and lactation”.

3.4.2.3. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

3.4.3. Plans for post-authorisation efficacy studies

3.4.3.1. Summary of Post authorisation efficacy development plan

No post-authorisation safety studies (PAES) are proposed.

3.4.4. Risk minimisation measures

3.4.4.1. Routine risk minimisation measures

Routine risk minimisation measures are proposed for all safety concerns.

3.4.4.2. Summary of additional risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Use in patients with severe hepatic impairment	Routine risk minimisation measures: *SmPC section 4.2* *SmPC section 4.4* *SmPC section 5.2* *PL section 3* Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in pregnancy and lactation	Routine risk minimisation measures: *SmPC section 4.6* *SmPC section 5.3* *PL section 2* Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Routine risk minimisation measures have been considered by the applicant sufficient to manage the safety concerns and no additional risk minimisation measures were proposed.

The proposed risk minimisation measures are considered sufficient to mitigate the proposed missing information on “use in patients with severe hepatic impairment” and “use in pregnancy and lactation”.

3.4.4.3. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

3.4.5. Summary of the risk management plan

The public summary of the RMP does not require revision.

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic safety update reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

The proposed indication for omecamtiv mecarbil (KINHARTO) is the treatment of adult patients with symptomatic chronic heart failure and reduced ejection fraction of less than 30%. Omecamtiv mecarbil is a selective cardiac myosin activator that increases cardiac contractility by specifically binding to myosin at an allosteric site stabilising its lever arm in a primed position, increasing the number of myosin heads that can bind to actin filaments and undergo a powerstroke once the cardiac cycle starts. As a cardiac myotrope, OM increases the contraction of cardiac myocytes by direct action on the sarcomere, increasing the extent and duration of the cardiac contraction.

The proposed posology is a starting dose of 25 mg twice daily. After 2 weeks at the starting dose of 25 mg twice daily, the dose should be increased to 37.5 mg twice daily, and after another 2 weeks, increased to the maximum dose of 50 mg twice daily.

Symptomatic chronic HFrEF of less than 30% is a condition in which the hearts' ability to pump enough blood to meet the body's needs is severely impaired. This leads to symptoms such as fatigue, dyspnoea, orthopnoea, reduced exercise tolerance and oedema in the legs and ankles. The condition is more common in older adults, and risk factors include coronary artery disease, previous myocardial infarction, hypertension, and diabetes. Heart failure is a progressive condition; factors associated with a faster progression are lower ejection fraction, lower blood pressure, higher NT-proBNP, recent hospitalisation and more severe symptoms (higher NYHA class). Moreover, although significant progress has been made in the management of HFrEF, and prognosis remains particularly poor after hospitalisation, with a the 5-year survival after hospitalisation for HFrEF of 25%. The overall goals of medicinal therapy in HFrEF are to reduce morbidity (decrease the rate of hospitalisation, reduce symptoms, and improve health-related quality of life and functional status) and to reduce mortality.

4.1.2. Available therapies and unmet medical need

Symptomatic treatment of volume overload consists of diuretics, mostly loop diuretics. Furthermore, unless there are specific contraindications, all patients with HFrEF should be treated with a β-blocker and one of an angiotensin receptor–neprilysin inhibitor, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker as foundational therapy, with the addition of a mineralocorticoid receptor antagonist in patients with persistent symptoms. More recently, sodium-glucose cotransporter 2-inhibitors have also been added to this arsenal. Despite these treatments, HFrEF remains a leading cause of hospitalisation and death, and there is still an unmet medical need for more effective therapies to improve outcomes in this patient population.

4.1.3. Main clinical studies

The clinical efficacy and safety profile of OM in support of the proposed indication is based primarily on data from the pivotal phase 3 study 20110203, also known as GALACTIC-HF. The study included 8,256 patients with symptomatic heart failure with a LVEF ≤35% who were either currently hospitalised or recently hospitalised (in the last year) and on standard-of-care treatment. Patients were randomised to either OM or placebo. The OM group was dosed using a PK-guided dosing strategy, aiming at a target predose plasma concentration in the range of 300 to 750 ng/mL, which was informed by concentration-response analyses in studies CY 1111, CY 1121, and 20110151, which demonstrated that OM was able to beneficially influence various echocardiographic PD markers at concentration >300

ng/ml, whereas events of myocardial ischaemia or infarction were observed in 6 of 16 participants with excessive plasma concentrations of OM >1,200 ng/mL. Patients started on a dose of 25 mg twice daily. At week 2 and 6, predose OM levels were determined to guide dose titration at week 4 and 8, respectively. The maximal dose was 50 mg twice daily. The primary endpoint in this trial was a composite of time to CV death or first HF event, whichever occurred first. HF events were defined as HF hospitalisation or urgent HF clinic/office/emergency department visit. Secondary outcomes included the time to CV death, time to HF hospitalisation, time to all-cause death and the change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) from baseline to week 24. The study was event-driven and will conclude when approximately 1590 CV death events have occurred.

4.2. Favourable effects

Primary endpoint

Full analysis set GALACTIC-HF

Treatment with OM resulted in a significant 8% relative hazard reduction in the positively adjudicated primary composite endpoint of CV death or first HF event, whichever occurred first (37.0% vs. 39.1% for the OM and placebo group, respectively; HR (95%) 0.92 (0.86, 0.99); p=0.0252). The absolute risk reduction is 2.1 per 100 patient-years. The effect was consistent for both components of the primary endpoint. The effect was mainly driven by HF events, with HF event as the first event for 28.6% of subjects in the OM group and 30.1% in the placebo group and CV death as the first event for 8.4% vs. 9.0%, respectively. Sensitivity analyses supported the primary endpoint. Further, the effect was consistent for most of the subgroups, but not all (see uncertainties). Compared with the placebo group, greater reductions on the exploratory evaluation of NT-proBNP were observed at Week 24 in the OM group. The mean treatment difference for omecamtiv mecarbil compared with placebo was -791.1 (-1,449.6; -132.7) pg/mL among inpatient participants, and -455.2 (-654.1; -256.4) among outpatient participants.

LVEF<30% subgroup of GALACTIC-HF (proposed target indication)

Treatment with OM resulted in a 15% relative hazard reduction in the primary composite endpoint of CV death or first HF event, whichever occurred first (38.0% vs. 42.9% for the OM and placebo group, respectively; HR (95%) 0.85 (0.77, 0.93). The effect was consistent for both components of the primary endpoint. The absolute risk reduction is 4.9 per 100 patient-years. The effect was mainly driven by HF events, with an HF event as the first event for 29.3% of subjects in the OM group and 33.3% in the placebo group and CV death as the first event for 8.7% vs. 9.5%, respectively. Sensitivity analyses supported the primary endpoint. Further, the primary effect was consistent for (sub)subgroups. Also, secondary endpoints appear to support the primary endpoint with numerically improvements (HR range 0.84 to 0.92), except that only a small effect on Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) was found (see uncertainties). Greater reductions on the exploratory evaluation of NT-proBNP were observed at Week 24 in the OM group.

4.3. Uncertainties and limitations about favourable effects

Posology

In post-hoc analyses of a concentration-response relationship, a decreased risk for the primary efficacy endpoint with increasing OM concentrations has been observed (HR of 0.85 (0.75, 0.97), 0.83 (0.73, 0.95), 0.77 (0.68, 0.87) for >144 to ≤225 ng/ml, >225 to ≤300 ng/ml and, >300 to ≤377 ng/ml, respectively, and a slightly less obvious beneficial effect in the highest OM concentration quintile

of >377 ng/ml, (HR 0.91 (95% CI: 0.80, 1.02)). In the subpopulation of subjects with LVEF<30%, the same pattern can be observed.

Endpoints

Full analysis set GALACTIC-HF

None of the secondary endpoints reached statistical significance failing to support the primary endpoint. Hierarchical testing stopped after testing CV death, hampering further statistical interpretation of the other secondary endpoints. For the time to CV death, the hazard ratio of OM over placebo was 1.01 (0.92; 1.11). It is worth noting that the apparent contribution of CV mortality to the primary endpoint (8.4% vs 9.0% OM and placebo, respectively) result was due to competing risks in the primary endpoint analysis, despite of the fact that the study showed absence of a beneficial effect on CV mortality (19.6% vs. 19.4% for OM and placebo,respectively).

The least squares (LS) mean (SE) changes from baseline to week 24 in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) in the OM was only slightly larger than the placebo group in inpatient subjects (23.65 (0.70) and 21.15 (0.71), respectively) and outpatient subjects (5.83 (0.34) and 6.29 (0.34)), but did not reach statistical significance adjusting for multiplicity. Overall, 1142 (27.7%) participants in the OM group and 1,179 (28.7%) in the placebo group had a first HF hospitalisation. The HR was numerically in favour of OM, yet not significant (HR: 0.95 (0.87, 1.03); p=0.19). Overall, a positively adjudicated all-cause death was reported for 1 067 (25.9%) participants in the OM group and 1 065 (25.9%) in the placebo group with a HR (95% CI) of 1.00 (0.92, 1.09), p=0.9633). In outpatient subjects, the hazard ratio was numerically in favour of placebo (1.07 (0.96, 1.18)).

There was heterogeneity of effect for both the primary composite endpoint and secondary endpoint of CV death among some subgroups including LVEF categories and for atrial fibrillation/flutter at baseline. More specifically, in patients with LVEF above the median LVEF of 28% (PE HR (95% CI): 1.04 (0.94;1.16) (p interaction=0.0034) and CV death HR 1.15 (0.98; 1.34) (p interaction=0.0308)) and patients with atrial fibrillation/flutter at baseline (PE HR (95% CI): 1.05 (0.93; 1.18) (p interaction=0.0120) and CV death HR 1.26 (1.07; 1.49) (p interacion=0.0014)), OM shows apparently no beneficial effect on the composite primary endpoint. Such observation was also present for the CV death endpoint. The increased risk of CV mortality in AF patients seems concentrated in those patients concomitantly using digoxin. This has been addressed in the SmPC.

LVEF<30% subgroup of GALACTIC-HF (proposed target indication):

The subgroup with LVEF<30% was not included in any formal testing strategy; all results are exploratory or based on post-hoc analyses.

The mean (SD) changes from baseline to Week 24 in KCCQ-TSS in the OM and placebo groups, respectively, were only small with 24.6 (29.0) and 21.6 (31.1) among inpatient participants and 6.6 (21.7) and 5.6 (21.5) among outpatient participants.

A total of 664 (28.4%) patients in the OM group and 754 (31.9%) patients in the placebo group had recurrent hospitalisations. The rate ratio appears reduced with OM versus placebo for times to the recurrent event HF hospitalisation (rate ratio: 0.86, 95% CI 0.75, 0.98) based on a negative binomial model. This was consistent with a joint frailty model's estimated hazard ratio of 0.84 (95% CI 0.74, 0.94). However, the endpoint was only defined as exploratory and not controller under alpha spending.

4.4. Unfavourable effects

Full analysis set GALACTIC-HF

Adverse events. Slightly lower percentages of subjects with TEAEs (87.4% vs. 88.3%), Grade ≥4 (31.6% vs 32.5%, respectively), serious adverse events (SAEs) (57.7% vs 59.4%) and AEs leading to discontinuation (10.5% vs 10.9%) were reported in the OM group compared with placebo. The most frequent AEs (≥5% of subjects in the OM group) with a higher incidence in the OM group compared with the placebo group were *hypotension* (7.5% vs. 6.6%), *dizziness* (5.8% vs. 4.6%), and *acute kidney injury* (5.6% vs. 5.5%). Generally, similar results were observed in the in- and outpatient subjects.

Serious adverse events. The incidence of SAE was relatively high; however, a slightly lower in the OM group compared with the placebo group (57.7% vs. 59.4%). Overall, no patterns indicative of a safety signal for OM in the total population were observed.

Deaths. The incidence of all-cause death was similar between the OM and placebo groups (25.9% (n=1067) vs. 25.9% (n=1065]), respectively) and mainly driven by CV death (19.6% vs. 19.4%, respectively).

Adverse events of special interest. *Cardiotoxicity.* Several phase I and II studies identified the risk of cardiac ischaemia at OM concentrations ≥1200 ng/ml due to exaggerated pharmacology. Six out of 16 subjects with OM plasma concentrations >1200 ng/ml experienced events of myocardial ischaemia or infarction (chest discomfort, ECG ST segment depression, non-ST elevation MI, and unstable angina). In the full population of the pivotal study, the incidence of *adjudicated major cardiac ischaemic events* (MI, coronary revascularisation, and unstable angina) was slightly higher the OM group compared with the placebo group (4.9% and 4.6%, respectively) due to an imbalance in the randomisation setting subgroup of inpatient subjects (4.5% vs. 2.7, respectively; see below). Interestingly, the incidence of adjudicated stroke is lower in the OM group compared with the placebo group (1.9% vs. 2.7%).

Renal disorders. OM appears not to have a detrimental effect on the kidneys as no imbalance in the SOC “Renal and urinary disorders” in terms of TEAEs (17.5% vs. 17.4%), SAEs (5.6% vs 6.2%), and AEs leading to discontinuation of study drug (0.9% vs 0.6%) in the OM group compared with the placebo group were observed. Also, renal function laboratory parameters were generally comparable between both treatment groups.

Laboratory findings. No clinically relevant changes in clinical chemistry terms of creatinine, total bilirubin, direct bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALA), aspartate aminotransferase (AST), potassium were observed between the OM and placebo groups.

Discontinuation due to AEs. The incidence of AEs leading to study discontinuation was slightly lower in the OM group (10.5%) than in the placebo group (10.9%). The most frequent AEs leading to discontinuations was cardiac failure (2.3% vs. 2.0%, respectively), while all other AES leading to discontinuation occurred in less than 0.5% of the study population. No pattern for increased risk of AE leading to discontinuation of study drug could be observed in the total population.

LVEF <30% subgroup of GALACTIC-HF (proposed target indication)
Generally similar results in the subgroup of subjects with LVEF <30% (n=4704; 57.1% of the full population) as those in the full population were observed. In this subgroup, the incidences of TEAs (87.4% vs. 88.7%), Grade ≥4 (31.8% vs. 34.7%), SAEs (58.8% vs. 61.9%) and AEs leading to discontinuation (10.7% vs. 12.6%) were slightly lower in the OM group compared with placebo. Similar to in the full population, the most frequent AEs (by ≥5 % in OM group) with a higher incidence in the OM group compared with the placebo group were *hypotension* (8.2% vs. 7.1%), *acute kidney injury*

(6.3% vs. 6.1%), and dizziness (5.8% vs. 4.6%). The same ADRs as in the full population were identified, i.e. *dizziness* (5.8% vs 4.6% for OM and placebo, respectively), *myocardial infarction* (3.1% vs. 3.1%), and *angina pectoris* (4.5% vs. 2.9%). While the incidence of all-cause death was similar between the OM and placebo groups in the full population (25.9% (n=1067) vs. 25.9% (n=1065]), respectively), the incidence of all-cause death in the subgroup of LVEF<30% was somewhat lower in the OM group compared with the placebo group (27.0% (n=633) vs. 28.7% (n=679), respectively). Similarly, a lower incidence in CV death was observed in the OM group compared with the placebo group in the LVEF <30% population (20.3% (n=476) vs. 22.1% (n=522), respectively), whereas in the LVEF >30% CV death occurred more often in subjects in the OM group (18.7%) compared with the placebo group (15.8%). Regarding AEs of special interest, similarly as observed in the full population, the incidence in adjudicated major cardiac ischaemic events was slightly higher in the OM group compared with the placebo group (4.5% vs. 4.2% for OM and placebo, respectively), while the incidences in ventricular tachyarrhythmias were generally similar between both treatment groups in the subgroup of LVEF <30% (8.0% each). Also, as in the full population, the incidence in adjudicated stroke is lower in the OM group compared with the placebo group (1.6% and 2.9%).

4.5. Uncertainties and limitations about unfavourable effects

Full analysis set GALACTIC-HF

Safety in special populations. Although the full population showed similar incidences between both treatment groups, inconsistent safety results have been observed in subgroup analysis in the full population regarding the randomisation setting (in- and outpatient) for, among others, time to CV death (HR (95%): 1.08 (0.96, 1.21) vs. 0.87 (0.73, 1.04) for outpatients vs. inpatients subjects, respectively), adjudicated major cardiac ischaemic events (HR (95%): 0.96 (0.77, 1.20) vs. 1.62 (1.01, 2.59) for outpatients vs. inpatients subjects) and discontinuations due to adverse events (10.3% vs. 11.4% and 11.3% vs. 9.4% for OM vs. placebo for outpatients and inpatients, respectively).

Adverse drug reactions (ADR). Two adverse drug reactions have been identified, i.e. dizziness (5.8% vs. 4.6% for the OM and placebo group, respectively) and angina pectoris (4.6% vs 3.3%).

Adverse events of special interest. *E*xposure-safety response analyses showed a higher incidence of AEs and SAE in the OM group in the highest concentration group compared to other OM concentration groups and placebo. There was no trend of higher incidences of individual AEs with increasing concentration, with the exception of hypotension and cardiogenic shock, although further details could not identify any specific pattern. Further, there were no patterns of increasing incidence of ventricular tachyarrhythmias, adjudicated major cardiac ischaemic events, or adjudicated stroke with increasing OM exposure bins.

Laboratory findings. Increased values of cardiac biomarkers, including troponin-I and creatine kinase-MB in the OM groups compared with the placebo groups were observed; The peak increase for both biomarkers occurred at week 6 (0.0080 vs. 0.000 ng/ml for Troponin I and 0.80 vs. 0.10 to 0.40 ng/ml for creatine kinase-MB in the OM and placebo group, respectively). A poor correlation was found between OM plasma levels and maximum change from baseline in troponin-I (r2= 0.00), and there was no imbalance in adjudicated MI and continuous or categorical analyses of maximal troponin excursion.

LVEF <30% subgroup of GALACTIC-HF (proposed target indication)
The incidence of AEs was generally similar in both treatment groups regardless of the randomisation status (i.e., outpatients or inpatients at randomisation). The incidence of serious or severe AEs was lower for the OM group compared with the placebo group. The incidence of SAEs by PT were similar

between treatment groups or lower in the OM group compared with placebo in both the outpatient and inpatient subgroups in the LVEF <30% population, with the exception of cardiogenic shock. The incidence of SAE of cardiogenic shock was approximately similar between treatments in the outpatient subgroup (2.2% vs. 1.7% for OM and placebo, respectively) whereas this incidence was higher for OM compared with placebo in the inpatient subgroup (3.1% vs. 1.1% for OM and placebo, respectively). The incidence of positively adjudicated major ischaemic events was approximately similar between treatments in the outpatient subgroup (4.6% vs. 4.9% for OM and placebo, respectively), whereas this incidence was higher for OM compared with placebo in the inpatient subgroup (4.1% vs. 2.0% for OM and placebo, respectively). These results are consistent with time to first positively adjudicated major ischaemic events (including death due to MI) in the outpatient and inpatient subgroups (HR=0.96 [95% CI: 0.71, 1.29]) and HR=1.93 [95% CI: 0.98, 3.79], respectively.

4.6. Effects Table

Table 102. Effects Table for omecamtiv mecarbil (KINHARTO) for the proposed indication of treatment of adult patients with symptomatic chronic heart failure for the full analysis set, based on Galactic HF in HFrEF.

Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects				
Composite endpoint of CV death or first HF event	n (%)	1110 (36.1)	1054 (34.3)	Primary endpoint SoE: HR (95% CI): 0.92 (0.86; 0.99); similar effect size in inpatient and outpatient patients. Consistent effect for components of the primary endpoint. Unc: Largely driven by HF events (both hopitalisation as well as urgent HF ER/ED visit); not supported by CV death as secondary endpoint HR 1.01 (0.92, 1.11). No hierarchical testing possible for other secondary endpoints. Higher risk for both PE and CV death endpoints in subgroups of patients with atrial fibrillation/flutter at baseline, and for higher LVEF >28% at baseline, with significant p for interaction. Exploratory endpoint of recurrent hopsitalisations not clearly supportive (738 (17.9) vs 704 (17.1%); HR (95% CI): 0.98 (0.88; 1.08)
Unfavourable Effects				
Major Cardiac Ischaemic Events (adjudicated)	n (%)	200 (4.9)	188 (4.6)	Unc: Inconsistencies in the full population regarding the randomisationisation setting (in- and outpatient)
- Myocardial infarction	n (%)	122 (3.0)	118 (2.9)	
- Hospitalisation for unstable angina	n (%)	25 (0.6)	12 (0.3)	
- Coronary revascularisation	n (%)	115 (2.8)	117 (2.9)	
Angina Pectoris (includes angina unstable, myocardial ischaemia)	n (%)	189 (4.6)	137 (3.3)	
Ventricular tachyarrhythmia (SMQ)	n (%)	290 (7.1)	304 (7.4)	

Abbreviations: CV: cardiovascular; HR: hazard ratio; CI: confidence interval; LVEF: left ventricular ejection fraction.

Table 103. Effects Table for omecamtiv mecarbil () for the proposed indication of treatment of adult patients with symptomatic chronic heart failure for the full analysis set, based on Galactic HF in LVEF <30% subgroup.

Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects				
Composite endpoint of CV death or first HF event	n (%)	889 (38.0)	1014 (42.9)	Primary endpoint, exploratory subgroup analysis SoE: HR (95% CI): 0.85 (0.77; 0.93); similar effect size in inpatient and outpatient patients. Consistent effect for components of the primary endpoint. Numerical improvement for all secondary endpoints. Exploratory endpoint of recurrent hopsitalisations supportive (664 (28.1) vs 754 (31.9%); HR (95% CI): 0.86 (0.75; 0.98); consistent with joint frailty model, estimated HR (95% CI): 0.84 (0.74; 0.94) Unc: Analyses are all post-hoc and exploratory; Largely driven by HF events; higher risk of CV mortality in patients with atrial fibrillation/flutter at baseline (HR (95% CI): 1.06 (0.85, 1.32)), but not for the primary endpoint.
Unfavourable Effects				
Major Cardiac Ischaemic Events (adjudicated)	n (%)	104 (4.5)	98 (4.2)	Unc: Inconsistencies in the full population regarding the randomisationisation setting (in- and outpatient)
- Myocardial infarction	n (%)	67 (2.9)	65 (2.8)	
- Hospitalisation for unstable angina	n (%)	8 (0.3)	4 (0.2)	
- Coronary revascularisation	n (%)	60 (2.6)	60 (2.5)	
Angina Pectoris (includes angina unstable, myocardial ischaemia)	n (%)	105 (4.5)	68 (2.9)	
Ventricular tachyarrhythmia (SMQ)	n (%)	187 (8.0)	188 (8.0)	

Abbreviations: CV: cardiovascular; HR: hazard ratio; CI: confidence interval; LVEF: left ventricular ejection fraction.

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Heart failure (HF) is a progressive disease associated with a high mortality rate, frequent hospitalisations and poor quality of life. Despite available treatments, heart failure with reduced ejection fraction (HFrEF) remains a leading cause of hospitalisation and death, and there is an unmet medical need for more effective therapies to improve outcomes in this patient population.

The current application is based on the results of a single pivotal study (GALACTIC-HF). The investigated endpoints are relevant since the main therapeutic goals in treating HFrEF are to reduce cardiovascular mortality and prevent deterioration of the clinical status and hospitalisations. However, the beneficial effect on the primary composite endpoint of CV death or first HF event has not been convincingly shown due to several reasons. Although the effect was statistically significant with unidirectional effect of both components, CV death as a secondary endpoint could not show a beneficial effect. Further, the Scientific Advice Working Party was not in favour of using non-hospitalisation HF events, especially if this would drive efficacy. Yet, these events contributed to approximately 30% for the event difference between treatment arms. However, such events are accepted in the Hicks definition and used in other large HF trials. Moreover, other secondary endpoints could not support the primary analysis due to hierarchical testing which was stopped after testing the CV death endpoint. Further, it may be considered disappointing that a convincing effect on health-related quality of life did not accompany the effect on HF events, although this may be related to suboptimal sensitivity due to the infrequent evaluation and short timeframe of 24 weeks. Also, while the limits of the analyses are acknowledged, the treatment effect does not seem to be linear across the exposure range. Although mortality risk was not found to be increased in this patient population, based on the mechanism of action, presumed increase in left ventricular function and other factors, the expectancy would be to see a decrease in mortality for OM.

An exploratory subgroup analysis appears to show a greater benefit on the primary endpoint with low LVEF at baseline. The applicant proposed limiting the indication to subjects with LVEF <30%. For this subgroup, the post-hoc analyses on the primary endpoint and all secondary endpoints seem to show greater benefit than for the overall population. However, the credibility to select this subgroup has not been sufficiently demonstrated according to the criteria as detailed in the guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013) following scenario 2, in which biological plausibility and the ability to find replication are considered key elements. First, in the statistical analyses plan or the protocol, LVEF <30% (or 28%) has not been identified as a key subgroup for which particularly attention should be followed for analyses; this subgroup was only pre-specified as one of the 23 subgroups. However, according to the EMA subgroup guideline, the absence of pre-specification cannot be taken as a direct argument that results in particular lack of credibility, nor can the absence of stratification given the large sample size. Second, the biological plausibility is questionable. According to the applicant, greater cardiac contractility would have greater benefit in patients with lower LVEF due to insufficient compensatory mechanisms. However, such an assumption seems to fail somewhat, as for LVEF >30% (to LVEF 35%) there is a suggestion of harm (HR 1.04 ((0.94-1.16)). Moreover, it is not entirely understood how improving contractility would provide greater benefit with very low LVEF and not with slightly higher LVEF, where the effects/symptoms of HF can also occur (due to insufficient compensatory mechanisms) (MO). Additionally, replication of subgroup findings from other relevant trials (internal to the MAA or external trials that are relevant) could not sufficiently been shown. The company has only presented and discussed replication of findings based on PD effects (NT-proBNP) between the COSMIC-HF study and GALACTIC-HF study upon treatment with OM. Any replication based on clinical outcome data is not available. Although the current understanding of the relationship between NT-proBNP and clinical outcomes has been further

clarified, this PD effect is not considered to be a surrogate for clinical treatment outcomes in HF. For other HF therapies (with substantially different mechanism of actions (except digoxin)) including ARB, ARNi, MRA and digitalis, a comparable relationship between LVEF and treatment HR has been shown, although the level at which the HR reaches unity is much higher than with OM (based on current study) of at least LVEF 65%, as based on an editorial in the EHJ 2022 by Kondo et al. Overall, this cannot be considered credible and exceptionally compelling, especially in the context of a single clinical trial (MO).

While the limitations of subgroup analyses for drawing (strong) conclussions are acknowledged (especially for subgroups within subgroups), another subgroup analysis (patients with AF [approximately 25% of the patients]) did show an increased risk for both the primary endpoint and the secondary CV death endpoint in the full analysis set. This could be of importance as HF and AF appear to be interrelated in the cause of both pathophysiologies. Furthermore, results in patients with AF, remains somewhat inconclusive in the LVEF <30% subgroup as well: despite a beneficial effect on the primary endpoint, an increased risk of CV mortality in patients with atrial fibrillation/flutter seems to be present. This appears to be (partly) driven by the subgroup of patients using digoxin, and has been appropriately addressed in the SmPC by inclusion of the contra-indication “Patients with atrial fibrillation/flutter with concomitant digoxin usage”, although any other (unidentified) factors cannot be entirely excluded with these analyses. Given the high incidence of both paroxysmal and permanent atrial fibrillation in this patient group, safety data are primarily based on the single pivotal GALACTIC-HF study supplemented with phase 1 and phase 2 studies, providing 5637 subjects with a mean drug exposure of 14.28 months. Generally, OM at the target predose plasma concentration range of 300-750 ng/ml appears to be well tolerated.

4.7.2. Balance of benefits and risks

The modest treatment effect does not appear to be robust or clinically relevant. While for the subpopulation of subjects with an LVEF <30% the treatment effects appears to be greater overall, the applicant is not able to provide credible arguments or proposing this subgroup, which does not exclude that the effects may be data-driven. In addition, any convincing replication of data is missing for this subgroup. With regard to safety, OM at the target pre-dose plasma concentration range of 300- 750 ng/ml appears to be well tolerated.

Considering all favourable and unfavourable effects, the benefit-risk balance is currently negative.

4.7.3. Additional considerations on the benefit-risk balance

N/A

4.8. Conclusions

The overall benefit/risk balance of omecamtiv mecarbil (KINHARTO) is currently negative, given the major objections raised in the list of questions.