2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Omecamtiv mecarbil injection

Name of Active Ingredient: Omecamtiv mecarbil (AMG 423)

Title of Study: A double-blind, randomized, placebo-controlled, multicenter study to evaluate the safety and efficacy of IV infusion treatment with omecamtiv mecarbil in subjects with left ventricular systolic dysfunction hospitalized for acute heart failure

Investigators and Study Centers: This study was conducted at 111 centers in 19 countries in Europe, Australia and North America; 106 centers enrolled subjects. The study centers and principal investigators are listed in Section 16.1.4.

Publication(s): None at the time this report was prepared.

Study Period: 18 May 2011 (first subject enrolled [cohort 1]) to 18 April 2013 (last subject [US] EOS [cohort 3])

Development Phase: 2

Objectives:

The primary objective was to evaluate the effect of 48 hours of intravenous (IV) omecamtiv mecarbil compared with placebo on dyspnea in subjects with left ventricular systolic dysfunction hospitalized for acute heart failure (AHF).

The secondary objectives were to:

- assess the safety and tolerability of 3 dose levels of IV omecamtiv mecarbil compared with placebo in subjects with left ventricular systolic dysfunction hospitalized for AHF
- to evaluate the effects of 48 hours treatment with IV omecamtiv mecarbil on additional measures of dyspnea, patient global assessment (PGA), change in N-terminal pro-brain-type natriuretic peptide (NT-proBNP) and short-term clinical outcomes
- to characterize pharmacokinetics (PK) of omecamtiv mecarbil, including metabolites, following IV infusion and to evaluate the relationship between omecamtiv mecarbil plasma concentration and echocardiographic parameters in subjects with AHF

Exploratory objectives are detailed in the body of this clinical study report.

Methodology:

This was a multicenter, randomized, double-blind, placebo-controlled study with 3 dose cohorts enrolled sequentially in order of ascending dose strength of omecamtiv mecarbil. In each cohort, subjects were randomized 1:1 to omecamtiv mecarbil or placebo. In addition to the protocol-defined safety monitoring by Amgen, the safety risk to study subjects was evaluated on an ongoing basis through regular review of unblinded data by an independent Data Monitoring Committee (DMC). Before each dose escalation, the DMC issued a recommendation whether to proceed to the next cohort or to modify the study.

Number of Subjects Planned: approximately 600 subjects

Diagnosis and Main Criteria for Eligibility: Subjects were to have been admitted to the hospital for a primary diagnosis of AHF and were to have dyspnea at rest, or with minimal exertion, at least 2 hours after having received a total of ≥ 40 mg IV furosemide (or equivalent dose of an alternative IV loop diuretic).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Omecamtiv mecarbil was provided as a colorless, sterile, injectable solution formulated at a concentration of 1 mg/mL [redacted] The infusion solution at the required concentration was prepared at the center using normal saline ([redacted] sodium chloride) as diluent.

Each cohort was dosed at the specified dose rates for the loading and maintenance infusions listed in the table below. For day 1, the loading dose infusion rate was 30 mL/hr over 4 hours and the maintenance dose infusion rate was 6 mL/hr over the remaining 20 hours. For day 2, the infusion rate was 6 mL/hr over 24 hours. The table below displays the loading and maintenance doses and infusion periods for each cohort.

	Loading Infusion		Maintenance Infusion	
	Loading dose (mg/hr)	**Infusion period (hr)**	**Maintenance dose (mg/hr)**	**Infusion period (hr)**
Cohort 1	7.5 mg/hr	4	1.5 mg/hr	44
Cohort 2	15 mg/hr	4	3.0 mg/hr	44
Cohort 3	20 mg/hr	4	4.0 mg/hr	44

Manufacturing batch numbers are provided in Section 16.1.6.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo was presented in identical containers and stored/packaged the same as omecamtiv mecarbil. Dosing procedures were as reported above.

Manufacturing batch numbers are provided in Section 16.1.6.

Duration of Treatment: Omecamtiv mecarbil or placebo was infused IV over 48 hours (4 hours loading infusion, followed by 44 hours maintenance infusion).

Study Endpoints:

Efficacy Endpoints:
Primary Endpoint:

- dyspnea symptom response (minimally, moderately or markedly better by 7-point Likert scale at 6 hours after investigational product (IP) initiation AND moderately or markedly better at 24 and 48 hours after IP initiation without worsening heart failure (WHF) or death from any cause by 48 hours

Secondary Endpoints:

- death from any cause or WHF within 7 days of initiation of IP
- worsening heart failure within 7 days of initiation of IP
- dyspnea area under the curve (AUC) as measured by subject self-assessed Numerical Rating Scale (NRS)
- dyspnea by 7-point Likert scale at each scheduled assessment

- patient global assessment response (minimally, moderately or markedly better by subject self-assessed 7- point Likert scale at 6 hours after IP initiation, AND moderately or markedly better at 24 and 48 hours after IP initiation)
- patient global assessment at each scheduled assessment
- change from baseline in NT-proBNP at each scheduled assessment
- length of initial hospital stay
- days alive out of hospital until day 30

Refer to Protocol Section 10.1.3 (Section 16.1.1 of this report) for the definition of worsening heart failure and for the list of exploratory efficacy endpoints, including CEC-adjudicated potential endpoints (PEPs).

PK Endpoints (All Subjects):

- plasma concentration of omecamtiv mecarbil at selected time points
- plasma concentration of circulating metabolites, including omecamtiv mecarbil metabolites at selected time points

PK/PD Substudy Endpoints:

- omecamtiv mecarbil PK parameters including, but not limited to, area under the plasma concentration-time curve (AUC) from time 0 to time of the last quantifiable sample (AUC_{last}), AUC from time 0 to infinity (AUC_{inf}), plasma clearance (CL), maximum observed plasma concentration after dosing (C_{max}), time of maximum omecamtiv mecarbil plasma concentration (t_{max}), terminal half-life ($t_{½}$)
- pharmacookinetic parameters of M3 and M4 metabolites including, but not limited to, AUC_{last}, $AUC_{inf,}$ C_{max}, t_{max}, $t_{1/2}$ and metabolite to parent and metabolite to total drug material AUC ratios, when feasible
- change from baseline in echocardiographic parameters including, but not limited to, systolic ejection time (SET), stroke volume, and cardiac output at 6 and 48 hours

Safety Endpoints:

- subject incidence of adverse events and serious adverse events
- change from baseline in laboratory measurements and vital signs
- change from baseline electrocardiography (ECG)

Statistical Methods:

Fisher's protected least significant difference (LSD) method (Hsu, 1996) is used to ensure that the overall type I error rate is controlled at a significance level of 0.05 under the complete null hypothesis for the primary endpoint. Initially, the 3 omecamtiv mecarbil groups and the pooled placebo group were compared by using Cochran-Mantel-Haenszel (CMH) test (Stokes, 2000) with region as stratification factor; if significant at the 0.05 significance level, comparisons were then made between each omecamtiv mecarbil group with the pooled placebo group to claim significant effect. If the overall CMH test was not significant at 0.05 level, all of the following comparisons between each omecamtiv mecarbil group and the pooled placebo group were descriptive and exploratory. The LSD approach was then repeated in comparing each omecamtiv mecarbil group with its own placebo group in the same cohort. Additional analyses were performed to compare the 3 placebo groups. Pairwise comparison among the 3 omecamtiv mecarbil groups was conducted and nominal p-values provided.

Binary secondary endpoints (death or WHF, WHF and PGA response) were analyzed by using CMH. Continuous secondary endpoints (dyspnea AUC, and change from baseline NT-pro BNP at each scheduled assessment) were analyzed using Analysis of Covariance model. Ordinal endpoints (dyspnea scale and PGA at each scheduled assessment, days alive out of hospital) were analyzed using the van Elteren test. Length of initial hospital stay was evaluated using Kaplan-Meier estimates.

The CEC-adjudicated PEPs (exploratory endpoint) were summarized.

Pharmacokinetic concentrations of omecamtiv mecarbil and its metabolites were summarized for all subjects by cohort and nominal time. For subjects enrolled in the PK/PD substudy, PK of omecamtiv mecarbil and metabolites were estimated using non-compartmental analysis by Phoenix WinNonlin. Mean and/or median concentration-time plots for each cohort were presented graphically and PK parameters were summarized descriptively. In addition, PK and PD endpoints were summarized by scheduled assessment. Scatter plots were generated to show the estimated dose/concentration relationship as well as the 90% confidence region the curves. The PK of omecamtiv mecarbil and its metabolites were simultaneously modeled using a non-linear mixed effects modeling approach and the effect of covariates on PK variability was evaluated.

Safety endpoints were analyzed using the safety analysis set, which included all subjects who received at least 1 dose of IP. The subject incidence of each adverse event was tabulated by system organ class (SOC), preferred term (PT), severity, seriousness and relationship to treatment. Events of interest Ischemic Heart Disease and Myocardial Infarction SMQ events and Troponins Increased events of interest [EOI]) were tabulated. Incidences of supraventricular tachycardia and ventricular tachycardia arrhythmias were summarized. Clinical laboratory parameters and vital signs were summarized using descriptive statistics and/or shift tables. Electrocardiographic (ECG) data were summarized by scheduled assessment.

Summary of Results:

Subject Disposition: Eight-hundred seven subjects were screened (ie, signed Informed Consent) and 613 were eligible for enrollment and randomized. A total of 606 subjects received at least 1 dose of study treatment (303 received omecamtiv mecarbil and 303 received placebo) and 563 completed IP (282 on omecamtiv mecarbil and 281 on placebo) .

Baseline Demographics:

Sex: 466 (76.9%) men; 140 (23.1%) women

Age: The mean (SD) age was 66.0 (10.8) years (range: 59.0 to 75.0)

Ethnicity/Race: 591 (97.5%) Non Hispanic or Latino; 15 (2.5%) Hispanic or Latino / 530 (87.5%) white; 65 (10.7%) black; 7 (1.2%) other; 2 (0.3%) Asian; and 1 (0.2%) each American Indian or Alaska Native and Mixed Race.

Efficacy Results:

The study did not meet its primary endpoint of demonstrating significant improvement in dyspnea symptom response without WHF or death from any cause by 48 hours in AHF subjects hospitalized due to acute decompensated HF as measured by the 7-point Likert scale following a 48-hour infusion (p-value = 0.331). Proportions of responders in omecamtiv mecarbil cohorts 1, 2, and 3 were 42%, 47%, and 51%, respectively, compared with 41% of the pooled placebo group, showing a numerically increasing trend. An exploratory analysis demonstrated nominal statistically significant increases in

dyspnea response rate for omecamtiv mecarbil dose and concentration relationship (p-value = 0.025 and 0.007 respectively).

Omecamtiv mecarbil did not significantly reduce the rate of death from any cause or WHF within 7 days of IP initiation. A trend towards a reduction in WHF within 7 days of IP initiation was observed at higher omecamtiv mecarbil doses compared to placebo. The incidence of WHF within 7 days of initiating treatment was 17% in the pooled placebo group and was 13%, 8% and 9% on omecamtiv mecarbil in the first, second and third cohorts, respectively.

Omecamtiv mecarbil did not significantly improve dyspnea AUC as measured by NRS, PGA response by 7-point Likert scale, dyspnea by 7-point Likert scale or PGA at each schedule assessment. Omecamtiv mecarbil did not significantly reduce NT-proBNP compared to pooled placebo.

The CEC adjudicated the post-randomization PEPs as follows: deaths (all from cardiovascular death): 3.3% in the pooled placebo group and 2.6% in the pooled omecamtiv mecarbil group; rehospitalization: 12.2% in the pooled placebo group and 9.6% in pooled omecamtiv mecarbil group; stroke/transient ischemic attack: 1 placebo subject; myocardial infarctions: 2.3% in the omecamtiv mecarbil group and 1.0% in placebo group. Five of the adjudicated myocardial infarctions in omecamtiv mecarbil-treated subjects occurred in cohort 3, however, 2 occurred more than 7 days after completion of drug infusion and 1 occurred subsequent to a percutaneous coronary intervention.

Treatment with omecamtiv mecarbil did not significantly reduce the length of initial hospital stay nor increase the number of days alive out of hospital until day 30 compared to pooled placebo. At the 6 month vital status assessment, 38 (12.6%) subjects in the omecamtiv mecarbil groups died compared with 39 (12.9%) subjects in the placebo groups.

Pharmacokinetic Results:

During a single IV infusion over 48 hours of 96 mg, 192 mg or 256 mg of omecamtiv mecarbil to subjects with left ventricular systolic dysfunction hospitalized for AHF, omecamtiv mecarbil and its metabolites, M3 and M4, exhibited dose linear PK. Omecamtiv mecarbil, M3 and M4 concentrations declined log-linearly following the end of infusion. The mean observed C_{max} and omecamtiv mecarbil concentrations at the end of the infusion (C_{48}) were 485 and 425 ng/mL, respectively, for the highest dose cohort. The mean omecamtiv mecarbil clearance values ranged from 9.47 to 9.71 L/hr and the mean omecamtiv mecarbil $t_{½}$ ranged from 21.6 to 23.3 hours.

The mean exposure (AUC_{inf}) ratios of metabolite M3 relative to omecamtiv mecarbil and to total drug material ranged from 12.6% to 14.3%, and 9.97% to 11.0%, respectively, among the 3 dose cohorts. Similar relative ratios of M4 ranged from 11.4% to 13.5% and 8.99% to 10.3%, respectively. The mean $t_{½}$ of M3 and M4 ranged from 43.3 to 44.7 hours and from 40.3 to 42.4 hours, respectively.

There appeared to be no relationship between the pharmacokinetics of omecamtiv mecarbil and metabolites M3 and M4 and the range of estimated glomerular filtration rates observed in this study (eGFR range = 16.9 to 104 mL/min). The omecamtiv mecarbil concentrations observed were generally consistent though modestly higher to those predicted based on a PK model generated using data from earlier studies. There were no clinically relevant differences in omecamtiv mecarbil PK parameters between the subjects enrolled in the main study and the PK/PD substudy.

PK/PD Relationship Results:

A small decrease in heart rate (HR) and increase in systolic blood pressure relative to placebo was observed with increasing omecamtiv mecarbil concentrations. Regression analysis of echocardiographic parameters showed a significant increase in systolic ejection time (SET) with increasing omecamtiv mecarbil concentration (slope = 0.113 msec/ng/mL; $p < 0.0001$). No significant association was observed between C_{max} and maximum troponin change from baseline.

Safety Results:

The mean (SD) total doses of omecamtiv mecarbil were 92.9 (13.1) mg in cohort 1, 186.3 (23.6) mg in cohort 2 and 250.0 (29.0) mg in cohort 3.

In each cohort, treatment groups had similar rates of treatment emergent adverse events and, by ascending dose, there was no dose-related trend. The incidence of treatment emergent adverse events was similar between the pooled placebo and omecamtiv mecarbil groups (63.0% and 58.4%, respectively) as was the incidence of treatment emergent serious adverse events (23.1% and 21.8%, respectively).

Adverse event PTs reported in ≥ 5% of subjects in either pooled treatment group included cardiac failure (16.5% pooled placebo, 13.5% pooled omecamtiv mecarbil), hypotension (4.6% placebo, 7.9% omecamtiv mecarbil) and hypokalemia (5.9% placebo, 6.6% omecamtiv mecarbil).

For the EOI assessment, treatment emergent Ischemic Heart Disease SMQ events were reported in 14 subjects overall; 5 (5.0%) of these subjects were in the cohort 3 omecamtiv mecarbil treatment group. Incidence rates across the other 5 groups ranged from 1.0 to 2.0%. Treatment emergent events within the Myocardial Infarction SMQ occurred in 7 subjects overall (1 placebo subject; 2, 1, and 3 subjects in omecamtiv mecarbil cohorts 1, 2, and 3, respectively). For the EOI Troponins Increased events, 1 subject (omecamtiv mecarbil, cohort 1) had troponin T increased and 2 subjects (omecamtiv mecarbil, cohort 3) had troponin I increased adverse events reported.

Hypotension was more common among omecamtiv mecarbil-treated subjects than placebo subjects (7.9% and 4.6%, respectively). The imbalance was largely driven by cohort 1 (13.6%, compared with 7.8%). In cohort 2, rates of hypotension were 5.1% in the omecamtiv mecarbil group, compared with 2.0% in placebo and, in cohort 3, 5.0%, compared with 4.0%.

Supraventricular tachyarrhythmia adverse events were observed in a lower proportion of omecamtiv mecarbil-treated subjects than placebo-treated subjects (3.6% and 6.6%, respectively) whereas the rates of ventricular tachyarrhythmia adverse events were generally similar (5.3% and 5.9%, respectively).

Overall, 21.8% of study subjects experienced adverse events of severity Grade 3, or higher; 24.1% in pooled placebo group and 19.5% in pooled omecamtiv mecarbil and events within the cardiac disorders SOC were the most common such events in each pooled group. Cardiac failure (7.4%; 6.6% omecamtiv mecarbil and 8.3% placebo), cardiac failure congestive (1.7%), renal failure acute (1.7%), and pneumonia (1.2%) were the most commonly–reported serious adverse events overall. Twenty subjects (3.3%; 3.0% omecamtiv mecarbil and 3.6% placebo) had a fatal adverse event n the 30 days following enrollment in this study.

At baseline before IP infusion, the median cardiac troponin in the pooled omecamtiv groups was higher than in pooled placebo at 0.054 and 0.044 ng/mL respectively (upper reference limit [URL] 0.04 ng/mL). The median changes from baseline at the end of IP infusion (48 hours) between the pooled omecamtiv mecarbil vs the pooled placebo were 0.000 ng/mL and -0.004 ng/mL, respectively, and in the cohort 3 omecamtiv mecarbil

group vs cohort 3 placebo group were 0.001 ng/mL and -0.005 ng/mL, respectively. There was no apparent relationship between increasing omecamtiv mecarbil exposure (assessed by either C_{max} or $AUC_{0\text{-}48hrs}$) and maximal changes from baseline in cardiac troponin I.

Conclusions:

This study tested the hypothesis that at least 1 dose level of omecamtiv mecarbil IV would result in improvement of dyspnea without WHF or death from any cause by 48 hours in subjects with LVSD hospitalized for AHF compared with placebo. The study did not meet its primary efficacy endpoint of statistically significant improvement in dyspnea as measured by the 7-point Likert scale. The proportion of dyspnea responders increased with increasing omecamtiv mecarbil dose and concentrations and a trend for reduction of WHF was observed.

Omecamtiv mecarbil exhibited dose linear pharmacokinetics. The mean $t_{½}$ of omecamtiv mecarbil is approximately 22 to 23 hours. Omecamtiv mecarbil metabolites constituted approximately 15% of the total drug material in systemic circulation.

The rates and characteristics of death, hospitalizations, adverse events and serious adverse events reported in the omecamtiv mecarbil-treated subjects were similar to that in the placebo-treated subjects. Troponin I increases occurred in more omecamtiv mecarbil than placebo subjects although there was not a relationship of maximum troponin increase to omecamtiv mecarbil C_{max} or AUC. There was a numerical imbalance in adjudicated myocardial infarctions in omecamtiv mecarbil-treated subjects in cohort 3. The possibility that the imbalance of myocardial infarction events is associated with omecamtiv mecarbil cannot be ruled out and hence the risk of myocardial infarction has been added to the risk profile of omecamtiv mecarbil. [redacted].