Clinical trial results:
A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Effect of Omecamtiv Mecarbil on Exercise Capacity in Subjects with Heart Failure with Reduced Ejection Fraction and Decreased Exercise Tolerance

Summary

EudraCT number	2018-001233-40
Trial protocol	FR DE HU PL NL IT
Global end of trial date	06 January 2022

Results information

Result version number	v1 (current)
This version publication date	21 January 2023
First version publication date	21 January 2023

Trial information

Trial identification

Sponsor protocol code	CY1031

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03759392
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cytokinetics, Inc.
Sponsor organisation address	350 Oyster Point Blvd, South San Francisco, United States, 94080
Public contact	Medical Affairs, Cytokinetics Inc., +1 650 624 2929, medicalaffairs@cytokinetics.com
Scientific contact	Medical Affairs, Cytokinetics Inc., +1 650 624 2929, medicalaffairs@cytokinetics.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of treatment with omecamtiv mecarbil compared with placebo on exercise capacity as determined by CPET following 20 weeks of treatment with omecamtiv mecarbil or placebo

Protection of trial subjects:

The protocol and consent form were submitted by each investigator to an institutional review board (IRB), an ethics committee (EC), or a research ethics board (REB) for review and approval before study initiation. All amendments to the protocol or revisions to the consent form (if applicable) after initial IRB/EC/REB approval were submitted by the investigator to the IRB/EC/REB for review and approval before implementation. This study was conducted in accordance with the United States Code of Federal Regulations and applicable International Council on Harmonisation (ICH) guidelines, consistent with Good Clinical Practice (GCP). All patients provided informed written consent before any protocol-specific procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 41
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	United States: 155
Country: Number of subjects enrolled	Canada: 19
Worldwide total number of subjects	276
EEA total number of subjects	102

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	140
From 65 to 84 years	134
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted in subjects between 09-April-2019 (date first subject enrolled) through 06-January-2022 (date last subject completed) at 63 sites in Canada, France, Germany, Hungary, Italy, Netherlands, Poland, Sweden, and United States.

Pre-assignment

Screening details:

A total of 474 subjects were screened for the study; 198 failed screening, primarily due to not satisfying eligibility criteria. Of 474 subjects, 276 subjects were enrolled and randomised in the study in 2:1 ratio i.e., 185 and 91 subjects received omecamtiv mecarbil and placebo, respectively.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects self-administered placebo (matched to omecamtiv mecarbil) at doses 25 milligrams (mg), 37.5 mg, or 50 mg tablets orally, twice a day (BID) from Day 1 up to Week 20.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered placebo (matched to omecamtiv mecarbil) tablets orally BID.

Arm title	Omecamtiv Mecarbil

Arm description:

Subjects Self-administered omecamtiv mecarbil oral tablets at doses 25 mg, 37.5 mg, or 50 mg, BID from Day 1 up to Week 20. All subjects started at a dose of 25 mg BID and the omecamtiv mecarbil dose was adjusted at Week 4 and Week 8 based on predose omecamtiv mecarbil plasma concentrations from blood collected at Week 2 and Week 6, respectively.

Arm type	Experimental
Investigational medicinal product name	Omecamtiv Mecarbil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered film-coated, white to off-white, oval, modified-release tablets in doses of 25 mg, 37.5 mg, or 50 mg, orally BID.

Number of subjects in period 1	Placebo	Omecamtiv Mecarbil
Started	91	185
Completed	85	164
Not completed	6	21
Physician decision	1	-
Consent withdrawn by subject	-	2
Adverse event, non-fatal	4	12
Death	1	2
Other-unspecified	-	3
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects self-administered placebo (matched to omecamtiv mecarbil) at doses 25 milligrams (mg), 37.5 mg, or 50 mg tablets orally, twice a day (BID) from Day 1 up to Week 20.	
Reporting group title	Omecamtiv Mecarbil
Reporting group description:	
Subjects Self-administered omecamtiv mecarbil oral tablets at doses 25 mg, 37.5 mg, or 50 mg, BID from Day 1 up to Week 20. All subjects started at a dose of 25 mg BID and the omecamtiv mecarbil dose was adjusted at Week 4 and Week 8 based on predose omecamtiv mecarbil plasma concentrations from blood collected at Week 2 and Week 6, respectively.	

Reporting group values	Placebo	Omecamtiv Mecarbil	Total
Number of subjects	91	185	276
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	98	140
From 65-84 years	48	86	134
85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	64.4	63.3	
standard deviation	± 11.41	± 9.64	-
Gender categorical Units: Subjects			
Female	15	27	42
Male	76	158	234
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	2	3	5
Black or African American	6	16	22
White	82	163	245
Other	1	2	3
Ethnicity Units: Subjects			
Hispanic or Latino	8	12	20
Not Hispanic or Latino	81	167	248
Unknown	2	6	8

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects self-administered placebo (matched to omecamtiv mecarbil) at doses 25 milligrams (mg), 37.5 mg, or 50 mg tablets orally, twice a day (BID) from Day 1 up to Week 20.	
Reporting group title	Omecamtiv Mecarbil
Reporting group description:	
Subjects Self-administered omecamtiv mecarbil oral tablets at doses 25 mg, 37.5 mg, or 50 mg, BID from Day 1 up to Week 20. All subjects started at a dose of 25 mg BID and the omecamtiv mecarbil dose was adjusted at Week 4 and Week 8 based on predose omecamtiv mecarbil plasma concentrations from blood collected at Week 2 and Week 6, respectively.	

Primary: Change in Peak Oxygen Uptake (pVO2) on Cardiopulmonary Exercise Testing (CPET) From Baseline to Week 20 (Multiple Imputation)

End point title	Change in Peak Oxygen Uptake (pVO2) on Cardiopulmonary Exercise Testing (CPET) From Baseline to Week 20 (Multiple Imputation)
End point description:	
The change in pVO2 from baseline to Week 20 was analysed using an analysis of covariance (ANCOVA) model which included terms of treatment, Baseline respiratory exchange ratio (RER) randomisation strata (less than [<] 1.15, greater than equal to [≥] 1.15), persistent atrial fibrillation (yes/no), age, sex, baseline pVO2, Baseline hemoglobin level, and Baseline body weight. pVO2 assessed effect of treatment on exercise capacity by assessing total workload and ventilatory efficiency during CPET by evaluating CPET with gas-exchange analysis. Analysis was performed on full analysis set (FAS) population that included all randomised subjects who had received at least 1 dose of randomised investigational product (IP). Here, "Subjects analysed" signifies number of subjects with available data at the specified timepoint for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline, Week 20	

End point values	Placebo	Omecamtiv Mecarbil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	162		
Units: millilitre per minute per kilogram				
least squares mean (standard error)	0.207 (± 0.2412)	-0.239 (± 0.1718)		

Statistical analyses

Statistical analysis title	Omecamtiv Mecarbil versus Placebo
Statistical analysis description:	
Each completed dataset was analysed using ANCOVA with fixed effects of treatment, RER (<1.15,≥1.15), persistent atrial fibrillation (Y/N) at randomisation, age, sex, baseline pVO2, hemoglobin (Hb), and weight. Missing Week 20 pVO2 were imputed using regression multiple imputation including estimated glomerular filtration rate (eGFR), Kansas City Cardiomyopathy Questionnaire Total Symptom	

(KCCQ TSS), NYHA and average daily activity units along with parameters mentioned for complete dataset.

Comparison groups	Omecamtiv Mecarbil v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [1]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-0.447
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.024
upper limit	0.131
Variability estimate	Standard error of the mean
Dispersion value	0.2931

Notes:

[1] - Threshold for significance at 0.05 level.

Secondary: Change in Total Workload During Cardiopulmonary Exercise Testing (CPET) From Baseline to Week 20 (Multiple Imputation)

End point title	Change in Total Workload During Cardiopulmonary Exercise Testing (CPET) From Baseline to Week 20 (Multiple Imputation)

End point description:

The change in total workload during CPET from Baseline to Week 20 using an ANCOVA model which included terms of treatment, baseline RER randomisation strata (<1.15, ≥1.15), persistent atrial fibrillation (yes/no), age, sex, baseline workload, Baseline hemoglobin level, and Baseline body weight. The pVO2 assessed effect of treatment on exercise capacity by assessing total workload and ventilatory efficiency during CPET by evaluating CPET with gas-exchange analysis. Analysis was performed on FAS population. Here, "Subjects analysed" signifies number of subjects with available data at the specified timepoint for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 20

End point values	Placebo	Omecamtiv Mecarbil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	162		
Units: Watts				
least squares mean (standard error)	1.590 (± 1.9477)	-3.798 (± 1.3352)		

Statistical analyses

Statistical analysis title	Omecamtiv Mecarbil versus Placebo

Statistical analysis description:

Each completed dataset was analysed using ANCOVA with fixed effects of treatment, RER (<1.15, ≥1.15), persistent atrial fibrillation (Yes/No) at randomisation, age, sex, baseline workload, Hb, and weight. Missing Week 20 workload were imputed using regression multiple imputation including eGFR, KCCQ TSS, NYHA and average daily activity units along with parameters mentioned for complete

Comparison groups	Omecamtiv Mecarbil v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025 [2]
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-5.388
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.108
upper limit	-0.668
Variability estimate	Standard error of the mean
Dispersion value	2.3937

Notes:

[2] - Threshold for significance at 0.05 level.

Secondary: Change in Ventilatory Efficiency, as Measured by the slope of Change in Ventilation (VE) divided by the change in Carbon Dioxide Output (VCO2), During Cardiopulmonary Exercise Testing (CPET) From Baseline to Week 20 (Multiple Imputation)

End point title	Change in Ventilatory Efficiency, as Measured by the slope of Change in Ventilation (VE) divided by the change in Carbon Dioxide Output (VCO2), During Cardiopulmonary Exercise Testing (CPET) From Baseline to Week 20 (Multiple Imputation)

End point description:

The change in ventilatory efficiency during CPET from Baseline to Week 20 was analyzed using an ANCOVA model which included terms of treatment, baseline RER randomisation strata (<1.15, ≥1.15), persistent atrial fibrillation (yes/no), age, sex, baseline ventilatory efficiency, Baseline hemoglobin level, and Baseline body weight. Analysis was performed on FAS population. Here, "Subjects analysed" signifies number of subjects with available data at the specified timepoint for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 20

End point values	Placebo	Omecamtiv Mecarbil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	162		
Units: VE/VCO2 slope				
least squares mean (standard error)	-0.138 (± 0.5065)	0.277 (± 0.3616)		

Statistical analyses

Statistical analysis title	Omecamtiv Mecarbil versus Placebo

Statistical analysis description:

Each completed dataset was analysed using ANCOVA with fixed effects of treatment, RER (<1.15, ≥1.15), persistent atrial fibrillation (Yes/No) at randomisation, age, sex, baseline ventilatory efficiency, Hb, and weight. Missing Week 20 ventilatory efficiency were imputed using regression multiple imputation including eGFR, KCCQ TSS, NYHA and average daily activity units along with parameters mentioned for complete dataset.

Comparison groups	Omecamtiv Mecarbil v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51 [3]
Method	ANCOVA
Parameter estimate	Least Sqaure Mean Difference
Point estimate	0.414
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	1.639
Variability estimate	Standard error of the mean
Dispersion value	0.6215

Notes:

[3] - Threshold for significance at 0.05 level.

Secondary: Change in the Average Daily Activity Units From Baseline (Week -2 to Day 1) to Weeks 18 to 20 (≥7 Days of Wear ≥10 hours During Awake Time)

End point title	Change in the Average Daily Activity Units From Baseline (Week -2 to Day 1) to Weeks 18 to 20 (≥7 Days of Wear ≥10 hours During Awake Time)

End point description:

The change in the average daily activity units measured over a 2-week period from baseline (Week −2 to Day 1) to Week 18-20 was analysed using a repeated measures mixed model with terms such as treatment, baseline value, visit, RER randomization strata (<1.15, ≥1.15), and persistent atrial fibrillation (yes/no) as well as interaction terms of treatment-by-visit and baseline-by-visit with an unstructured covariance matrix. Analysis was performed on FAS population. Here, "Subjects analysed" signifies number of subjects with available data at the specified timepoint for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (Week -2 to Day 1), Weeks 18 to 20

End point values	Placebo	Omecamtiv Mecarbil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	147		
Units: Activity Units (10^5)				
least squares mean (standard error)	-0.5 (± 0.38)	-0.2 (± 0.30)		

Statistical analyses

Statistical analysis title	Omecamtiv Mecarbil versus Placebo

Statistical analysis description:

Change from baseline in average daily activity units use a mixed model repeated measures model with fixed effect of treatment, visit, baseline average daily activity units, baseline RER (<1.15, >=1.15) and persistent atrial fibrillation (Yes/No) at randomization and interaction terms of treatment-by-visit, and baseline-by-visit.

Comparison groups	Omecamtiv Mecarbil v Placebo
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54 [4]
Method	Mixed model repeated measures
Parameter estimate	Least Sqaure Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.42

Notes:

[4] - Threshold for significance at 0.05 level.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to 4 weeks following the last visit (Week 24) regardless of seriousness or relationship to IP.

Adverse event reporting additional description:

Reported AEs are treatment-emergent AEs that developed/worsened during 'on-treatment period' (time form first dose of study drug up to end of study [i.e., 4 weeks following last visit [Week 24]). Safety population included all randomised subjects who had received at least 1 dose of IP. 1 of 4 deaths occurred after end of treatment (Week 20).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects self-administered placebo (matched to omecamtiv mecarbil) at doses 25 milligrams (mg), 37.5 mg, or 50 mg tablets orally, twice a day (BID) from Day 1 up to Week 20.

Reporting group title	Omecamtiv Mecarbil

Reporting group description:

Subjects Self-administered omecamtiv mecarbil oral tablets at doses 25 mg, 37.5 mg, or 50 mg, BID from Day 1 up to Week 20. All subjects started at a dose of 25 mg BID and the omecamtiv mecarbil dose was adjusted at Week 4 and Week 8 based on predose omecamtiv mecarbil plasma concentrations from blood collected at Week 2 and Week 6, respectively.

Serious adverse events	Placebo	Omecamtiv Mecarbil	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 91 (14.29%)	30 / 185 (16.22%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Complications of transplanted heart			
subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thermal burn			

subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 91 (0.00%)	2 / 185 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	3 / 91 (3.30%)	2 / 185 (1.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 91 (1.10%)	7 / 185 (3.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 91 (0.00%)	2 / 185 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 91 (2.20%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	2 / 91 (2.20%)	5 / 185 (2.70%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			

subjects affected / exposed	1 / 91 (1.10%)	2 / 185 (1.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 91 (0.00%)	2 / 185 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Palpitations			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Heart transplant			
subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Ischaemic stroke			
subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 91 (1.10%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary oedema			
subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 91 (1.10%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 91 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Omecamtiv Mecarbil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 91 (59.34%)	121 / 185 (65.41%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 91 (3.30%)	3 / 185 (1.62%)	
occurrences (all)	3	4	
Hypotension			
subjects affected / exposed	1 / 91 (1.10%)	4 / 185 (2.16%)	
occurrences (all)	1	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 91 (4.40%)	9 / 185 (4.86%)	
occurrences (all)	4	9	
Non-cardiac chest pain			
subjects affected / exposed	3 / 91 (3.30%)	4 / 185 (2.16%)	
occurrences (all)	4	4	
Asthenia			
subjects affected / exposed	0 / 91 (0.00%)	4 / 185 (2.16%)	
occurrences (all)	0	5	
Chest discomfort			
subjects affected / exposed	0 / 91 (0.00%)	4 / 185 (2.16%)	
occurrences (all)	0	4	
Oedema peripheral			
subjects affected / exposed	0 / 91 (0.00%)	4 / 185 (2.16%)	
occurrences (all)	0	5	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	8 / 91 (8.79%)	5 / 185 (2.70%)	
occurrences (all)	9	5	
Cough			
subjects affected / exposed	1 / 91 (1.10%)	5 / 185 (2.70%)	
occurrences (all)	1	5	
Dyspnoea exertional			

subjects affected / exposed	0 / 91 (0.00%)	4 / 185 (2.16%)	
occurrences (all)	0	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 91 (1.10%)	5 / 185 (2.70%)	
occurrences (all)	1	5	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 91 (1.10%)	7 / 185 (3.78%)	
occurrences (all)	1	8	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	3 / 91 (3.30%)	4 / 185 (2.16%)	
occurrences (all)	4	28	
Atrial fibrillation			
subjects affected / exposed	3 / 91 (3.30%)	4 / 185 (2.16%)	
occurrences (all)	3	4	
Cardiac failure			
subjects affected / exposed	2 / 91 (2.20%)	5 / 185 (2.70%)	
occurrences (all)	2	6	
Palpitations			
subjects affected / exposed	2 / 91 (2.20%)	1 / 185 (0.54%)	
occurrences (all)	2	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 91 (5.49%)	9 / 185 (4.86%)	
occurrences (all)	6	10	
Headache			
subjects affected / exposed	3 / 91 (3.30%)	4 / 185 (2.16%)	
occurrences (all)	3	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 91 (4.40%)	7 / 185 (3.78%)	
occurrences (all)	4	7	
Nausea			

subjects affected / exposed	3 / 91 (3.30%)	3 / 185 (1.62%)	
occurrences (all)	3	4	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 91 (1.10%)	4 / 185 (2.16%)	
occurrences (all)	1	4	
Rash			
subjects affected / exposed	4 / 91 (4.40%)	0 / 185 (0.00%)	
occurrences (all)	4	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 91 (1.10%)	4 / 185 (2.16%)	
occurrences (all)	1	5	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 91 (4.40%)	5 / 185 (2.70%)	
occurrences (all)	4	5	
Arthralgia			
subjects affected / exposed	0 / 91 (0.00%)	6 / 185 (3.24%)	
occurrences (all)	0	7	
Myalgia			
subjects affected / exposed	1 / 91 (1.10%)	5 / 185 (2.70%)	
occurrences (all)	1	6	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 91 (2.20%)	2 / 185 (1.08%)	
occurrences (all)	2	2	
Urinary tract infection			
subjects affected / exposed	2 / 91 (2.20%)	1 / 185 (0.54%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	3 / 91 (3.30%)	4 / 185 (2.16%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2019	Amendment 1: • Modified inclusion criteria to specify that screening assessments were to be completed prior to randomisation • Modified exclusion criteria to: − Qualify that a subject would be excluded if they had paroxysmal atrial fibrillation or flutter that required treatment − Lower the screening CPET for chronotropic incompetence from 60% to <55% of maximum predicted heart rate • Specified permanent discontinuation of IP if a subject had an acute ST-segment elevation myocardial infarction • Specified permanent discontinuation of IP and treatment unblinding if the omecamtiv mecarbil plasma concentration was ≥1000 nanograms per millilitre (ng/mL) at an unscheduled visit • Added electrocardiogram (ECG) assessments at Weeks −2, 2, and 6 • Added iron testing (iron, ferritin, total iron binding capacity) to laboratory assessments • For interim analysis, reduced the conditional power to 0.1
31 July 2020	Amendment 2: Revised the time between screening CPET and randomization to not more than 3 weeks to harmonize timing between subjects who had 2 screening visits and those having a combined screening visit • Clarified that if the Week 2 or Week 6 PK assessment was missed, the subjects randomised to omecamtiv mecarbil would be titrated to, or maintained at a dose of 25 mg to ensure omecamtiv mecarbil plasma concentrations remained <1000 ng/mL • Reduced the number of in-person study visits to reduce potential COVID-19 exposure, with the following specific changes: − Changed Week 14 clinic visit to a telephone visit − Removed the omecamtiv mecarbil concentration assessment, vital signs assessment, and IP tablet count at Week 14 • Provided additional flexibility in the conduct of the study because of the COVID-19 pandemic, with the following specific changes: − Added the ability to extend the treatment duration when the Week 20 CPET was delayed − Extended the potential study duration − Added the option of a second rescreening if a prior screen failure was due to the COVID-19 pandemic − Added the ability to use an alternative IP dispensing method − Added the option to complete the KCCQ over the telephone − Added unscheduled visits to perform the Week 20 CPET, if it could not be performed in the planned Week 20 window − Added the ability to increase sample size (to overcome the loss of information due to possible important protocol deviations due to COVID-19 • Added statistical analyses to assess the impact of the COVID-19 pandemic • Added the ability to perform remote source data verification (to overcome possible on-site or travel restrictions due to COVID-19)
30 June 2021	Amendment 3: Updated the study sponsor from Amgen to Cytokinetics • Updated data from GALACTIC-HF study • Made administrative changes to align with the change in sponsor, including updates of contact personnel and safety reporting procedures

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 April 2020	The new screening within the study was temporarily suspended due to COVID-19. On 04-Jun-2020, the decision to re-open screening on site by site basis was made.	04 June 2020

Notes:

Limitations and caveats

None reported