Clinical trial results:
Impact of EMpagliflozin on cardiac function and biomarkers of heart failure in patients with acute MYocardial infarction (EMMY-Trial) – a phase III Study

Summary

EudraCT number	2016-004591-22
Trial protocol	AT
Global end of trial date	03 May 2022

Results information

Result version number	v1 (current)
This version publication date	08 September 2023
First version publication date	08 September 2023
Summary attachment (see zip file)	Final Report EMMY Trial (ICH E3 STRUCTURED CLINICAL STUDY REPORT_EMMY_V1.1_clean.pdf)

Trial information

Trial identification

Sponsor protocol code	HS-2017-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03087773
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Graz
Sponsor organisation address	Neue Stiftingtalstrasse 6, Graz, Austria, 8010
Public contact	Dr. Norbert Tripolt, Medical University of Graz, 43 316385 81310, norbert.tripolt@medunigraz.at
Scientific contact	Prof. Harald Sourij, MBA, Medical University of Graz, 43 316385 81310, ha.sourij@medunigraz.at

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	29 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2022
Global end of trial reached?	Yes
Global end of trial date	03 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to investigate the impact of Empagliflozin on biomarkers of heart failure in patients with myocardial infarction with and without type 2 diabetes mellitus within 6 months after the event.

Protection of trial subjects:

ethical standards were followed, the trial adhere to strict ethical standards to ensure that participants were treated fairly and with respect
protecting the privacy and confidentiality of participants
education and training in protection of clinical trials participants for all study team members

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 April 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 476
Worldwide total number of subjects	476
EEA total number of subjects	476

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)	361

From 65 to 84 years	115
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study sites recruited competively and the clinic staff of the intensive care unit informed patients about the possibility of being enrolled in this study. No study-related procedures were undertaken before obtaining informed consent.

Pre-assignment

Screening details:

After obtaining ICF at the screening visit, subject´s eligibility was further assessed and documented by using a SDF with a list of inclusion/exclusion criteria, medical history were acquired and the following measurements were performed: body weight, height, blood parameters. Lab results up to 2 days before screening were used to test eligibility.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin

Arm description:

Participants of this group received empagliflozin (10mg)

Arm type	Experimental
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	A10BK03
Other name	Jardiance
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

orally once daily for 6 months (10mg).

Arm title	Placebo

Arm description:

Participants of this group received placebo

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:

10mg oral per day

Number of subjects in period 1	Empagliflozin	Placebo
Started	237	239
Completed	217	227
Not completed	20	12
Consent withdrawn by subject	8	4
Lost to follow-up	12	8

Baseline characteristics

Reporting groups	
Reporting group title	Baseline Period

Reporting group description: -

Reporting group values	Baseline Period	Total	
Number of subjects	476	476	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	57		
inter-quartile range (Q1-Q3)	52 to 64	-	
Gender categorical Units: Subjects			
Female	84	84	
Male	392	392	

End points

End points reporting groups

Reporting group title	Empagliflozin
Reporting group description:	
Participants of this group received empagliflozin (10mg)	
Reporting group title	Placebo
Reporting group description:	
Participants of this group received placebo	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The primary endpoint (change in NT-proBNP from baseline to week 26) was analysed in the intention-to-treat (ITT) population using a robust linear mixed effect model (LMEM) in which the dependent variable was log-transformed NT-proBNP and the fixed effects were treatment, visit, treatment-by-visit interaction, the stratification factors sex and presence/absence of type 2 diabetes, and baseline NT-proBNP concentration.	

Primary: NT-proBNP

End point title	NT-proBNP
End point description:	
Median and IQR of NTproBNP percent change according to treatment and visits	
End point type	Primary
End point timeframe:	
Baseline to Week 26	

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	209		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	-84.9 (-91.7 to -72.6)	-82.2 (-89.2 to -69.8)		

Statistical analyses

Statistical analysis title	Linear mixed effect model
Statistical analysis description:	
The primary endpoint (change in NT-proBNP from baseline to week 26) was analysed in the intention-to-treat (ITT) population using a robust linear mixed effect model (LMEM) in which the dependent variable was log-transformed NT-proBNP and the fixed effects were treatment, visit, treatment-by-visit interaction, the stratification factors sex and presence/absence of type 2 diabetes, and baseline NT-proBNP concentration. For the primary analysis no missing data were imputed.	
Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [1]
Method	t-test, 2-sided

Notes:

[1] - To claim superiority of empagliflozin over placebo, the primary efficacy analysis was required to demonstrate a statistically significant treatment at week 26 at a 5% alpha level with a two-sided test.

Secondary: Left ventricular ejection fraction

End point title	Left ventricular ejection fraction

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	209		
Units: %				
median (inter-quartile range (Q1-Q3))	4.7 (3.6 to 5.8)	7.6 (5.2 to 9.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: E/é Ratio

End point title	E/é Ratio

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	209		
Units: ratio				
median (inter-quartile range (Q1-Q3))	-9.7 (-13.1 to -6.4)	-3.5 (-7.4 to -0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Left ventricular end-systolic volume

End point title	Left ventricular end-systolic volume

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	209		
Units: ml				
median (inter-quartile range (Q1-Q3))	-2.2 (-6.4 to 2.0)	12.1 (6.4 to 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Left ventricular end-diastolic volume

End point title	Left ventricular end-diastolic volume

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	209		
Units: ml				
median (inter-quartile range (Q1-Q3))	5.9 (1.8 to 10.1)	14.8 (10.2 to 19.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event date was collected over 5 years from May 2017 (first patient first visit) until May 2022 (last patient last visit)

Adverse event reporting additional description:

Adverse events (AE) that occured during this study were recorded on AE case report forms. The Sponsor reported all SAEs and AEs which were relevant for a reported SAE as well as Adverse Events of Special Interest by fax or other secure method using Böhringer Ingelheim (BI) IIS SAE form to the BI Unique Entry Point. The sponsor reported the SAEs to

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Empagliflozin Group
Reporting group description: -	
Reporting group title	Placebo Group

Reporting group description: -

Serious adverse events	Empagliflozin Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 237 (15.19%)	41 / 239 (17.15%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events		0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pulmonary carcinoma			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Benign mass			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Haematoma Retroperitoneal			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Weber B fracture			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Morphine intoxication			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 237 (0.42%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hernia			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Mitral valve disease			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
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 / 237 (0.00%)	2 / 239 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	6 / 237 (2.53%)	2 / 239 (0.84%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 237 (1.27%)	3 / 239 (1.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stress Dyspnoea			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	2 / 237 (0.84%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Elevated troponin I			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ICD-implantation			
subjects affected / exposed	2 / 237 (0.84%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute heart failure			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	6 / 237 (2.53%)	2 / 239 (0.84%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 237 (0.42%)	2 / 239 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac decompensation			
subjects affected / exposed	1 / 237 (0.42%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 237 (0.42%)	2 / 239 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral regurgitation			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac scintigraphy			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bleeding			

subjects affected / exposed	0 / 237 (0.00%)	2 / 239 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epigastrial pain			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
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			
Pulmonary embolism			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive sleep apnoea syndrome			
subjects affected / exposed	0 / 237 (0.00%)	2 / 239 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 237 (0.84%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 237 (0.42%)	1 / 239 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Gout attack			
subjects affected / exposed	2 / 237 (0.84%)	0 / 239 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Empagliflozin Group	Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	129 / 237 (54.43%)	109 / 239 (45.61%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	10	1	
Vascular disorders			
Syncope			
subjects affected / exposed	4 / 237 (1.69%)	3 / 239 (1.26%)	
occurrences (all)	4	6	
Periarterial occlusive disease			
subjects affected / exposed	1 / 237 (0.42%)	1 / 239 (0.42%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Sleep disorder			
subjects affected / exposed	3 / 237 (1.27%)	0 / 239 (0.00%)	
occurrences (all)	4	0	
Hair disorder			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
Muscle fatigue			
subjects affected / exposed	3 / 237 (1.27%)	0 / 239 (0.00%)	
occurrences (all)	3	0	
Fatigue			
subjects affected / exposed	7 / 237 (2.95%)	5 / 239 (2.09%)	
occurrences (all)	10	7	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	11 / 237 (4.64%)	4 / 239 (1.67%)	
occurrences (all)	19	10	
Haemoptysis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	3 / 237 (1.27%)	0 / 239 (0.00%)	
occurrences (all)	4	0	
pulmonary emphysema			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
Dyspnoea exertional			
subjects affected / exposed	8 / 237 (3.38%)	9 / 239 (3.77%)	
occurrences (all)	15	11	
Bronchitis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	4	0	
Injury, poisoning and procedural complications			
Haematoma			
subjects affected / exposed	1 / 237 (0.42%)	4 / 239 (1.67%)	
occurrences (all)	1	5	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	2	
Tachycardia			
subjects affected / exposed	1 / 237 (0.42%)	2 / 239 (0.84%)	
occurrences (all)	1	2	
elevated Troponin values			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	

Paroxysmal arrhythmia			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	3 / 237 (1.27%)	1 / 239 (0.42%)	
occurrences (all)	3	4	
Hypotension			
subjects affected / exposed	2 / 237 (0.84%)	1 / 239 (0.42%)	
occurrences (all)	2	1	
Vertigo			
subjects affected / exposed	8 / 237 (3.38%)	9 / 239 (3.77%)	
occurrences (all)	14	13	
Angina pectoris			
subjects affected / exposed	7 / 237 (2.95%)	6 / 239 (2.51%)	
occurrences (all)	7	6	
Chest pain			
subjects affected / exposed	13 / 237 (5.49%)	12 / 239 (5.02%)	
occurrences (all)	13	16	
Pressure in the chest			
subjects affected / exposed	9 / 237 (3.80%)	5 / 239 (2.09%)	
occurrences (all)	12	9	
Bradycardia			
subjects affected / exposed	0 / 237 (0.00%)	3 / 239 (1.26%)	
occurrences (all)	0	5	
Apex thrombus			
subjects affected / exposed	2 / 237 (0.84%)	0 / 239 (0.00%)	
occurrences (all)	3	0	
Ventricular thrombus			
subjects affected / exposed	1 / 237 (0.42%)	1 / 239 (0.42%)	
occurrences (all)	1	1	
Stenosis			
subjects affected / exposed	3 / 237 (1.27%)	1 / 239 (0.42%)	
occurrences (all)	3	1	
Acute coronary syndrome			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	

Heart failure			
subjects affected / exposed	0 / 237 (0.00%)	2 / 239 (0.84%)	
occurrences (all)	0	2	
Cardial decompensation			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Mitral valve incompetence			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
Nervous system disorders			
Tremor			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	2 / 237 (0.84%)	2 / 239 (0.84%)	
occurrences (all)	3	2	
Paraesthesia			
subjects affected / exposed	0 / 237 (0.00%)	2 / 239 (0.84%)	
occurrences (all)	0	3	
loss of strength			
subjects affected / exposed	2 / 237 (0.84%)	1 / 239 (0.42%)	
occurrences (all)	2	1	
Dysaesthesia			
subjects affected / exposed	1 / 237 (0.42%)	1 / 239 (0.42%)	
occurrences (all)	1	1	
Radiculitis brachial			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Elevated CK values			
subjects affected / exposed	1 / 237 (0.42%)	1 / 239 (0.42%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	2 / 237 (0.84%)	3 / 239 (1.26%)	
occurrences (all)	5	3	
Elevated albumin-creatinin levels			

subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Increas lipoprotein (a)			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
Elevated Transaminasis			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 237 (0.84%)	0 / 239 (0.00%)	
occurrences (all)	2	0	
Otitis media			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	2 / 237 (0.84%)	3 / 239 (1.26%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Appendicitis perforated			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	4 / 237 (1.69%)	0 / 239 (0.00%)	
occurrences (all)	10	0	
Obstipation			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	2 / 237 (0.84%)	4 / 239 (1.67%)	
occurrences (all)	4	6	
Hunger			
subjects affected / exposed	3 / 237 (1.27%)	0 / 239 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			

subjects affected / exposed	4 / 237 (1.69%)	2 / 239 (0.84%)	
occurrences (all)	5	2	
Flatulence			
subjects affected / exposed	2 / 237 (0.84%)	0 / 239 (0.00%)	
occurrences (all)	3	0	
Haematochezia			
subjects affected / exposed	2 / 237 (0.84%)	0 / 239 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	3 / 237 (1.27%)	1 / 239 (0.42%)	
occurrences (all)	3	1	
Reflux gastritis			
subjects affected / exposed	2 / 237 (0.84%)	0 / 239 (0.00%)	
occurrences (all)	2	0	
Hepatic infection			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
elevated GGT values			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
elevated Bilirubin			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	5 / 237 (2.11%)	3 / 239 (1.26%)	
occurrences (all)	6	6	
Exanthema subitum			
subjects affected / exposed	3 / 237 (1.27%)	4 / 239 (1.67%)	
occurrences (all)	3	4	
Endocrine disorders			

elevated TSH values			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
HbA1c increase			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	2	0	
Hyperthyroidism			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Mastodynia			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Thyroid nodules			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Muscle pain			
subjects affected / exposed	1 / 237 (0.42%)	2 / 239 (0.84%)	
occurrences (all)	2	2	
Pain in extremity			
subjects affected / exposed	6 / 237 (2.53%)	3 / 239 (1.26%)	
occurrences (all)	7	3	
Oedema			
subjects affected / exposed	2 / 237 (0.84%)	0 / 239 (0.00%)	
occurrences (all)	2	0	
Swelling			
subjects affected / exposed	1 / 237 (0.42%)	2 / 239 (0.84%)	
occurrences (all)	1	2	
Fracture			

subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Rhabdomyolysis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
joint inflammation			
subjects affected / exposed	1 / 237 (0.42%)	2 / 239 (0.84%)	
occurrences (all)	1	2	
Thoracic pain			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	11 / 237 (4.64%)	7 / 239 (2.93%)	
occurrences (all)	18	8	
Genital fungal infection			
subjects affected / exposed	7 / 237 (2.95%)	2 / 239 (0.84%)	
occurrences (all)	7	2	
COVID-19			
subjects affected / exposed	1 / 237 (0.42%)	2 / 239 (0.84%)	
occurrences (all)	1	3	
Cold burn			
subjects affected / exposed	2 / 237 (0.84%)	2 / 239 (0.84%)	
occurrences (all)	2	5	
Epididymitis			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	3 / 237 (1.27%)	1 / 239 (0.42%)	
occurrences (all)	3	1	
Tooth infection			
subjects affected / exposed	1 / 237 (0.42%)	1 / 239 (0.42%)	
occurrences (all)	1	1	
Herpes zoster			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	

Pharyngitis lateralis			
subjects affected / exposed	0 / 237 (0.00%)	1 / 239 (0.42%)	
occurrences (all)	0	1	
athletes food			
subjects affected / exposed	1 / 237 (0.42%)	0 / 239 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 237 (0.00%)	3 / 239 (1.26%)	
occurrences (all)	0	6	
Gout arthritis			
subjects affected / exposed	1 / 237 (0.42%)	1 / 239 (0.42%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2017	New study site Klinikum Klagenfurt am Wörthersee
21 November 2017	Announcement of a cardiac ultrasound sub-study
29 November 2017	New study site Klinikum Rudolfstiftung
08 March 2018	Change of the upper limit of age from 75 to 80 years in the inclusion criteria & new study site Kardinal Schwarzenberg Klinikum Schwarzach
22 August 2018	New study sites LKH Graz West and University Hospital Linz
14 November 2018	New study sites BHB Eisenstadt and University Hospital St. Pölten
04 February 2020	Change of Principal Investigator at study site Klinikum Klagenfurt
02 October 2020	Additional sub-study in participants at study site University Hospital Graz for microbiome analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36036746