



Clinical trial results:

MACH 2 - Magnesium orotate in severe congestive heart failure - Part 2

Summary

EudraCT number	2016-004600-53
Trial protocol	DE
Global end of trial date	04 September 2023

Results information

Result version number	v1 (current)
This version publication date	27 June 2025
First version publication date	27 June 2025
Summary attachment (see zip file)	Clinical Trial Report Synopsis (241004_MACH2_Synopsis_CTR_V1.0_blackened.pdf)

Trial information

Trial identification

Sponsor protocol code	RBK03-16-00389
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	WÖRWAG Pharma GmbH & Co. KG
Sponsor organisation address	Flugfeld-Allee 24, Böblingen, Germany, 71034
Public contact	Global Clinical Research, WÖRWAG Pharma GmbH & Co. KG, 0049 73162040, GCR@woerwagpharma.com
Scientific contact	Global Clinical Research, WÖRWAG Pharma GmbH & Co. KG, 0049 7316204416, GCR@woerwagpharma.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	04 June 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2023
Global end of trial reached?	Yes
Global end of trial date	04 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the study was to demonstrate the significant reduction in NTproBNP by the regular intake of magnesium orotate compared to placebo in participants with HFrEF.

Protection of trial subjects:

The trial was in compliance with the ethical principles outlined in the Declaration of Helsinki and the International Council for Harmonisation's Good Clinical Practice (ICH GCP) guidelines. Additionally, all local regulatory requirements related to participant safety were followed throughout the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 June 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	13
From 65 to 84 years	16
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

FPFV 21. November 2019; LPLV 04. September 2023; Recruitment stop due to COVID19 pandemic 06.04.2020 – 22.06.2020; 67 participants were screened and 30 were randomized.

Pre-assignment

Screening details:

The screening period began once patients had signed the study informed consent. Screening evaluations were performed at baseline visit (V1). After screening, the treatment period started on Visit 1 Day 1.

Period 1

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

Blinding implementation details:

This was a double-blind, randomized, placebo-controlled cross-over trial. Participants, the investigator, including the whole trial team at trial site and the sponsor, including monitoring and data management personnel were blinded to the identity of the treatment from the time of randomization until official unblinding. Serum magnesium levels were not accessible until database closure.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo - Verum

Arm description:

Day 1-84 Placebo;
Day 85-140 Wash-out;
Day 141-224 Verum

Arm type	Crossover: Placebo - Verum
Investigational medicinal product name	Magnesium orotate dihydrate
Investigational medicinal product code	
Other name	magnerot® CLASSIC N
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered orally three times a day as 3 tablets per dose for 4 weeks, followed by 2 tablets per dose for an additional 8 weeks. This was followed by a wash-out phase. Magnesium orotate dihydrate was administered orally three times a day as 3 tablets per dose (4500 mg/day) for 4 weeks, followed by as 2 tablets per dose (3000 mg/day) for an additional 8 weeks.

Arm title	Verum - Placebo
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Arm description:

Day 1-84 Verum;
Day 85-140 Wash-out;
Day 141-224 Placebo

Arm type	Crossover: Verum - Placebo
Investigational medicinal product name	Magnesium orotate dihydrate
Investigational medicinal product code	
Other name	magnerot® CLASSIC N
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Magnesium orotate dihydrate was administered orally three times a day as 3 tablets per dose (4500 mg/day) for 4 weeks, followed by as 2 tablets per dose (3000 mg/day) for an additional 8 weeks. This was followed by a wash-out phase. Placebo was administered orally three times a day as 3 tablets per dose for 4 weeks, followed by 2 tablets per dose for an additional 8 weeks.

Number of subjects in period 1	Placebo - Verum	Verum - Placebo
Started	15	15
Wash-out	14	14
Completed	13	14
Not completed	2	1
Worsening of general condition	1	-
Consent withdrawn by subject	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo - Verum
Reporting group description: Day 1-84 Placebo; Day 85-140 Wash-out; Day 141-224 Verum	
Reporting group title	Verum - Placebo
Reporting group description: Day 1-84 Verum; Day 85-140 Wash-out; Day 141-224 Placebo	

Reporting group values	Placebo - Verum	Verum - Placebo	Total
Number of subjects	15	15	30
Age categorical Units: Subjects			
Adults (18-64 years)	5	8	13
From 65-84 years	10	6	16
85 years and over	0	1	1
Age continuous Units: years			
median	73	61	
inter-quartile range (Q1-Q3)	59 to 79	55 to 71	-
Gender categorical Units: Subjects			
Female	5	5	10
Male	10	10	20

Subject analysis sets

Subject analysis set title	Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

The analysis was carried out "per protocol" (PP), i.e., only those test individuals for whom there are no major protocol violations, who have received a predetermined minimum proportion of the planned treatment (at least 80%) and for whom the examinations required to assess the target criteria have been carried out at predetermined points in time are analysed. In this trial, the per protocol analysis was defined as the primary analysis. Criteria for per protocol analysis were fulfilled by 27 participants. The 3 drop-outs didn't fulfil the PP criteria and therefore, were not included into efficacy analysis.

Day 1-84 Placebo or Verum; Day 85-140 Wash-out; Day 141-224 Verum or Placebo

Subject analysis set title	Verum
Subject analysis set type	Per protocol

Subject analysis set description:

The analysis was carried out "per protocol" (PP), i.e., only those test individuals for whom there are no major protocol violations, who have received a predetermined minimum proportion of the planned treatment (at least 80%) and for whom the examinations required to assess the target criteria have been carried out at predetermined points in time are analysed. In this trial, the per protocol analysis was defined as the primary analysis. Criteria for per protocol analysis were fulfilled by 27 participants. The 3 drop-outs didn't fulfil the PP criteria and therefore, were not included into efficacy analysis.

Day 1-84 Placebo or Verum; Day 85-140 Wash-out; Day 141-224 Verum or Placebo

Reporting group values	Placebo	Verum	
Number of subjects	27	27	
Age categorical Units: Subjects			
Adults (18-64 years)	12	12	
From 65-84 years	14	14	
85 years and over	1	1	
Age continuous Units: years			
median	65.67	65.67	
inter-quartile range (Q1-Q3)	56.00 to 77.00	56.00 to 77.00	
Gender categorical Units: Subjects			
Female	9	9	
Male	18	18	

End points

End points reporting groups

Reporting group title	Placebo - Verum
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Reporting group description:

Day 1-84 Placebo;
Day 85-140 Wash-out;
Day 141-224 Verum

Reporting group title	Verum - Placebo
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Reporting group description:

Day 1-84 Verum;
Day 85-140 Wash-out;
Day 141-224 Placebo

Subject analysis set title	Placebo
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Subject analysis set type	Per protocol
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Subject analysis set description:

The analysis was carried out "per protocol" (PP), i.e., only those test individuals for whom there are no major protocol violations, who have received a predetermined minimum proportion of the planned treatment (at least 80%) and for whom the examinations required to assess the target criteria have been carried out at predetermined points in time are analysed. In this trial, the per protocol analysis was defined as the primary analysis. Criteria for per protocol analysis were fulfilled by 27 participants. The 3 drop-outs didn't fulfil the PP criteria and therefore, were not included into efficacy analysis.

Day 1-84 Placebo or Verum; Day 85-140 Wash-out; Day 141-224 Verum or Placebo

Subject analysis set title	Verum
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Subject analysis set type	Per protocol
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Subject analysis set description:

The analysis was carried out "per protocol" (PP), i.e., only those test individuals for whom there are no major protocol violations, who have received a predetermined minimum proportion of the planned treatment (at least 80%) and for whom the examinations required to assess the target criteria have been carried out at predetermined points in time are analysed. In this trial, the per protocol analysis was defined as the primary analysis. Criteria for per protocol analysis were fulfilled by 27 participants. The 3 drop-outs didn't fulfil the PP criteria and therefore, were not included into efficacy analysis.

Day 1-84 Placebo or Verum; Day 85-140 Wash-out; Day 141-224 Verum or Placebo

Primary: Change of NTproBNP

End point title	Change of NTproBNP
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End point description:

Differences on the change of NTproBNP between Verum and Placebo after 12 weeks of treatment.

End point type	Primary
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End point timeframe:

Visit 1 to visit 3 (12 weeks)

End point values	Placebo	Verum		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	-199.0 (-368.0 to 18.0)	-70.0 (-291.0 to 174.0)		

Statistical analyses

Statistical analysis title	Change of NTproBNP: Verum vs. Placebo
Comparison groups	Verum v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.486
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - As it is a cross-over study, in total 27 participants were analysed and every one received Placebo and Verum for 12 weeks.

Secondary: Change of LVEF

End point title	Change of LVEF
End point description: Difference on change of Left Ventricular Ejection Fraction (LVEF) under Verum and Placebo after 12 weeks of treatment.	
End point type	Secondary
End point timeframe: Visit 1 to visit 3 (12 weeks)	

End point values	Placebo	Verum		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: %				
median (inter-quartile range (Q1-Q3))	0 (-2.0 to 4.0)	1 (-3.0 to 4.0)		

Statistical analyses

Statistical analysis title	Change of LVEF: Verum vs. Placebo
Comparison groups	Placebo v Verum
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.776
Method	t-test, 2-sided

Notes:

[2] - As this is a cross-over study, 27 participants were analyzed, with each participant receiving Verum or Placebo for 12 weeks.

Secondary: Change of KCCQ questionnaire OSS

End point title	Change of KCCQ questionnaire OSS
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End point description:

Differences on the change KCCQ questionnaire Overall Summary Score (OSS) under Verum and Placebo after 12 weeks of treatment.

End point type	Secondary
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End point timeframe:

Visit 1 to Visit 3 (12 weeks)

End point values	Placebo	Verum		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: Change of score				
median (inter-quartile range (Q1-Q3))	0 (-5.729 to 4.688)	1.771 (-2.344 to 5.208)		

Statistical analyses

Statistical analysis title	Change of KCCQ OSS: Verum vs. Placebo
Comparison groups	Placebo v Verum
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.564
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - As this is a cross-over study, 27 participants were analyzed, with each participant receiving Verum or Placebo for 12 weeks.

Secondary: Change of KCCQ questionnaire CSS

End point title	Change of KCCQ questionnaire CSS
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End point description:

Differences on the change KCCQ questionnaire Clinical Summary Score (CSS) under Verum and Placebo after 12 weeks of treatment.

End point type	Secondary
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End point timeframe:

Visit 1 to visit 3 (12 weeks)

End point values	Placebo	Verum		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: Change of score				
median (inter-quartile range (Q1-Q3))	-1.04 (-5.21 to 4.17)	0 (-6.25 to 8.85)		

Statistical analyses

Statistical analysis title	Change of KCCQ CSS: Verum vs. Placebo
Comparison groups	Verum v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	= 0.435
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - As this is a cross-over study, 27 participants were analyzed, with each participant receiving Verum or Placebo for 12 weeks.

Secondary: Change of EQ-5D-5L VAS

End point title	Change of EQ-5D-5L VAS
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End point description:

Differences on the change EQ-5D-5L (Visual Analog Scale) VAS under Verum and Placebo after 12 weeks of treatment.

End point type	Secondary
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End point timeframe:

Visit 1 to visit 3 (12 weeks)

End point values	Placebo	Verum		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: Score change				
median (inter-quartile range (Q1-Q3))	0.000 (-5.000 to 5.000)	1.000 (0.000 to 10.000)		

Statistical analyses

Statistical analysis title	Change of EQ-5D-5L VAS: Verum vs. Placebo
Comparison groups	Placebo v Verum
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	= 0.152
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - As this is a cross-over study, 27 participants were analyzed, with each participant receiving Verum or Placebo for 12 weeks.

Secondary: Change of EQ-5D-5L Index

End point title	Change of EQ-5D-5L Index
End point description:	Differences on the change EQ-5D-5L Index under Verum and Placebo after 12 weeks of treatment.
End point type	Secondary
End point timeframe:	Visit 1 to visit 3 (12 weeks)

End point values	Placebo	Verum		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: Score change				
median (inter-quartile range (Q1-Q3))	0.000 (-0.049 to 0.057)	0.000 (0.000 to 0.050)		

Statistical analyses

Statistical analysis title	Change of EQ-5D-5L Index: Verum vs. Placebo
Comparison groups	Placebo v Verum
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	= 0.274
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - As this is a cross-over study, 27 participants were analyzed, with each participant receiving Verum or Placebo for 12 weeks.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study at week 32.

Adverse event reporting additional description:

Adverse Events (AEs) are any untoward sign or symptom that occurs during the study treatment. Adverse events are evaluated in the safety analysis set that includes all participants who received at least one dose of the investigational medicinal product.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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Reporting groups

Reporting group title	Verum
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Reporting group description:

Reported adverse events occurred during intake of magnesium orotate dihydrate.

Reporting group title	Placebo
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Reporting group description:

Reported adverse events occurred during intake of Placebo.

Reporting group title	Wash-out after Verum
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Reporting group description:

Reported adverse events occurred during wash-out after magnesium orotate dihydrate.

Reporting group title	Wash-out after Placebo
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Reporting group description:

Reported adverse events occurred during wash-out after Placebo.

Reporting group title	N/A, occurred after trial discontinuation
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Reporting group description:

Reported adverse events occurred after end of trial.

For one participant who dropped out of the trial 12 events including 9 SAEs were documented after end of trial, as part of an SAE follow-up. For another dropout participant one AE was documented after end of treatment with start date on the same day as the last visit.

Serious adverse events	Verum	Placebo	Wash-out after Verum
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 30 (16.67%)	1 / 30 (3.33%)	2 / 30 (6.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Failed weaning from the ventilator			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative renal failure			

subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distal radius fracture			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Acute occlusion of left arteria poplitea			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular collapse			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Independent shock delivery by ICD (implanted cardioverter defibrillator)			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			

subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiorenal syndrome			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normofrequent atrial flutter			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NSTEMI			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericard effusion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Possible critical illness neuropathy			

subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Appendicitis epiploica			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epigastric pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter cloacae infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Wash-out after Placebo	N/A, occurred after trial discontinuation	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Failed weaning from the ventilator			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative renal failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distal radius fracture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Acute occlusion of left arteria poplitea			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular collapse			

subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Independent shock delivery by ICD (implanted cardioverter defibrillator)			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiorenal syndrome			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normofrequent atrial flutter			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NSTEMI			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pericard effusion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible critical illness neuropathy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Appendicitis epiploica			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epigastric pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial infection			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter cloacae infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Verum	Placebo	Wash-out after Verum
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 30 (90.00%)	24 / 30 (80.00%)	12 / 30 (40.00%)
Vascular disorders			
Vascular disorders			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	5 / 30 (16.67%)	6 / 30 (20.00%)	0 / 30 (0.00%)
occurrences (all)	6	10	0
Respiratory, thoracic and mediastinal			

disorders Respiratory, thoracic, and mediastinal disorders subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 6	6 / 30 (20.00%) 9	4 / 30 (13.33%) 4
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Investigations Examinations subjects affected / exposed occurrences (all)	9 / 30 (30.00%) 11	5 / 30 (16.67%) 9	6 / 30 (20.00%) 17
Injury, poisoning and procedural complications Injury, poisoning, and procedure- related complications subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 4	4 / 30 (13.33%) 4	1 / 30 (3.33%) 1
Cardiac disorders Cardiac disorders subjects affected / exposed occurrences (all)	8 / 30 (26.67%) 21	10 / 30 (33.33%) 17	10 / 30 (33.33%) 18
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	7 / 30 (23.33%) 9	5 / 30 (16.67%) 7	3 / 30 (10.00%) 3
Blood and lymphatic system disorders Blood and lymphatic system disorders subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	12 / 30 (40.00%) 24	9 / 30 (30.00%) 13	0 / 30 (0.00%) 0
Skin and subcutaneous tissue disorders			

Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	4 / 30 (13.33%) 5	2 / 30 (6.67%) 2
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	4 / 30 (13.33%) 4	2 / 30 (6.67%) 3
Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Musculoskeletal and connective tissue disorders Musculoskeletal, connective tissue, and bone disorders subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 4	11 / 30 (36.67%) 18	1 / 30 (3.33%) 1
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	4 / 30 (13.33%) 4	1 / 30 (3.33%) 1
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 5	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1

Non-serious adverse events	Wash-out after Placebo	N/A, occurred after trial discontinuation	
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 30 (40.00%)	2 / 30 (6.67%)	
Vascular disorders Vascular disorders subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Surgical and medical procedures Surgical and medical procedures subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	
General disorders and administration site conditions			

General disorders and administration site conditions subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	0 / 30 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic, and mediastinal disorders subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 3	0 / 30 (0.00%) 0	
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Investigations Examinations subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 6	0 / 30 (0.00%) 0	
Injury, poisoning and procedural complications Injury, poisoning, and procedure-related complications subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Cardiac disorders Cardiac disorders subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 7	0 / 30 (0.00%) 0	
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Blood and lymphatic system disorders Blood and lymphatic system disorders subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	
Gastrointestinal disorders			

Gastrointestinal disorders subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 2	1 / 30 (3.33%) 1	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Musculoskeletal and connective tissue disorders Musculoskeletal, connective tissue, and bone disorders subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2018	Implementation of changes required for regulatory approval
10 July 2018	Principal investigator change
31 January 2019	In- and exclusion criteria change
22 March 2019	Implementation of changes required for regulatory approval
07 June 2019	In- and exclusion criteria change
01 October 2020	Extension of trial duration, adjustment of statistics details.
20 June 2022	Principal investigator and deputy change, extension of trial duration

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 April 2020	Recruitment stop due to COVID19 pandemic 06.04.2020 – 22.06.2020	22 June 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Small number of participants (pilot study)

Notes: