Clinical trial results:
REPETITIVE LEVOSIMENDAN INFUSIONS FOR PATIENTS WITH ADVANCED CHRONIC HEART FAILURE

Summary

EudraCT number	2017-002429-39
Trial protocol	AT DE HU SI FI DK IT
Global end of trial date	31 December 2021

Results information

Result version number	v1 (current)
This version publication date	08 January 2023
First version publication date	08 January 2023

Trial information

Trial identification

Sponsor protocol code	Leodor2017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03437226
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University Innsbruck
Sponsor organisation address	Christoph-Probst-Platz 1, Innrain 52, Innsbruck, Austria, 6020
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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 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2021
Global end of trial reached?	Yes
Global end of trial date	31 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of the study is to compare the effects of pulsed application of levosimendan versus placebo in patients with advanced chronic heart failure during a vulnerable period of 14 weeks following a recent hospitalisation on a global rank endpoint in which all participants are ranked across three hierarchical groups:

- time to death or high-urgent heart transplantation or ventricular assist device (VAD),
- time to non-fatal HF event requiring i.v. vasoactive therapy (i.v. diuretics, i.v. vasodilators or i. v. inotropes) and
- time-averaged proportional change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) from baseline to 14 weeks.

Protection of trial subjects:

The patients will be under optimal medical treatment for HF and the study drug will be administered ontop of the patients' on-going medication. Thus placebo as a control can be ethically justified.

Background therapy:

Patients should be on optimised background therapy according to the ESC guidelines 2016 for the diagnosis and treatment of acute and chronic heart failure. Changes or improvement in heart failure medication – if needed – are allowed throughout the study period except for the additional administration of levosimendan.

Evidence for comparator:

-

Actual start date of recruitment	08 November 2017
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	Slovenia: 10
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Austria: 39
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 51
Country: Number of subjects enrolled	Italy: 26
Worldwide total number of subjects	148
EEA total number of subjects	148

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)	50
From 65 to 84 years	94
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Candidates for the study will be screened during their hospitalisation for acute decompensated HF. If the patient meets all the inclusion criteria and none of the exclusion criteria, a baseline visit will be arranged.

Pre-assignment

Screening details:

Candidates for the study will be screened during their hospitalisation for acute decompensated HF. If the patient meets all the inclusion criteria and none of the exclusion criteria, a baseline visit will be arranged.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The randomisation will be performed by the Department of Medical Statistics, Informatics and Health Economics at Medical University Innsbruck and the treatment codes will be stored in the eCRF database. The codes will be delivered to the accredited pharmacy responsible of labelling the study medications. Each study centre is provided with unblinders containing information on the study treatments.

Arms

Are arms mutually exclusive?	Yes
Arm title	6-hour infusion group Levosimendan

Arm description:

Patients will receive a 6-hour infusion every 2 weeks up to 12 weeks,followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.

Arm type	Experimental
Investigational medicinal product name	Levosimendan
Investigational medicinal product code	
Other name	Simdax
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For the 6-hour infusion group, the study drug is administered at a continuous infusion rate of 0.2 µg/kg/min, for 6 hours.

Arm title	24-hour infusion group Levosimendan

Arm description:

Patients will receive a 24-hour infusion every 3 weeks up to 12 weeks, followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.

Arm type	Experimental
Investigational medicinal product name	Levosimendan
Investigational medicinal product code	
Other name	Simdax
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For the 24-hour infusion group, the study drug is administered at a continuous infusion rate of 0.1 µg/kg/min, for 24 hours.

Arm title	6-hour infusion group Placebo

Arm description:

Patients will receive a 6-hour infusion every 2 weeks up to 12 weeks,followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For the 6-hour infusion group, the study drug/Placebo is administered at a continuous infusion rate of 0.1 µg/kg/min, for 24 hours.

Arm title	24-hour infusion group Placebo

Arm description:

Patients will receive a 24-hour infusion every 3 weeks up to 12 weeks, followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For the 24-hour infusion group, the study drug/Placebo is administered at a continuous infusion rate of 0.1 µg/kg/min, for 24 hours.

Number of subjects in period 1	6-hour infusion group Levosimendan	24-hour infusion group Levosimendan	6-hour infusion group Placebo
Started	38	57	22
Completed	26	39	17
Not completed	12	18	5
Adverse event, serious fatal	3	10	1
Physician decision	1	2	2
Consent withdrawn by subject	4	2	-
Screening failure	1	-	-
Adverse event, non-fatal	2	4	-
Covid 19	1	-	1
Lost to follow-up	-	-	1

Number of subjects in period 1	24-hour infusion group Placebo
Started	31
Completed	23
Not completed	8
Adverse event, serious fatal	3
Physician decision	2
Consent withdrawn by subject	2

Screening failure	-
Adverse event, non-fatal	1
Covid 19	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	6-hour infusion group Levosimendan
Reporting group description:	
Patients will receive a 6-hour infusion every 2 weeks up to 12 weeks,followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.	
Reporting group title	24-hour infusion group Levosimendan
Reporting group description:	
Patients will receive a 24-hour infusion every 3 weeks up to 12 weeks, followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.	
Reporting group title	6-hour infusion group Placebo
Reporting group description:	
Patients will receive a 6-hour infusion every 2 weeks up to 12 weeks,followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.	
Reporting group title	24-hour infusion group Placebo
Reporting group description:	
Patients will receive a 24-hour infusion every 3 weeks up to 12 weeks, followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.	

Reporting group values	6-hour infusion group Levosimendan	24-hour infusion group Levosimendan	6-hour infusion group Placebo
Number of subjects	38	57	22
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)	7	23	9
From 65-84 years	28	34	12
85 years and over	3	0	1
Age continuous Units: years			
arithmetic mean	72.1	67.4	67.4
full range (min-max)	52 to 86	49 to 84	46 to 87
Gender categorical Units: Subjects			
Female	6	14	17
Male	32	43	5

Reporting group values	24-hour infusion group Placebo	Total	
Number of subjects	31	148	
Age categorical Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	49	
From 65-84 years	21	95	
85 years and over	0	4	
Age continuous			
Units: years			
arithmetic mean	68.5		
full range (min-max)	51 to 82	-	
Gender categorical			
Units: Subjects			
Female	6	43	
Male	25	105	

End points

End points reporting groups

Reporting group title	6-hour infusion group Levosimendan
Reporting group description:	
Patients will receive a 6-hour infusion every 2 weeks up to 12 weeks,followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.	
Reporting group title	24-hour infusion group Levosimendan
Reporting group description:	
Patients will receive a 24-hour infusion every 3 weeks up to 12 weeks, followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.	
Reporting group title	6-hour infusion group Placebo
Reporting group description:	
Patients will receive a 6-hour infusion every 2 weeks up to 12 weeks,followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.	
Reporting group title	24-hour infusion group Placebo
Reporting group description:	
Patients will receive a 24-hour infusion every 3 weeks up to 12 weeks, followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.	

Primary: Heart transplantation

End point title	Heart transplantation[1]
End point description:	
The primary efficacy objective of the study is to compare the effects of pulsed application of levosimendan versus placebo in patients with advanced chronic heart failure during a vulnerable period of 14 weeks.	
End point type	Primary
End point timeframe:	
Week 0-week 14	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: With total of 264 patients, study has approximately 90% power to detect statistically significant difference between treatments. Only 148 patients were enrolled.

End point values	6-hour infusion group Levosimendan	24-hour infusion group Levosimendan	6-hour infusion group Placebo	24-hour infusion group Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	57	22	31
Units: number				
number (not applicable)	0	0	2	0

Statistical analyses

No statistical analyses for this end point

Primary: Implantation of a VAD

End point title	Implantation of a VAD[2]

End point description:

The primary efficacy objective of the study is to compare the effects of pulsed application of levosimendan versus placebo in patients with advanced chronic heart failure during a vulnerable period of 14 weeks.

End point type	Primary

End point timeframe:

Week 0-week 14

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: With total of 264 patients, study has approximately 90% power to detect statistically significant difference between treatments. Only 148 patients were enrolled.

End point values	6-hour infusion group Levosimendan	24-hour infusion group Levosimendan	6-hour infusion group Placebo	24-hour infusion group Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	57	22	31
Units: number				
number (not applicable)	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Death

End point title	Death[3]

End point description:

The primary efficacy objective of the study is to compare the effects of pulsed application of levosimendan versus placebo in patients with advanced chronic heart failure during a vulnerable period of 14 weeks.

End point type	Primary

End point timeframe:

Week 0- week 14

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: With total of 264 patients, study has approximately 90% power to detect statistically significant difference between treatments. Only 148 patients were enrolled.

End point values	6-hour infusion group Levosimendan	24-hour infusion group Levosimendan	6-hour infusion group Placebo	24-hour infusion group Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	57	22	31
Units: number				
number (not applicable)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 08.11.2017-31.12.2021	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	6.0

Reporting groups	
Reporting group title	6-hour infusion group Levosimendan
Reporting group description: Patients will receive a 6-hour infusion every 2 weeks up to 12 weeks,followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.	
Reporting group title	24-hour infusion group Levosimendan
Reporting group description: Patients will receive a 24-hour infusion every 3 weeks up to 12 weeks, followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.	
Reporting group title	6-hour infusion group Placebo
Reporting group description: Patients will receive a 6-hour infusion every 2 weeks up to 12 weeks,followed by a follow-up visit (FUP1) at week 14 and another follow-up visit (FUP2) at 6 months.	
Reporting group title	24-hour infusion group Placebo
Reporting group description: -	

Serious adverse events	6-hour infusion group Levosimendan	24-hour infusion group Levosimendan	6-hour infusion group Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 38 (34.21%)	33 / 57 (57.89%)	11 / 22 (50.00%)
number of deaths (all causes)	3	10	1
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Cardiac decompensation			
subjects affected / exposed	6 / 38 (15.79%)	3 / 57 (5.26%)	6 / 22 (27.27%)
occurrences causally related to treatment / all	0 / 19	0 / 19	0 / 19
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Worsening of heart failure			
subjects affected / exposed	2 / 38 (5.26%)	15 / 57 (26.32%)	4 / 22 (18.18%)
occurrences causally related to treatment / all	0 / 23	0 / 23	0 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			

subjects affected / exposed	2 / 38 (5.26%)	5 / 57 (8.77%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 57 (1.75%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Edema			
subjects affected / exposed	2 / 38 (5.26%)	3 / 57 (5.26%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	0 / 8	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 38 (2.63%)	1 / 57 (1.75%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 7	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 38 (0.00%)	4 / 57 (7.02%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthopnoea			
subjects affected / exposed	1 / 38 (2.63%)	1 / 57 (1.75%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 38 (5.26%)	1 / 57 (1.75%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 8	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	24-hour infusion group Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 31 (48.39%)		
number of deaths (all causes)	3		

number of deaths resulting from adverse events	0		
Cardiac disorders			
Cardiac decompensation			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences causally related to treatment / all	0 / 19		
deaths causally related to treatment / all	0 / 0		
Worsening of heart failure			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	0 / 23		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Edema			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Orthopnoea			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	6-hour infusion group Levosimendan	24-hour infusion group Levosimendan	6-hour infusion group Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 38 (60.53%)	42 / 57 (73.68%)	14 / 22 (63.64%)
Cardiac disorders			
Worsening of heart failure			
subjects affected / exposed	5 / 38 (13.16%)	13 / 57 (22.81%)	6 / 22 (27.27%)
occurrences (all)	25	25	25
Cardiac decompensation			
subjects affected / exposed	6 / 38 (15.79%)	3 / 57 (5.26%)	2 / 22 (9.09%)
occurrences (all)	14	14	14
Ventricular tachycardia			
subjects affected / exposed	1 / 38 (2.63%)	8 / 57 (14.04%)	3 / 22 (13.64%)
occurrences (all)	13	13	13
Heart failure			
subjects affected / exposed	0 / 38 (0.00%)	3 / 57 (5.26%)	0 / 22 (0.00%)
occurrences (all)	5	5	5
Atrial fibrillation			
subjects affected / exposed	3 / 38 (7.89%)	0 / 57 (0.00%)	0 / 22 (0.00%)
occurrences (all)	4	4	4
Cardiogenic shock			
subjects affected / exposed	2 / 38 (5.26%)	2 / 57 (3.51%)	0 / 22 (0.00%)
occurrences (all)	4	4	4
Blood and lymphatic system disorders			

Hypotension			
subjects affected / exposed	10 / 38 (26.32%)	9 / 57 (15.79%)	3 / 22 (13.64%)
occurrences (all)	28	28	28
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	0 / 38 (0.00%)	3 / 57 (5.26%)	0 / 22 (0.00%)
occurrences (all)	4	4	4
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 38 (5.26%)	1 / 57 (1.75%)	1 / 22 (4.55%)
occurrences (all)	11	11	11
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 38 (2.63%)	2 / 57 (3.51%)	1 / 22 (4.55%)
occurrences (all)	4	4	4

Non-serious adverse events	24-hour infusion group Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 31 (67.74%)		
Cardiac disorders			
Worsening of heart failure			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	25		
Cardiac decompensation			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	14		
Ventricular tachycardia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	13		
Heart failure			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	5		
Atrial fibrillation			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	4		
Cardiogenic shock			

subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 4		
Blood and lymphatic system disorders Hypotension subjects affected / exposed occurrences (all)	 6 / 31 (19.35%) 28		
Respiratory, thoracic and mediastinal disorders Pneumonia subjects affected / exposed occurrences (all)	 1 / 31 (3.23%) 4		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	 7 / 31 (22.58%) 11		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	 0 / 31 (0.00%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2018	*Revised protocol, V1.5 *ICF V1.2 *New subinvestigators
17 September 2019	*Revised protocol V1.8 *Additional sites in Italy, Sweden and Danmark *Trial duration extended to 31-DEC-2021 *New Subinvestigtors *Change of sponsor contact
04 June 2020	Amendment of exclusion criteria 11

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 March 2020	The safety and well-being of patients participating in LeoDOR, as well as the personnel at each site, are of the utmost importance to the sponsor. The sponsor has decided to conduct a temporary hold until the situation is considerably improved .	11 May 2020

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30378288