Clinical trial results:
A multicenter, open-label study to investigate the effectiveness and safety of AOP Landiolol in controlling supraventricular tachycardia in pediatric patients (LANDI-PED).

Summary

EudraCT number	2015-001129-17
Trial protocol	AT DE LT HU
Global end of trial date	31 July 2023

Results information

Result version number	v1 (current)
This version publication date	13 April 2024
First version publication date	13 April 2024

Trial information

Trial identification

Sponsor protocol code	LDLL300.301

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AOP Orphan Pharmaceuticals GmbH
Sponsor organisation address	Leopold-Ungar-Platz 2, Vienna, Austria, A-1190
Public contact	Clinical Operations, AOP Orphan Pharmaceuticals GmbH, 0043 1 5037244, landi-ped@aoporphan.com
Scientific contact	Clinical Operations, AOP Orphan Pharmaceuticals GmbH, 0043 1 5037244, landi-ped@aoporphan.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001150-PIP02-13
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 January 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2023
Global end of trial reached?	Yes
Global end of trial date	31 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the pharmacokinetic (PK) and pharmacodynamic (PD) profile of LDLL300 in the pediatric population.

Protection of trial subjects:

The Investigator obtained a freely given signed ICF, with name, date and time noted by the patient/parents/legal representative, before the patient was exposed to any study-related procedure (or other country-specific documentation, as required). The study was carried out in compliance with protocol, the principles laid down in the "Declaration of Helsinki", the principles of Good Clinical Practice (GCP), data protection and confidentiality were handled in compliance with local laws.

Background therapy:

The type, dose and duration of further treatment/rescue therapy after LDLL300 infusion end was at the Investigator’s discretion (e.g. any alternative antiarrhythmic therapy). All concomitant treatment/rescue therapy (including dose change) with start date before or at Follow-up Visit III (V8) was recorded in detail. No antiarrhythmic agents Class I-V could be administered in parallel to LDLL300 infusion for the purpose of controlling HR or terminating the SVT. Concomitant treatment with pharmaceutical agents with potential antiarrhythmic properties administered for other reasons than HR control or SVT termination (e.g. dexmedetomidine for sedation) was permitted.

Evidence for comparator: -

Actual start date of recruitment	15 November 2018
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	Austria: 20
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Spain: 1
Worldwide total number of subjects	61
EEA total number of subjects	61

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	6
Infants and toddlers (28 days-23 months)	34
Children (2-11 years)	16
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study population comprised surgical (peri- and postoperative, cardiac and non-cardiac surgery) and non-surgical pediatric patients with IST, JET, AFL, AFib and FAT. Patients with AVRT or AVNRT were only treated with LDLL300 if they relapse, do not respond or show contraindications to first line treatment (adenosine).

Pre-assignment

Screening details:

Of 61 enrolled patients, one was not treated in Group II + III due to screening failure.

Period 1

Period 1 title	Overall treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group I

Arm description:

Patients with age range from day of birth to the day before the 2nd birthday.

Arm type	Experimental
Investigational medicinal product name	LDLL300
Investigational medicinal product code	LDLL300
Other name	Landiolol hydrochloride
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Treatment Phase (up to 210 min after treatment start):
Following the initial dose of 5 µg/kg/min, LDLL300 was up-titrated in order to achieve HR response:

- Dose level 1: 5 µg/kg/min
- Dose level 2: 10 µg/kg/min
- Dose level 3: 20 µg/kg/min
- Dose level 4: 40 µg/kg/min

If the HR response was not achieved or HR reduction above 20% was medically indicated and safe, after 10 min, the dose was increased to the next higher dose level. Upon achievement of HR response, the effective dose was to be maintained until minute 210 unless a further up-titration (up to a maximum of 40 µg/kg/min) to achieve a more profound HR reduction was medically indicated and safe, or the patient experienced ADR necessitating LDLL300 infusion reduction or termination.
Prolongation Phase (211 min – 24 h after treatment start):
If a longer infusion duration was medically indicated and deemed safe and efficacious by the Investigator, prolongation of infusion duration up to 24 hours was allowed.

Arm title	Group II + III

Arm description:

Patients with age range from day of 2nd birthday to the day before the 18th birthday.

Arm type	Experimental
Investigational medicinal product name	LDLL300
Investigational medicinal product code	LDLL300
Other name	Landiolol hydrochloride
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Treatment Phase (up to 210 min after treatment start):

Following the initial dose of 5 µg/kg/min, LDLL300 was up-titrated in order to achieve HR response:
- Dose level 1: 5 µg/kg/min
- Dose level 2: 10 µg/kg/min
- Dose level 3: 20 µg/kg/min
- Dose level 4: 40 µg/kg/min

If the HR response was not achieved or HR reduction above 20% was medically indicated and safe, after 10 min, the dose was increased to the next higher dose level. Upon achievement of HR response, the effective dose was to be maintained until minute 210 unless a further up-titration (up to a maximum of 40 µg/kg/min) to achieve a more profound HR reduction was medically indicated and safe, or the patient experienced ADR necessitating LDLL300 infusion reduction or termination.
Prolongation Phase (211 min – 24 h after treatment start):
If a longer infusion duration was medically indicated and deemed safe and efficacious by the Investigator, prolongation of infusion duration up to 24 hours was allowed.

Number of subjects in period 1	Group I	Group II + III
Started	40	21
Treated (Safety set)	40	20
Full analysis set (FAS)	40	20
Per-protocol set (PPS)	36 [1]	19
Completed	39	19
Not completed	1	2
Transfer to other hospital	1	-
Screening Failure	-	1
Lost to follow-up	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One patient was transfer to another hospital.

Baseline characteristics

Reporting groups	
Reporting group title	Group I
Reporting group description:	
Patients with age range from day of birth to the day before the 2nd birthday.	
Reporting group title	Group II + III
Reporting group description:	
Patients with age range from day of 2nd birthday to the day before the 18th birthday.	

Reporting group values	Group I	Group II + III	Total
Number of subjects	40	21	61
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	6	0	6
Infants and toddlers (28 days-23 months)	34	0	34
Children (2-11 years)	0	16	16
Adolescents (12-17 years)	0	5	5
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: months			
median	5.0	67.2	
inter-quartile range (Q1-Q3)	2.7 to 8.2	50.4 to 133.2	-
Gender categorical Units: Subjects			
Female	24	10	34
Male	16	11	27
Heart rate Units: beats per minute			
arithmetic mean	170.1	152.5	
standard deviation	± 21.89	± 36.18	-

Subject analysis sets	
Subject analysis set title	Group I FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All 0-2 years old patients who entered the Tratment Phase regardless of violation of eligibility criteria and protocol deviations.	
Subject analysis set title	Group II + III FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All 2-18 years old patients who entered the Tratment Phase regardless of violation of eligibility criteria and protocol deviations.	

Subject analysis set title	Group I PPS
Subject analysis set type	Per protocol

Subject analysis set description:

Patients from the Group I FAS set who have no major protocol deviations which might affect the evaluation of the study outcome measures.

Subject analysis set title	Group II + III PPS
Subject analysis set type	Per protocol

Subject analysis set description:

Patients from the Group II + III FAS set who have no major protocol deviations which might affect the evaluation of the study outcome measures.

Subject analysis set title	Group I PK FAS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients from the Group I FAS set who have evaluable PK profile.

Subject analysis set title	Group II + III PK FAS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients from the Group II + III FAS set who have evaluable PK profile.

Subject analysis set title	Group I PK PPS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients from the Group I PK FAS set who completed the study without major protocol deviations which might affect the evaluation of the PK endpoints.

Subject analysis set title	Group II + III PK PPS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients from the Group II + III PK FAS set who completed the study without major protocol deviations which might affect the evaluation of the PK endpoints.

Reporting group values	Group I FAS	Group II + III FAS	Group I PPS
Number of subjects	40	20	36
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	6	0	6
Infants and toddlers (28 days-23 months)	34	0	30
Children (2-11 years)	0	15	0
Adolescents (12-17 years)	0	5	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: months			
median	5.0	67.2	5.4
inter-quartile range (Q1-Q3)	2.7 to 8.2	51.6 to 138.6	3.1 to 8.4
Gender categorical Units: Subjects			
Female	24	10	20
Male	16	10	16

Heart rate			
Units: beats per minute			
arithmetic mean	170.1	152.5	168.6
standard deviation	± 21.89	± 36.18	± 21.82

Reporting group values	Group II + III PPS	Group I PK FAS	Group II + III PK FAS
Number of subjects	19	11	5
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	3	0
Infants and toddlers (28 days-23 months)	0	8	0
Children (2-11 years)	14	0	2
Adolescents (12-17 years)	5	0	3
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: months			
median	67.2	4.7	147.6
inter-quartile range (Q1-Q3)	50.4 to 144.0	0.7 to 5.3	63.6 to 188.4
Gender categorical			
Units: Subjects			
Female	9	7	2
Male	10	4	3
Heart rate			
Units: beats per minute			
arithmetic mean	152.9	179.6	153.8
standard deviation	± 37.13	± 14.34	± 18.99

Reporting group values	Group I PK PPS	Group II + III PK PPS	
Number of subjects	6	4	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	2	0	
Infants and toddlers (28 days-23 months)	4	0	
Children (2-11 years)	0	1	
Adolescents (12-17 years)	0	3	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: months			
median	3.4	168	
inter-quartile range (Q1-Q3)	0.3 to 7.6	97.2 to 190.8	

Gender categorical Units: Subjects			
Female	5	2	
Male	1	2	
Heart rate Units: beats per minute			
arithmetic mean	188.0	149.3	
standard deviation	± 14.23	± 18.52	

End points

End points reporting groups

Reporting group title	Group I
Reporting group description:	
Patients with age range from day of birth to the day before the 2nd birthday.	
Reporting group title	Group II + III
Reporting group description:	
Patients with age range from day of 2nd birthday to the day before the 18th birthday.	
Subject analysis set title	Group I FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All 0-2 years old patients who entered the Tratment Phase regardless of violation of eligibility criteria and protocol deviations.	
Subject analysis set title	Group II + III FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All 2-18 years old patients who entered the Tratment Phase regardless of violation of eligibility criteria and protocol deviations.	
Subject analysis set title	Group I PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients from the Group I FAS set who have no major protocol deviations which might affect the evaluation of the study outcome measures.	
Subject analysis set title	Group II + III PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients from the Group II + III FAS set who have no major protocol deviations which might affect the evaluation of the study outcome measures.	
Subject analysis set title	Group I PK FAS
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients from the Group I FAS set who have evaluable PK profile.	
Subject analysis set title	Group II + III PK FAS
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients from the Group II + III FAS set who have evaluable PK profile.	
Subject analysis set title	Group I PK PPS
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients from the Group I PK FAS set who completed the study without major protocol deviations which might affect the evaluation of the PK endpoints.	
Subject analysis set title	Group II + III PK PPS
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients from the Group II + III PK FAS set who completed the study without major protocol deviations which might affect the evaluation of the PK endpoints.	

Primary: Conversion to normal sinus rhythm response

End point title	Conversion to normal sinus rhythm response[1]

End point description:

The primary efficacy endpoint was defined as the percentage of patients converting to normal sinus rhythm (cardioversion) within 3.5 hours (210 min) (or earlier if infusion ended before 210 min) of the commencement of the LDLL300 infusion. 95% asymptotic Wald's confidence interval is presented as presicion estimate.

End point type	Primary

End point timeframe:

Up to 210 minutes (or earlier if infusion ended before 210 min) of the commencement of the LDLL300 infusion.

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: There is no statistical hypothesis to be tested. Asymptotic Wald’s confidence interval for the the percentage of patients converting to sinus rhythm were calculated per age group. Age groups were not compared with any statistical test.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: percent				
number (confidence interval 95%)	17.50 (5.72 to 29.28)	40.00 (18.53 to 61.47)	19.44 (6.52 to 32.37)	42.11 (19.90 to 64.31)

End point values	Group I PK FAS	Group II + III PK FAS	Group I PK PPS	Group II + III PK PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	5	6	4
Units: percent				
number (confidence interval 95%)	36.36 (7.94 to 64.79)	40.00 (0.00 to 82.94)	100.00 (100.00 to 100.00)	25.00 (0.00 to 67.43)

Statistical analyses

No statistical analyses for this end point

Secondary: Relative HR response at each dosing level

End point title	Relative HR response at each dosing level

End point description:

Relative heart rate response (at least 20% reduction from baseline HR) rates at each dosing level (before increase of treatment dose).

End point type	Secondary

End point timeframe:

Up to 210 minutes (or earlier if infusion ended before 210 min) of the commencement of the LDLL300 infusion.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40[2]	20[3]	36[4]	19[5]
Units: Percentage of patients				
number (confidence interval 95%)				
5 ug/kg/min	5 (0 to 11.75)	10 (0 to 23.15)	5.56 (0 to 13.04)	10.53 (0 to 24.33)
10 ug/kg/min	2.63 (0 to 7.72)	5.26 (0 to 15.3)	2.94 (0 to 8.62)	5.56 (0 to 16.14)
20 ug/kg/min	11.43 (0.89 to 21.97)	11.11 (0 to 25.63)	9.68 (0 to 20.08)	11.76 (0 to 27.08)
40 ug/kg/min	35.48 (18.64 to 52.33)	50 (26.9 to 73.1)	35.71 (17.97 to 53.46)	52.94 (29.21 to 76.67)
20 ug/kg/min post-reduction	50 (1 to 99)	100 (100 to 100)	50 (1 to 99)	100 (100 to 100)
5 ug/kg/min post-reduction	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

Notes:

[2] - Number of patients exposed to each dosing level is different.

[3] - Number of patients exposed to each dosing level is different.

[4] - Number of patients exposed to each dosing level is different.

[5] - Number of patients exposed to each dosing level is different.

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative HR response at each dosing level

End point title	Cumulative HR response at each dosing level

End point description:

Cumulative heart rate response (at least 20% reduction from baseline HR) rates at each dosing level (before increase of treatment dose).

End point type	Secondary

End point timeframe:

Up to 210 minutes (or earlier if infusion ended before 210 min) of the commencement of the LDLL300 infusion.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: Percentage of patients				
number (confidence interval 95%)				
10 ug/kg/min	5 (0 to 11.75)	15 (0 to 30.65)	5.56 (0 to 13.04)	15.79 (0 to 32.19)
20 ug/kg/min	15 (3.93 to 26.07)	20 (2.47 to 37.53)	13.89 (2.59 to 25.19)	21.05 (2.72 to 39.38)
40 ug/kg/min	42.5 (27.18 to 57.82)	60 (38.53 to 81.47)	41.67 (25.56 to 57.77)	63.16 (41.47 to 84.85)

20 ug/kg/min post-reduction	45 (29.58 to 60.42)	65 (44.1 to 85.9)	44.44 (28.21 to 60.68)	68.42 (47.52 to 89.32)
5 ug/kg/min post-reduction	45 (29.58 to 60.42)	65 (44.1 to 85.9)	44.44 (28.21 to 60.68)	68.42 (47.52 to 89.32)

Statistical analyses

No statistical analyses for this end point

Secondary: Relative non-response rates at each dosing level

End point title	Relative non-response rates at each dosing level

End point description:

Relative non-response rates at each dosing level, where non-response is defined as no HR response and/or no conversion to normal sinus rhythm.

End point type	Secondary

End point timeframe:

Up to 210 minutes (or earlier if infusion ended before 210 min) of the commencement of the LDLL300 infusion.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40[6]	20[7]	36[8]	19[9]
Units: Percentage of patients				
number (confidence interval 95%)				
5 ug/kg/min	95 (88.25 to 100)	90 (76.85 to 100)	94.44 (86.96 to 100)	89.47 (75.67 to 100)
10 ug/kg/min	97.37 (92.28 to 100)	94.74 (84.7 to 100)	97.06 (91.38 to 100)	94.44 (83.86 to 100)
20 ug/kg/min	88.57 (78.03 to 99.11)	88.89 (74.37 to 100)	90.32 (79.92 to 100)	88.24 (72.92 to 100)
40 ug/kg/min	64.52 (47.67 to 81.36)	50 (26.9 to 73.1)	64.29 (46.54 to 82.03)	47.06 (23.33 to 79.79)
20 ug/kg/min post-reduction	50 (1 to 99)	0 (0 to 0)	50 (1 to 99)	0 (0 to 0)
5 ug/kg/min post-reduction	100 (100 to 100)	0 (0 to 0)	100 (100 to 100)	0 (0 to 0)

Notes:

[6] - Number of patients exposed to each dosing level is different.

[7] - Number of patients exposed to each dosing level is different.

[8] - Number of patients exposed to each dosing level is different.

[9] - Number of patients exposed to each dosing level is different.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in HR by visit and timepoint

End point title	Percentage change from baseline in HR by visit and timepoint

End point description:

Percentage change from baseline in heart rate by visit and time point.

End point type	Secondary

End point timeframe:

From treatment start up to the end of study.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: Percentage change				
arithmetic mean (standard deviation)				
Infusion Phase I - 5 min	-1.86 (± 6.444)	-3.10 (± 5.489)	-1.85 (± 6.379)	-3.10 (± 5.489)
Infusion Phase I - 10 min	-3.67 (± 8.063)	-6.01 (± 8.647)	-3.83 (± 8.135)	-6.01 (± 8.647)
Infusion Phase I - 15 min	-4.78 (± 8.437)	-5.21 (± 9.216)	-5.00 (± 8.606)	-5.55 (± 9.333)
Infusion Phase I - 20 min	-4.20 (± 6.804)	-5.46 (± 5.867)	-4.20 (± 6.630)	-5.46 (± 5.867)
Infusion Phase I - 25 min	-4.46 (± 7.652)	-7.13 (± 10.717)	-4.26 (± 7.606)	-7.13 (± 10.717)
Infusion Phase I - 30 min	-5.26 (± 6.311)	-5.90 (± 9.389)	-5.19 (± 6.100)	-6.27 (± 9.521)
Infusion Phase II - 40 min	-5.50 (± 8.268)	-11.2 (± 12.699)	-5.36 (± 8.050)	-11.7 (± 12.866)
Infusion Phase II - 50 min	-6.59 (± 10.053)	-11.5 (± 13.354)	-6.53 (± 9.860)	-12.0 (± 13.593)
Infusion Phase II - 60 min	-7.25 (± 9.622)	-12.6 (± 12.906)	-6.84 (± 9.291)	-13.0 (± 13.154)
Infusion Phase II - 70 min	-8.77 (± 10.419)	-13.6 (± 14.095)	-8.21 (± 9.634)	-14.1 (± 14.353)
Infusion Phase II - 80 min	-7.41 (± 9.019)	-13.8 (± 16.083)	-6.71 (± 7.260)	-14.3 (± 16.419)
Infusion Phase II - 90 min	-6.72 (± 9.274)	-14.7 (± 12.813)	-6.21 (± 8.390)	-15.2 (± 13.014)
Infusion Phase II - 100 min	-7.77 (± 9.436)	-14.7 (± 12.806)	-7.45 (± 8.910)	-15.0 (± 13.118)
Infusion Phase II - 110 min	-9.01 (± 10.099)	-14.8 (± 13.594)	-8.56 (± 9.562)	-15.3 (± 13.880)
Infusion Phase II - 120 min	-8.52 (± 9.601)	-17.1 (± 16.102)	-7.19 (± 8.895)	-17.7 (± 16.406)
Infusion Phase II - 130 min	-9.04 (± 9.975)	-15.7 (± 17.530)	-7.66 (± 9.233)	-16.3 (± 18.005)
Infusion Phase II - 140 min	-9.20 (± 8.968)	-16.8 (± 16.489)	-8.49 (± 8.452)	-17.5 (± 16.823)
Infusion Phase II - 150 min	-9.30 (± 9.792)	-17.0 (± 15.996)	-8.60 (± 8.759)	-17.8 (± 16.198)
Infusion Phase II - 160 min	-10.4 (± 10.976)	-18.5 (± 16.749)	-9.93 (± 10.636)	-19.0 (± 17.214)
Infusion Phase II - 170 min	-10.4 (± 11.100)	-18.2 (± 14.455)	-9.62 (± 11.172)	-18.4 (± 14.897)
Infusion Phase II - 180 min	-10.1 (± 10.858)	-17.5 (± 12.659)	-9.53 (± 10.995)	-17.8 (± 13.037)
Infusion Phase II - 190 min	-9.36 (± 9.369)	-18.3 (± 14.925)	-8.84 (± 9.076)	-18.4 (± 15.435)
Infusion Phase II - 200 min	-10.0 (± 8.834)	-18.4 (± 13.091)	-9.68 (± 8.420)	-18.4 (± 13.520)

Infusion Phase II - 210 min	-10.4 (± 9.330)	-17.9 (± 13.359)	-9.78 (± 8.656)	-18.1 (± 13.778)
Prolongation Phase - 450 min	-19.9 (± 8.189)	-35.0 (± 17.563)	-17.1 (± 6.022)	-35.0 (± 17.563)
Prolongation Phase - 690 min	-20.5 (± 7.870)	-37.9 (± 10.376)	-18.1 (± 6.341)	-37.9 (± 10.376)
Prolongation Phase - 930 min	-19.7 (± 9.870)	-40.5 (± 17.053)	-15.3 (± 5.950)	-40.5 (± 17.053)
Prolongation Phase - 1170 min	-23.5 (± 5.564)	-29.1 (± 15.679)	-22.2 (± 3.390)	-29.1 (± 15.679)
Prolongation Phase - 1410 min	-26.9 (± 6.389)	-44.8 (± 17.302)	-23.3 (± 1.649)	-44.8 (± 17.302)
Infusion End	-12.3 (± 13.921)	-23.3 (± 16.456)	-11.6 (± 12.652)	-23.7 (± 16.793)
Follow-up Visit I - 10 min	-10.6 (± 12.770)	-18.0 (± 20.638)	-10.1 (± 11.937)	-18.3 (± 21.179)
Follow-up Visit I - 20 min	-11.0 (± 12.487)	-18.3 (± 21.911)	-10.8 (± 12.306)	-18.3 (± 21.911)
Follow-up Visit I - 30 min	-11.6 (± 13.076)	-18.2 (± 20.815)	-10.9 (± 11.929)	-18.5 (± 21.415)
Follow-up Visit I - 60 min	-11.3 (± 13.398)	-20.3 (± 18.743)	-11.1 (± 12.974)	-20.5 (± 19.340)
Follow-up Visit II	-18.8 (± 14.166)	-27.1 (± 22.146)	-18.6 (± 14.710)	-26.1 (± 22.311)
Follow-up Visit III	-21.7 (± 14.796)	-27.5 (± 20.573)	-20.9 (± 14.810)	-27.4 (± 21.168)
First response up to 210 min or infusion end	-23.9 (± 4.066)	-30.1 (± 13.595)	-23.8 (± 4.402)	-30.1 (± 13.595)
FR from 210 min till end of prolongation phase	-22.5 (± 1.174)	-23.0 (± 1.635)	-22.5 (± 1.174)	-23.0 (± 1.635)
First response up to Follow-up II	-24.3 (± 3.925)	-29.7 (± 12.578)	-24.3 (± 4.109)	-28.4 (± 12.201)
First response up to Follow-up III	-25.3 (± 5.651)	-29.7 (± 12.578)	-24.5 (± 4.116)	-28.4 (± 12.201)

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship between change from baseline in HR and patient’s age

End point title	Relationship between change from baseline in HR and patient’s age

End point description:

Relationship between absolute and relative change from baseline in heart rate and patient’s age.

End point type	Secondary

End point timeframe:

From treatment start up to the end of study or up to 210 min (or earlier if infusion ended before 210 min) depending on the type statistical analysis.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: Subjects	40	20	36	19

Statistical analyses

Statistical analysis title	Absolute change up to EOS (FAS)

Statistical analysis description:

Difference of mean estimates of absolute change from baseline in HR up to the end of study.

Comparison groups	Group I FAS v Group II + III FAS
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	18.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.05
upper limit	20.52

Notes:

[10] - Mixed model with repeated measures with Visit, Age group, Sex and the baseline HR value as covariates was used

Statistical analysis title	Absolute change within 210 minutes (FAS)

Statistical analysis description:

Difference of mean estimates of absolute change from baseline in HR within first 210 minutes.

Comparison groups	Group I FAS v Group II + III FAS
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	14.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.3
upper limit	16.87

Notes:

[11] - Mixed model with repeated measures with Visit, Age group, Sex and the baseline HR value as covariates was used

Statistical analysis title	Percentage change up to EOS (FAS)

Statistical analysis description:

Difference of mean estimates of percentage change from baseline in HR up to the end of study.

Comparison groups	Group I FAS v Group II + III FAS
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	10.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.83
upper limit	11.34

Notes:

[12] - Mixed model with repeated measures with Visit, Age group, Sex and the baseline HR value as covariates was used

Statistical analysis title	Percentage change within 210 min (FAS)

Statistical analysis description:

Difference of mean estimates of percentage change from baseline in HR within first 210 minutes.

Comparison groups	Group II + III FAS v Group I FAS
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	8.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.18
upper limit	9.82

Notes:

[13] - Mixed model with repeated measures with Visit, Age group, Sex and the baseline HR value as covariates was used

Statistical analysis title	Absolute change up to EOS (PPS)

Statistical analysis description:

Difference of mean estimates of absolute change from baseline in HR up to the end of study.

Comparison groups	Group I PPS v Group II + III PPS
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	18.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	16.63
upper limit	21.19

Notes:

[14] - Mixed model with repeated measures with Visit, Age group, Sex and the baseline HR value as covariates was used

Statistical analysis title	Absolute change within 210 minutes (PPS)

Statistical analysis description:

Difference of mean estimates of absolute change from baseline in HR within first 210 minutes.

Comparison groups	Group I PPS v Group II + III PPS
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	15.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.95
upper limit	17.57

Notes:

[15] - Mixed model with repeated measures with Visit, Age group, Sex and the baseline HR value as covariates was used

Statistical analysis title	Percentage change up to EOS (PPS)

Statistical analysis description:

Difference of mean estimates of percentage change from baseline in HR up to the end of study.

Comparison groups	Group I PPS v Group II + III PPS
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	10.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.15
upper limit	11.73

Notes:

[16] - Mixed model with repeated measures with Visit, Age group, Sex and the baseline HR value as covariates was used

Statistical analysis title	Percentage change within 210 min (PPS)

Statistical analysis description:

Difference of mean estimates of percentage change from baseline in HR within first 210 minutes.

Comparison groups	Group I PPS v Group II + III PPS

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	8.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.58
upper limit	10.27

Notes:

[17] - Mixed model with repeated measures with Visit, Age group, Sex and the baseline HR value as covariates was used

Secondary: Relative restoration of sinus rhythm by time period

End point title	Relative restoration of sinus rhythm by time period

End point description:

Percentage of patients who had restoration of sinus rhythm by pre-specified time periods.

End point type	Secondary

End point timeframe:

From treatment start up to the end of study.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: Percentage of patients				
number (not applicable)				
within 210 min	17.5	40	19.44	42.11
after 210 min	2.5	0	2.78	0
during Prolongation Phase	12.5	10	11.11	10.53
after infusion end up to Follow-up II	25	10	27.78	10.53
after Follow-up II up to Follow-up III	20	25	19.44	21.05

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative restoration of sinus rhythm by time period

End point title	Cumulative restoration of sinus rhythm by time period

End point description:

Cumulative percentage of patients who had restoration of sinus rhythm by pre-specified time periods.

End point type	Secondary

End point timeframe:

From treatment start up to the end of study.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: Percentage of patients				
number (not applicable)				
after 210 min	20	40	22.22	42.11
during Prolongation phase	32.5	50	33.33	52.63
after infusion end up to Follow-up II	57.5	60	61.11	63.16
after Follow-up II up to Follow-up III	77.5	85	80.56	84.21

Statistical analyses

No statistical analyses for this end point

Secondary: Patients who entered the Prolongation Phase and duration of prolongation

End point title	Patients who entered the Prolongation Phase and duration of prolongation

End point description:

Number of patients who entered the Prolongation Phase and duration of prolongation.

End point type	Secondary

End point timeframe:

Prolongation Phase

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11[18]	6[19]	9[20]	6[21]
Units: hours				
arithmetic mean (standard deviation)	17.45 (± 3.839)	15.96 (± 7.493)	16.84 (± 4.017)	15.96 (± 7.493)

Notes:

[18] - The number of patients who entered the Prolongation Phase

[19] - The number of patients who entered the Prolongation Phase

[20] - The number of patients who entered the Prolongation Phase

[21] - The number of patients who entered the Prolongation Phase

Statistical analyses

No statistical analyses for this end point

Secondary: Relative restoration of sinus rhythm or HR response by time period

End point title	Relative restoration of sinus rhythm or HR response by time

	period

End point description:

Percentage of patients who had achieved either restoration of sinus rhythm or HR response by pre-specified time periods

End point type	Secondary

End point timeframe:

From treatment start up to the end of study.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: Percentage of patients				
number (not applicable)				
within 210 min	35	50	33.33	52.63
after 210 min	2.5	5	2.78	5.26
during Prolongation phase	22.5	30	19.44	31.58
after infusion end up to Follow-up II	62.5	70	63.89	68.42
after Follow-up II up to Follow-up III	60	75	58.33	73.68

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative restoration of sinus rhythm or HR response by time period

End point title	Cumulative restoration of sinus rhythm or HR response by time period

End point description:

Cumulative percentage of patients who had achieved either restoration of sinus rhythm or HR response by pre-specified time periods.

End point type	Secondary

End point timeframe:

From treatment start up to the end of study.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: Percentage of patients				
number (not applicable)				
after 210 min	37.5	50	36.11	52.63
during Prolongation phase	45	65	44.44	68.42
after infusion end up to Follow-up II	70	80	72.22	78.95
after Follow-up II up to Follow-up III	82.5	95	83.33	94.74

Statistical analyses

No statistical analyses for this end point

Secondary: Time to HR response up to infusion end

End point title	Time to HR response up to infusion end

End point description:

Time to HR response from infusion start up to infusion end.

End point type	Secondary

End point timeframe:

From infusion start up to infusion end.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40[22]	20[23]	36[24]	19[25]
Units: minutes				
arithmetic mean (standard deviation)	282.39 (± 408.886)	127.15 (± 135.844)	311.13 (± 426.065)	127.15 (± 135.844)

Notes:

[22] - Responders only - 18 patients

[23] - Responders only - 13 patients

[24] - Responders only - 16 patients

[25] - Responders only - 13 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Time to conversion to normal sinus rhythm up to infusion end

End point title	Time to conversion to normal sinus rhythm up to infusion end

End point description:

Time to conversion to normal sinus rhythm from infusion start to infusion end.

End point type	Secondary

End point timeframe:

From infusion start up to infusion end.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40[26]	20[27]	36[28]	19[29]
Units: minutes				
arithmetic mean (standard deviation)	453.77 (± 471.442)	158.20 (± 136.419)	414.42 (± 469.574)	158.20 (± 136.419)

Notes:

[26] - Responders only - 13 patients

[27] - Responders only - 10 patients

[28] - Responders only - 12 patients

[29] - Responders only - 10 patients

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters of Landiolol

End point title	PK parameters of Landiolol

End point description:

Descriptive summary of the following PK parameters for Landiolol: Time to peak drug concentration (T max [min]), Maximum blood concentration (C max [ng/mL]), AUC from administration (0 h) to the last quantified concentration (AUC 0-t [min*ug/mL]), AUC from 0 h extrapolated to infinity (AUC 0-inf [min*ug/mL]), Half-life (t 1/2 [min]), Total clearance (CL tot [mL/min]), Volume of distribution (Vd [mL]), Total clearance adjusted for body weight (CLwa tot [mL/min/kg]), Volume of distribution adjusted for body weight (Vdwa [mL/kg]).

End point type	Secondary

End point timeframe:

From infusion start up to the end of elimination phase

End point values	Group I PK FAS	Group II + III PK FAS	Group I PK PPS	Group II + III PK PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	5	6	4
Units: individual				
arithmetic mean (standard deviation)				
T max [min]	527.1 (± 580.91)	819.6 (± 649.14)	630.0 (± 557.18)	1016.5 (± 550.81)
C max [ng/mL]	750.0 (± 615.97)	2168.2 (± 1860.61)	1021.5 (± 667.23)	2435.3 (± 2034.80)
AUC 0-t [min*ug/mL]	429.512 (± 457.8161)	1455.656 (± 1214.7227)	634.827 (± 478.9989)	1444.216 (± 1402.3298)
AUC 0-inf [min*ug/mL]	397.649 (± 435.9146)	1459.921 (± 1219.6874)	673.583 (± 452.4203)	1449.515 (± 1408.1173)
t 1/2 [min]	4.245 (± 0.8063)	4.130 (± 2.8408)	4.088 (± 0.8621)	4.708 (± 2.9218)

Cl tot [mL/min]	462.6 (± 378.43)	1136.2 (± 1075.52)	422.0 (± 418.58)	1251.3 (± 1205.85)
Vd [mL]	2594.6 (± 1665.23)	5133.6 (± 4418.38)	2256.0 (± 1829.74)	5973.0 (± 4618.67)
Clwa tot [mL/min/kg]	95.5 (± 72.62)	27.8 (± 13.37)	67.3 (± 32.57)	25.3 (± 13.96)
Vdwa [mL/kg]	558.5 (± 371.35)	140.2 (± 64.35)	377.3 (± 133.07)	150.5 (± 69.38)

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters of Landiolol Metabolite M1

End point title	PK parameters of Landiolol Metabolite M1

End point description:

Descriptive summary of the following PK parameters for Landiolol Metabolite M1: Time to peak drug concentration (T max [min]), Maximum blood concentration (C max [ng/mL]), AUC from administration (0 h) to the last quantified concentration (AUC 0-t [min*ug/mL]).

End point type	Secondary

End point timeframe:

From infusion start up to the last quantified concentration.

End point values	Group I PK FAS	Group II + III PK FAS	Group I PK PPS	Group II + III PK PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	5	6	4
Units: individual				
arithmetic mean (standard deviation)				
T max [min]	701.5 (± 579.66)	1101.6 (± 509.97)	860.2 (± 549.96)	1018.0 (± 547.87)
C max [ng/mL]	7774.5 (± 7499.27)	5961.2 (± 3668.89)	11035.0 (± 8098.07)	6084.0 (± 4224.59)
AUC 0-t [min*ug/mL]	4049.545 (± 4724.0080)	3141.756 (± 2559.5043)	5965.170 (± 5167.6622)	2780.451 (± 2804.3674)

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters of Landiolol Metabolite M2

End point title	PK parameters of Landiolol Metabolite M2

End point description:

Descriptive summary of the following PK parameters for Landiolol Metabolite M2: Time to peak drug concentration (T max [min]), Maximum blood concentration (C max [ng/mL]), AUC from administration (0 h) to the last quantified concentration (AUC 0-t [min*ug/mL]).

End point type	Secondary

End point timeframe:

From infusion start up to the last quantified concentration.

End point values	Group I PK FAS	Group II + III PK FAS	Group I PK PPS	Group II + III PK PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	5	6	4
Units: individual				
arithmetic mean (standard deviation)				
T max [min]	703.7 (± 576.92)	1103.6 (± 507.42)	861.8 (± 546.31)	1018.5 (± 543.16)
C max [ng/mL]	1154.9 (± 1050.03)	744.8 (± 487.32)	1605.3 (± 1138.65)	633.5 (± 483.79)
AUC 0-t [min*ug/mL]	591.574 (± 702.5463)	403.026 (± 377.3202)	879.335 (± 772.2095)	289.445 (± 322.2157)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Relative conversion to normal sinus rhythm at each dosing level

End point title	Relative conversion to normal sinus rhythm at each dosing level

End point description:

Relative conversion to normal sinus rhythm rates at each dosing level (before increase of treatment dose).

End point type	Other pre-specified

End point timeframe:

Up to 210 minutes (or earlier if infusion ended before 210 min) of the commencement of the LDLL300 infusion.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: Percentage of patients				
number (confidence interval 95%)				
5 ug/kg/min	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
10 ug/kg/min	2.63 (0.00 to 7.72)	5.26 (0.00 to 15.30)	2.94 (0.00 to 8.62)	5.56 (0.00 to 16.14)
20 ug/kg/min	2.86 (0.00 to 8.38)	0 (0 to 0)	3.23 (0.00 to 9.45)	0 (0 to 0)
40 ug/kg/min	32.26 (15.80 to 48.71)	50.00 (26.90 to 73.10)	32.14 (14.84 to 49.44)	52.94 (29.21 to 76.67)
20 ug/kg/min post-reduction	25.00 (0.00 to 67.43)	0 (0 to 0)	25.00 (0.00 to 67.43)	0 (0 to 0)
5 ug/kg/min post-reduction	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cumulative conversion to normal sinus rhythm at each dosing level

End point title	Cumulative conversion to normal sinus rhythm at each dosing level

End point description:

Cumulative conversion to normal sinus rhythm rates at each dosing level (before increase of treatment dose).

End point type	Other pre-specified

End point timeframe:

Up to 210 minutes (or earlier if infusion ended before 210 min) of the commencement of the LDLL300 infusion.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: Percentage of patients				
number (confidence interval 95%)				
10 ug/kg/min	2.50 (0.00 to 7.34)	5.00 (0.00 to 14.55)	2.78 (0.00 to 8.15)	5.26 (0.00 to 15.30)
20 ug/kg/min	5.00 (0.00 to 11.75)	5.00 (0.00 to 14.55)	5.56 (0.00 to 13.04)	5.26 (0.00 to 15.30)
40 ug/kg/min	30.00 (15.80 to 44.20)	50.00 (28.09 to 71.91)	30.56 (15.51 to 45.60)	52.63 (30.18 to 75.08)
5 ug/kg/min post-reduction	32.50 (17.99 to 47.01)	50.00 (28.09 to 71.91)	33.33 (17.93 to 48.73)	52.63 (30.18 to 75.08)
20 ug/kg/min post-reduction	32.50 (17.99 to 47.01)	50.00 (28.09 to 71.91)	33.33 (17.93 to 48.73)	52.63 (30.18 to 75.08)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to conversion to normal sinus rhythm up to 210 min

End point title	Time to conversion to normal sinus rhythm up to 210 min

End point description:

Time to conversion to normal sinus rhythm from infusion start up to 210 min (or earlier if infusion ended before 210 min).

End point type	Other pre-specified

End point timeframe:

From infusion start up to 210 minutes (or earlier if infusion ended before 210 min) of the commencement of the LDLL300 infusion.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40[30]	20[31]	36[32]	19[33]
Units: minute				
arithmetic mean (standard deviation)	105.1 (± 60.889)	101.0 (± 64.009)	105.1 (± 60.889)	101.0 (± 64.009)

Notes:

[30] - Responders only - 7 patients

[31] - Responders only - 8 patients

[32] - Responders only - 7 patients

[33] - Responders only - 8 patients

Statistical analyses

No statistical analyses for this end point

Other pre-specified: HR response

End point title	HR response

End point description:

Percentage of patients with a heart rate reduction of at least 20% within 210 min (or earlier if infusion ended before 210 min) of the commencement of the LDLL300 infusion. 95% asymptotic Wald's confidence interval is presented

End point type	Other pre-specified

End point timeframe:

Up to 210 minutes (or earlier if infusion ended before 210 min) of the commencement of the LDLL300 infusion.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: percent				
number (confidence interval 95%)	35.00 (20.22 to 49.78)	50.00 (28.09 to 71.91)	33.33 (17.93 to 48.73)	52.63 (30.18 to 75.08)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cumulative HR response

End point title	Cumulative HR response

End point description:

Cumulative HR response by visit and time point.

End point type	Other pre-specified

End point timeframe:

From treatment start up to the end of study.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	20	36	19
Units: Subjects				
Up to Infusion Phase I - 5 min	0	0	0	0
Up to Infusion Phase I - 10 min	1	2	1	2
Up to Infusion Phase I - 15 min	1	2	1	2
Up to Infusion Phase I - 20 min	1	2	1	2
Up to Infusion Phase I - 25 min	1	2	1	2
Up to Infusion Phase I - 30 min	1	3	1	3
Up to Infusion Phase II - 40 min	3	4	2	4
Up to Infusion Phase II - 50 min	4	6	3	6
Up to Infusion Phase II - 60 min	4	6	3	6
Up to Infusion Phase II - 70 min	5	7	3	7
Up to Infusion Phase II - 80 min	5	7	3	7
Up to Infusion Phase II - 90 min	6	7	4	7
Up to Infusion Phase II - 100 min	7	7	5	7
Up to Infusion Phase II - 110 min	9	9	7	9
Up to Infusion Phase II - 120 min	9	9	7	9
Up to Infusion Phase II - 130 min	10	9	8	9
Up to Infusion Phase II - 140 min	10	9	8	9
Up to Infusion Phase II - 150 min	11	9	9	9
Up to Infusion Phase II - 160 min	12	10	10	10
Up to Infusion Phase II - 170 min	14	10	12	10
Up to Infusion Phase II - 180 min	14	10	12	10
Up to Infusion Phase II - 190 min	14	10	12	10
Up to Infusion Phase II - 200 min	14	10	12	10
Up to Infusion Phase II - 210 min	14	10	12	10
Up to Prolongation Phase - 450 min	15	13	13	13
Up to Prolongation Phase - 690 min	15	13	13	13
Up to Prolongation Phase - 930 min	16	13	14	13
Up to Prolongation Phase - 1170 min	17	13	15	13
Up to Prolongation Phase - 1410 min	18	13	16	13
Up to Infusion End	18	13	16	13
Up to Follow-up Visit I - 10 min	18	13	16	13
Up to Follow-up Visit I - 20 min	18	13	16	13
Up to Follow-up Visit I - 30 min	18	13	16	13
Up to Follow-up Visit I - 60 min	19	13	17	13

Up to Follow-up Visit II	23	14	21	13
Up to Follow-up Visit III	27	14	24	13

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to HR response up to 210 min

End point title	Time to HR response up to 210 min

End point description:

Time to HR response from infusion start up to 210 minutes (or earlier if infusion ended before 210 min).

End point type	Other pre-specified

End point timeframe:

From infusion start up to 210 minutes (or earlier if infusion ended before 210 min) of the commencement of the LDLL300 infusion.

End point values	Group I FAS	Group II + III FAS	Group I PPS	Group II + III PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40[34]	20[35]	36[36]	19[37]
Units: minute				
arithmetic mean (standard deviation)	98.43 (± 54.206)	62.70 (± 48.687)	106.1 (± 54.741)	62.70 (± 48.687)

Notes:

[34] - Responders only - 14 patients

[35] - Responders only - 10 patients

[36] - Responders only - 12 patients

[37] - Responders only - 10 patients

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring during the course of the clinical trial from LDLL300 infusion start until Follow-up Visit III (V8) were collected, documented and reported by the Investigator.

Adverse event reporting additional description:

Any SAE occurring at any other time after completion of the study was to be promptly reported, especially if a causal relationship to LDLL300 was suspected.
Follow-up of AEs was required after Follow-up Visit III (V8), if the AE or its sequelae persisted.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	Group I

Reporting group description:

Patients with age range from day of 2nd birthday to the day before the 18th birthday.

Reporting group title	Group II + III

Reporting group description:

Patients with age range from day of 2nd birthday to the day before the 18th birthday.

Serious adverse events	Group I	Group II + III	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 40 (7.50%)	1 / 20 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 40 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac tamponade			

subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypoperfusion			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Group I	Group II + III	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 40 (57.50%)	9 / 20 (45.00%)	
Investigations			
Chest x-ray abnormal			
subjects affected / exposed	0 / 40 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Ejection fraction decreased			
subjects affected / exposed	0 / 40 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Electrocardiogram QRS complex prolonged			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 40 (17.50%)	0 / 20 (0.00%)	
occurrences (all)	7	0	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 40 (2.50%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Supraventricular tachycardia			
subjects affected / exposed	2 / 40 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	2	1	

Aortic valve incompetence			
subjects affected / exposed	0 / 40 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Hypertonia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Infusion site erythema			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 40 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Pleural effusion			
subjects affected / exposed	2 / 40 (5.00%)	3 / 20 (15.00%)	
occurrences (all)	2	3	
Stridor			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Infection			
subjects affected / exposed	3 / 40 (7.50%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Oral candidiasis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Systemic bacterial infection			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 40 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2017	Protocol Amendment 1: Version 2.0
28 September 2017	Protocol Amendment 2: Version 3.0
24 May 2018	Protocol Amendment 3: Version 4.0
04 September 2018	Protocol Amendment 4: Version 5.0
22 August 2019	Protocol Amendment 5: Version 6.0
06 May 2021	Protocol Amendment 6: Version 7.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

There were limitations to the assessment of the PK profile in blood volume amount, potential dose change, and the number of patients who/whose legal representative(s)/parents/care givers agreed to a second indwelling catheter.

Notes: