Clinical trial results:
A multi-center, randomized, double-blind, parallel-group dose-finding study to assess the effect of 3 doses of LIK066 compared to placebo or empagliflozin in type 2 diabetes mellitus patients with heart failure

Summary

EudraCT number	2016-003084-19
Trial protocol	AT GB DE CZ DK NO NL HU ES BE BG PL HR IT
Global end of trial date	06 June 2018

Results information

Result version number	v2 (current)
This version publication date	05 July 2019
First version publication date	15 May 2019
Version creation reason	• Correction of full data set Clarification of previously reported data.

Trial information

Trial identification

Sponsor protocol code	CLIK066B2204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03152552
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, Novartis.email@novartis.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	06 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 June 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the dose-response signal and assess the dose-response relationship of LIK066 2.5mg, 10mg, and 50mg qd as measured by the change from baseline (BL) in NT-proBNP relative to placebo after 12 weeks of treatment in T2DM patients with HF.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 July 2017
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	Argentina: 11
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Croatia: 8
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Spain: 21

Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	124
EEA total number of subjects	87

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)	40
From 65 to 84 years	81
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Patients were randomized in a 1:1:2:2:2 ratio to one of 5 regimens (LIK066 2.5mg, 10mg, 50 mg, EMPA 25mg, Pbo) at Visit 201 (randomization) with a plan to be treated for 36 weeks.

Pre-assignment

Screening details:

A placebo run-in period (Epoch 2) running up to 2 weeks before randomization was used to assess eligibility

Period 1

Period 1 title	Treatment Period 1 (12 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	LIK066 2.5mg

Arm description:

LIK066 2.5mg once daily

Arm type	Experimental
Investigational medicinal product name	LIK066
Investigational medicinal product code	LIK066
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

LIK066 2.5mg qd at bedtime

Arm title	LIK066 10mg

Arm description:

LIk066 10mg once daily

Arm type	Experimental
Investigational medicinal product name	LIK066
Investigational medicinal product code	LIK066
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

LIK066 10mg qd at bedtime

Arm title	LIK066 50mg

Arm description:

LIK066 50mg once daily

Arm type	Experimental

Investigational medicinal product name	LIK066
Investigational medicinal product code	LIK066
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
LIK066 50mg qd at bedtime

Arm title	EMPA 25mg

Arm description:
Empagliflozin 25 mg once daily

Arm type	Active comparator
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
Empagliflozin (up-titrated from 10mg qd to 25mg qd after 2 weeks); in the morning

Arm title	Placebo

Arm description:
LIK066 matching placebo and empagliflozin matching placebo

Arm type	Placebo
Investigational medicinal product name	Placebo LIK066
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
Placebo LIK066 at bedtime/Placebo Empagliflozin in the morning

Number of subjects in period 1	LIK066 2.5mg	LIK066 10mg	LIK066 50mg
Started	15	16	30
Full Analysis Set (FAS)	15	16	30
Completed	7	5	10
Not completed	8	11	20
Adverse event, serious fatal	-	1	-
Protocol deviation	-	1	-
Study terminated by sponsor	8	9	19
Lost to follow-up	-	-	1
Subject/guardian decision	-	-	-

Number of subjects in period 1	EMPA 25mg	Placebo
Started	30	33
Full Analysis Set (FAS)	30	33

Completed	10	12
Not completed	20	21
Adverse event, serious fatal	-	1
Protocol deviation	-	-
Study terminated by sponsor	19	20
Lost to follow-up	-	-
Subject/guardian decision	1	-

Period 2

Period 2 title	Treatment Period 2 (24 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	LIK066 2.5mg
Arm description: LIK066 2.5mg once daily	
Arm type	Experimental
Investigational medicinal product name	LIK066
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: LIK066 2.5mg qd at bedtime	
Arm title	LIK066 10mg
Arm description: LIk066 10mg once daily	
Arm type	Experimental
Investigational medicinal product name	LIK066
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: LIK066 10mg qd at bedtime	
Arm title	LIK066 50mg
Arm description: LIK066 50mg once daily	
Arm type	Experimental

Investigational medicinal product name	LIK066
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
LIK066 50mg qd at bedtime

Arm title	EMPA 25mg

Arm description:
Empagliflozin 25 mg once daily

Arm type	Active comparator
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Intratumoral use, Oral use

Dosage and administration details:
Empagliflozin (up-titrated from 10mg qd to 25mg qd after 2 weeks); in the morning

Arm title	Placebo

Arm description:
LIK066 matching placebo and empagliflozin matching placebo

Arm type	Placebo
Investigational medicinal product name	Placebo LIK066
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
Placebo LIK066 at bedtime/Placebo Empagliflozin in the morning

Number of subjects in period 2[1]	LIK066 2.5mg	LIK066 10mg	LIK066 50mg
Started	7	5	9
Completed	1	0	0
Not completed	6	5	9
Study terminated by sponsor	6	5	9

Number of subjects in period 2[1]	EMPA 25mg	Placebo
Started	9	11
Completed	0	0
Not completed	9	11
Study terminated by sponsor	9	11

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all patients who completed Period 1 went into period 2.

Baseline characteristics

Reporting groups	
Reporting group title	LIK066 2.5mg
Reporting group description: LIK066 2.5mg once daily	
Reporting group title	LIK066 10mg
Reporting group description: LIk066 10mg once daily	
Reporting group title	LIK066 50mg
Reporting group description: LIK066 50mg once daily	
Reporting group title	EMPA 25mg
Reporting group description: Empagliflozin 25 mg once daily	
Reporting group title	Placebo
Reporting group description: LIK066 matching placebo and empagliflozin matching placebo	

Reporting group values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg
Number of subjects	15	16	30
Age categorical Units: Subjects			
Adults (18-64 years)	5	2	13
From 65-84 years	10	14	16
85 years and over	0	0	1
Age Continuous Units: Years			
arithmetic mean	68.2	69.8	65.8
standard deviation	± 7.10	± 9.69	± 9.08
Sex: Female, Male Units: Subjects			
Female	1	4	6
Male	14	12	24
Race/Ethnicity, Customized Units: Subjects			
Caucasian	14	14	28
Black	0	0	0
Asian	1	2	2
Other	0	0	0

Reporting group values	EMPA 25mg	Placebo	Total
Number of subjects	30	33	124
Age categorical Units: Subjects			
Adults (18-64 years)	10	10	40
From 65-84 years	20	21	81
85 years and over	0	2	3

Age Continuous Units: Years			
arithmetic mean	68.6	67.8	
standard deviation	± 7.89	± 10.93	-
Sex: Female, Male Units: Subjects			
Female	10	14	35
Male	20	19	89
Race/Ethnicity, Customized Units: Subjects			
Caucasian	28	29	113
Black	0	1	1
Asian	1	3	9
Other	1	0	1

End points

End points reporting groups

Reporting group title	LIK066 2.5mg
Reporting group description: LIK066 2.5mg once daily	
Reporting group title	LIK066 10mg
Reporting group description: LIk066 10mg once daily	
Reporting group title	LIK066 50mg
Reporting group description: LIK066 50mg once daily	
Reporting group title	EMPA 25mg
Reporting group description: Empagliflozin 25 mg once daily	
Reporting group title	Placebo
Reporting group description: LIK066 matching placebo and empagliflozin matching placebo	
Reporting group title	LIK066 2.5mg
Reporting group description: LIK066 2.5mg once daily	
Reporting group title	LIK066 10mg
Reporting group description: LIk066 10mg once daily	
Reporting group title	LIK066 50mg
Reporting group description: LIK066 50mg once daily	
Reporting group title	EMPA 25mg
Reporting group description: Empagliflozin 25 mg once daily	
Reporting group title	Placebo
Reporting group description: LIK066 matching placebo and empagliflozin matching placebo	

Primary: Change from Baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP) at Week 12

End point title	Change from Baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP) at Week 12[1][2]
End point description: Evaluation of NT-proBNP was performed by a central laboratory. For Change from baseline, Geometric mean is the geometric mean of the endpoint to baseline ratio. Pre-planned statistical analysis was not performed for this primary endpoint due to early study termination. Only descriptive statistics are presented.	
End point type	Primary
End point timeframe: Baseline, Week 12	

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: Statistical analysis was not done for this arm.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was not done for this arm.

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	33
Units: ratio				
geometric mean (confidence interval 95%)				
Change from BL at Week 12(n=9, 8,12,16)	0.8 (0.5 to 1.2)	0.6 (0.2 to 1.7)	0.8 (0.7 to 1.1)	1.1 (0.8 to 1.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in glycated hemoglobin (HbA1c) at Weeks 12 and 36

End point title	Change from Baseline in glycated hemoglobin (HbA1c) at Weeks 12 and 36

End point description:

HbA1c was measured from a blood sample and analyzed using a National Glycohemoglobin Standardization Program (NGSP) certified method at a central laboratory. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	30
Units: Percentage (%)				
arithmetic mean (standard deviation)				
Baseline(n=15,16,30,30,33)	8.26 (± 0.684)	7.51 (± 0.642)	7.82 (± 0.795)	7.92 (± 0.863)
Change from BL at Week 12(n=9,8,12,14,18)	-0.29 (± 0.836)	-0.01 (± 0.508)	-0.58 (± 0.335)	-0.44 (± 1.176)
Change from BL at Week 36(n=3,0,1,0,3)	0.13 (± 0.961)	0.00 (± 0.00)	-0.60 (± 999)	0.00 (± 0.00)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage (%)				
arithmetic mean (standard deviation)				

Baseline(n=15,16,30,30,33)	8.12 (± 0.886)			
Change from BL at Week 12(n=9,8,12,14,18)	-0.04 (± 0.913)			
Change from BL at Week 36(n=3,0,1,0,3)	-1.83 (± 0.321)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG) at Weeks 12 and 36

End point title	Change from Baseline in Fasting Plasma Glucose (FPG) at Weeks 12 and 36

End point description:

FPG was measured from a blood sample after an overnight fast; patients were not allowed to eat or drink anything (except water) for at least 8 h before each study visit. Samples were analyzed at a central laboratory. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	30
Units: millimoles per litre (mmol/L)				
arithmetic mean (standard deviation)				
Baseline(n=15,14,29,28,30)	10.076 (± 3.1466)	9.581 (± 3.2087)	9.105 (± 2.8418)	9.231 (± 3.0525)
Change from BL at Week 12(n=8,6,12,13,15)	-1.021 (± 1.0368)	-2.041 (± 4.9772)	-0.426 (± 2.1451)	-1.303 (± 2.4386)
Change from BL at Week 36(n=3,0,1,0,3)	0.392 (± 1.1119)	0.00 (± 0.00)	-1.200 (± 999)	0.00 (± 0.00)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: millimoles per litre (mmol/L)				
arithmetic mean (standard deviation)				
Baseline(n=15,14,29,28,30)	8.921 (± 2.3119)			
Change from BL at Week 12(n=8,6,12,13,15)	-1.187 (± 3.9653)			
Change from BL at Week 36(n=3,0,1,0,3)	-4.733 (± 0.3055)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Weight at Weeks 12 and 36

End point title	Change from Baseline in Body Weight at Weeks 12 and 36

End point description:

Body weight was measured to the nearest 0.1 kg on a calibrated scale (weight and bio-impedance measurements), provided by the sponsor. Exceptionally (e.g. if the body weight exceeded the limits of the provided scale) sites were allowed to use another scale for weight measurement as available, but during the study the same scale was to be used for the same patient. The measurement was performed with the study patient in underwear and without shoes. Indoor clothing was also acceptable, but measurements were to be done consistently (either with underwear or with indoor clothing) throughout the study. Voiding before weight measurement was required. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	30
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Baseline(n=15,16,30,30,33)	100.16 (± 19.331)	92.29 (± 18.010)	96.32 (± 19.746)	93.35 (± 22.906)
Change from BL at Week 12(n=9,8,13,14,18)	-0.78 (± 2.734)	-1.83 (± 1.402)	-2.15 (± 2.397)	-2.25 (± 1.894)
Change from BL at Week 36(n=3,0,1,0,3)	-2.21 (± 1.586)	0.00 (± 0.00)	-3.90 (± 999)	0.00 (± 0.00)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Baseline(n=15,16,30,30,33)	90.30 (± 17.998)			
Change from BL at Week 12(n=9,8,13,14,18)	-0.34 (± 2.115)			
Change from BL at Week 36(n=3,0,1,0,3)	0.47 (± 6.158)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Composition assessed by bio-impedance (Total Body Fat Mass) at Weeks 12 and 36

End point title	Change from Baseline in Body Composition assessed by bio-impedance (Total Body Fat Mass) at Weeks 12 and 36

End point description:

Body composition was measured in all patients using bio-impedance, except in patients where it was contra-indicated, e.g. those using an implantable cardioverter-defibrillator. Body composition parameters were assessed as available for the different models of calibrated bio-impedance scales. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	30
Units: Percentage of body fat mass				
arithmetic mean (standard deviation)				
Baseline (n = 12, 13, 27, 23, 28)	28.40 (± 10.388)	35.55 (± 8.003)	34.79 (± 9.263)	34.36 (± 9.299)
Wk 12 Chge from BL (n=6,7,11,12,15)	-0.77 (± 2.276)	-1.51 (± 5.048)	-0.32 (± 4.675)	1.63 (± 3.639)
Wk 36 Chge from BL (n=2,0,1,0,2)	2.25 (± 1.485)	0.00 (± 0.00)	0.20 (± 999)	0.00 (± 0.00)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of body fat mass				
arithmetic mean (standard deviation)				
Baseline (n = 12, 13, 27, 23, 28)	36.49 (± 9.217)			
Wk 12 Chge from BL (n=6,7,11,12,15)	-1.77 (± 7.812)			
Wk 36 Chge from BL (n=2,0,1,0,2)	6.70 (± 20.082)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Composition assessed by bio-impedance (Visceral Fat Level) at Weeks 12 and 36

End point title	Change from Baseline in Body Composition assessed by bio-impedance (Visceral Fat Level) at Weeks 12 and 36

End point description:

Body composition was measured in all patients using bio-impedance, except in patients where it was contra-indicated, e.g. those using an implantable cardioverter-defibrillator. Body composition parameters were assessed as available for the different models of calibrated bio-impedance scales. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented. Visceral fat levels were measured by Omron device. Levels ranged from 1 - 30 and are relative (not absolute) values.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	30
Units: Level				
arithmetic mean (standard deviation)				
Baseline (n = 13, 13, 27, 23, 26)	18.077 (± 6.1164)	19.077 (± 5.8944)	17.796 (± 6.2553)	16.348 (± 6.4499)
Wk 12 Chge from BL (n=7,7,11,12,15)	-2.429 (± 4.6853)	-2.857 (± 3.8914)	-0.436 (± 4.6877)	-0.417 (± 1.3114)
Wk 36 Chge from BL (n=2,0,1,0,2)	0.000 (± 1.4142)	999 (± 999)	0.000 (± 999)	999 (± 999)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Level				
arithmetic mean (standard deviation)				
Baseline (n = 13, 13, 27, 23, 26)	15.538 (± 4.5540)			
Wk 12 Chge from BL (n=7,7,11,12,15)	-3.200 (± 4.7988)			
Wk 36 Chge from BL (n=2,0,1,0,2)	3.500 (± 7.7782)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Composition assessed by bio-impedance (Lean Body Mass) at Weeks 12 and 36

End point title	Change from Baseline in Body Composition assessed by bio-impedance (Lean Body Mass) at Weeks 12 and 36

End point description:

Body composition was measured in all patients using bio-impedance, except in patients where it was contra-indicated, e.g. those using an implantable cardioverter-defibrillator. Body composition parameters were assessed as available for the different models of calibrated bio-impedance scales. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	30
Units: Percentage of body fat mass				
arithmetic mean (standard deviation)				
Baseline (n = 12, 12, 26, 23, 25)	33.03 (± 4.682)	38.39 (± 20.028)	28.28 (± 4.221)	40.83 (± 62.377)
Wk 12 Chge from BL (n=6,6,10,12,14)	-2.32 (± 7.063)	-2.32 (± 5.774)	-0.24 (± 2.022)	-0.68 (± 2.454)
Wk 36 Chge from BL (n=2,0,1,0,2)	-0.85 (± 1.344)	999 (± 999)	-0.30 (± 999)	999 (± 999)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of body fat mass				
arithmetic mean (standard deviation)				
Baseline (n = 12, 12, 26, 23, 25)	30.94 (± 12.419)			
Wk 12 Chge from BL (n=6,6,10,12,14)	1.64 (± 4.584)			
Wk 36 Chge from BL (n=2,0,1,0,2)	-5.35 (± 13.223)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Composition assessed by DXA (Total Body Fat Mass) at Weeks 12 and 36

End point title	Change from Baseline in Body Composition assessed by DXA (Total Body Fat Mass) at Weeks 12 and 36

End point description:

A whole body DXA scan was performed to assess Total Body Fat Mass (Whole Body Minus Head Hologic, Whole Body Minus Head Lunar). DXA data were transferred to a central reading vendor for independent review and analysis. Only descriptive statistics done.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0[3]	4	4
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
BL Whole Body Minus Head Hologic(n=1,0,0,1,1)	35.970 (± 999)	()	0.00 (± 0.00)	18.870 (± 999)
Wk 12 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	-0.310 (± 999)	()	0.00 (± 0.00)	0.00 (± 0.00)
Wk 36 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	-3.800 (± 999)	()	0.00 (± 0.00)	0.00 (± 0.00)
BL Whole Body Minus Head Lunar(n=0,0,3,2,0)	0.00 (± 0.00)	()	29.350 (± 4.9403)	37.455 (± 6.0175)
Wk 12 Whole Body - Hd Lunar Chge BL(n=0,0,1,1,0)	0.00 (± 0.00)	()	-1.260 (± 999)	1.190 (± 999)
Wk 36 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	0.00 (± 0.00)	()	0.00 (± 0.00)	0.00 (± 0.00)

Notes:

[3] - Subject discontinued before time point

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
BL Whole Body Minus Head Hologic(n=1,0,0,1,1)	27.550 (± 999)			
Wk 12 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	-4.280 (± 999)			

Wk 36 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	-5.590 (± 999)			
BL Whole Body Minus Head Lunar(n=0,0,3,2,0)	0.00 (± 0.00)			
Wk 12 Whole Body - Hd Lunar Chge BL(n=0,0,1,1,0)	0.00 (± 0.00)			
Wk 36 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	0.00 (± 0.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Composition assessed by DXA (Visceral Fat Mass) at Weeks 12 and 36

End point title	Change from Baseline in Body Composition assessed by DXA (Visceral Fat Mass) at Weeks 12 and 36

End point description:

A whole body DXA scan was performed to assess Visceral Fat Mass (Whole Body Minus Head Hologic, Whole Body Minus Head Lunar). DXA data were transferred to a central reading vendor for independent review and analysis. Only descriptive statistics done.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0[4]	4	4
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
BL Whole Body Minus Head Hologic(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)
Wk 12 Whole Body - Hd Hologic Chge BL(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)
Wk 36 Whole Body - Hd Hologic Chge BL(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)
BL Whole Body Minus Head Lunar(n=0,0,0,0,0)9	999 (± 999)	()	999 (± 999)	999 (± 999)
Wk 12 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)
Wk 36 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)

Notes:

[4] - Subject discontinued before time point

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: kilogram (kg)				

arithmetic mean (standard deviation)				
BL Whole Body Minus Head Hologic(n=0,0,0,0,0)	999 (± 999)			
Wk 12 Whole Body - Hd Hologic Chge BL(n=0,0,0,0,0)	999 (± 999)			
Wk 36 Whole Body - Hd Hologic Chge BL(n=0,0,0,0,0)	999 (± 999)			
BL Whole Body Minus Head Lunar(n=0,0,0,0,0)9	999 (± 999)			
Wk 12 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)			
Wk 36 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Composition assessed by DXA (Lean Body Mass) at Weeks 12 and 36

End point title	Change from Baseline in Body Composition assessed by DXA (Lean Body Mass) at Weeks 12 and 36

End point description:

A whole body DXA scan was performed to assess Lean Body Mass (Whole Body Minus Head Hologic, Whole Body Minus Head Lunar). DXA data were transferred to a central reading vendor for independent review and analysis. Only descriptive statistics done.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0[5]	4	4
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
BL Whole Body Minus Head Hologic(n=1,0,0,1,1)	29.490 (± 999)	()	999 (± 999)	38.990 (± 999)
Wk 12 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	-1.910 (± 999)	()	999 (± 999)	999 (± 999)
Wk 36 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	0.860 (± 999)	()	999 (± 999)	999 (± 999)
BL Whole Body Minus Head Lunar(n=0,0,3,2,0)	999 (± 999)	()	48.220 (± 13.0748)	59.335 (± 4.1224)
Wk 12 Whole Body - Hd Lunar Chge BL(n=0,0,1,1,0)	999 (± 999)	()	-1.290 (± 999)	-2.960 (± 999)
Wk 36 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)

Notes:

[5] - Subject discontinued before time point

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
BL Whole Body Minus Head Hologic(n=1,0,0,1,1)	58.400 (± 999)			
Wk 12 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	4.980 (± 999)			
Wk 36 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	1.700 (± 999)			
BL Whole Body Minus Head Lunar(n=0,0,3,2,0)	999 (± 999)			
Wk 12 Whole Body - Hd Lunar Chge BL(n=0,0,1,1,0)	999 (± 999)			
Wk 36 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Composition assessed by DXA (Total Body Water) at Weeks 12 and 36

End point title	Change from Baseline in Body Composition assessed by DXA (Total Body Water) at Weeks 12 and 36

End point description:

A whole body DXA scan was performed to assess Total Body Water (Whole Body Minus Head Hologic, Whole Body Minus Head Lunar). DXA data were transferred to a central reading vendor for independent review and analysis. Only descriptive statistics done.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0[6]	4	4
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
BL Whole Body Minus Head Hologic(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)
Wk 12 Whole Body - Hd Hologic Chge BL(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)
Wk 36 Whole Body - Hd Hologic Chge BL(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)
BL Whole Body Minus Head Lunar(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)
Wk 12 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)
Wk 36 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 999)

Notes:

[6] - Subject discontinued before time point

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
BL Whole Body Minus Head Hologic(n=0,0,0,0,0)	999 (± 999)			
Wk 12 Whole Body - Hd Hologic Chge BL(n=0,0,0,0,0)	999 (± 999)			
Wk 36 Whole Body - Hd Hologic Chge BL(n=0,0,0,0,0)	999 (± 999)			
BL Whole Body Minus Head Lunar(n=0,0,0,0,0)	999 (± 999)			
Wk 12 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)			
Wk 36 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in sitting Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at Weeks 12 and 36

End point title	Change from Baseline in sitting Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at Weeks 12 and 36

End point description:

Three sitting BP measurements were performed. At each visit, sitting BP was derived as the mean of three readings of the sitting SBP/DBP at that visit. Pre-planned statistical analyses were not performed for these secondary endpoints due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	30
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline SBP(n=15,16,30,30,33)	132.20 (± 7.992)	133.94 (± 15.575)	129.17 (± 12.811)	130.64 (± 14.918)
SBP Change from BL at Week 12(n=9,8,13,14,18)	5.15 (± 13.485)	0.17 (± 15.373)	-9.54 (± 16.884)	-6.98 (± 15.031)
SBP Change from BL at Week 36(n=3,0,1,0,3)	13.78 (± 17.900)	999 (± 999)	-4.00 (± 999)	999 (± 999)

Baseline DBP(n=15,16,30,30,33)	78.67 (± 9.665)	77.56 (± 8.961)	75.70 (± 9.520)	76.47 (± 7.853)
DBP Change from BL at Week 12(n=9,8,13,14,18)	-2.00 (± 6.582)	4.50 (± 12.746)	-4.46 (± 11.238)	-1.81 (± 10.421)
DBP Change from BL at Week 36(n=3,0,1,0,3)	1.12 (± 3.975)	999 (± 999)	3.66 (± 999)	999 (± 999)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline SBP(n=15,16,30,30,33)	128.10 (± 12.467)			
SBP Change from BL at Week 12(n=9,8,13,14,18)	-2.85 (± 11.967)			
SBP Change from BL at Week 36(n=3,0,1,0,3)	0.00 (± 8.627)			
Baseline DBP(n=15,16,30,30,33)	72.73 (± 10.603)			
DBP Change from BL at Week 12(n=9,8,13,14,18)	-2.00 (± 8.596)			
DBP Change from BL at Week 36(n=3,0,1,0,3)	-0.44 (± 8.517)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Lipid Profile (Triglycerides (TG)) at Weeks 12 and 36

End point title	Change from Baseline in Fasting Lipid Profile (Triglycerides (TG)) at Weeks 12 and 36

End point description:

TG was measured on blood samples obtained after an overnight fast and analyzed at a central laboratory. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	30
Units: percent change				
arithmetic mean (standard deviation)				

% Change from BL at Week 12(n=9,6,12,13,15)	-1.623 (± 35.2838)	19.089 (± 31.4798)	9.878 (± 30.3065)	8.865 (± 35.0872)
% Change from BL at Week 36(n=3,0,1,0,3)	4.324 (± 31.4438)	999 (± 999)	14.286 (± 999)	999 (± 999)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percent change				
arithmetic mean (standard deviation)				
% Change from BL at Week 12(n=9,6,12,13,15)	-2.979 (± 25.1049)			
% Change from BL at Week 36(n=3,0,1,0,3)	-1.111 (± 18.3586)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Lipid Profile (Lipoproteins) at Weeks 12 and 36

End point title	Change from Baseline in Fasting Lipid Profile (Lipoproteins) at Weeks 12 and 36

End point description:

Lipoproteins (High Density Lipoprotein (HDL) Cholesterol, Low Density Lipoprotein (LDL) Cholesterol) were measured on blood samples obtained after an overnight fast and analyzed at a central laboratory. Pre-planned statistical analysis were not performed for these secondary endpoints due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	30
Units: percent change				
arithmetic mean (standard deviation)				
HDL % Change from BL at Week 12(n=9,8,7,12,12)	9.33 (± 16.735)	-10.54 (± 20.590)	0.26 (± 9.772)	2.18 (± 12.179)
HDL % Change from BL at Week 36(n=3,0,1,0,2)	10.70 (± 16.257)	999 (± 999)	0.00 (± 999)	999 (± 999)
LDL % Change from BL at Week 12(n=9,8,7,12,12)	22.02 (± 35.466)	2.62 (± 17.525)	16.40 (± 36.928)	22.24 (± 35.145)
LDL % Change from BL at Week 36(n=3,0,1,0,2)	22.73 (± 31.690)	999 (± 999)	-3.57 (± 999)	999 (± 999)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percent change				
arithmetic mean (standard deviation)				
HDL % Change from BL at Week 12(n=9,8,7,12,12)	-0.67 (± 13.322)			
HDL % Change from BL at Week 36(n=3,0,1,0,2)	35.00 (± 49.497)			
LDL % Change from BL at Week 12(n=9,8,7,12,12)	-1.59 (± 31.970)			
LDL % Change from BL at Week 36(n=3,0,1,0,2)	0.22 (± 13.163)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Fasting Lipid Profile (Total Cholesterol) at Weeks 12 and 36

End point title	Change from Baseline in Fasting Lipid Profile (Total Cholesterol) at Weeks 12 and 36

End point description:

Total Cholesterol was measured on blood samples obtained after an overnight fast and analyzed at a central laboratory. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	30
Units: percent change				
arithmetic mean (standard deviation)				
% Change from BL at Week 12(n=9,8,7,12,12)	9.69 (± 23.892)	-2.66 (± 13.202)	6.32 (± 22.667)	10.83 (± 11.330)
% Change from BL at Week 36(n=3,0,1,0,2)	14.72 (± 13.147)	999 (± 999)	2.04 (± 999)	999 (± 999)

End point values	Placebo			

Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percent change				
arithmetic mean (standard deviation)				
% Change from BL at Week 12(n=9,8,7,12,12)	1.46 (± 16.741)			
% Change from BL at Week 36(n=3,0,1,0,2)	10.27 (± 28.326)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in High sensitive C-reactive protein (hsCRP) at Weeks 12 and 36

End point title	Change from Baseline in High sensitive C-reactive protein (hsCRP) at Weeks 12 and 36

End point description:

hs-CRP is an inflammation biomarker. For Change from baseline, Geometric mean is the geometric mean of the endpoint to baseline ratio. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	30
Units: milligram per litre (mg/L)				
geometric mean (confidence interval 95%)				
Baseline(n=9,13,20,24,22)	4.477 (1.114 to 18.001)	2.970 (1.617 to 5.453)	2.531 (1.424 to 4.500)	3.932 (2.582 to 5.988)
Change from BL at Week 12(n=7,7,7,11,10)	0.543 (0.086 to 3.446)	0.722 (0.157 to 3.321)	1.997 (0.758 to 5.263)	0.714 (0.353 to 1.443)
Change from BL at Week 36(n=3,0,1,0,3)	0.953 (0.221 to 4.112)	0.00 (0.00 to 0.00)	0.620 (0 to 999)	0.00 (0.00 to 0.00)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: milligram per litre (mg/L)				
geometric mean (confidence interval 95%)				
Baseline(n=9,13,20,24,22)	3.373 (1.773 to 6.417)			

Change from BL at Week 12(n=7,7,7,11,10)	1.018 (0.661 to 1.566)			
Change from BL at Week 36(n=3,0,1,0,3)	0.578 (0.172 to 1.945)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 24 hour Urinary Glucose Excretion (UGE) at Weeks 12 and 36

End point title	Change from Baseline in 24 hour Urinary Glucose Excretion (UGE) at Weeks 12 and 36

End point description:

UGE was measured from a 24h urine collection from about 25% of randomized patients and analyzed at a central laboratory. Only descriptive analysis done.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	11	7	12
Units: millimoles per 24 hours (mmol/24h)				
arithmetic mean (standard deviation)				
Baseline(n=2,6,3,9,11)	102.325 (± 135.1635)	27.343 (± 36.4044)	3.590 (± 3.8192)	2.510 (± 3.6456)
Change from BL at Week 12(n=2,2,1,2,5)	256.245 (± 129.0682)	346.360 (± 107.3671)	305.110 (± 999)	254.270 (± 198.8243)
Change from BL at Week 36 (n=0,0,0,0,0)	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: millimoles per 24 hours (mmol/24h)				
arithmetic mean (standard deviation)				
Baseline(n=2,6,3,9,11)	91.535 (± 201.7728)			
Change from BL at Week 12(n=2,2,1,2,5)	84.778 (± 222.6565)			
Change from BL at Week 36 (n=0,0,0,0,0)	999 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 24 hour Sodium Excretion at Weeks 12 and 36

End point title	Change from Baseline in 24 hour Sodium Excretion at Weeks 12 and 36

End point description:

Sodium excretion was measured from a 24h urine collection from about 25% of randomized patients and analyzed at a central laboratory. Only descriptive statistics were done.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	11	7	12
Units: millimoles per 24 hours (mmol/24h)				
arithmetic mean (standard deviation)				
Baseline(n=2,7,6,9,13)	160.3 (± 148.14)	209.9 (± 99.86)	167.4 (± 71.62)	186.4 (± 98.03)
Change from BL at Week 12(n=2,2,2,2,7)	-38.5 (± 86.69)	45.6 (± 40.52)	-42.6 (± 28.50)	82.3 (± 98.29)
Change from BL at Week 36 (n=0,0,0,0,0)	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: millimoles per 24 hours (mmol/24h)				
arithmetic mean (standard deviation)				
Baseline(n=2,7,6,9,13)	195.4 (± 125.07)			
Change from BL at Week 12(n=2,2,2,2,7)	-43.9 (± 112.48)			
Change from BL at Week 36 (n=0,0,0,0,0)	999 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Left Atrial Size at Weeks 12 and 36

End point title	Change from Baseline in Left Atrial Size at Weeks 12 and 36[7]

End point description:

A limited two-dimensional and Doppler ECHO examination was performed to assess ECHO parameters. The images were sent to a central reading vendor for independent review and analysis. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was not done for this arm.

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	33
Units: milliliter per square meter (mL/m^2)				
arithmetic mean (standard deviation)				
Baseline (n = 13,16, 28, 30)	46.608 (± 17.6085)	57.088 (± 22.1322)	41.446 (± 13.6345)	42.783 (± 16.3363)
Change from BL at Week 12 (n = 3, 4, 7, 11)	-1.167 (± 14.8123)	0.075 (± 6.7884)	2.700 (± 7.2155)	-1.045 (± 11.0223)
Change from BL at Week 36 (n=3,0,1,3)	16.333 (± 20.9194)	999 (± 999)	0.300 (± 999)	5.100 (± 6.2960)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Left Atrial Volume at Weeks 12 and 36

End point title	Change from baseline in Left Atrial Volume at Weeks 12 and

End point description:

A limited two-dimensional and Doppler ECHO examination was performed to assess ECHO parameters. The images were sent to a central reading vendor for independent review and analysis.Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was not done for this arm.

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	33
Units: milliliter (mL)				
arithmetic mean (standard deviation)				
Baseline (n=14,16,29,30)	91.457 (± 37.8730)	115.869 (± 45.1660)	86.083 (± 30.3583)	86.120 (± 33.9823)
Change from BL at Week 12 (n=5,4,8,11)	12.360 (± 42.7067)	0.225 (± 15.4157)	7.725 (± 16.9351)	-3.591 (± 22.8382)
Change from BL at Week 36(n=3,0,1,3)	34.800 (± 51.0409)	999 (± 999)	-0.900 (± 999)	11.333 (± 12.7892)

Statistical analyses

No statistical analyses for this end point

Secondary: Nunmber of subjects with New York Heart Association (NYHA) class I, II, II or IV

End point title	Nunmber of subjects with New York Heart Association (NYHA) class I, II, II or IV[9]

End point description:

The NYHA Functional Classification classifies patients' heart failure according to the severity of their symptoms. The classification is as follows: Class I: no limitation of physical activity, ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath); Class II: slight limitation to physical activity, comfortable at rest, ordinary physical activity results in fatigue, palpitation or dyspnea; Class III: marked limitation of physical activity, comfortable at rest, less than ordinary activity causes fatigue, palpitation or dyspnea; Class IV: unable to carry on any physical activity without discomfort, symptoms of heart failure at rest, if any physical activity is undertaken, discomfort increases. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was not done for this arm.

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	33
Units: Subjects				
Baseline (n=15,16,30,33)|Class I	0	0	0	0
Week 12 (n=9,8,13,18)|Class I	13	14	26	25
Week 36 (n=3,0,1,3)|Class I	2	2	3	8
Baseline (n=15,16,30,33)|Class II	0	0	1	0
Week 12 (n=9,8,13,18)|Class II	1	1	1	1
Week 36 (n=3,0,1,3)|Class II	6	6	10	13
Baseline (n=15,16,30,33)|Class III	2	1	2	4
Week 12 (n=9,8,13,18)|Class III	0	0	0	0
Week 36 (n=3,0,1,3)|Class III	0	0	0	0
Baseline (n=15,16,30,33)|Class IV	3	0	1	3
Week 12 (n=9,8,13,18)|Class IV	0	0	0	0

Week 36 (n=3,0,1,3)|Class IV	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with change from Baseline in New York Heart Association (NYHA) Class at Week 12 and 36

End point title	Number of subjects with change from Baseline in New York Heart Association (NYHA) Class at Week 12 and 36[10]

End point description:

The change from BL in NYHA class at a given visit is a three-category ordinal variable (improved/unchanged/worsened) with the following definition: 1. Improved, if NYHA class decreases at least one level from BL; 2. Unchanged, if NYHA class is unchanged from BL; 3. Worsened, if NYHA class increases at least one level from BL. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are presented.

End point type	Secondary

End point timeframe:

Week 12, Week 36

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was not done for this arm.

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	33
Units: Subjects				
Week 12 (n=9,8,13,18)|Improved	1	1	1	4
Week 36 (n=3,0,1,3)|Improved	8	7	12	13
Week 12 (n=9,8,13,18)|Unchanged	0	0	0	1
Week 36 (n=3,0,1,3)|Unchanged	0	0	0	0
Week 12 (n=9,8,13,18)|Worsened	3	0	1	3
Week 36 (n=3,0,1,3)|Worsened	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP) at Week 36

End point title	Change from Baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP) at Week 36[11]

End point description:

Evaluation of NT-proBNP was performed by a central laboratory. For Change from baseline, Geometric mean is the geometric mean of the endpoint to baseline ratio. Pre-planned statistical analysis was not performed for this secondary endpoint due to early study termination. Only descriptive statistics are

presented.

End point type	Secondary

End point timeframe:

Baseline, Week 36

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis was not done for this arm.

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	30	33
Units: ratio				
geometric mean (confidence interval 95%)				
Change from BL at Week 36(n=3,0,1,3)	0.7 (0.4 to 1.4)	0.00 (0.00 to 0.00)	1.3 (0 to 999)	1.0 (0.5 to 1.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 24 hour urinary calcium excretion at Weeks 12 and 36

End point title	Change from Baseline in 24 hour urinary calcium excretion at Weeks 12 and 36

End point description:

Urinary calcium excretion was measured from a 24h urine collection from about 25% of randomized patients and analyzed at a central laboratory. Only descriptive analysis done.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	11	7	12
Units: millimoles per day (mmol/d)				
arithmetic mean (standard deviation)				
Baseline(n=1,5,5,7,9)	1.60 (± 999)	3.54 (± 1.540)	2.04 (± 1.146)	3.36 (± 1.896)
Change from BL at Week 12(n=1,1,2,1,5)	1.40 (± 999)	3.80 (± 999)	0.10 (± 0.566)	0.60 (± 999)
Change from BL at Week 36(n=0,0,0,0,0)	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: millimoles per day (mmol/d)				
arithmetic mean (standard deviation)				
Baseline(n=1,5,5,7,9)	6.07 (± 5.427)			
Change from BL at Week 12(n=1,1,2,1,5)	-0.49 (± 3.202)			
Change from BL at Week 36(n=0,0,0,0,0)	999 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: 24 hour urinary phosphate excretion at Weeks 12 and 36

End point title	24 hour urinary phosphate excretion at Weeks 12 and 36

End point description:

Urinary phosphate excretion was measured from a 24h urine collection from about 25% of randomized patients and analyzed at a central laboratory. Only descriptive statistics were done.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	11	7	12
Units: millimoles per day (mmol/d)				
arithmetic mean (standard deviation)				
Baseline(n=2,5,6,7,12)	184.95 (± 69.650)	263.24 (± 33.864)	184.32 (± 116.065)	155.27 (± 45.636)
Change from BL at Week 12(n=2,2,2,1,6)	55.35 (± 25.809)	19.25 (± 55.225)	-125.95 (± 105.571)	5.30 (± 999)
Change from BL at Week 36(n=0,0,0,0,0)	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: millimoles per day (mmol/d)				
arithmetic mean (standard deviation)				
Baseline(n=2,5,6,7,12)	215.20 (± 102.259)			
Change from BL at Week 12(n=2,2,2,1,6)	26.07 (± 142.536)			

Change from BL at Week 36(n=0,0,0,0,0)	999 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bone Mineral Density (BMD) at Weeks 12 and 36

End point title	Change from Baseline in Bone Mineral Density (BMD) at Weeks 12 and 36

End point description:

To evaluate bone mineral density as assessed by bone mineral content after 12 weeks and after 36 weeks of treatment. Only descriptive statistics were done.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 36

End point values	LIK066 2.5mg	LIK066 10mg	LIK066 50mg	EMPA 25mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0[12]	4	4
Units: grams (g)				
arithmetic mean (standard deviation)				
BL Whole Body Minus Head Hologic(n=1,0,0,1,1)	1633.710 (± 999)	()	999 (± 999)	1991.270 (± 999)
Wk 12 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	-13.250 (± 999)	()	999 (± 999)	999 (± 999)
Wk 36 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	-58.220 (± 999)	()	999 (± 999)	999 (± 999)
BL Whole Body Minus Head, Lunar N=0,0,3,2,0)	999 (± 999)	()	2167.063 (± 550.9181)	2723.345 (± 74.6493)
Wk 12 Whole Body - Hd Lunar Chge BL(n=0,0,1,1,0)	999 (± 999)	()	-78.750 (± 999)	37.350 (± 999)
Wk 36 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)	()	999 (± 999)	999 (± 9999)

Notes:

[12] - Subject discontinued before time point

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: grams (g)				
arithmetic mean (standard deviation)				
BL Whole Body Minus Head Hologic(n=1,0,0,1,1)	2435.000 (± 999)			
Wk 12 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	-3.340 (± 999)			

Wk 36 Whole Body - Hd Hologic Chge BL(n=1,0,0,0,1)	64.620 (± 999)			
BL Whole Body Minus Head, Lunar N=0,0,3,2,0)	999 (± 9999)			
Wk 12 Whole Body - Hd Lunar Chge BL(n=0,0,1,1,0)	999 (± 999)			
Wk 36 Whole Body - Hd Lunar Chge BL(n=0,0,0,0,0)	999 (± 999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent AEs are represented for the double-blind period (i.e., starting from randomization to the end of the double-blind period). Total duration of the double-blind period was planned to be approximately 36 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	LIK066 2.5mg
Reporting group description:	
LIK066 2.5mg	
Reporting group title	LIK066 10mg
Reporting group description:	
LIK066 10mg	
Reporting group title	LIK066 50mg
Reporting group description:	
LIK066 50mg	
Reporting group title	EMPA 25mg
Reporting group description:	
EMPA 25mg	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	LIK066 2.5mg	LIK066 10mg	LIK066 50mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	2 / 16 (12.50%)	3 / 30 (10.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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
Wound dehiscence			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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

Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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
Atrial fibrillation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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
Cardiac failure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (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 failure chronic			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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
Coronary artery disease			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	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
Nervous system disorders			
Cerebral vascular occlusion			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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
General disorders and administration site conditions			
Cardiac death			

subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	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 / 1	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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
Infections and infestations			
Diarrhoea infectious			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (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
Gastroenteritis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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
Wound infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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

Serious adverse events	EMPA 25mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 30 (16.67%)	3 / 33 (9.09%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Hip fracture			

subjects affected / exposed	1 / 30 (3.33%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 30 (3.33%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 30 (3.33%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 30 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 30 (3.33%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebral vascular occlusion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cardiac death			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 33 (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			
Respiratory failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Diarrhoea infectious			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (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	LIK066 2.5mg	LIK066 10mg	LIK066 50mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 15 (46.67%)	6 / 16 (37.50%)	8 / 30 (26.67%)
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 15 (13.33%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	3	0	2
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Thirst			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Cough			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			

Anxiety			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Investigations			
Heart rate irregular			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Liver function test increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysaesthesia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	4
Enteritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Vomiting			

subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Breast abscess			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Genital infection fungal			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	2 / 15 (13.33%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Fluid retention			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0

Hypoglycaemia			
subjects affected / exposed	1 / 15 (6.67%)	2 / 16 (12.50%)	2 / 30 (6.67%)
occurrences (all)	15	7	2
Hypokalaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	EMPA 25mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 30 (40.00%)	9 / 33 (27.27%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 30 (10.00%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 30 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Thirst			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 30 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 30 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Epistaxis			

subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Investigations			
Heart rate irregular			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Liver function test increased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 30 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Nervous system disorders			
Dysaesthesia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 30 (3.33%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	2 / 30 (6.67%)	1 / 33 (3.03%)	
occurrences (all)	2	2	
Enteritis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Flatulence			

subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Breast abscess			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Bronchitis			
subjects affected / exposed	1 / 30 (3.33%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Genital infection fungal			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	1 / 30 (3.33%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Fluid retention			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	

Hyperglycaemia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Hypoglycaemia			
subjects affected / exposed	3 / 30 (10.00%)	2 / 33 (6.06%)	
occurrences (all)	7	5	
Hypokalaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2017	Amendment 1 introduced the following changes: - The protocol was amended to add a newly identified risk (lower limb amputation) observed with the SGLT-2 inhibitor canagliflozin, and preventive measures were provided. - The inclusion criterion for NT-proBNP was lowered from >400 to >300 pg/mL. When designing the study protocol, a NT-proBNP value of >400 pg/mL was selected to make a patient eligible for the study. This was based on the experience and results from the PARAMOUNT study, which included patients with chronic HF and preserved left ventricular ejection fraction (LVEF). Based on more recent guidelines defining patients with preserved LVEF by NT-proBNP >125 pg/mL, the NT-proBNP value to qualify patients for this study was changed to >300 pg/mL, as this cut-off has a robust predictive value to identify chronic HF patients with preserved LVEF. - In addition, the inclusion criterion for serum potassium was changed from ≤ 5.2 mM to ≤ 5.3 mM to be in line with the reference range used by the Central laboratory in this study. - The HbA1c inclusion criterion was modified from 7.0% - 10.0% to 6.5% - 10.0% to allow for exploration of LIK066 effects in the group of patients with HbA1c 6.5% - 7.0%.
04 February 2018	Amendment 2 introduced the following changes: - The protocol was amended to provide the option for patients to be pre-screened for certain laboratory parameters (NT-proBNP, HbA1c, eGFR, serum potassium) assessed by the central laboratory before patients entered the study at screening (Visit 1). This measure was expected to significantly decrease the number of screen failure patients which reduces the burden on many patients, who otherwise had to undergo the full range of screening assessments but did not qualify for the study. - Other changes included adjustments and/or clarifications for several technical and logistical procedures, such as for body weight, bio-impedance and echocardiography assessments.

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.

Due to early discontinuation of the study, the analysis of efficacy was done on the available data (mostly for Epoch 3 (double-blind period 1) only). Because of the small sample sizes the interpretation of the results remained limited.

Notes: