



## 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          | v1          |
| This version publication date  | 15 May 2019 |
| First version publication date | 15 May 2019 |

### 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?                     | No           |

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:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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 |
|------------------------------|-----|

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | 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

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | 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

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | 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:<br>LIK066 50mg qd at bedtime   |                    |
| <b>Arm title</b>  | EMPA 25mg          |
| Arm description:<br>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:<br>Empagliflozin (up-titrated from 10mg qd to 25mg qd after 2 weeks); in the morning |                    |
| <b>Arm title</b>  | Placebo            |
| Arm description:<br>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:<br>Placebo LIK066 at bedtime/Placebo Empagliflozin in the morning                    |                    |

| <b>Number of subjects in period 1</b> | 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             | -            | -           | -           |

| <b>Number of subjects in period 1</b> | 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          |
| <b>Arm title</b>             | 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

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | 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

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | 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   |                            |
| <b>Arm title</b>  | 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 |                            |
| <b>Arm title</b>  | 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                    |                            |

| <b>Number of subjects in period 2<sup>[1]</sup></b> | 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           |

| <b>Number of subjects in period 2<sup>[1]</sup></b> | EMPA 25mg | Placebo |
|---|-----------|---------|
| Started   | 9         | 11      |
| Completed   | 0         | 0       |
| Not completed                                       | 9         | 11      |
| Study terminated by sponsor                         | 9         | 11      |

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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<br>Units: Years<br>arithmetic mean<br>standard deviation | 68.6<br>± 7.89 | 67.8<br>± 10.93 | -   |
| Sex: Female, Male<br>Units: Subjects                                    |                |                 |     |
| Female  | 10             | 14              | 35  |
| Male  | 20             | 19              | 89  |
| Race/Ethnicity, Customized<br>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:<br>LIK066 2.5mg once daily                                    |              |
| Reporting group title  | LIK066 10mg  |
| Reporting group description:<br>LIK066 10mg once daily                                     |              |
| Reporting group title  | LIK066 50mg  |
| Reporting group description:<br>LIK066 50mg once daily                                     |              |
| Reporting group title  | EMPA 25mg    |
| Reporting group description:<br>Empagliflozin 25 mg once daily                             |              |
| Reporting group title  | Placebo      |
| Reporting group description:<br>LIK066 matching placebo and empagliflozin matching placebo |              |
| Reporting group title  | LIK066 2.5mg |
| Reporting group description:<br>LIK066 2.5mg once daily                                    |              |
| Reporting group title  | LIK066 10mg  |
| Reporting group description:<br>LIK066 10mg once daily                                     |              |
| Reporting group title  | LIK066 50mg  |
| Reporting group description:<br>LIK066 50mg once daily                                     |              |
| Reporting group title  | EMPA 25mg    |
| Reporting group description:<br>Empagliflozin 25 mg once daily                             |              |
| Reporting group title  | Placebo      |
| Reporting group description:<br>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 <sup>[1][2]</sup> |
| End point description:<br>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:<br>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: No statistical analysis was planned for this endpoint.

[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: The objective was to evaluate the effect of all LIK066 doses only (not EMPA) vs placebo

| 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: pg/mL                             |                          |                          |                        |                         |
| geometric mean (confidence interval 95%) |                          |                          |                        |                         |
| Baseline(n=15,16,30,33)                  | 1189.3 (774.5 to 1826.4) | 1023.5 (688.5 to 1521.5) | 672.1 (542.8 to 832.0) | 993.7 (702.6 to 1405.5) |
| 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 ( $\pm$ 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 ( $\pm$ 19.331) | 92.29 ( $\pm$ 18.010) | 96.32 ( $\pm$ 19.746) | 93.35 ( $\pm$ 22.906) |
| Change from BL at Week 12(n=9,8,13,14,18) | -0.78 ( $\pm$ 2.734)   | -1.83 ( $\pm$ 1.402)  | -2.15 ( $\pm$ 2.397)  | -2.25 ( $\pm$ 1.894)  |
| Change from BL at Week 36(n=3,0,1,0,3)    | -2.21 ( $\pm$ 1.586)   | 0.00 ( $\pm$ 0.00)    | -3.90 ( $\pm$ 999)    | 0.00 ( $\pm$ 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 ( $\pm$ 17.998) |  |  |  |
| Change from BL at Week 12(n=9,8,13,14,18) | -0.34 ( $\pm$ 2.115)  |  |  |  |
| Change from BL at Week 36(n=3,0,1,0,3)    | 0.47 ( $\pm$ 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 (%)                |                  |                 |                 |                 |
| 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 (%)                |                 |  |  |  |
| 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

|                |           |
|----------------|-----------|
| 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: Unit                          |                        |                        |                        |                        |
| arithmetic mean (standard deviation) |                        |                        |                        |                        |
| Baseline (n = 13, 13, 27, 23, 26)    | 18.077 ( $\pm$ 6.1164) | 19.077 ( $\pm$ 5.8944) | 17.796 ( $\pm$ 6.2553) | 16.348 ( $\pm$ 6.4499) |
| Wk 12 Chge from BL (n=7,7,11,12,15)  | -2.429 ( $\pm$ 4.6853) | -2.857 ( $\pm$ 3.8914) | -0.436 ( $\pm$ 4.6877) | -0.417 ( $\pm$ 1.3114) |
| Wk 36 Chge from BL (n=2,0,1,0,2)     | 0.000 ( $\pm$ 1.4142)  | 999 ( $\pm$ 999)       | 0.000 ( $\pm$ 999)     | 999 ( $\pm$ 999)       |

| End point values                     | Placebo                |  |  |  |
|--------------------------------------|------------------------|--|--|--|
| Subject group type                   | Reporting group        |  |  |  |
| Number of subjects analysed          | 33                     |  |  |  |
| Units: Unit                          |                        |  |  |  |
| arithmetic mean (standard deviation) |                        |  |  |  |
| Baseline (n = 13, 13, 27, 23, 26)    | 15.538 ( $\pm$ 4.5540) |  |  |  |
| Wk 12 Chge from BL (n=7,7,11,12,15)  | -3.200 ( $\pm$ 4.7988) |  |  |  |
| Wk 36 Chge from BL (n=2,0,1,0,2)     | 3.500 ( $\pm$ 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 (%)                |                 |                  |                 |                  |
| 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 (%)                |                  |  |  |  |
| 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 <sup>[3]</sup> | 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<br>BL(n=1,0,0,0,1) | -5.590 (± 999) |  |  |  |
| BL Whole Body Minus Head<br>Lunar(n=0,0,3,2,0)        | 0.00 (± 0.00)  |  |  |  |
| Wk 12 Whole Body - Hd Lunar Chge<br>BL(n=0,0,1,1,0)   | 0.00 (± 0.00)  |  |  |  |
| Wk 36 Whole Body - Hd Lunar Chge<br>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 <sup>[4]</sup> | 4               | 4               |
| Units: kilogram (kg)  |                 |                  |                 |                 |
| arithmetic mean (standard deviation)                        |                 |                  |                 |                 |
| BL Whole Body Minus Head<br>Hologic(n=0,0,0,0,0)            | 999 (± 999)     | ()               | 999 (± 999)     | 999 (± 999)     |
| Wk 12 Whole Body - Hd Hologic Chge<br>BL(n=0,0,0,0,0)       | 999 (± 999)     | ()               | 999 (± 999)     | 999 (± 999)     |
| Wk 36 Whole Body - Hd Hologic Chge<br>BL(n=0,0,0,0,0)       | 999 (± 999)     | ()               | 999 (± 999)     | 999 (± 999)     |
| BL Whole Body Minus Head<br>Lunar(n=0,0,0,0,0) <sup>9</sup> | 999 (± 999)     | ()               | 999 (± 999)     | 999 (± 999)     |
| Wk 12 Whole Body - Hd Lunar Chge<br>BL(n=0,0,0,0,0)         | 999 (± 999)     | ()               | 999 (± 999)     | 999 (± 999)     |
| Wk 36 Whole Body - Hd Lunar Chge<br>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 <sup>[5]</sup> | 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 <sup>[6]</sup> | 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: millimoles per litre (mmol/L) |                 |                 |                 |                 |
| arithmetic mean (standard deviation) |                 |                 |                 |                 |

|   |                    |                    |                   |                   |
|---|--------------------|--------------------|-------------------|-------------------|
| Baseline(n=14,14,29,28,30)                  | 2.381 (± 1.2366)   | 1.618 (± 0.7786)   | 2.269 (± 1.0461)  | 1.689 (± 0.6482)  |
| % 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: millimoles per litre (mmol/L)        |                    |  |  |  |
| arithmetic mean (standard deviation)        |                    |  |  |  |
| Baseline(n=14,14,29,28,30)                  | 1.630 (± 0.9569)   |  |  |  |
| % 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: millimoles per litre (mmol/L)           |                  |                   |                 |                 |
| arithmetic mean (standard deviation)           |                  |                   |                 |                 |
| Baseline HDL(n=10,13,21,24,22)                 | 1.07 (± 0.396)   | 1.36 (± 0.576)    | 1.10 (± 0.314)  | 1.09 (± 0.333)  |
| 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)     |
| Baseline LDL(n=10,13,21,24,22)                 | 1.66 (± 0.894)   | 2.44 (± 0.957)    | 1.94 (± 0.681)  | 2.00 (± 0.795)  |



|  |                  |                 |                  |                  |
|--|------------------|-----------------|------------------|------------------|
| 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: millimoles per litre (mmol/L)           |                  |  |  |  |
| arithmetic mean (standard deviation)           |                  |  |  |  |
| Baseline HDL(n=10,13,21,24,22)                 | 1.14 (± 0.350)   |  |  |  |
| 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) |  |  |  |
| Baseline LDL(n=10,13,21,24,22)                 | 1.85 (± 0.515)   |  |  |  |
| 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: millimoles per litre (mmol/L)       |                  |                  |                 |                  |
| arithmetic mean (standard deviation)       |                  |                  |                 |                  |
| Baseline(n=10,13,21,24,22)                 | 3.60 (± 1.172)   | 4.52 (± 1.249)   | 4.00 (± 0.884)  | 3.85 (± 0.973)   |
| % 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: millimoles per litre (mmol/L)       |                  |  |  |  |
| arithmetic mean (standard deviation)       |                  |  |  |  |
| Baseline(n=10,13,21,24,22)                 | 3.71 (± 9.586)   |  |  |  |
| % 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 <sup>[7]</sup> |
|-----------------|--|

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: The objective was to evaluate the effect of all LIK066 doses only (not EMPA) vs placebo

| 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 <sup>2</sup> ) |                    |                    |                    |                    |
| 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: The objective was to evaluate the effect of all LIK066 doses only (not EMPA) vs placebo

| 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: Percentage of participants with New York Heart Association (NYHA) class I, II, III or IV

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with New York Heart Association (NYHA) class I, II, III or IV <sup>[9]</sup> |
|-----------------|---|

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: The objective was to evaluate the effect of all LIK066 doses only (not EMPA) vs placebo

| 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: Participants               |                 |                 |                 |                 |
| Baseline (n=15,16,30,33) Class I  | 0               | 0               | 0               | 0               |
| Week 12 (n=9,8,13,18) Class I     | 1               | 1               | 1               | 1               |
| Week 36 (n=3,0,1,3) Class I       | 0               | 0               | 0               | 0               |
| Baseline (n=15,16,30,33) Class II | 13              | 14              | 26              | 25              |

|                                    |   |   |    |    |
|------------------------------------|---|---|----|----|
| Week 12 (n=9,8,13,18) Class II     | 6 | 6 | 10 | 13 |
| Week 36 (n=3,0,1,3) Class II       | 3 | 0 | 1  | 3  |
| Baseline (n=15,16,30,33) Class III | 2 | 2 | 3  | 8  |
| Week 12 (n=9,8,13,18) Class III    | 2 | 1 | 2  | 4  |
| Week 36 (n=3,0,1,3) Class III      | 0 | 0 | 0  | 0  |
| Baseline (n=15,16,30,33) Class IV  | 0 | 0 | 1  | 0  |
| 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: Percentage of participants with change from Baseline in New York Heart Association (NYHA) Class at Week 12 and 36

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with change from Baseline in New York Heart Association (NYHA) Class at Week 12 and 36 <sup>[10]</sup> |
|-----------------|---|

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: The objective was to evaluate the effect of all LIK066 doses only (not EMPA) vs placebo

| 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: Participants             |                 |                 |                 |                 |
| Week 12 (n=9,8,13,18) Improved  | 1               | 1               | 1               | 4               |
| Week 36 (n=3,0,1,3) Improved    | 0               | 0               | 0               | 0               |
| Week 12 (n=9,8,13,18) Unchanged | 8               | 7               | 12              | 13              |
| Week 36 (n=3,0,1,3) Unchanged   | 3               | 0               | 1               | 3               |
| Week 12 (n=9,8,13,18) Worsened  | 0               | 0               | 0               | 1               |
| 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 <sup>[11]</sup> |
|-----------------|--|

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: The objective was to evaluate the effect of all LIK066 doses only (not EMPA) vs placebo

| 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: pg/mL                             |                          |                          |                        |                         |
| geometric mean (confidence interval 95%) |                          |                          |                        |                         |
| Baseline(n=15,16,30,33)                  | 1189.3 (774.5 to 1826.4) | 1023.5 (688.5 to 1521.5) | 672.1 (542.8 to 832.0) | 993.7 (702.6 to 1405.5) |
| 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 <sup>[12]</sup> | 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<br>Hologic(n=1,0,0,1,1)      | 2435.000 (± 999) |  |  |  |
| Wk 12 Whole Body - Hd Hologic Chge<br>BL(n=1,0,0,0,1) | -3.340 (± 999)   |  |  |  |
| Wk 36 Whole Body - Hd Hologic Chge<br>BL(n=1,0,0,0,1) | 64.620 (± 999)   |  |  |  |
| BL Whole Body Minus Head, Lunar<br>N=0,0,3,2,0)       | 999 (± 9999)     |  |  |  |
| Wk 12 Whole Body - Hd Lunar Chge<br>BL(n=0,0,1,1,0)   | 999 (± 999)      |  |  |  |
| Wk 36 Whole Body - Hd Lunar Chge<br>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 10mg  |
| Reporting group description: |              |
| LIK066 10mg                  |              |
| Reporting group title        | LIK066 2.5mg |
| Reporting group description: |              |
| LIK066 2.5mg                 |              |
| Reporting group title        | EMPA 25mg    |
| Reporting group description: |              |
| EMPA 25mg                    |              |
| Reporting group title        | Placebo      |
| Reporting group description: |              |
| Placebo                      |              |
| Reporting group title        | LIK066 50mg  |
| Reporting group description: |              |
| LIK066 50mg                  |              |

| Serious adverse events                            | LIK066 10mg     | LIK066 2.5mg    | EMPA 25mg       |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events |                 |                 |                 |
| subjects affected / exposed                       | 2 / 16 (12.50%) | 2 / 15 (13.33%) | 5 / 30 (16.67%) |
| number of deaths (all causes)                     | 1               | 0               | 0               |
| number of deaths resulting from adverse events    | 0               | 0               | 0               |
| Injury, poisoning and procedural complications    |                 |                 |                 |
| Hip fracture                                      |                 |                 |                 |
| subjects affected / exposed                       | 0 / 16 (0.00%)  | 0 / 15 (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           |
| Wound dehiscence                                  |                 |                 |                 |
| subjects affected / exposed                       | 0 / 16 (0.00%)  | 0 / 15 (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 disorders                                    |                |                |                |
| Angina pectoris                                      |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 15 (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          |
| Atrial fibrillation                                  |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 15 (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                                      |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 1 / 15 (6.67%) | 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          |
| Cardiac failure chronic                              |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 15 (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 congestive                           |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 15 (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                          | 1 / 16 (6.25%) | 0 / 15 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                             |                |                |                |
| Cerebral vascular occlusion                          |                |                |                |
| subjects affected / exposed                          | 0 / 16 (0.00%) | 0 / 15 (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          |
| General disorders and administration site conditions |                |                |                |
| Cardiac death  |                |                |                |

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

|   |                |                 |  |
|---|----------------|-----------------|--|
| <b>Serious adverse events</b>                     | Placebo        | LIK066 50mg     |  |
| Total subjects affected by serious adverse events |                |                 |  |
| subjects affected / exposed                       | 3 / 33 (9.09%) | 3 / 30 (10.00%) |  |
| number of deaths (all causes)                     | 1              | 0               |  |
| number of deaths resulting from adverse events    | 0              | 0               |  |
| Injury, poisoning and procedural complications    |                |                 |  |
| Hip fracture                                      |                |                 |  |

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

|   |                                  |                                  |  |
|---|----------------------------------|----------------------------------|--|
| Cerebral vascular occlusion<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 30 (3.33%)<br>0 / 1<br>0 / 0 |  |
| General disorders and administration<br>site conditions<br>Cardiac death<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all    | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 30 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Reproductive system and breast<br>disorders<br>Benign prostatic hyperplasia<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 30 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Respiratory failure<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 1 / 33 (3.03%)<br>0 / 1<br>0 / 1 | 0 / 30 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Infections and infestations<br>Diarrhoea infectious<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                         | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 30 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 30 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Wound infection<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 30 (3.33%)<br>0 / 1<br>0 / 0 |  |



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

| <b>Non-serious adverse events</b>                     | LIK066 10mg     | LIK066 2.5mg    | EMPA 25mg        |
|---|-----------------|-----------------|------------------|
| Total subjects affected by non-serious adverse events |                 |                 |                  |
| subjects affected / exposed                           | 6 / 16 (37.50%) | 7 / 15 (46.67%) | 12 / 30 (40.00%) |
| Vascular disorders                                    |                 |                 |                  |
| Hypotension   |                 |                 |                  |
| subjects affected / exposed                           | 0 / 16 (0.00%)  | 2 / 15 (13.33%) | 3 / 30 (10.00%)  |
| occurrences (all)                                     | 0               | 3               | 3                |
| General disorders and administration site conditions  |                 |                 |                  |
| Oedema peripheral                                     |                 |                 |                  |
| subjects affected / exposed                           | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 30 (0.00%)   |
| occurrences (all)                                     | 1               | 0               | 0                |
| Pyrexia   |                 |                 |                  |
| subjects affected / exposed                           | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 30 (0.00%)   |
| occurrences (all)                                     | 1               | 0               | 0                |
| Thirst  |                 |                 |                  |
| subjects affected / exposed                           | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 30 (0.00%)   |
| occurrences (all)                                     | 1               | 0               | 0                |
| Reproductive system and breast disorders              |                 |                 |                  |
| Gynaecomastia   |                 |                 |                  |
| subjects affected / exposed                           | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 30 (0.00%)   |
| occurrences (all)                                     | 0               | 1               | 0                |
| Respiratory, thoracic and mediastinal disorders       |                 |                 |                  |
| Cough   |                 |                 |                  |
| subjects affected / exposed                           | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 30 (0.00%)   |
| occurrences (all)                                     | 0               | 1               | 0                |
| Dyspnoea  |                 |                 |                  |
| subjects affected / exposed                           | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  | 0 / 30 (0.00%)   |
| occurrences (all)                                     | 1               | 0               | 0                |
| Epistaxis   |                 |                 |                  |
| subjects affected / exposed                           | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  | 0 / 30 (0.00%)   |
| occurrences (all)                                     | 0               | 1               | 0                |
| Psychiatric disorders                                 |                 |                 |                  |

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

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

|                             |                 |                |                 |
|-----------------------------|-----------------|----------------|-----------------|
| Hypoglycaemia               |                 |                |                 |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 15 (6.67%) | 3 / 30 (10.00%) |
| occurrences (all)           | 7               | 15             | 7               |
| Hypokalaemia                |                 |                |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 15 (0.00%) | 0 / 30 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0               |

| <b>Non-serious adverse events</b>                     | Placebo         | LIK066 50mg     |  |
|---|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                 |                 |  |
| subjects affected / exposed                           | 9 / 33 (27.27%) | 8 / 30 (26.67%) |  |
| Vascular disorders                                    |                 |                 |  |
| Hypotension   |                 |                 |  |
| subjects affected / exposed                           | 1 / 33 (3.03%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                                     | 1               | 2               |  |
| General disorders and administration site conditions  |                 |                 |  |
| Oedema peripheral                                     |                 |                 |  |
| subjects affected / exposed                           | 1 / 33 (3.03%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                                     | 1               | 1               |  |
| Pyrexia   |                 |                 |  |
| subjects affected / exposed                           | 0 / 33 (0.00%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                                     | 0               | 0               |  |
| Thirst  |                 |                 |  |
| subjects affected / exposed                           | 0 / 33 (0.00%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                                     | 0               | 0               |  |
| Reproductive system and breast disorders              |                 |                 |  |
| Gynaecomastia   |                 |                 |  |
| subjects affected / exposed                           | 0 / 33 (0.00%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                                     | 0               | 0               |  |
| Respiratory, thoracic and mediastinal disorders       |                 |                 |  |
| Cough   |                 |                 |  |
| subjects affected / exposed                           | 1 / 33 (3.03%)  | 0 / 30 (0.00%)  |  |
| occurrences (all)                                     | 1               | 0               |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                           | 1 / 33 (3.03%)  | 1 / 30 (3.33%)  |  |
| occurrences (all)                                     | 1               | 1               |  |
| Epistaxis   |                 |                 |  |

|  |   |   |  |
|--|---|---|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 33 (0.00%)<br>0   | 0 / 30 (0.00%)<br>0   |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)   | 0 / 33 (0.00%)<br>0   | 1 / 30 (3.33%)<br>1   |  |
| Investigations<br>Heart rate irregular<br>subjects affected / exposed<br>occurrences (all)<br><br>Liver function test increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 33 (0.00%)<br>0<br><br>0 / 33 (0.00%)<br>0                            | 0 / 30 (0.00%)<br>0<br><br>0 / 30 (0.00%)<br>0                            |  |
| Injury, poisoning and procedural complications<br>Limb injury<br>subjects affected / exposed<br>occurrences (all)  | 0 / 33 (0.00%)<br>0   | 0 / 30 (0.00%)<br>0   |  |
| Cardiac disorders<br>Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)   | 1 / 33 (3.03%)<br>1   | 0 / 30 (0.00%)<br>0   |  |
| Nervous system disorders<br>Dysaesthesia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 33 (0.00%)<br>0   | 0 / 30 (0.00%)<br>0   |  |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Enteritis<br>subjects affected / exposed<br>occurrences (all)<br><br>Flatulence | 1 / 33 (3.03%)<br>1<br><br>1 / 33 (3.03%)<br>2<br><br>0 / 33 (0.00%)<br>0 | 0 / 30 (0.00%)<br>0<br><br>2 / 30 (6.67%)<br>4<br><br>0 / 30 (0.00%)<br>0 |  |

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

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| Hyperglycaemia              |                |                |  |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 30 (0.00%) |  |
| occurrences (all)           | 2              | 0              |  |
| Hypoglycaemia               |                |                |  |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 30 (6.67%) |  |
| occurrences (all)           | 5              | 2              |  |
| Hypokalaemia                |                |                |  |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 30 (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 | <p>Amendment 1 introduced the following changes:</p> <ul style="list-style-type: none"><li>- 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.</li><li>- The inclusion criterion for NT-proBNP was lowered from &gt;400 to &gt;300 pg/mL. When designing the study protocol, a NT-proBNP value of &gt;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 &gt;125 pg/mL, the NT-proBNP value to qualify patients for this study was changed to &gt;300 pg/mL, as this cut-off has a robust predictive value to identify chronic HF patients with preserved LVEF.</li><li>- In addition, the inclusion criterion for serum potassium was changed from <math>\leq 5.2</math> mM to <math>\leq 5.3</math> mM to be in line with the reference range used by the Central laboratory in this study.</li><li>- 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%.</li></ul> |
| 04 February 2018  | <p>Amendment 2 introduced the following changes:</p> <ul style="list-style-type: none"><li>- 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.</li><li>- Other changes included adjustments and/or clarifications for several technical and logistical procedures, such as for body weight, bio-impedance and echocardiography assessments.</li></ul>   |

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: