

**Clinical trial results:**

**A phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of linagliptin 5 mg/empagliflozin 25 mg and linagliptin 5 mg/empagliflozin 10 mg Fixed Dose Combination tablets compared with the individual components (linagliptin 5 mg, empagliflozin 25 mg, and empagliflozin 10 mg) for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycaemic control.**

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

**Summary**

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2011-000383-10       |
| Trial protocol           | EE ES HU SE DK IT BG |
| Global end of trial date | 10 September 2013    |

**Results information**

|                                |  |
|--------------------------------|--|
| Result version number          | v2 (current)   |
| This version publication date  | 23 July 2016   |
| First version publication date | 17 April 2015  |
| Version creation reason        | • Correction of full data set<br>Data correction due to system error in EudraCT- Results |

**Trial information****Trial identification**

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 1275.1 |
|-----------------------|--------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01422876 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Boehringer Ingelheim  |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216  |
| Public contact               | QRPE Processes and Systems Coordination<br>Clinical Trial Information Disclosure, Boehringer Ingelheim ,<br>+1 800-243-0127, clintrriage.rdg@boehringer-ingelheim.com |
| Scientific contact           | QRPE Processes and Systems Coordination<br>Clinical Trial Information Disclosure, Boehringer Ingelheim ,<br>+1 800-243-0127, clintrriage.rdg@boehringer-ingelheim.com |

Notes:

**Paediatric regulatory details**

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No                          | No |

|  |    |
|--|----|
| 1901/2006 apply to this trial?                                       |    |
| 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                       | 07 October 2013   |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 10 September 2013 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 10 September 2013 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The objective of the study is to investigate the efficacy, safety and tolerability of empagliflozin 25 mg/linagliptin 5 mg FDC qd and of empagliflozin 10 mg/linagliptin 5 mg FDC qd compared to the individual components (empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg) given for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycaemic control.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 31 August 2011 |
| 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 | Poland: 26     |
| Country: Number of subjects enrolled | Romania: 154   |
| Country: Number of subjects enrolled | Spain: 107     |
| Country: Number of subjects enrolled | Sweden: 95     |
| Country: Number of subjects enrolled | Bulgaria: 15   |
| Country: Number of subjects enrolled | Denmark: 40    |
| Country: Number of subjects enrolled | Estonia: 55    |
| Country: Number of subjects enrolled | Hungary: 48    |
| Country: Number of subjects enrolled | Italy: 26      |
| Country: Number of subjects enrolled | Argentina: 110 |
| Country: Number of subjects enrolled | Australia: 27  |
| Country: Number of subjects enrolled | Brazil: 38     |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Canada: 130            |
| Country: Number of subjects enrolled | Colombia: 68           |
| Country: Number of subjects enrolled | Lebanon: 82            |
| Country: Number of subjects enrolled | Malaysia: 23           |
| Country: Number of subjects enrolled | Mexico: 79             |
| Country: Number of subjects enrolled | Peru: 75               |
| Country: Number of subjects enrolled | Philippines: 109       |
| Country: Number of subjects enrolled | Russian Federation: 69 |
| Country: Number of subjects enrolled | Taiwan: 56             |
| Country: Number of subjects enrolled | United States: 1073    |
| Worldwide total number of subjects   | 2505                   |
| EEA total number of subjects         | 566                    |

Notes:

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### Subjects enrolled per age group

|   |      |
|---|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 1957 |
| From 65 to 84 years                       | 543  |
| 85 years and over                         | 5    |

## Subject disposition

### Recruitment

Recruitment details:

Of the 1405 patients enrolled and randomized the data for 42 randomized patients were excluded from all analyses due to serious non-compliance. Therefore, 1363 patients were included in the analyses.

### Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subject) met all strictly implemented inclusion/exclusion criteria. Subjects were not randomised to trial treatment if any one of the specific entry criteria were violated.

### Period 1

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

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | No   |
| <b>Arm title</b>             | Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg |

Arm description:

Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$  mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral

|  |                             |
|--|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | Empagliflozin + Linagliptin |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Tablet                      |
| Routes of administration               | Oral use                    |

Dosage and administration details:

Empagliflozin/linagliptin Fixed Dose Combination (FDC) tablets, dose: 25 mg/5 mg q.d.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg |
|------------------|--|

Arm description:

Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$  mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral

|  |                             |
|--|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | Empagliflozin + Linagliptin |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Tablet                      |
| Routes of administration               | Oral use                    |

Dosage and administration details:

Empagliflozin/linagliptin Fixed Dose Combination (FDC) tablets, dose: 10 mg/5 mg q.d

|                  |   |
|------------------|---|
| <b>Arm title</b> | Metformin Background: Empagliflozin 25 mg |
|------------------|---|

Arm description:

Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$  mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged

for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Empagliflozin     |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Empagliflozin tablets 25 mg q.d.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Metformin Background: Empagliflozin 10 mg |
|------------------|---|

Arm description:

Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$  mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Empagliflozin     |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Empagliflozin tablets 10 mg q.d.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Metformin Background: Linagliptin 5 mg |
|------------------|--|

Arm description:

Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$  mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Linagliptin       |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Linagliptin tablets 5 mg q.d.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg |
|------------------|---|

Arm description:

Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral

|  |                             |
|--|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | Empagliflozin + Linagliptin |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Tablet                      |
| Routes of administration               | Oral use                    |

Dosage and administration details:

Empagliflozin/linagliptin FDC tablets, 25 mg/5 mg q.d.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg |
|------------------|---|

Arm description:

Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral

|  |                             |
|--|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | Empagliflozin + Linagliptin |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Tablet                      |
| Routes of administration               | Oral use                    |

Dosage and administration details:

Empagliflozin/linagliptin FDC tablets 10 mg/5 mg q.d.

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Treatment Naive: Empagliflozin 25 mg |
|------------------|--------------------------------------|

Arm description:

Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Empagliflozin     |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Empagliflozin tablets 25 mg q.d.

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Treatment Naive: Empagliflozin 10 mg |
|------------------|--------------------------------------|

Arm description:

Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Empagliflozin     |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Empagliflozin tablets 10 mg q.d.

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | Treatment Naive: Linagliptin 5 mg |
|------------------|-----------------------------------|

Arm description:

Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Linagliptin       |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Linagliptin tablets 5 mg q.d.

| <b>Number of subjects in period 1</b> | Metformin Background:<br>Empagliflozin 25 mg/linagliptin 5 mg | Metformin Background:<br>Empagliflozin 10 mg/linagliptin 5 mg | Metformin Background:<br>Empagliflozin 25 mg |
|---------------------------------------|---|---|--|
| Started                               | 137   | 136   | 141  |
| Week 24 (continuing trial medication) | 126   | 129   | 131  |
| Week 52 (completed trial medication)  | 121 <sup>[1]</sup>  | 124 <sup>[2]</sup>  | 125 <sup>[3]</sup>                           |
| Week 24 (remaining in the trial)      | 131   | 133   | 136  |
| Week 52 (completed trial)             | 125   | 126   | 128  |
| Completed                             | 125   | 126   | 128  |
| Not completed                         | 12  | 10  | 13   |
| Adverse event, serious fatal          | -   | 1   | -  |
| Consent withdrawn by subject          | 9   | 4   | 6  |
| Lost to follow-up                     | 3   | 5   | 7  |

| <b>Number of subjects in period 1</b> | Metformin Background:<br>Empagliflozin 10 mg | Metformin Background:<br>Linagliptin 5 mg | Treatment Naive:<br>Empagliflozin 25 mg/linagliptin 5 mg |
|---------------------------------------|--|---|--|
| Started                               | 140  | 132                                       | 137  |
| Week 24 (continuing trial medication) | 124  | 118                                       | 125  |
| Week 52 (completed trial medication)  | 118 <sup>[4]</sup>                           | 113 <sup>[5]</sup>                        | 114 <sup>[6]</sup>                                       |
| Week 24 (remaining in the trial)      | 132  | 125                                       | 131  |
| Week 52 (completed trial)             | 122  | 117                                       | 120  |
| Completed                             | 122  | 117                                       | 120  |
| Not completed                         | 18   | 15  | 17   |
| Adverse event, serious fatal          | 1  | -   | -  |
| Consent withdrawn by subject          | 12   | 7   | 12   |
| Lost to follow-up                     | 5  | 8   | 5  |

| <b>Number of subjects in period 1</b> | Treatment Naive:<br>Empagliflozin 10 mg/linagliptin 5 mg | Treatment Naive:<br>Empagliflozin 25 mg | Treatment Naive:<br>Empagliflozin 10 mg |
|---------------------------------------|--|---|---|
| Started                               | 136  | 135                                     | 134                                     |
| Week 24 (continuing trial medication) | 124  | 121                                     | 121                                     |
| Week 52 (completed trial medication)  | 116 <sup>[7]</sup>                                       | 114                                     | 110 <sup>[8]</sup>                      |
| Week 24 (remaining in the trial)      | 130  | 128                                     | 128                                     |
| Week 52 (completed trial)             | 120  | 112                                     | 113                                     |
| Completed                             | 120  | 112                                     | 113                                     |
| Not completed                         | 16   | 23                                      | 21                                      |
| Adverse event, serious fatal          | 1  | 3                                       | 1                                       |
| Consent withdrawn by subject          | 10   | 12                                      | 13                                      |
| Lost to follow-up                     | 5  | 8                                       | 7                                       |

| Number of subjects in period 1        | Treatment Naive:<br>Linagliptin 5 mg |
|---------------------------------------|--------------------------------------|
| Started                               | 135                                  |
| Week 24 (continuing trial medication) | 123                                  |
| Week 52 (completed trial medication)  | 116 <sup>[9]</sup>                   |
| Week 24 (remaining in the trial)      | 125                                  |
| Week 52 (completed trial)             | 118                                  |
| Completed                             | 118                                  |
| Not completed                         | 17                                   |
| Adverse event, serious fatal          | -                                    |
| Consent withdrawn by subject          | 9                                    |
| Lost to follow-up                     | 8                                    |

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Notes:

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

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg at week 52 but not the trial.

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

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg at week 52 but not the trial.

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

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Metformin Background: Empagliflozin 25 mg at week 52 but not the trial.

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

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Metformin Background: Empagliflozin 10 mg at week 52 but not the trial.

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

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Metformin Background: Linagliptin 5 mg at week 52 but not the trial.

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

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Naive: Empagliflozin 25 mg/linagliptin 5 mg at week 52 but not the trial.

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



completed, minus those who left.

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Naive: Empagliflozin 10 mg/linagliptin 5 mg at week 52 but not the trial.

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

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Naive: Empagliflozin 10 mg at week 52 but not the trial.

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

Justification: This was a randomised, double-blind, multi-national, parallel-group comparison study. The number that completed are those patient who completd the trial. The patient could discontinue study medication while still in the trial. Thus this milestone represent the number of subjects who completed the trial medication Naive: Linagliptin 5 mg at week 52 but not the trial.

## Baseline characteristics

### Reporting groups<sup>[1]</sup>

|  |  |
|--|--|
| Reporting group title  | Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg |
| Reporting group description:<br>Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$ mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral |  |
| Reporting group title  | Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg |
| Reporting group description:<br>Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$ mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral |  |
| Reporting group title  | Metformin Background: Empagliflozin 25 mg                  |
| Reporting group description:<br>Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$ mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral               |  |
| Reporting group title  | Metformin Background: Empagliflozin 10 mg                  |
| Reporting group description:<br>Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$ mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral               |  |
| Reporting group title  | Metformin Background: Linagliptin 5 mg                     |
| Reporting group description:<br>Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$ mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral                  |  |
| Reporting group title  | Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg      |
| Reporting group description:<br>Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral   |  |
| Reporting group title  | Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg      |
| Reporting group description:<br>Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral   |  |
| Reporting group title  | Treatment Naive: Empagliflozin 25 mg                       |
| Reporting group description:<br>Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral   |  |
| Reporting group title  | Treatment Naive: Empagliflozin 10 mg                       |
| Reporting group description:<br>Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral   |  |
| Reporting group title  | Treatment Naive: Linagliptin 5 mg                          |
| Reporting group description:<br>Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral  |  |

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: The baseline characteristics represents the number of patients randomized and analyzed whereas the worldwide number represents the number of patients enrolled.

| Reporting group values             | Metformin Background:<br>Empagliflozin 25 mg/linagliptin 5 mg | Metformin Background:<br>Empagliflozin 10 mg/linagliptin 5 mg | Metformin Background:<br>Empagliflozin 25 mg |
|------------------------------------|---|---|--|
| Number of subjects                 | 137   | 136   | 141  |
| Age categorical<br>Units: Subjects |   |   |  |

|   |        |        |        |
|---|--------|--------|--------|
| Age Continuous  |        |        |        |
| Randomised set (RS) – including all patients from the screened set who were randomised to trial medication, regardless of whether any trial medication was taken. |        |        |        |
| Units: years  |        |        |        |
| arithmetic mean   | 57.1   | 56.2   | 55.4   |
| standard deviation  | ± 10.2 | ± 10.3 | ± 10.1 |
| Gender, Male/Female   |        |        |        |
| Units: participants   |        |        |        |
| Female  | 64     | 52     | 75     |
| Male  | 73     | 84     | 66     |

| Reporting group values             | Metformin Background:<br>Empagliflozin 10 mg | Metformin Background:<br>Linagliptin 5 mg | Treatment Naive:<br>Empagliflozin 25 mg/linagliptin 5 mg |
|------------------------------------|--|---|--|
| Number of subjects                 | 140  | 132                                       | 137  |
| Age categorical<br>Units: Subjects |  |   |  |

|   |        |       |      |
|---|--------|-------|------|
| Age Continuous  |        |       |      |
| Randomised set (RS) – including all patients from the screened set who were randomised to trial medication, regardless of whether any trial medication was taken. |        |       |      |
| Units: years  |        |       |      |
| arithmetic mean   | 55.9   | 56.3  | 54.3 |
| standard deviation  | ± 10.5 | ± 9.9 | ± 10 |
| Gender, Male/Female   |        |       |      |
| Units: participants   |        |       |      |
| Female  | 59     | 65    | 65   |
| Male  | 81     | 67    | 72   |

| Reporting group values             | Treatment Naive:<br>Empagliflozin 10 mg/linagliptin 5 mg | Treatment Naive:<br>Empagliflozin 25 mg | Treatment Naive:<br>Empagliflozin 10 mg |
|------------------------------------|--|---|---|
| Number of subjects                 | 136  | 135                                     | 134                                     |
| Age categorical<br>Units: Subjects |  |   |   |

|   |       |       |        |
|---|-------|-------|--------|
| Age Continuous  |       |       |        |
| Randomised set (RS) – including all patients from the screened set who were randomised to trial medication, regardless of whether any trial medication was taken. |       |       |        |
| Units: years  |       |       |        |
| arithmetic mean   | 55.2  | 55.7  | 53.8   |
| standard deviation  | ± 9.7 | ± 9.5 | ± 10.4 |

|                     |    |    |    |
|---------------------|----|----|----|
| Gender, Male/Female |    |    |    |
| Units: participants |    |    |    |
| Female              | 62 | 57 | 70 |
| Male                | 74 | 78 | 64 |

|                               |                                      |       |  |
|-------------------------------|--------------------------------------|-------|--|
| <b>Reporting group values</b> | Treatment Naive:<br>Linagliptin 5 mg | Total |  |
| Number of subjects            | 135                                  | 1341  |  |
| Age categorical               |                                      |       |  |
| Units: Subjects               |                                      |       |  |

|   |        |     |  |
|---|--------|-----|--|
| Age Continuous  |        |     |  |
| Randomised set (RS) – including all patients from the screened set who were randomised to trial medication, regardless of whether any trial medication was taken. |        |     |  |
| Units: years  |        |     |  |
| arithmetic mean   | 53.7   |     |  |
| standard deviation  | ± 11.4 | -   |  |
| Gender, Male/Female   |        |     |  |
| Units: participants   |        |     |  |
| Female  | 60     | 620 |  |
| Male  | 75     | 721 |  |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg |
| Reporting group description:<br>Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$ mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral |  |
| Reporting group title  | Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg |
| Reporting group description:<br>Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$ mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral |  |
| Reporting group title  | Metformin Background: Empagliflozin 25 mg                  |
| Reporting group description:<br>Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$ mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral               |  |
| Reporting group title  | Metformin Background: Empagliflozin 10 mg                  |
| Reporting group description:<br>Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$ mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral               |  |
| Reporting group title  | Metformin Background: Linagliptin 5 mg                     |
| Reporting group description:<br>Study population on a stable background of metformin defined as pre-treated with metformin ( $\geq 1500$ mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral                  |  |
| Reporting group title  | Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg      |
| Reporting group description:<br>Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral   |  |
| Reporting group title  | Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg      |
| Reporting group description:<br>Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral   |  |
| Reporting group title  | Treatment Naive: Empagliflozin 25 mg                       |
| Reporting group description:<br>Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral   |  |
| Reporting group title  | Treatment Naive: Empagliflozin 10 mg                       |
| Reporting group description:<br>Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral   |  |
| Reporting group title  | Treatment Naive: Linagliptin 5 mg                          |
| Reporting group description:<br>Study population treatment naive defined as an absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomisation. Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral  |  |

## Primary: Change from baseline in glycosylated hemoglobin (HbA1c) for Metformin Background patients

|                 |  |
|-----------------|--|
| End point title | Change from baseline in glycosylated hemoglobin (HbA1c) for Metformin Background patients <sup>[1]</sup> |
|-----------------|--|

End point description:

Glycosylated hemoglobin (HbA1c) is a measurement of the percentage of hemoglobin that is glycated. The change from baseline in HbA1c is calculated as the week 24 HbA1c minus the baseline HbA1c. Since HbA1c is measured as a percentage the change from baseline is also a percentage. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all Metformin Background patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and 24 weeks

Notes:

[1] - 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: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

| End point values                    | Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg | Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg | Metformin Background: Empagliflozin 25 mg | Metformin Background: Empagliflozin 10 mg |
|-------------------------------------|--|--|---|---|
| Subject group type                  | Reporting group  | Reporting group  | Reporting group                           | Reporting group                           |
| Number of subjects analysed         | 134 <sup>[2]</sup>   | 135 <sup>[3]</sup>   | 140 <sup>[4]</sup>                        | 137 <sup>[5]</sup>                        |
| Units: % change from baseline       |  |  |   |   |
| least squares mean (standard error) | -1.19 (± 0.06)   | -1.08 (± 0.06)   | -0.62 (± 0.06)                            | -0.66 (± 0.06)                            |

Notes:

[2] - FAS (LOCF)

[3] - FAS (LOCF)

[4] - FAS (LOCF)

[5] - FAS (LOCF)

| End point values                    | Metformin Background: Linagliptin 5 mg |  |  |  |
|-------------------------------------|--|--|--|--|
| Subject group type                  | Reporting group                        |  |  |  |
| Number of subjects analysed         | 128 <sup>[6]</sup>                     |  |  |  |
| Units: % change from baseline       |  |  |  |  |
| least squares mean (standard error) | -0.7 (± 0.06)                          |  |  |  |

Notes:

[6] - FAS (LOCF)

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Metformin: Empa/Lina 25/5 versus Empa 25 |
|----------------------------|--|

Statistical analysis description:

Model for Week 24 includes baseline HbA1c ( $p < 0.0001$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.0038$ ), geographical region ( $p < 0.0001$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.

|   |  |
|---|--|
| Comparison groups                       | Metformin Background: Empagliflozin 25 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 274  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001   |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Mean difference (net)  |
| Point estimate                          | -0.58  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.75  |
| upper limit                             | -0.41  |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 0.09   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Metformin: Empa/Lina 25/5 versus Lina 5 |
|-----------------------------------|---|

Statistical analysis description:

Model for Week 24 includes baseline HbA1c ( $p < 0.0001$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.0038$ ), geographical region ( $p < 0.0001$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.

|   |   |
|---|---|
| Comparison groups                       | Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 262   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (net)   |
| Point estimate                          | -0.5  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.67   |
| upper limit                             | -0.32   |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.09  |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Metformin: Empa/Lina 10/5 versus Empa 10 |
|-----------------------------------|--|

Statistical analysis description:

Model for Week 24 includes baseline HbA1c ( $p < 0.0001$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.0038$ ), geographical region ( $p < 0.0001$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.

|                   |  |
|-------------------|--|
| Comparison groups | Metformin Background: Empagliflozin 10 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg |
|-------------------|--|

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 272                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.0001                   |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | Mean difference (net)      |
| Point estimate                          | -0.42                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.59                      |
| upper limit                             | -0.25                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.09                       |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Metformin: Empa/Lina 10/5 versus Lina 5 |
|-----------------------------------|---|

Statistical analysis description:

Model for Week 24 includes baseline HbA1c (p<0.0001) as linear covariate(s) and baseline eGFR (MDRD) (p=0.0038), geographical region (p<0.0001), treatment (p<0.0001) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Lina 5.

|   |   |
|---|---|
| Comparison groups                       | Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 263   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (net)   |
| Point estimate                          | -0.39   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.56   |
| upper limit                             | -0.21   |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.09  |

### **Primary: Change from baseline in glycosylated hemoglobin (HbA1c) for Treatment Naive patients**

|                 |   |
|-----------------|---|
| End point title | Change from baseline in glycosylated hemoglobin (HbA1c) for Treatment Naive patients <sup>[7]</sup> |
|-----------------|---|

End point description:

Glycosylated hemoglobin (HbA1c) is a measurement of the percentage of hemoglobin that is glycated. The change from baseline in HbA1c is calculated as the week 24 HbA1c minus the baseline HbA1c. Since HbA1c is measured as a percentage the change from baseline is also a percentage. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all treatment naive patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|



End point timeframe:

Baseline and 24 weeks

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: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

| End point values                    | Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg | Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg | Treatment Naive: Empagliflozin 25 mg | Treatment Naive: Empagliflozin 10 mg |
|-------------------------------------|---|---|--------------------------------------|--------------------------------------|
| Subject group type                  | Reporting group                                       | Reporting group                                       | Reporting group                      | Reporting group                      |
| Number of subjects analysed         | 134 <sup>[8]</sup>                                    | 135 <sup>[9]</sup>                                    | 133 <sup>[10]</sup>                  | 132 <sup>[11]</sup>                  |
| Units: % change from baseline       |   |   |                                      |                                      |
| least squares mean (standard error) | -1.08 (± 0.07)  | -1.24 (± 0.07)  | -0.95 (± 0.07)                       | -0.83 (± 0.07)                       |

Notes:

[8] - FAS (LOCF)

[9] - FAS (LOCF)

[10] - FAS (LOCF)

[11] - FAS (LOCF)

| End point values                    | Treatment Naive: Linagliptin 5 mg |  |  |  |
|-------------------------------------|-----------------------------------|--|--|--|
| Subject group type                  | Reporting group                   |  |  |  |
| Number of subjects analysed         | 133 <sup>[12]</sup>               |  |  |  |
| Units: % change from baseline       |                                   |  |  |  |
| least squares mean (standard error) | -0.67 (± 0.07)                    |  |  |  |

Notes:

[12] - FAS (LOCF)

## Statistical analyses

| Statistical analysis title | Naive: Empa/Lina 25/5 versus Empa 25 |
|----------------------------|--------------------------------------|
|----------------------------|--------------------------------------|

Statistical analysis description:

Model for Week 24 includes baseline HbA1c ( $p < 0.0001$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.8627$ ), geographical region ( $p = 0.0008$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.

|   |   |
|---|---|
| Comparison groups                       | Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg v<br>Treatment Naive: Empagliflozin 25 mg |
| Number of subjects included in analysis | 267   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.1785  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (net)   |
| Point estimate                          | -0.14   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -0.33                      |
| upper limit          | 0.06                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.1                        |

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| <b>Statistical analysis title</b> | Naive: Empa/Lina 10/5 versus Empa 10 |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Model for Week 24 includes baseline HbA1c ( $p < 0.0001$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.8627$ ), geographical region ( $p = 0.0008$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.

|   |  |
|---|--|
| Comparison groups                       | Treatment Naive: Empagliflozin 10 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 267  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | $< 0.0001$   |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Mean difference (net)  |
| Point estimate                          | -0.41  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.61  |
| upper limit                             | -0.21  |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 0.1  |

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | Naive: Empa/Lina 25/5 versus Lina 5 |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Model for Week 24 includes baseline HbA1c ( $p < 0.0001$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.8627$ ), geographical region ( $p = 0.0008$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.

|   |   |
|---|---|
| Comparison groups                       | Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 267   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | $< 0.0001$  |
| Method                                  | Cochran-Mantel-Haenszel   |
| Parameter estimate                      | Mean difference (net)   |
| Point estimate                          | -0.41   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -0.61                      |
| upper limit          | -0.22                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.1                        |

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | Naive: Empa/Lina 10/5 versus Lina 5 |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Model for Week 24 includes baseline HbA1c ( $p < 0.0001$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.8627$ ), geographical region ( $p = 0.0008$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.

|   |  |
|---|--|
| Comparison groups                       | Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg v<br>Treatment Naive: Linagliptin 5 mg |
| Number of subjects included in analysis | 268  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | $< 0.0001$   |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Mean difference (net)  |
| Point estimate                          | -0.57  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.76  |
| upper limit                             | -0.37  |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 0.1  |

## Secondary: Change from baseline in fasting plasma glucose at week 24 for Metformin Background patients

|                 |   |
|-----------------|---|
| End point title | Change from baseline in fasting plasma glucose at week 24 for Metformin Background patients <sup>[13]</sup> |
|-----------------|---|

End point description:

Change from baseline in fasting plasma glucose at week 24 for Metformin Background patients. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all Metformin Background patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 24 Weeks

Notes:

[13] - 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: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

| <b>End point values</b>             | Metformin Background:<br>Empagliflozin 25 mg/linagliptin 5 mg | Metformin Background:<br>Empagliflozin 10 mg/linagliptin 5 mg | Metformin Background:<br>Empagliflozin 25 mg | Metformin Background:<br>Empagliflozin 10 mg |
|-------------------------------------|---|---|--|--|
| Subject group type                  | Reporting group   | Reporting group   | Reporting group                              | Reporting group                              |
| Number of subjects analysed         | 133 <sup>[14]</sup>   | 134 <sup>[15]</sup>   | 139 <sup>[16]</sup>                          | 136 <sup>[17]</sup>                          |
| Units: mg/dL change from baseline   |   |   |  |  |
| least squares mean (standard error) | -35.25 ( $\pm$ 2.53)  | -32.18 ( $\pm$ 2.52)  | -18.83 ( $\pm$ 2.47)                         | -20.84 ( $\pm$ 2.5)                          |

Notes:

[14] - FAS (LOCF)

[15] - FAS (LOCF)

[16] - FAS (LOCF)

[17] - FAS (LOCF)

| <b>End point values</b>             | Metformin Background:<br>Linagliptin 5 mg |  |  |  |
|-------------------------------------|---|--|--|--|
| Subject group type                  | Reporting group                           |  |  |  |
| Number of subjects analysed         | 127 <sup>[18]</sup>                       |  |  |  |
| Units: mg/dL change from baseline   |   |  |  |  |
| least squares mean (standard error) | -13.05 ( $\pm$ 2.59)                      |  |  |  |

Notes:

[18] - FAS (LOCF)

## Statistical analyses

| <b>Statistical analysis title</b> | Metformin: Empa/Lina 25/5 versus Empa 25 |
|-----------------------------------|--|
|-----------------------------------|--|

Statistical analysis description:

Model for Week 24 includes baseline fasting plasma glucose ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.6082$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.3685$ ), geographical region ( $p = 0.0104$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.

|   |  |
|---|--|
| Comparison groups                       | Metformin Background: Empagliflozin 25 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 272  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | $< 0.0001$   |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Mean difference (net)  |
| Point estimate                          | -16.43   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -23.37   |
| upper limit                             | -9.48  |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 3.54   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Metformin: Empa/Lina 25/5 versus Lina 5   |
| Statistical analysis description:   |   |
| Model for Week 24 includes baseline fasting plasma glucose ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.6082$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.3685$ ), geographical region ( $p = 0.0104$ ), treatment ( $p < 0.0001$ ) as fixed effect(s). |   |
| Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.  |   |
| Comparison groups   | Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis   | 260   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | $< 0.0001$  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (net)   |
| Point estimate  | -22.2   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -29.3   |
| upper limit   | -15.1   |
| Variability estimate  | Standard error of the mean  |
| Dispersion value  | 3.62  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Metformin: Empa/Lina 10/5 versus Empa 10   |
| Statistical analysis description:   |  |
| Model for Week 24 includes baseline fasting plasma glucose ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.6082$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.3685$ ), geographical region ( $p = 0.0104$ ), treatment ( $p < 0.0001$ ) as fixed effect(s). |  |
| Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.   |  |
| Comparison groups   | Metformin Background: Empagliflozin 10 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis   | 270  |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | $= 0.0015$   |
| Method  | ANCOVA   |
| Parameter estimate  | Mean difference (net)  |
| Point estimate  | -11.34   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | -18.31   |
| upper limit   | -4.37  |
| Variability estimate  | Standard error of the mean   |
| Dispersion value  | 3.55   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Metformin: Empa/Lina 10/5 versus Lina 5   |
| Statistical analysis description:   |   |
| Model for Week 24 includes baseline fasting plasma glucose (p<0.0001), baseline HbA1c (p=0.6082) as linear covariate(s) and baseline eGFR (MDRD) (p=0.3685), geographical region (p=0.0104), treatment (p<0.0001) as fixed effect(s). |   |
| Treatment difference calculated as: Empa/Lina 10/5 minus Lina 5.  |   |
| Comparison groups   | Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis   | 261   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | < 0.0001  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (net)   |
| Point estimate  | -19.12  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -26.21  |
| upper limit   | -12.03  |
| Variability estimate  | Standard error of the mean  |
| Dispersion value  | 3.61  |

## Secondary: Change from baseline in fasting plasma glucose at week 24 for Treatment Naive patients

|   |  |
|---|--|
| End point title   | Change from baseline in fasting plasma glucose at week 24 for Treatment Naive patients <sup>[19]</sup> |
| End point description:  |  |
| Change from baseline in fasting plasma glucose at week 24 for Treatment Naive patients. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all treatment naive patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline and 24 Weeks   |  |

### Notes:

[19] - 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: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

| <b>End point values</b>     | Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg | Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg | Treatment Naive: Empagliflozin 25 mg | Treatment Naive: Empagliflozin 10 mg |
|-----------------------------|---|---|--------------------------------------|--------------------------------------|
| Subject group type          | Reporting group                                       | Reporting group                                       | Reporting group                      | Reporting group                      |
| Number of subjects analysed | 134 <sup>[20]</sup>                                   | 135 <sup>[21]</sup>                                   | 133 <sup>[22]</sup>                  | 132 <sup>[23]</sup>                  |

|                                     |                      |                      |                      |                      |
|-------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Units: mg/dL change from baseline   |                      |                      |                      |                      |
| least squares mean (standard error) | -29.55 ( $\pm$ 2.67) | -28.21 ( $\pm$ 2.66) | -24.24 ( $\pm$ 2.68) | -22.39 ( $\pm$ 2.69) |

Notes:

[20] - FAS (LOCF)

[21] - FAS (LOCF)

[22] - FAS (LOCF)

[23] - FAS (LOCF)

|                                     |                                      |  |  |  |
|-------------------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>             | Treatment Naive:<br>Linagliptin 5 mg |  |  |  |
| Subject group type                  | Reporting group                      |  |  |  |
| Number of subjects analysed         | 133 <sup>[24]</sup>                  |  |  |  |
| Units: mg/dL change from baseline   |                                      |  |  |  |
| least squares mean (standard error) | -5.92 ( $\pm$ 2.68)                  |  |  |  |

Notes:

[24] - FAS (LOCF)

## Statistical analyses

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| <b>Statistical analysis title</b> | Naive: Empa/Lina 25/5 versus Empa 25 |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Model for Week 24 includes baseline fasting plasma glucose ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.4591$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.7413$ ), geographical region ( $p = 0.1504$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.

|   |   |
|---|---|
| Comparison groups                       | Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg v<br>Treatment Naive: Empagliflozin 25 mg |
| Number of subjects included in analysis | 267   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.1605  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (net)   |
| Point estimate                          | -5.31   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -12.74  |
| upper limit                             | 2.11  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 3.78  |

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| <b>Statistical analysis title</b> | Naive: Empa/Lina 10/5 versus Empa 10 |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Model for Week 24 includes baseline fasting plasma glucose ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.4591$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.7413$ ), geographical region ( $p = 0.1504$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.

|   |  |
|---|--|
| Comparison groups                       | Treatment Naive: Empagliflozin 10 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 267  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.1246   |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Mean difference (net)  |
| Point estimate                          | -5.82  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -13.25   |
| upper limit                             | 1.61   |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 3.78   |

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | Naive: Empa/Lina 25/5 versus Lina 5 |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Model for Week 24 includes baseline fasting plasma glucose ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.4591$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.7413$ ), geographical region ( $p = 0.1504$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.

|   |   |
|---|---|
| Comparison groups                       | Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 267   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (net)   |
| Point estimate                          | -23.63  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -31.06  |
| upper limit                             | -16.21  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 3.78  |

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | Naive: Empa/Lina 10/5 versus Lina 5 |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Model for Week 24 includes baseline fasting plasma glucose ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.4591$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.7413$ ), geographical region ( $p = 0.1504$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Lina 5.

|                   |   |
|-------------------|---|
| Comparison groups | Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg |
|-------------------|---|



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 268                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.0001                   |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | Mean difference (net)      |
| Point estimate                          | -22.29                     |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -29.71                     |
| upper limit                             | -14.88                     |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 3.77                       |

### Secondary: Change from baseline in body weight for Metformin Background patients

|                 |   |
|-----------------|---|
| End point title | Change from baseline in body weight for Metformin Background patients <sup>[25]</sup> |
|-----------------|---|

End point description:

Change from baseline in body weight for Metformin Background patients. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all Metformin Background patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 24 Weeks

Notes:

[25] - 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: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

| End point values                    | Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg | Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg | Metformin Background: Empagliflozin 25 mg | Metformin Background: Empagliflozin 10 mg |
|-------------------------------------|--|--|---|---|
| Subject group type                  | Reporting group  | Reporting group  | Reporting group                           | Reporting group                           |
| Number of subjects analysed         | 134 <sup>[26]</sup>  | 135 <sup>[27]</sup>  | 140 <sup>[28]</sup>                       | 137 <sup>[29]</sup>                       |
| Units: kg change from baseline      |  |  |   |   |
| least squares mean (standard error) | -2.99 (± 0.31)   | -2.6 (± 0.3)   | -3.18 (± 0.3)                             | -2.53 (± 0.3)                             |

Notes:

[26] - FAS (LOCF)

[27] - FAS (LOCF)

[28] - FAS (LOCF)

[29] - FAS (LOCF)

|                  |  |  |  |  |
|------------------|--|--|--|--|
| End point values | Metformin Background: Linagliptin 5 mg |  |  |  |
|------------------|--|--|--|--|

|                                     |                     |  |  |  |
|-------------------------------------|---------------------|--|--|--|
| Subject group type                  | Reporting group     |  |  |  |
| Number of subjects analysed         | 128 <sup>[30]</sup> |  |  |  |
| Units: kg change from baseline      |                     |  |  |  |
| least squares mean (standard error) | -0.69 (± 0.31)      |  |  |  |

Notes:

[30] - FAS (LOCF)

## Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Metformin: Empa/Lina 25/5 versus Empa 25 |
|-----------------------------------|--|

Statistical analysis description:

Model for Week 24 includes baseline weight ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.1610$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.3685$ ), geographical region ( $p = 0.0162$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.

|   |  |
|---|--|
| Comparison groups                       | Metformin Background: Empagliflozin 25 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 274  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.6604 <sup>[31]</sup>   |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Mean difference (net)  |
| Point estimate                          | 0.19   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.65  |
| upper limit                             | 1.03   |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 0.43   |

Notes:

[31] - Not an alpha protected test.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Metformin: Empa/Lina 25/5 versus Lina 5 |
|-----------------------------------|---|

Statistical analysis description:

Model for Week 24 includes baseline weight ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.1610$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.3685$ ), geographical region ( $p = 0.0162$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.

|   |   |
|---|---|
| Comparison groups                       | Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 262   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (net)   |
| Point estimate                          | -2.3  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -3.15                      |
| upper limit          | -1.44                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.44                       |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Metformin: Empa/Lina 10/5 versus Empa 10 |
|-----------------------------------|--|

Statistical analysis description:

Model for Week 24 includes baseline weight ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.1610$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.3685$ ), geographical region ( $p = 0.0162$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.

|   |  |
|---|--|
| Comparison groups                       | Metformin Background: Empagliflozin 10 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 272  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.8757 <sup>[32]</sup>   |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Mean difference (net)  |
| Point estimate                          | -0.07  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.91  |
| upper limit                             | 0.77   |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 0.43   |

Notes:

[32] - Not an alpha protected test.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Metformin: Empa/Lina 10/5 versus Lina 5 |
|-----------------------------------|---|

Statistical analysis description:

Model for Week 24 includes baseline weight ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.1610$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.3685$ ), geographical region ( $p = 0.0162$ ), treatment ( $p < 0.0001$ ) as fixed effect(s).

Treatment difference calculated as: Empa/Lina 10/5 minus Lina 5.

|   |   |
|---|---|
| Comparison groups                       | Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 263   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (net)   |
| Point estimate                          | -1.91   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -2.77                      |
| upper limit          | -1.05                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.44                       |

## Secondary: Change from baseline in body weight for Treatment Naive patients

|                 |  |
|-----------------|--|
| End point title | Change from baseline in body weight for Treatment Naive patients <sup>[33]</sup> |
|-----------------|--|

End point description:

Change from baseline in body weight for Treatment Naive patients. Full Analysis Set (FAS) with last observation carried forward (LOCF). FAS - all treatment naive patients randomised and treated who had a baseline and at least 1 on treatment HbA1c value.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 24 Weeks

Notes:

[33] - 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: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

| End point values                    | Treatment Naive:<br>Empagliflozin 25 mg/linagliptin 5 mg | Treatment Naive:<br>Empagliflozin 10 mg/linagliptin 5 mg | Treatment Naive:<br>Empagliflozin 25 mg | Treatment Naive:<br>Empagliflozin 10 mg |
|-------------------------------------|--|--|---|---|
| Subject group type                  | Reporting group  | Reporting group  | Reporting group                         | Reporting group                         |
| Number of subjects analysed         | 134 <sup>[34]</sup>                                      | 135 <sup>[35]</sup>                                      | 133 <sup>[36]</sup>                     | 132 <sup>[37]</sup>                     |
| Units: kg change from baseline      |  |  |   |   |
| least squares mean (standard error) | -2 (± 0.36)  | -2.74 (± 0.36)   | -2.13 (± 0.36)                          | -2.27 (± 0.37)                          |

Notes:

[34] - FAS (LOCF)

[35] - FAS (LOCF)

[36] - FAS (LOCF)

[37] - FAS (LOCF)

| End point values                    | Treatment Naive:<br>Linagliptin 5 mg |  |  |  |
|-------------------------------------|--------------------------------------|--|--|--|
| Subject group type                  | Reporting group                      |  |  |  |
| Number of subjects analysed         | 133 <sup>[38]</sup>                  |  |  |  |
| Units: kg change from baseline      |                                      |  |  |  |
| least squares mean (standard error) | -0.78 (± 0.36)                       |  |  |  |

Notes:

[38] - FAS (LOCF)

## Statistical analyses

| Statistical analysis title  | Naive: Empa/Lina 25/5 versus Empa 25   |
|---|--|
| Statistical analysis description:   |  |
| Model for Week 24 includes baseline weight ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.0023$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.0316$ ), geographical region ( $p = 0.0134$ ), treatment ( $p = 0.0031$ ) as fixed effect(s). |  |
| Treatment difference calculated as: Empa/Lina 25/5 minus Empa 25.   |  |
| Comparison groups   | Treatment Naive: Empagliflozin 25 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis   | 267  |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.801 <sup>[39]</sup>  |
| Method  | ANCOVA   |
| Parameter estimate  | Mean difference (net)  |
| Point estimate  | 0.13   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | -0.88  |
| upper limit   | 1.14   |
| Variability estimate  | Standard error of the mean   |
| Dispersion value  | 0.51   |

Notes:

[39] - Not an alpha protected test.

| Statistical analysis title  | Naive: Empa/Lina 10/5 versus Empa 10   |
|---|--|
| Statistical analysis description:   |  |
| Model for Week 24 includes baseline weight ( $p < 0.0001$ ), baseline HbA1c ( $p = 0.0023$ ) as linear covariate(s) and baseline eGFR (MDRD) ( $p = 0.0316$ ), geographical region ( $p = 0.0134$ ), treatment ( $p = 0.0031$ ) as fixed effect(s). |  |
| Treatment difference calculated as: Empa/Lina 10/5 minus Empa 10.   |  |
| Comparison groups   | Treatment Naive: Empagliflozin 10 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis   | 267  |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.3616 <sup>[40]</sup>   |
| Method  | ANCOVA   |
| Parameter estimate  | Mean difference (net)  |
| Point estimate  | -0.47  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | -1.48  |
| upper limit   | 0.54   |
| Variability estimate  | Standard error of the mean   |
| Dispersion value  | 0.51   |

Notes:

[40] - Not an alpha protected test.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Naive: Empa/Lina 25/5 versus Lina 5   |
| Statistical analysis description:   |   |
| Model for Week 24 includes baseline weight (p<0.0001), baseline HbA1c (p=0.0023) as linear covariate(s) and baseline eGFR (MDRD) (p=0.0316), geographical region (p=0.0134), treatment (p=0.0031) as fixed effect(s). |   |
| Treatment difference calculated as: Empa/Lina 25/5 minus Lina 5.  |   |
| Comparison groups   | Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis   | 267   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.0178  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (net)   |
| Point estimate  | -1.22   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -2.23   |
| upper limit   | -0.21   |
| Variability estimate  | Standard error of the mean  |
| Dispersion value  | 0.51  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Naive: Empa/Lina 10/5 versus Lina 5   |
| Statistical analysis description:   |   |
| Model for Week 24 includes baseline weight (p<0.0001), baseline HbA1c (p=0.0023) as linear covariate(s) and baseline eGFR (MDRD) (p=0.0316), geographical region (p=0.0134), treatment (p=0.0031) as fixed effect(s). |   |
| Treatment difference calculated as: Empa/Lina 10/5 minus Lina 5.  |   |
| Comparison groups   | Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis   | 268   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.0001  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (net)   |
| Point estimate  | -1.96   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -2.97   |
| upper limit   | -0.95   |
| Variability estimate  | Standard error of the mean  |
| Dispersion value  | 0.51  |

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## Secondary: Occurrence of treat to target efficacy response for Metformin

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## Background patients

|                 |   |
|-----------------|---|
| End point title | Occurrence of treat to target efficacy response for Metformin Background patients <sup>[41]</sup> |
|-----------------|---|

End point description:

Occurrence of the treat-to-target efficacy response for Metformin Background patients measured as HbA1c < 7.0% after 24 weeks of treatment for patients with HbA1c ≥ 7.0% at baseline. Full Analysis Set (FAS) with non-completers considered failures (NCF). FAS- Metformin background patients randomised and treated who had a baseline (HbA1c ≥ 7% at baseline are included) and at least 1 on treatment HbA1c value with NCF approach, in which missing data due to premature discontinuation of a patient were considered as failure.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 Weeks

Notes:

[41] - 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: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

| End point values                             | Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg | Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg | Metformin Background: Empagliflozin 25 mg | Metformin Background: Empagliflozin 10 mg |
|--|--|--|---|---|
| Subject group type                           | Reporting group  | Reporting group  | Reporting group                           | Reporting group                           |
| Number of subjects analysed                  | 123 <sup>[42]</sup>  | 128 <sup>[43]</sup>  | 132 <sup>[44]</sup>                       | 125 <sup>[45]</sup>                       |
| Units: % of patients satisfying HbA1c < 7.0% |  |  |   |   |
| number (confidence interval 95%)             | 61.8 (52.6 to 70.4)  | 57.8 (48.8 to 66.5)  | 32.6 (24.7 to 41.3)                       | 28 (20.3 to 36.7)                         |

Notes:

[42] - FAS (NCF)

[43] - FAS (NCF)

[44] - FAS (NCF)

[45] - FAS (NCF)

| End point values                             | Metformin Background: Linagliptin 5 mg |  |  |  |
|--|--|--|--|--|
| Subject group type                           | Reporting group                        |  |  |  |
| Number of subjects analysed                  | 119 <sup>[46]</sup>                    |  |  |  |
| Units: % of patients satisfying HbA1c < 7.0% |  |  |  |  |
| number (confidence interval 95%)             | 36.1 (27.5 to 45.4)                    |  |  |  |

Notes:

[46] - FAS (NCF)

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Metformin: Empa/Lina 25/5 versus Empa 25 |
|----------------------------|--|

Statistical analysis description:

Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.

Odds ratio for Empa/Lina 25/5 versus Empa 25.

|   |  |
|---|--|
| Comparison groups                       | Metformin Background: Empagliflozin 25 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 255  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | < 0.0001   |
| Method                                  | Regression, Logistic   |
| Parameter estimate                      | Odds ratio (OR)  |
| Point estimate                          | 4.191  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 2.319  |
| upper limit                             | 7.573  |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Metformin: Empa/Lina 10/5 versus Empa 10 |
|-----------------------------------|--|

Statistical analysis description:

Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.

Odds ratio for Empa/Lina 10/5 versus Empa 10

|   |  |
|---|--|
| Comparison groups                       | Metformin Background: Empagliflozin 10 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 253  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | < 0.0001   |
| Method                                  | Regression, Logistic   |
| Parameter estimate                      | Odds ratio (OR)  |
| Point estimate                          | 4.5  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 2.474  |
| upper limit                             | 8.184  |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Metformin: Empa/Lina 25/5 versus Lina 5 |
|-----------------------------------|---|

Statistical analysis description:

Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.

Odds ratio for Empa/Lina 25/5 versus Lina 5.

|   |   |
|---|---|
| Comparison groups                       | Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 242   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | < 0.0001  |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)   |
| Point estimate                          | 3.495   |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 1.92    |
| upper limit         | 6.363   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Metformin: Empa/Lina 10/5 versus Lina 5 |
|-----------------------------------|---|

Statistical analysis description:

Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c.

Odds ratio for Empa/Lina 10/5 versus Lina 5.

|   |   |
|---|---|
| Comparison groups                       | Metformin Background: Linagliptin 5 mg v Metformin Background: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis | 247   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | = 0.0005  |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)   |
| Point estimate                          | 2.795   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 1.562   |
| upper limit                             | 5.001   |

## Secondary: Occurrence of treat to target efficacy response for Treatment Naive patients

|                 |  |
|-----------------|--|
| End point title | Occurrence of treat to target efficacy response for Treatment Naive patients <sup>[47]</sup> |
|-----------------|--|

End point description:

Occurrence of the treat-to-target efficacy response for Treatment Naive patients measured as HbA1c < 7.0% after 24 weeks of treatment for patients with HbA1c ≥ 7.0% at baseline.

Full Analysis Set (FAS) with non-completers considered failures (NCF). FAS-treatment naive patients randomised and treated who had a baseline (HbA1c ≥ 7% at baseline are included) and at least 1 on treatment HbA1c value with NCF approach, in which missing data due to premature discontinuation of a patient were considered as failure.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 Weeks

Notes:

[47] - 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: Endpoints are presented separately for metformin patients versus treatment naive patients. Baseline characteristics are presented for both groups combined.

| <b>End point values</b>                     | Treatment Naive:<br>Empagliflozin 25 mg/linagliptin 5 mg | Treatment Naive:<br>Empagliflozin 10 mg/linagliptin 5 mg | Treatment Naive:<br>Empagliflozin 25 mg | Treatment Naive:<br>Empagliflozin 10 mg |
|---|--|--|---|---|
| Subject group type                          | Reporting group  | Reporting group  | Reporting group                         | Reporting group                         |
| Number of subjects analysed                 | 121 <sup>[48]</sup>                                      | 122 <sup>[49]</sup>                                      | 118 <sup>[50]</sup>                     | 121 <sup>[51]</sup>                     |
| Units: % of patients satisfying HbA1c <7.0% |  |  |   |   |
| number (confidence interval 95%)            | 55.4 (46.1 to 64.4)                                      | 62.3 (53.1 to 70.9)                                      | 41.5 (32.5 to 51)                       | 38.8 (30.1 to 48.1)                     |

Notes:

[48] - FAS (NCF)

[49] - FAS (NCF)

[50] - FAS (NCF)

[51] - FAS (NCF)

| <b>End point values</b>                     | Treatment Naive:<br>Linagliptin 5 mg |  |  |  |
|---|--------------------------------------|--|--|--|
| Subject group type                          | Reporting group                      |  |  |  |
| Number of subjects analysed                 | 127 <sup>[52]</sup>                  |  |  |  |
| Units: % of patients satisfying HbA1c <7.0% |                                      |  |  |  |
| number (confidence interval 95%)            | 32.3 (24.3 to 41.2)                  |  |  |  |

Notes:

[52] - FAS (NCF)

## Statistical analyses

| <b>Statistical analysis title</b>   | Naive: Empa/Lina 25/5 versus Empa 25   |
|---|--|
| Statistical analysis description:   |  |
| Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c. |  |
| Odds ratio for Empa/Lina 25/5 versus Empa 25.   |  |
| Comparison groups   | Treatment Naive: Empagliflozin 25 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis   | 239  |
| Analysis specification  | Pre-specified  |
| Analysis type   | other  |
| P-value   | = 0.0224   |
| Method  | Regression, Logistic   |
| Parameter estimate  | Odds ratio (OR)  |
| Point estimate  | 1.893  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 1.095  |
| upper limit   | 3.274  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Naive: Empa/Lina 10/5 versus Empa 10   |
| Statistical analysis description:   |  |
| Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c. |  |
| Odds ratio for Empa/Lina 10/5 versus Empa 10.   |  |
| Comparison groups   | Treatment Naive: Empagliflozin 10 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg |
| Number of subjects included in analysis   | 243  |
| Analysis specification  | Pre-specified  |
| Analysis type   | other  |
| P-value   | = 0.0001   |
| Method  | Regression, Logistic   |
| Parameter estimate  | Odds ratio (OR)  |
| Point estimate  | 2.961  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 1.697  |
| upper limit   | 5.169  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Naive: Empa/Lina 25/5 versus Lina 5   |
| Statistical analysis description:   |   |
| Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c. |   |
| Odds ratio for Empa/Lina 25/5 versus Lina 5.  |   |
| Comparison groups   | Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 25 mg/linagliptin 5 mg |
| Number of subjects included in analysis   | 248   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other   |
| P-value   | < 0.0001  |
| Method  | Regression, Logistic  |
| Parameter estimate  | Odds ratio (OR)   |
| Point estimate  | 3.065   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 1.768   |
| upper limit   | 5.314   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Naive: Empa/Lina 10/5 versus Lina 5   |
| Statistical analysis description:   |   |
| Logistic regression includes treatment, baseline eGFR (MDRD), geographical region and baseline HbA1c. |   |
| Odds ratio for Empa/Lina 10/5 versus Lina 5.  |   |
| Comparison groups   | Treatment Naive: Linagliptin 5 mg v Treatment Naive: Empagliflozin 10 mg/linagliptin 5 mg |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 249                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | other                |
| P-value                                 | < 0.0001             |
| Method                                  | Regression, Logistic |
| Parameter estimate                      | Odds ratio (OR)      |
| Point estimate                          | 4.303                |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 2.462                |
| upper limit                             | 7.522                |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first trial medication intake until 7 days after last drug intake during the 52-week study period.

Adverse event reporting additional description:

One patient was randomized to treatment with Empa/Lina 25/5 but was treated with Empa 10 from the start of trial for 6 weeks. For efficacy, the patient was analyzed as randomized (Empa/Lina 25/5) and for safety the patient was analyzed as first medication taken (Empa 10).

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Empagliflozin 25 mg/Linagliptin 5 mg |
|-----------------------|--------------------------------------|

Reporting group description:

Test product: Empagliflozin/linagliptin FDC tablets dose: 25 mg/5 mg q.d. mode of admin.: Oral

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Empagliflozin 10 mg/Linagliptin 5 mg |
|-----------------------|--------------------------------------|

Reporting group description:

Test product: Empagliflozin/linagliptin FDC tablets dose: 10 mg/5 mg q.d. mode of admin.: Oral

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Empagliflozin 25 mg |
|-----------------------|---------------------|

Reporting group description:

Reference therapy 1: Empagliflozin tablets dose: 25 mg q.d. mode of admin.: Oral

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Empagliflozin 10 mg |
|-----------------------|---------------------|

Reporting group description:

Reference therapy 1: Empagliflozin tablets dose: 10 mg q.d. mode of admin.: Oral

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Linagliptin 5 mg |
|-----------------------|------------------|

Reporting group description:

Reference therapy 2: Linagliptin tablets dose: 5 mg q.d. mode of admin.: Oral

| Serious adverse events  | Empagliflozin 25 mg/Linagliptin 5 mg | Empagliflozin 10 mg/Linagliptin 5 mg | Empagliflozin 25 mg |
|---|--------------------------------------|--------------------------------------|---------------------|
| Total subjects affected by serious adverse events                   |                                      |                                      |                     |
| subjects affected / exposed   | 12 / 273 (4.40%)                     | 16 / 272 (5.88%)                     | 19 / 276 (6.88%)    |
| number of deaths (all causes)                                       | 0                                    | 2                                    | 3                   |
| number of deaths resulting from adverse events                      | 0                                    | 0                                    | 1                   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                      |                                      |                     |
| Adenoid cystic carcinoma  |                                      |                                      |                     |
| subjects affected / exposed   | 0 / 273 (0.00%)                      | 0 / 272 (0.00%)                      | 0 / 276 (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               |
| Basal cell carcinoma  |                                      |                                      |                     |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Breast cancer                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Clear cell renal cell carcinoma                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal carcinoma                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Lung adenocarcinoma                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Lung neoplasm                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Metastases to peritoneum                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Non-small cell lung cancer metastatic           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Ovarian cancer                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Parathyroid tumour benign                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal cancer                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Squamous cell carcinoma                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Uterine leiomyoma                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Hypotension                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Varicose vein                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Surgical and medical procedures                 |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Finger amputation                                    |                 |                 |                 |
| subjects affected / exposed                          | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Chest pain   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 273 (0.00%) | 2 / 272 (0.74%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Non-cardiac chest pain                               |                 |                 |                 |
| subjects affected / exposed                          | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Reproductive system and breast disorders             |                 |                 |                 |
| Ovarian cyst   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Postmenopausal haemorrhage                           |                 |                 |                 |
| subjects affected / exposed                          | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectocele  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| 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      |                 |                 |                 |
| Acute respiratory failure                            |                 |                 |                 |
| subjects affected / exposed                          | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Pulmonary embolism                                   |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Psychiatric disorders                           |                 |                 |                 |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mental status changes                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Troponin increased                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Chemical injury                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Fibula fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint dislocation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Lower limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Road traffic accident                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Seroma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Tendon rupture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| 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                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery occlusion                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Hypertensive heart disease                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Palpitations                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Silent myocardial infarction                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Brain oedema                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Cerebral infarction                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Dementia Alzheimer's type                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Encephalopathy                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic stroke                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Lethargy  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal adhesions                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Abdominal strangulated hernia                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis ischaemic                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Intestinal perforation                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Mechanical ileus                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Pancreatitis chronic                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 2 / 276 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic mass                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Diabetic foot                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Renal and urinary disorders                     |                 |                 |                 |
| Calculus bladder                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Calculus ureteric                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hydronephrosis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal colic                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Renal failure acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Flank pain                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myofascial pain syndrome                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rotator cuff syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Infections and infestations                     |                 |                 |                 |
| Bacterial infection                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cystitis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 1 / 272 (0.37%) | 0 / 276 (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           |
| Encephalitis viral                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Meningitis tuberculous                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Peritonitis                                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Pneumonia viral                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Pyelonephritis acute                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Pyelonephritis chronic                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tooth abscess                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 273 (0.37%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Alkalosis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Dehydration                                     |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 1 / 276 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperglycaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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           |
| Hypokalaemia                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 273 (0.00%) | 0 / 272 (0.00%) | 0 / 276 (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>                                       | Empagliflozin 10 mg | Linagliptin 5 mg |  |
|---|---------------------|------------------|--|
| Total subjects affected by serious adverse events                   |                     |                  |  |
| subjects affected / exposed   | 16 / 275 (5.82%)    | 10 / 267 (3.75%) |  |
| number of deaths (all causes)                                       | 2                   | 0                |  |
| number of deaths resulting from adverse events                      | 0                   | 0                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |                  |  |
| Adenoid cystic carcinoma  |                     |                  |  |
| subjects affected / exposed   | 1 / 275 (0.36%)     | 0 / 267 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1               | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0            |  |
| Basal cell carcinoma  |                     |                  |  |
| subjects affected / exposed   | 0 / 275 (0.00%)     | 0 / 267 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0            |  |
| Breast cancer   |                     |                  |  |
| subjects affected / exposed   | 0 / 275 (0.00%)     | 0 / 267 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0            |  |
| Clear cell renal cell carcinoma                                     |                     |                  |  |
| subjects affected / exposed   | 0 / 275 (0.00%)     | 0 / 267 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0            |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Gastrointestinal carcinoma                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung adenocarcinoma                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung neoplasm                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Metastases to peritoneum                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Non-small cell lung cancer metastatic           |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Ovarian cancer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Parathyroid tumour benign                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prostate cancer                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal cancer                                    |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma                              |                 |                 |  |
| subjects affected / exposed                          | 0 / 275 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Uterine leiomyoma                                    |                 |                 |  |
| subjects affected / exposed                          | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                   |                 |                 |  |
| Hypotension  |                 |                 |  |
| subjects affected / exposed                          | 0 / 275 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Varicose vein  |                 |                 |  |
| subjects affected / exposed                          | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                      |                 |                 |  |
| Finger amputation                                    |                 |                 |  |
| subjects affected / exposed                          | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Non-cardiac chest pain                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Reproductive system and breast disorders        |                 |                 |  |
| Ovarian cyst                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postmenopausal haemorrhage                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectocele                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mental status changes                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Troponin increased                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Chemical injury                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fibula fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint dislocation                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rib fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Seroma  |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tendon rupture                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery occlusion                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertensive heart disease                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Palpitations                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Silent myocardial infarction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Brain oedema                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dementia Alzheimer's type                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic stroke                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lethargy  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 275 (0.73%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal adhesions                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal strangulated hernia                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis ischaemic                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal perforation                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mechanical ileus                                |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis chronic                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic mass                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Diabetic foot                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Calculus bladder                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Calculus ureteric                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Hydronephrosis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal colic                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Flank pain                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myofascial pain syndrome                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rotator cuff syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Bacterial infection                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalitis viral                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis tuberculous                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia viral                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis acute                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis chronic                          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tooth abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Alkalosis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 275 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 275 (0.36%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Empagliflozin 25 mg/Linagliptin 5 mg | Empagliflozin 10 mg/Linagliptin 5 mg | Empagliflozin 25 mg |
|---|--------------------------------------|--------------------------------------|---------------------|
| Total subjects affected by non-serious adverse events |                                      |                                      |                     |
| subjects affected / exposed                           | 80 / 273 (29.30%)                    | 86 / 272 (31.62%)                    | 70 / 276 (25.36%)   |
| Nervous system disorders                              |                                      |                                      |                     |
| Headache  |                                      |                                      |                     |
| subjects affected / exposed                           | 16 / 273 (5.86%)                     | 15 / 272 (5.51%)                     | 13 / 276 (4.71%)    |
| occurrences (all)                                     | 18                                   | 27                                   | 18                  |
| Musculoskeletal and connective tissue disorders       |                                      |                                      |                     |
| Arthralgia  |                                      |                                      |                     |
| subjects affected / exposed                           | 5 / 273 (1.83%)                      | 14 / 272 (5.15%)                     | 13 / 276 (4.71%)    |
| occurrences (all)                                     | 6                                    | 16                                   | 17                  |
| Infections and infestations                           |                                      |                                      |                     |
| Nasopharyngitis                                       |                                      |                                      |                     |
| subjects affected / exposed                           | 18 / 273 (6.59%)                     | 16 / 272 (5.88%)                     | 10 / 276 (3.62%)    |
| occurrences (all)                                     | 19                                   | 18                                   | 13                  |
| Upper respiratory tract infection                     |                                      |                                      |                     |
| subjects affected / exposed                           | 19 / 273 (6.96%)                     | 19 / 272 (6.99%)                     | 18 / 276 (6.52%)    |
| occurrences (all)                                     | 23                                   | 23                                   | 22                  |
| Urinary tract infection                               |                                      |                                      |                     |
| subjects affected / exposed                           | 27 / 273 (9.89%)                     | 29 / 272 (10.66%)                    | 25 / 276 (9.06%)    |
| occurrences (all)                                     | 35                                   | 38                                   | 36                  |
| Metabolism and nutrition disorders                    |                                      |                                      |                     |
| Hyperglycaemia  |                                      |                                      |                     |
| subjects affected / exposed                           | 8 / 273 (2.93%)                      | 8 / 272 (2.94%)                      | 12 / 276 (4.35%)    |
| occurrences (all)                                     | 8                                    | 12                                   | 17                  |

| <b>Non-serious adverse events</b>                     | Empagliflozin 10 mg | Linagliptin 5 mg  |  |
|---|---------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                     |                   |  |
| subjects affected / exposed                           | 83 / 275 (30.18%)   | 94 / 267 (35.21%) |  |
| Nervous system disorders                              |                     |                   |  |
| Headache  |                     |                   |  |
| subjects affected / exposed                           | 19 / 275 (6.91%)    | 24 / 267 (8.99%)  |  |
| occurrences (all)                                     | 24                  | 28                |  |
| Musculoskeletal and connective tissue disorders       |                     |                   |  |

|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                        | 10 / 275 (3.64%)<br>13  | 12 / 267 (4.49%)<br>12  |  |
| Infections and infestations   |                         |                         |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 16 / 275 (5.82%)<br>18  | 20 / 267 (7.49%)<br>29  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 13 / 275 (4.73%)<br>15  | 16 / 267 (5.99%)<br>19  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 30 / 275 (10.91%)<br>34 | 27 / 267 (10.11%)<br>31 |  |
| Metabolism and nutrition disorders  |                         |                         |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                    | 12 / 275 (4.36%)<br>14  | 24 / 267 (8.99%)<br>28  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 27 January 2012  | <p>The amendment dated 27 Jan 2012 (approximately 5 months after trial initiation) introduced the following sponsor-initiated changes and clarifications after being approved by the IRB/IEC/CA: The protocol was revised to update the new co-ordinating investigator information in the trial. Increased number of entered patients: As per FDA request, the modified ITT population was to be used as the full analysis set, changed from the ITT population which included all randomised patients. The modified ITT population included all randomised patients who were treated with at least 1 dose of trial medication, had a baseline HbA1c measurement, and had at least 1 on-treatment HbA1c measurement. Considering the anticipated patient discontinuation in the trial before the first on-treatment HbA1c measurement, additional 30 patients were to be entered in the trial. The Screening study day in the flowchart was modified to clarify that the maximum time allowed from Visit 1 date to Visit 3 was 35 days.</p> <p>Description of DILI (drug-induced liver injury), definition of always serious AEs, and an appendix with further instruction on DILI handling were added in the protocol to fulfil the recommendation of the current FDA guidance. The CEC responsibility description was revised to clarify and reflect the current FDA guidance regarding evaluation of cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Known hypersensitivity or allergy to DPP4-inhibitors was added as exclusion criteria according to the FDA recommendation. A secondary analysis of the change from baseline in HbA1c after 24 weeks of treatment for the full analysis set including completers only was added according to FDA recommendation.</p> |
| 11 December 2012 | <p>The amendment dated 11 Dec 2012 (approximately 15.5 months after trial initiation) introduced the following sponsor-initiated changes and clarifications from logistical or administrative aspects which were implemented without the approval from IRB/IEC/CA: The other exploratory endpoint investigating the treat-to-target efficacy response of HbA1c &lt;7.0% after 24 weeks of treatment was redefined as a key secondary endpoint. The endpoint was included into the confirmatory testing structure performed at 24 weeks. For the key secondary endpoint of change in body weight after 24 weeks of treatment, the comparison between the FDCs and empagliflozin was removed and redefined as other efficacy endpoint. Detailed information on DBL, treatment unblinding, and data planned to be analysed for the Week 24 confirmatory analysis were added to clarify that all confirmatory statistical analyses on the primary and key secondary endpoints were to be performed at Week 24. Laboratory tests were added and description for the clinical evaluation of liver injury was corrected to be consistent with the ISF DILI checklist and DILI laboratory kit.</p>   |
| 07 June 2013     | <p>The amendment dated 07 Jun 2013 (approximately 1 year and 9 months after trial initiation) introduced the following sponsor-initiated changes and was implemented immediately in order to eliminate hazard and required IRB/IEC/CA to be notified of change with request for approval. Treatment discontinuation instructions were updated to include the criterion "if pancreatitis was suspected, the study treatment was to be stopped". This amendment was introduced after the DBL of primary analysis on 20 Mar 2013; hence it was not included in the primary analysis report.</p>   |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported