



## Clinical trial results:

**A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus.**

### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2016-000669-21             |
| Trial protocol           | PT Outside EU/EEA DE NL GB |
| Global end of trial date | 31 May 2023                |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 14 December 2023 |
| First version publication date | 14 December 2023 |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | 1218-0091 |
|-----------------------|-----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03429543 |
| 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               | Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127 x 001, clintrriage.rdg@boehringer-ingelheim.com |
| Scientific contact           | Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127 x 001, clintrriage.rdg@boehringer-ingelheim.com |

Notes:

### Paediatric regulatory details

|                                                                      |                     |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000498-PIP01-08 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No                  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes                 |

Notes:

## Results analysis stage

|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 20 June 2023 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 03 May 2023  |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 31 May 2023  |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The objective of DINAMO was to assess the efficacy and safety of 1 dose of linagliptin and an empagliflozin dosing regimen versus placebo after 26 weeks of treatment in children and adolescents with type 2 diabetes mellitus (T2DM) who were treated with metformin and/or insulin or who were not tolerating metformin. In addition, this trial assessed the long-term safety of empagliflozin and linagliptin after 52 weeks of treatment.

The objective of DINAMO Mono was to explore the effect of an empagliflozin dosing regimen and one dose of linagliptin as Monotherapy in children and adolescents with type 2 diabetes mellitus.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be 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 subjects as required.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 26 April 2018 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 2           |
| Country: Number of subjects enrolled | Brazil: 6              |
| Country: Number of subjects enrolled | Canada: 7              |
| Country: Number of subjects enrolled | China: 3               |
| Country: Number of subjects enrolled | Colombia: 2            |
| Country: Number of subjects enrolled | Germany: 3             |
| Country: Number of subjects enrolled | Israel: 10             |
| Country: Number of subjects enrolled | Korea, Republic of: 5  |
| Country: Number of subjects enrolled | Mexico: 48             |
| Country: Number of subjects enrolled | Russian Federation: 21 |
| Country: Number of subjects enrolled | Thailand: 4            |
| Country: Number of subjects enrolled | United Kingdom: 3      |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 187 |
| Worldwide total number of subjects   | 301                |
| EEA total number of subjects         | 3                  |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 19  |
| Adolescents (12-17 years)                 | 282 |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Randomised, double-blind, placebo-controlled and parallel group design of 3 treatment arms (placebo, linagliptin 5 mg, empagliflozin 10 mg) over 26 weeks with a possible dose increase of empagliflozin 10 mg to 25 mg at Week 14 in non-responder patients and an active treatment safety period up to 52 weeks.

### Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

### Period 1

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

Blinding implementation details:

Patients, investigators, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial remained blinded with regard to the randomised treatment assignments until after database lock.

### Arms

|                              |                                |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes                            |
| <b>Arm title</b>             | Placebo - DINAMO & DINAMO Mono |

Arm description:

Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily, until end of treatment.

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

Dosage and administration details:

1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily.

|                  |                                                   |
|------------------|---------------------------------------------------|
| <b>Arm title</b> | Placebo - Linagliptin 5 mg - DINAMO & DINAMO Mono |
|------------------|---------------------------------------------------|

Arm description:

Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily. At week 26, patients were re-randomised to receive 5 milligram (mg) Linagliptin, taken once daily, until end of treatment.

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

Dosage and administration details:

1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily.

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

Dosage and administration details:

1 film-coated tablet of 5 milligram (mg) Linagliptin once daily.

|                  |                                                      |
|------------------|------------------------------------------------------|
| <b>Arm title</b> | Placebo - Empagliflozin 10 mg - DINAMO & DINAMO Mono |
|------------------|------------------------------------------------------|

Arm description:

Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily. At week 26, patients were re-randomised to receive 10 milligram (mg) empagliflozin, taken once daily, until end of treatment.

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

Dosage and administration details:

1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily.

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

Dosage and administration details:

1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily.

|                  |                                                      |
|------------------|------------------------------------------------------|
| <b>Arm title</b> | Placebo - Empagliflozin 25 mg - DINAMO & DINAMO Mono |
|------------------|------------------------------------------------------|

Arm description:

Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily. At week 26, patients were re-randomised to receive 25 milligram (mg) empagliflozin, taken once daily, until end of treatment.

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

Dosage and administration details:

1 film-coated tablet of 25 milligram (mg) Empagliflozin once daily.

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

Dosage and administration details:

1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily.

|                  |                                         |
|------------------|-----------------------------------------|
| <b>Arm title</b> | Linagliptin 5 mg - DINAMO & DINAMO Mono |
|------------------|-----------------------------------------|

Arm description:

Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-

naïve patients or patients who are not on active treatment took 1 film-coated tablet of 5 milligram (mg) Linagliptin once daily, until end of treatment.

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

Dosage and administration details:

1 film-coated tablet of 5 milligram (mg) Linagliptin once daily.

|                  |                                            |
|------------------|--------------------------------------------|
| <b>Arm title</b> | Empagliflozin 10 mg - DINAMO & DINAMO Mono |
|------------------|--------------------------------------------|

Arm description:

Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily, until Week 14. Responder patients were not re-randomised at week 14 and continued 10 mg empagliflozin, taken once daily, until end of treatment. Non responder patients were re-randomised at Week 14 to receive 10 mg empagliflozin, taken once daily, until end of treatment.

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

Dosage and administration details:

1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily.

|                  |                                                    |
|------------------|----------------------------------------------------|
| <b>Arm title</b> | Empagliflozin 10 mg - 25 mg - DINAMO & DINAMO Mono |
|------------------|----------------------------------------------------|

Arm description:

Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily until Week 14. Non responder patients were re-randomised at Week 14 to receive 25 mg empagliflozin, taken once daily, until end of treatment.

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

Dosage and administration details:

1 film-coated tablet of 25 milligram (mg) Empagliflozin once daily.

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

Dosage and administration details:

1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily.

| Number of subjects in period 1 <sup>[1]</sup> | Placebo - DINAMO & DINAMO Mono | Placebo - Linagliptin 5 mg - DINAMO & DINAMO Mono | Placebo - Empagliflozin 10 mg - DINAMO & DINAMO Mono |
|-----------------------------------------------|--------------------------------|---------------------------------------------------|------------------------------------------------------|
|                                               |                                |                                                   |                                                      |
| Started                                       | 7                              | 19                                                | 16                                                   |
| Treated                                       | 7                              | 19                                                | 16                                                   |
| Completed                                     | 0                              | 17                                                | 15                                                   |
| Not completed                                 | 7                              | 2                                                 | 1                                                    |
| Consent withdrawn by subject                  | 5                              | -                                                 | 1                                                    |
| Adverse event, non-fatal                      | 1                              | 1                                                 | -                                                    |
| Other reason than listed                      | -                              | 1                                                 | -                                                    |
| Lost to follow-up                             | 1                              | -                                                 | -                                                    |
| Not treated                                   | -                              | -                                                 | -                                                    |

| Number of subjects in period 1 <sup>[1]</sup> | Placebo - Empagliflozin 25 mg - DINAMO & DINAMO Mono | Linagliptin 5 mg - DINAMO & DINAMO Mono | Empagliflozin 10 mg - DINAMO & DINAMO Mono |
|-----------------------------------------------|------------------------------------------------------|-----------------------------------------|--------------------------------------------|
|                                               |                                                      |                                         |                                            |
| Started                                       | 16                                                   | 59                                      | 45                                         |
| Treated                                       | 16                                                   | 58                                      | 45                                         |
| Completed                                     | 14                                                   | 47                                      | 36                                         |
| Not completed                                 | 2                                                    | 12                                      | 9                                          |
| Consent withdrawn by subject                  | 2                                                    | 6                                       | 3                                          |
| Adverse event, non-fatal                      | -                                                    | -                                       | 2                                          |
| Other reason than listed                      | -                                                    | 4                                       | 4                                          |
| Lost to follow-up                             | -                                                    | 1                                       | -                                          |
| Not treated                                   | -                                                    | 1                                       | -                                          |

| Number of subjects in period 1 <sup>[1]</sup> | Empagliflozin 10 mg - 25 mg - DINAMO & DINAMO Mono |
|-----------------------------------------------|----------------------------------------------------|
| Started                                       | 13                                                 |
| Treated                                       | 13                                                 |
| Completed                                     | 12                                                 |
| Not completed                                 | 1                                                  |
| Consent withdrawn by subject                  | 1                                                  |
| Adverse event, non-fatal                      | -                                                  |
| Other reason than listed                      | -                                                  |
| Lost to follow-up                             | -                                                  |
| Not treated                                   | -                                                  |

Notes:

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

Justification: Out of the 301 enrolled subjects, 175 were randomised.

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Placebo - DINAMO & DINAMO Mono                       |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily, until end of treatment.                                                                                                                                                                                                                                     |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Placebo - Linagliptin 5 mg - DINAMO & DINAMO Mono    |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily. At week 26, patients were re-randomised to receive 5 milligram (mg) Linagliptin, taken once daily, until end of treatment.                                                                                                                                  |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Placebo - Empagliflozin 10 mg - DINAMO & DINAMO Mono |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily. At week 26, patients were re-randomised to receive 10 milligram (mg) empagliflozin, taken once daily, until end of treatment.                                                                                                                               |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Placebo - Empagliflozin 25 mg - DINAMO & DINAMO Mono |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily. At week 26, patients were re-randomised to receive 25 milligram (mg) empagliflozin, taken once daily, until end of treatment.                                                                                                                               |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Linagliptin 5 mg - DINAMO & DINAMO Mono              |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of 5 milligram (mg) Linagliptin once daily, until end of treatment.                                                                                                                                                                                                                                                            |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Empagliflozin 10 mg - DINAMO & DINAMO Mono           |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily, until Week 14. Responder patients were not re-randomised at week 14 and continued 10 mg empagliflozin, taken once daily, until end of treatment. Non responder patients were re-randomised at Week 14 to receive 10 mg empagliflozin, taken once daily, until end of treatment. |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Empagliflozin 10 mg - 25 mg - DINAMO & DINAMO Mono   |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily until Week 14. Non responder patients were re-randomised at Week 14 to receive 25 mg empagliflozin, taken once daily, until end of treatment.                                                                                                                                    |                                                      |

| Reporting group values                                                                                   | Placebo - DINAMO & DINAMO Mono | Placebo - Linagliptin 5 mg - DINAMO & DINAMO Mono | Placebo - Empagliflozin 10 mg - DINAMO & DINAMO Mono |
|----------------------------------------------------------------------------------------------------------|--------------------------------|---------------------------------------------------|------------------------------------------------------|
| Number of subjects                                                                                       | 7                              | 19                                                | 16                                                   |
| Age categorical                                                                                          |                                |                                                   |                                                      |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |                                |                                                   |                                                      |
| Units: Subjects                                                                                          |                                |                                                   |                                                      |

|                         |   |    |   |
|-------------------------|---|----|---|
| <15 years               | 3 | 10 | 8 |
| >=15 years to <18 years | 4 | 9  | 8 |

|                                                                                                          |        |        |        |
|----------------------------------------------------------------------------------------------------------|--------|--------|--------|
| Age Continuous                                                                                           |        |        |        |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |        |        |        |
| Units: years                                                                                             |        |        |        |
| arithmetic mean                                                                                          | 15.3   | 14.3   | 14.1   |
| standard deviation                                                                                       | ± 1.4  | ± 1.7  | ± 2.2  |
| Sex: Female, Male                                                                                        |        |        |        |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |        |        |        |
| Units: Participants                                                                                      |        |        |        |
| Female                                                                                                   | 6      | 12     | 11     |
| Male                                                                                                     | 1      | 7      | 5      |
| Race/Ethnicity, Customized                                                                               |        |        |        |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |        |        |        |
| Units: Subjects                                                                                          |        |        |        |
| American Indian/Alaska Native                                                                            | 0      | 1      | 0      |
| Asian                                                                                                    | 0      | 1      | 1      |
| Black/African American                                                                                   | 5      | 4      | 3      |
| Native Hawaiian or other Pacific Islander                                                                | 0      | 0      | 1      |
| White                                                                                                    | 1      | 13     | 10     |
| Other including mixed or missing race                                                                    | 1      | 0      | 1      |
| Ethnicity (NIH/OMB)                                                                                      |        |        |        |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |        |        |        |
| Units: Subjects                                                                                          |        |        |        |
| Hispanic or Latino                                                                                       | 1      | 10     | 5      |
| Not Hispanic or Latino                                                                                   | 6      | 9      | 11     |
| Unknown or Not Reported                                                                                  | 0      | 0      | 0      |
| Glycated haemoglobin (HbA1c) (%)                                                                         |        |        |        |
| Glycated haemoglobin (HbA1c) (%)                                                                         |        |        |        |
| Units: Percentage                                                                                        |        |        |        |
| arithmetic mean                                                                                          | 7.40   | 8.01   | 8.00   |
| standard deviation                                                                                       | ± 0.77 | ± 1.42 | ± 1.28 |

| Reporting group values                                                                                   | Placebo -<br>Empagliflozin 25 mg<br>- DINAMO &<br>DINAMO Mono | Linagliptin 5 mg -<br>DINAMO & DINAMO<br>Mono | Empagliflozin 10 mg<br>- DINAMO &<br>DINAMO Mono |
|----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------|
| Number of subjects                                                                                       | 16                                                            | 59                                            | 45                                               |
| Age categorical                                                                                          |                                                               |                                               |                                                  |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |                                                               |                                               |                                                  |
| Units: Subjects                                                                                          |                                                               |                                               |                                                  |
| <15 years                                                                                                | 8                                                             | 29                                            | 21                                               |
| >=15 years to <18 years                                                                                  | 8                                                             | 30                                            | 24                                               |
| Age Continuous                                                                                           |                                                               |                                               |                                                  |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |                                                               |                                               |                                                  |
| Units: years                                                                                             |                                                               |                                               |                                                  |

|                    |       |       |       |
|--------------------|-------|-------|-------|
| arithmetic mean    | 14.8  | 14.4  | 14.6  |
| standard deviation | ± 1.8 | ± 2.1 | ± 1.8 |

|                                                                                                          |        |        |        |
|----------------------------------------------------------------------------------------------------------|--------|--------|--------|
| Sex: Female, Male                                                                                        |        |        |        |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |        |        |        |
| Units: Participants                                                                                      |        |        |        |
| Female                                                                                                   | 8      | 36     | 31     |
| Male                                                                                                     | 8      | 23     | 14     |
| Race/Ethnicity, Customized                                                                               |        |        |        |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |        |        |        |
| Units: Subjects                                                                                          |        |        |        |
| American Indian/Alaska Native                                                                            | 0      | 3      | 4      |
| Asian                                                                                                    | 1      | 5      | 2      |
| Black/African American                                                                                   | 6      | 17     | 20     |
| Native Hawaiian or other Pacific Islander                                                                | 0      | 2      | 0      |
| White                                                                                                    | 9      | 28     | 17     |
| Other including mixed or missing race                                                                    | 0      | 4      | 2      |
| Ethnicity (NIH/OMB)                                                                                      |        |        |        |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |        |        |        |
| Units: Subjects                                                                                          |        |        |        |
| Hispanic or Latino                                                                                       | 7      | 24     | 12     |
| Not Hispanic or Latino                                                                                   | 9      | 35     | 33     |
| Unknown or Not Reported                                                                                  | 0      | 0      | 0      |
| Glycated haemoglobin (HbA1c) (%)                                                                         |        |        |        |
| Glycated haemoglobin (HbA1c) (%)                                                                         |        |        |        |
| Units: Percentage                                                                                        |        |        |        |
| arithmetic mean                                                                                          | 8.14   | 7.98   | 7.78   |
| standard deviation                                                                                       | ± 1.17 | ± 1.09 | ± 1.33 |

|                                                                                                          |                                                    |       |  |
|----------------------------------------------------------------------------------------------------------|----------------------------------------------------|-------|--|
| <b>Reporting group values</b>                                                                            | Empagliflozin 10 mg - 25 mg - DINAMO & DINAMO Mono | Total |  |
| Number of subjects                                                                                       | 13                                                 | 175   |  |
| Age categorical                                                                                          |                                                    |       |  |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |                                                    |       |  |
| Units: Subjects                                                                                          |                                                    |       |  |
| <15 years                                                                                                | 7                                                  | 86    |  |
| >=15 years to <18 years                                                                                  | 6                                                  | 89    |  |
| Age Continuous                                                                                           |                                                    |       |  |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |                                                    |       |  |
| Units: years                                                                                             |                                                    |       |  |
| arithmetic mean                                                                                          | 13.9                                               |       |  |
| standard deviation                                                                                       | ± 2.2                                              | -     |  |
| Sex: Female, Male                                                                                        |                                                    |       |  |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |                                                    |       |  |
| Units: Participants                                                                                      |                                                    |       |  |

|        |   |     |  |
|--------|---|-----|--|
| Female | 8 | 112 |  |
| Male   | 5 | 63  |  |

  

|                                                                                                          |        |     |  |
|----------------------------------------------------------------------------------------------------------|--------|-----|--|
| Race/Ethnicity, Customized                                                                               |        |     |  |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |        |     |  |
| Units: Subjects                                                                                          |        |     |  |
| American Indian/Alaska Native                                                                            | 0      | 8   |  |
| Asian                                                                                                    | 0      | 10  |  |
| Black/African American                                                                                   | 4      | 59  |  |
| Native Hawaiian or other Pacific Islander                                                                | 0      | 3   |  |
| White                                                                                                    | 7      | 85  |  |
| Other including mixed or missing race                                                                    | 2      | 10  |  |
| Ethnicity (NIH/OMB)                                                                                      |        |     |  |
| The randomised set (RS) included all randomised patients, regardless whether they took trial medication. |        |     |  |
| Units: Subjects                                                                                          |        |     |  |
| Hispanic or Latino                                                                                       | 6      | 65  |  |
| Not Hispanic or Latino                                                                                   | 7      | 110 |  |
| Unknown or Not Reported                                                                                  | 0      | 0   |  |
| Glycated haemoglobin (HbA1c) (%)                                                                         |        |     |  |
| Glycated haemoglobin (HbA1c) (%)                                                                         |        |     |  |
| Units: Percentage                                                                                        |        |     |  |
| arithmetic mean                                                                                          | 8.24   |     |  |
| standard deviation                                                                                       | ± 1.08 | -   |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Placebo - DINAMO & DINAMO Mono                       |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily, until end of treatment.                                                                                                                                                                                                                                     |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Placebo - Linagliptin 5 mg - DINAMO & DINAMO Mono    |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily. At week 26, patients were re-randomised to receive 5 milligram (mg) Linagliptin, taken once daily, until end of treatment.                                                                                                                                  |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Placebo - Empagliflozin 10 mg - DINAMO & DINAMO Mono |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily. At week 26, patients were re-randomised to receive 10 milligram (mg) empagliflozin, taken once daily, until end of treatment.                                                                                                                               |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Placebo - Empagliflozin 25 mg - DINAMO & DINAMO Mono |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily. At week 26, patients were re-randomised to receive 25 milligram (mg) empagliflozin, taken once daily, until end of treatment.                                                                                                                               |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Linagliptin 5 mg - DINAMO & DINAMO Mono              |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of 5 milligram (mg) Linagliptin once daily, until end of treatment.                                                                                                                                                                                                                                                            |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Empagliflozin 10 mg - DINAMO & DINAMO Mono           |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily, until Week 14. Responder patients were not re-randomised at week 14 and continued 10 mg empagliflozin, taken once daily, until end of treatment. Non responder patients were re-randomised at Week 14 to receive 10 mg empagliflozin, taken once daily, until end of treatment. |                                                      |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Empagliflozin 10 mg - 25 mg - DINAMO & DINAMO Mono   |
| Reporting group description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin or treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily until Week 14. Non responder patients were re-randomised at Week 14 to receive 25 mg empagliflozin, taken once daily, until end of treatment.                                                                                                                                    |                                                      |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Placebo - DINAMO                                     |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Intention-to-treat                                   |
| Subject analysis set description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily.                                                                                                                                                                                                                                                                                                                                |                                                      |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Linagliptin 5 mg - DINAMO                            |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Intention-to-treat                                   |
| Subject analysis set description:<br>Patients treated with metformin and/or insulin or patients who do not tolerate metformin took 1 film-coated tablet of 5 milligram (mg) Linagliptin once daily.                                                                                                                                                                                                                                                                                                                                                       |                                                      |

|                            |                                                 |
|----------------------------|-------------------------------------------------|
| Subject analysis set title | Empagliflozin pooled (10 mg and 25 mg) - DINAMO |
| Subject analysis set type  | Intention-to-treat                              |

Subject analysis set description:

Patients treated with metformin and/or insulin or patients who do not tolerate metformin took 1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily. Patients who did not achieve an HbA1c value <7% at Week 12, were re-randomised to receive either 10 mg or 25 mg empagliflozin in a 1:1 ratio, taken once daily, until end of treatment.

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Empagliflozin 10 mg - DINAMO |
| Subject analysis set type  | Intention-to-treat           |

Subject analysis set description:

Patients treated with metformin and/or insulin or patients who do not tolerate metformin took 1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily. Responder (achieve an HbA1c value <7% at Week 12) patients were not re-randomised at week 14 and continued 10 mg empagliflozin, taken once daily, until end of treatment. Non responder patients were re-randomised at Week 14 to receive 10 mg empagliflozin, taken once daily, until end of treatment.

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Empagliflozin 25 mg - DINAMO |
| Subject analysis set type  | Intention-to-treat           |

Subject analysis set description:

Patients treated with metformin and/or insulin or patients who do not tolerate metformin took 1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily. Patients who did not achieve an HbA1c value <7% at Week 12, were re-randomised to receive 25 mg empagliflozin, taken once daily, until end of treatment.

|                            |                       |
|----------------------------|-----------------------|
| Subject analysis set title | Placebo - DINAMO Mono |
| Subject analysis set type  | Intention-to-treat    |

Subject analysis set description:

Treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of either Linagliptin or Empagliflozin matched placebo once daily.

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | Linagliptin 5 mg - DINAMO Mono |
| Subject analysis set type  | Intention-to-treat             |

Subject analysis set description:

Treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of 5 milligram (mg) Linagliptin once daily.

|                            |                                                      |
|----------------------------|------------------------------------------------------|
| Subject analysis set title | Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |
| Subject analysis set type  | Intention-to-treat                                   |

Subject analysis set description:

Treatment-naïve patients or patients who are not on active treatment took 1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily. Patients who did not achieve an HbAc value <7% at Week 12, were re-randomised to receive either 10 mg or 25 mg empagliflozin in a 1:1 ratio, taken once daily, until end of treatment.

## **Primary: Change in glycated haemoglobin (HbA1c) (%) from baseline to the end of 26 weeks - DINAMO**

|                 |                                                                                          |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | Change in glycated haemoglobin (HbA1c) (%) from baseline to the end of 26 weeks - DINAMO |
|-----------------|------------------------------------------------------------------------------------------|

End point description:

Adjusted means taken from three models:

Treatment group 1 (TG1): Placebo, Linagliptin 5 mg and Empagliflozin pooled

Treatment group 2 (TG2): Placebo, Empagliflozin 25mg

Treatment group 3 (TG3): Placebo, Empagliflozin 10mg

Description of model used to obtain adjusted values can be found in the statistical analyses.

mITT: patients treated with at least 1 dose of trial medication who had a baseline HbA1c measurement. All available data as observed were included. Any values after start of rescue medication and any on- and post-treatment values were kept. As pre-specified in the Protocol, endpoint only includes the main study DINAMO data.

9999= Adjusted mean (95%CI) per treatment group.

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

End point timeframe:

Baseline (Day 1) and week 26 of treatment.

| End point values                             | Placebo - DINAMO     | Linagliptin 5 mg - DINAMO | Empagliflozin pooled (10 mg and 25 mg) - DINAMO | Empagliflozin 10 mg - DINAMO |
|----------------------------------------------|----------------------|---------------------------|-------------------------------------------------|------------------------------|
| Subject group type                           | Subject analysis set | Subject analysis set      | Subject analysis set                            | Subject analysis set         |
| Number of subjects analysed                  | 53 <sup>[1]</sup>    | 52                        | 52                                              | 39                           |
| Units: Percent change                        |                      |                           |                                                 |                              |
| least squares mean (confidence interval 95%) | 9999 (9999 to 9999)  | 0.33 (-0.13 to 0.79)      | -0.17 (-0.64 to 0.31)                           | -0.49 (-1.03 to 0.04)        |

Notes:

[1] - 9999= Adj mean (95%CI):

TG1: 0.68 (0.23, 1.13)

TG2: 0.66 (0.12, 1.21)

TG3: 0.68 (0.19, 1.17)

| End point values                             | Empagliflozin 25 mg - DINAMO |  |  |  |
|----------------------------------------------|------------------------------|--|--|--|
| Subject group type                           | Subject analysis set         |  |  |  |
| Number of subjects analysed                  | 41                           |  |  |  |
| Units: Percent change                        |                              |  |  |  |
| least squares mean (confidence interval 95%) | 0.14 (-0.42 to 0.71)         |  |  |  |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Treatment group 1 (TG1) consisting of Placebo, Linagliptin 5 mg and Empagliflozin pooled Patients: Analysis of covariance (ANCOVA) model with a continuous covariate (baseline HbA1c) and categorical covariates (treatment and age). The effect of linagliptin and of empagliflozin (including responders and non-responders) was compared with placebo at an overall  $\alpha$  of 0.05 (2-sided) using the Hochberg method to account for multiple testing.

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| Comparison groups                       | Placebo - DINAMO v Linagliptin 5 mg - DINAMO |
| Number of subjects included in analysis | 105                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           |                                              |
| P-value                                 | = 0.2935                                     |
| Method                                  | ANCOVA                                       |
| Parameter estimate                      | Mean difference (final values)               |
| Point estimate                          | -0.34                                        |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -0.99                                        |
| upper limit                             | 0.3                                          |
| Variability estimate                    | Standard error of the mean                   |
| Dispersion value                        | 0.33                                         |

| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                   | Statistical analysis 2                                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                    |
| Treatment group 1 (TG1) consisting of Placebo, Linagliptin 5 mg and Empagliflozin pooled Patients: Analysis of covariance (ANCOVA) model with a continuous covariate (baseline HbA1c) and categorical covariates (treatment and age). The effect of linagliptin and of empagliflozin (including responders and non-responders) was compared with placebo at an overall $\alpha$ of 0.05 (2-sided) using the Hochberg method to account for multiple testing. |                                                                    |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                            | Placebo - DINAMO v Empagliflozin pooled (10 mg and 25 mg) - DINAMO |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                                                      | 105                                                                |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                                       | Pre-specified                                                      |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                    |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                                                                      | = 0.0116                                                           |
| Method                                                                                                                                                                                                                                                                                                                                                                                                                                                       | ANCOVA                                                             |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                                           | Mean difference (final values)                                     |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                                                               | -0.84                                                              |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                    |
| level                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 95 %                                                               |
| sides                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 2-sided                                                            |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                                                                  | -1.5                                                               |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                                                                  | -0.19                                                              |
| Variability estimate                                                                                                                                                                                                                                                                                                                                                                                                                                         | Standard error of the mean                                         |
| Dispersion value                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0.33                                                               |

| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Statistical analysis 3                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                 |
| Treatment group 2 (TG2) consisting of Placebo, Empagliflozin 25mg Patients: Analysis of covariance (ANCOVA) model with a continuous covariate (baseline HbA1c) and categorical covariates (treatment and age). The effect of linagliptin and of empagliflozin (including responders and non-responders) was compared with placebo at an overall $\alpha$ of 0.05 (2-sided) using the Hochberg method to account for multiple testing. Mean difference calculated as [Treatment] - Placebo. |                                                 |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Placebo - DINAMO v Empagliflozin 25 mg - DINAMO |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 94                                              |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Pre-specified                                   |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                 |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | = 0.1943                                        |
| Method                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | ANCOVA                                          |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Mean difference (final values)                  |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | -0.52                                           |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                 |
| level                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 95 %                                            |
| sides                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 2-sided                                         |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | -1.31                                           |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.27                                            |
| Variability estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Standard error of the mean                      |
| Dispersion value                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.4                                             |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Statistical analysis 4                          |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                 |
| Treatment group 2 (TG2) consisting of Placebo, Empagliflozin 25mg Patients: Analysis of covariance (ANCOVA) model with a continuous covariate (baseline HbA1c) and categorical covariates (treatment and age). The effect of linagliptin and of empagliflozin (including responders and non-responders) was compared with placebo at an overall $\alpha$ of 0.05 (2-sided) using the Hochberg method to account for multiple testing. Mean difference calculated as [Treatment] - Placebo. |                                                 |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Placebo - DINAMO v Empagliflozin 10 mg - DINAMO |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 92                                              |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Pre-specified                                   |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                 |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | = 0.0015                                        |
| Method                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | ANCOVA                                          |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Mean difference (final values)                  |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | -1.18                                           |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                 |
| level                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 95 %                                            |
| sides                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 2-sided                                         |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | -1.9                                            |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | -0.45                                           |
| Variability estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Standard error of the mean                      |
| Dispersion value                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.37                                            |

### Primary: Percentage of patients with treatment failure up to or at Week 26

|                                                                                                                                                                                                                                                                                                      |                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                      | Percentage of patients with treatment failure up to or at Week 26 |
| End point description:                                                                                                                                                                                                                                                                               |                                                                   |
| Percentage of patients with treatment failure up to or at Week 26 as a binary endpoint, defined as meeting at least one of the following criteria:                                                                                                                                                   |                                                                   |
| <ul style="list-style-type: none"> <li>- Use of rescue medication at any time up to Week 26</li> <li>- Increase from baseline in HbA1c by 0.5% at Week 26</li> <li>. Increase from baseline in HbA1c to above 7.0% at Week 26 in patients with baseline HbA1c &lt;7.0%.</li> </ul>                   |                                                                   |
| The modified intention-to-treat set (mITT) included all patients treated with at least 1 dose of trial medication who had a baseline HbA1c measurement. Missing values were regarded as 'failures'. As pre-specified in the Protocol, endpoint only includes the ancillary study (DINAMO Mono) data. |                                                                   |
| End point type                                                                                                                                                                                                                                                                                       | Primary                                                           |
| End point timeframe:                                                                                                                                                                                                                                                                                 |                                                                   |
| Up to 26 weeks.                                                                                                                                                                                                                                                                                      |                                                                   |

| End point values                 | Placebo -<br>DINAMO Mono | Linagliptin 5<br>mg - DINAMO<br>Mono | Empagliflozin<br>pooled (10 mg<br>and 25 mg) -<br>DINAMO Mono |  |
|----------------------------------|--------------------------|--------------------------------------|---------------------------------------------------------------|--|
| Subject group type               | Subject analysis set     | Subject analysis set                 | Subject analysis set                                          |  |
| Number of subjects analysed      | 3                        | 3                                    | 3                                                             |  |
| Units: Percentage of subjects    |                          |                                      |                                                               |  |
| number (confidence interval 90%) | 60.0 (18.9 to<br>92.4)   | 50.0 (15.3 to<br>84.7)               | 50.0 (15.3 to<br>84.7)                                        |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                       | Statistical analysis 6                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                |                                                                              |
| Risk difference of active treatments versus placebo was determined and assessed by an exact 2-sided 90% confidence interval based on the method of Chan and Zhang. Patients were assigned to the treatment they were randomised to at the initial randomisation. |                                                                              |
| Comparison groups                                                                                                                                                                                                                                                | Placebo - DINAMO Mono v Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |
| Number of subjects included in analysis                                                                                                                                                                                                                          | 6                                                                            |
| Analysis specification                                                                                                                                                                                                                                           | Pre-specified                                                                |
| Analysis type                                                                                                                                                                                                                                                    |                                                                              |
| P-value                                                                                                                                                                                                                                                          | = 1                                                                          |
| Method                                                                                                                                                                                                                                                           | Fisher exact                                                                 |
| Parameter estimate                                                                                                                                                                                                                                               | Risk difference (RD)                                                         |
| Point estimate                                                                                                                                                                                                                                                   | -10                                                                          |
| Confidence interval                                                                                                                                                                                                                                              |                                                                              |
| level                                                                                                                                                                                                                                                            | 90 %                                                                         |
| sides                                                                                                                                                                                                                                                            | 2-sided                                                                      |
| lower limit                                                                                                                                                                                                                                                      | -58.7                                                                        |
| upper limit                                                                                                                                                                                                                                                      | 43.7                                                                         |

| Statistical analysis title                                                                                                                                                                                                                                       | Statistical analysis 5                                 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                |                                                        |
| Risk difference of active treatments versus placebo was determined and assessed by an exact 2-sided 90% confidence interval based on the method of Chan and Zhang. Patients were assigned to the treatment they were randomised to at the initial randomisation. |                                                        |
| Comparison groups                                                                                                                                                                                                                                                | Placebo - DINAMO Mono v Linagliptin 5 mg - DINAMO Mono |
| Number of subjects included in analysis                                                                                                                                                                                                                          | 6                                                      |
| Analysis specification                                                                                                                                                                                                                                           | Pre-specified                                          |
| Analysis type                                                                                                                                                                                                                                                    |                                                        |
| P-value                                                                                                                                                                                                                                                          | = 1                                                    |
| Method                                                                                                                                                                                                                                                           | Fisher exact                                           |
| Parameter estimate                                                                                                                                                                                                                                               | Risk difference (RD)                                   |
| Point estimate                                                                                                                                                                                                                                                   | -10                                                    |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | -58.7   |
| upper limit         | 43.7    |

## Secondary: Change in HbA1c (%) from baseline to the end of 26 weeks - DINAMO Mono

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Change in HbA1c (%) from baseline to the end of 26 weeks - DINAMO Mono |
|-----------------|------------------------------------------------------------------------|

### End point description:

Change in Glycated haemoglobin (HbA1c) (%) from baseline to the end of 26 weeks. Adjusted values came from a restricted maximum likelihood (REML) approach with mixed model for repeated measures (MMRM). Analyses included fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. mITT: included all patients treated with at least 1 dose of trial medication who had a baseline HbA1c measurement. All available data as observed were included. Any values after start of rescue medication and any on- and post-treatment values were kept. As pre-specified in the Protocol, endpoint only includes the ancillary study (DINAMO Mono) data.

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

### End point timeframe:

Baseline (Day 1) and week 26 of treatment.

| End point values                             | Placebo - DINAMO Mono | Linagliptin 5 mg - DINAMO Mono | Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |  |
|----------------------------------------------|-----------------------|--------------------------------|------------------------------------------------------|--|
| Subject group type                           | Subject analysis set  | Subject analysis set           | Subject analysis set                                 |  |
| Number of subjects analysed                  | 4                     | 5                              | 4                                                    |  |
| Units: Percent change                        |                       |                                |                                                      |  |
| least squares mean (confidence interval 95%) | 0.15 (-1.45 to 1.75)  | -0.53 (-2.01 to 0.95)          | -0.23 (-1.83 to 1.37)                                |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 8 |
|----------------------------|------------------------|

### Statistical analysis description:

Restricted maximum likelihood (REML) approach with mixed model for repeated measures (MMRM). Fixed categorical effects of treatment, visit, and treatment-by-visit interaction and categorical covariate age (baseline) and continuous, fixed covariates of baseline of response variable and baseline of response variable-by-visit interaction. Covariate visit was treated as repeated measure with an unstructured covariance structure used to model within-patient measurements.

|                   |                                                                              |
|-------------------|------------------------------------------------------------------------------|
| Comparison groups | Placebo - DINAMO Mono v Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |
|-------------------|------------------------------------------------------------------------------|

|                                         |                          |
|-----------------------------------------|--------------------------|
| Number of subjects included in analysis | 8                        |
| Analysis specification                  | Pre-specified            |
| Analysis type                           |                          |
| P-value                                 | = 0.7047                 |
| Method                                  | Mixed models analysis    |
| Parameter estimate                      | Adjusted mean difference |
| Point estimate                          | -0.38                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | -2.64                    |
| upper limit                             | 1.88                     |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Restricted maximum likelihood (REML) approach with mixed model for repeated measures (MMRM). Fixed categorical effects of treatment, visit, and treatment-by-visit interaction and categorical covariate age (baseline) and continuous, fixed covariates of baseline of response variable and baseline of response variable-by-visit interaction. Covariate visit was treated as repeated measure with an unstructured covariance structure used to model within-patient measurements.

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO Mono v Linagliptin 5 mg - DINAMO Mono |
| Number of subjects included in analysis | 9                                                      |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| P-value                                 | = 0.4828                                               |
| Method                                  | Mixed models analysis                                  |
| Parameter estimate                      | Adjusted mean difference                               |
| Point estimate                          | -0.68                                                  |
| Confidence interval                     |                                                        |
| level                                   | 95 %                                                   |
| sides                                   | 2-sided                                                |
| lower limit                             | -2.86                                                  |
| upper limit                             | 1.49                                                   |

## Secondary: Time to treatment failure

|                 |                           |
|-----------------|---------------------------|
| End point title | Time to treatment failure |
|-----------------|---------------------------|

End point description:

Time to treatment failure was analysed by Kaplan-Meier estimates up to the end of the study (Week 52). Patients in the placebo group were censored after 26 weeks unless a prior treatment failure was observed. The modified intention-to-treat set (mITT) included all patients treated with at least 1 dose of trial medication who had a baseline HbA1c measurement. Missing values were regarded as 'failures'. As pre-specified in the Protocol, endpoint only includes the ancillary study (DINAMO Mono) data.

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

End point timeframe:

Up to 395 days.

| <b>End point values</b>          | Placebo -<br>DINAMO Mono  | Linagliptin 5<br>mg - DINAMO<br>Mono | Empagliflozin<br>pooled (10 mg<br>and 25 mg) -<br>DINAMO Mono |  |
|----------------------------------|---------------------------|--------------------------------------|---------------------------------------------------------------|--|
| Subject group type               | Subject analysis set      | Subject analysis set                 | Subject analysis set                                          |  |
| Number of subjects analysed      | 3                         | 4                                    | 3                                                             |  |
| Units: Days                      |                           |                                      |                                                               |  |
| arithmetic mean (standard error) | 65.600 ( $\pm$<br>19.941) | 72.167 ( $\pm$<br>20.280)            | 167.333 ( $\pm$<br>26.711)                                    |  |

## Statistical analyses

| <b>Statistical analysis title</b>                                                                                                                                                                                             | Statistical analysis 10                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Statistical analysis description:<br>Time to treatment failure was analysed by Kaplan-Meier estimates up to the end of the study. A log-rank test compared linagliptin and empagliflozin pooled versus placebo up to Week 26. |                                                                              |
| Comparison groups                                                                                                                                                                                                             | Placebo - DINAMO Mono v Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |
| Number of subjects included in analysis                                                                                                                                                                                       | 6                                                                            |
| Analysis specification                                                                                                                                                                                                        | Pre-specified                                                                |
| Analysis type                                                                                                                                                                                                                 |                                                                              |
| P-value                                                                                                                                                                                                                       | = 0.2827                                                                     |
| Method                                                                                                                                                                                                                        | Logrank                                                                      |

| <b>Statistical analysis title</b>                                                                                                                                                                                             | Statistical analysis 9                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| Statistical analysis description:<br>Time to treatment failure was analysed by Kaplan-Meier estimates up to the end of the study. A log-rank test compared linagliptin and empagliflozin pooled versus placebo up to Week 26. |                                                        |
| Comparison groups                                                                                                                                                                                                             | Placebo - DINAMO Mono v Linagliptin 5 mg - DINAMO Mono |
| Number of subjects included in analysis                                                                                                                                                                                       | 7                                                      |
| Analysis specification                                                                                                                                                                                                        | Pre-specified                                          |
| Analysis type                                                                                                                                                                                                                 |                                                        |
| P-value                                                                                                                                                                                                                       | = 0.8626                                               |
| Method                                                                                                                                                                                                                        | Logrank                                                |

## Secondary: Change in fasting plasma glucose (FPG, mg/dL) from baseline to the end of 26 weeks

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Change in fasting plasma glucose (FPG, mg/dL) from baseline to the end of 26 weeks |
|-----------------|------------------------------------------------------------------------------------|

### End point description:

Change in fasting plasma glucose (FPG, Milligrams Per Deciliter (mg/dL)) from baseline to the end of 26 weeks. Adjusted values taken from analysis of covariance (ANCOVA) model with treatment as a fixed

classification effect, baseline FPG as linear covariate and age at randomisation as categorical covariate. The random error was assumed to be normally distributed. The modified intention-to-treat set (mITT) included all patients treated with at least 1 dose of trial medication who had a baseline HbA1c measurement. All available data as observed were included. Any values after start of rescue medication and any on- and post-treatment values were kept, baseline observations were carried forward to impute the missing data. Only patients with non-missing data were included.

|                               |           |
|-------------------------------|-----------|
| End point type                | Secondary |
| End point timeframe:          |           |
| Baseline (Day 1) and week 26. |           |

| End point values                             | Placebo - DINAMO       | Linagliptin 5 mg - DINAMO | Empagliflozin pooled (10 mg and 25 mg) - DINAMO | Placebo - DINAMO Mono     |
|----------------------------------------------|------------------------|---------------------------|-------------------------------------------------|---------------------------|
| Subject group type                           | Subject analysis set   | Subject analysis set      | Subject analysis set                            | Subject analysis set      |
| Number of subjects analysed                  | 52                     | 51                        | 48                                              | 4                         |
| Units: Milligrams Per Deciliter (mg/dL)      |                        |                           |                                                 |                           |
| least squares mean (confidence interval 95%) | 15.70 (-0.53 to 31.93) | 10.29 (-6.12 to 26.69)    | -19.48 (-36.39 to -2.57)                        | -38.50 (-62.67 to -14.33) |

| End point values                             | Linagliptin 5 mg - DINAMO Mono | Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |  |  |
|----------------------------------------------|--------------------------------|------------------------------------------------------|--|--|
| Subject group type                           | Subject analysis set           | Subject analysis set                                 |  |  |
| Number of subjects analysed                  | 4                              | 5                                                    |  |  |
| Units: Milligrams Per Deciliter (mg/dL)      |                                |                                                      |  |  |
| least squares mean (confidence interval 95%) | 0.12 (-23.67 to 23.91)         | -18.45 (-40.00 to 3.10)                              |  |  |

## Statistical analyses

|                                                                                                                                                                                                                                     |                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                          | Statistical analysis 11                      |
| Statistical analysis description:                                                                                                                                                                                                   |                                              |
| Analysis of covariance (ANCOVA) model with treatment as a fixed classification effect, baseline FPG as linear covariate and age at randomisation as categorical covariate. The random error was assumed to be normally distributed. |                                              |
| Comparison groups                                                                                                                                                                                                                   | Placebo - DINAMO v Linagliptin 5 mg - DINAMO |
| Number of subjects included in analysis                                                                                                                                                                                             | 103                                          |
| Analysis specification                                                                                                                                                                                                              | Pre-specified                                |
| Analysis type                                                                                                                                                                                                                       |                                              |
| P-value                                                                                                                                                                                                                             | = 0.6438                                     |
| Method                                                                                                                                                                                                                              | ANCOVA                                       |
| Parameter estimate                                                                                                                                                                                                                  | Mean difference (final values)               |
| Point estimate                                                                                                                                                                                                                      | -5.41                                        |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -28.49  |
| upper limit         | 17.67   |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Analysis of covariance (ANCOVA) model with treatment as a fixed classification effect, baseline FPG as linear covariate and age at randomisation as categorical covariate. The random error was assumed to be normally distributed.

|                                         |                                                                    |
|-----------------------------------------|--------------------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO v Empagliflozin pooled (10 mg and 25 mg) - DINAMO |
| Number of subjects included in analysis | 100                                                                |
| Analysis specification                  | Pre-specified                                                      |
| Analysis type                           |                                                                    |
| P-value                                 | = 0.0035                                                           |
| Method                                  | ANCOVA                                                             |
| Parameter estimate                      | Mean difference (final values)                                     |
| Point estimate                          | -35.18                                                             |
| Confidence interval                     |                                                                    |
| level                                   | 95 %                                                               |
| sides                                   | 2-sided                                                            |
| lower limit                             | -58.61                                                             |
| upper limit                             | -11.74                                                             |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 13 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Analysis of covariance (ANCOVA) model with treatment as a fixed classification effect, baseline FPG as linear covariate and age at randomisation as categorical covariate. The random error was assumed to be normally distributed.

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO Mono v Linagliptin 5 mg - DINAMO Mono |
| Number of subjects included in analysis | 8                                                      |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| P-value                                 | = 0.031                                                |
| Method                                  | ANCOVA                                                 |
| Parameter estimate                      | Mean difference (final values)                         |
| Point estimate                          | 38.62                                                  |
| Confidence interval                     |                                                        |
| level                                   | 95 %                                                   |
| sides                                   | 2-sided                                                |
| lower limit                             | 4.54                                                   |
| upper limit                             | 72.7                                                   |

|                                                                                                                                                                                                                                     |                                                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                   | Statistical analysis 14                                                      |
| Statistical analysis description:                                                                                                                                                                                                   |                                                                              |
| Analysis of covariance (ANCOVA) model with treatment as a fixed classification effect, baseline FPG as linear covariate and age at randomisation as categorical covariate. The random error was assumed to be normally distributed. |                                                                              |
| Comparison groups                                                                                                                                                                                                                   | Placebo - DINAMO Mono v Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |
| Number of subjects included in analysis                                                                                                                                                                                             | 9                                                                            |
| Analysis specification                                                                                                                                                                                                              | Pre-specified                                                                |
| Analysis type                                                                                                                                                                                                                       |                                                                              |
| P-value                                                                                                                                                                                                                             | = 0.1994                                                                     |
| Method                                                                                                                                                                                                                              | ANCOVA                                                                       |
| Parameter estimate                                                                                                                                                                                                                  | Mean difference (final values)                                               |
| Point estimate                                                                                                                                                                                                                      | 20.05                                                                        |
| Confidence interval                                                                                                                                                                                                                 |                                                                              |
| level                                                                                                                                                                                                                               | 95 %                                                                         |
| sides                                                                                                                                                                                                                               | 2-sided                                                                      |
| lower limit                                                                                                                                                                                                                         | -13.01                                                                       |
| upper limit                                                                                                                                                                                                                         | 53.11                                                                        |

## Secondary: Change in body weight (kg) from baseline to the end of 26 weeks

|                 |                                                                 |
|-----------------|-----------------------------------------------------------------|
| End point title | Change in body weight (kg) from baseline to the end of 26 weeks |
|-----------------|-----------------------------------------------------------------|

End point description:

Change in body weight (kg) from baseline to the end of 26 weeks. Adjusted values taken from mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements.

The modified intention-to-treat set (mITT) included all patients treated with at least 1 dose of trial medication who had a baseline HbA1c measurement. All available data as observed were included. Any values after start of rescue medication and any on- and post-treatment values were kept. Only patients with non-missing data were included.

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

End point timeframe:

Baseline (Day 1) and week 26.

| <b>End point values</b>                      | Placebo - DINAMO      | Linagliptin 5 mg - DINAMO | Empagliflozin pooled (10 mg and 25 mg) - DINAMO | Placebo - DINAMO Mono |
|----------------------------------------------|-----------------------|---------------------------|-------------------------------------------------|-----------------------|
| Subject group type                           | Subject analysis set  | Subject analysis set      | Subject analysis set                            | Subject analysis set  |
| Number of subjects analysed                  | 50                    | 49                        | 48                                              | 4                     |
| Units: kilogram (kg)                         |                       |                           |                                                 |                       |
| least squares mean (confidence interval 95%) | -0.04 (-1.40 to 1.32) | 1.42 (0.04 to 2.81)       | -0.79 (-2.17 to 0.59)                           | 2.64 (-0.35 to 5.63)  |

| End point values                             | Linagliptin 5 mg - DINAMO Mono | Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |  |  |
|----------------------------------------------|--------------------------------|------------------------------------------------------|--|--|
| Subject group type                           | Subject analysis set           | Subject analysis set                                 |  |  |
| Number of subjects analysed                  | 6                              | 4                                                    |  |  |
| Units: kilogram (kg)                         |                                |                                                      |  |  |
| least squares mean (confidence interval 95%) | 2.69 (0.24 to 5.14)            | 1.29 (-1.75 to 4.33)                                 |  |  |

## Statistical analyses

| Statistical analysis title | Statistical analysis 15 |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements.

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| Comparison groups                       | Placebo - DINAMO v Linagliptin 5 mg - DINAMO |
| Number of subjects included in analysis | 99                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           |                                              |
| P-value                                 | = 0.1394                                     |
| Method                                  | Mixed models analysis                        |
| Parameter estimate                      | Mean difference (final values)               |
| Point estimate                          | 1.46                                         |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -0.48                                        |
| upper limit                             | 3.41                                         |

| Statistical analysis title | Statistical analysis 17 |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements.

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Linagliptin 5 mg - DINAMO Mono v Placebo - DINAMO Mono |
| Number of subjects included in analysis | 10                                                     |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| P-value                                 | = 0.9789                                               |
| Method                                  | Mixed models analysis                                  |
| Parameter estimate                      | Mean difference (final values)                         |
| Point estimate                          | 0.05                                                   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -3.8    |
| upper limit         | 3.9     |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 18 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements.

|                                         |                                                                              |
|-----------------------------------------|------------------------------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO Mono v Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |
| Number of subjects included in analysis | 8                                                                            |
| Analysis specification                  | Pre-specified                                                                |
| Analysis type                           |                                                                              |
| P-value                                 | = 0.5092                                                                     |
| Method                                  | Mixed models analysis                                                        |
| Parameter estimate                      | Mean difference (final values)                                               |
| Point estimate                          | -1.35                                                                        |
| Confidence interval                     |                                                                              |
| level                                   | 95 %                                                                         |
| sides                                   | 2-sided                                                                      |
| lower limit                             | -5.68                                                                        |
| upper limit                             | 2.99                                                                         |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 16 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements.

|                                         |                                                                    |
|-----------------------------------------|--------------------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO v Empagliflozin pooled (10 mg and 25 mg) - DINAMO |
| Number of subjects included in analysis | 98                                                                 |
| Analysis specification                  | Pre-specified                                                      |
| Analysis type                           |                                                                    |
| P-value                                 | = 0.4476                                                           |
| Method                                  | Mixed models analysis                                              |
| Parameter estimate                      | Mean difference (final values)                                     |
| Point estimate                          | -0.75                                                              |
| Confidence interval                     |                                                                    |
| level                                   | 95 %                                                               |
| sides                                   | 2-sided                                                            |
| lower limit                             | -2.68                                                              |
| upper limit                             | 1.19                                                               |

**Secondary: Change in systolic blood pressure (SBP, mmHg) from baseline to the end of 26 weeks**

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Change in systolic blood pressure (SBP, mmHg) from baseline to the end of 26 weeks |
|-----------------|------------------------------------------------------------------------------------|

## End point description:

Change in systolic blood pressure (SBP, millimeters of mercury (mmHg)) from baseline to the end of 26 weeks. Adjusted values taken from mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements. The modified intention-to-treat set (mITT) included all patients treated with at least 1 dose of trial medication who had a baseline HbA1c measurement. All available data as observed were included. Any values after start of rescue medication and any on- and post-treatment values were kept. Only patients with non-missing data were included.

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

## End point timeframe:

Baseline (Day 1) and week 26.

| End point values                             | Placebo - DINAMO     | Linagliptin 5 mg - DINAMO | Empagliflozin pooled (10 mg and 25 mg) - DINAMO | Placebo - DINAMO Mono |
|----------------------------------------------|----------------------|---------------------------|-------------------------------------------------|-----------------------|
| Subject group type                           | Subject analysis set | Subject analysis set      | Subject analysis set                            | Subject analysis set  |
| Number of subjects analysed                  | 50                   | 49                        | 48                                              | 4                     |
| Units: millimeters of mercury (mmHg)         |                      |                           |                                                 |                       |
| least squares mean (confidence interval 95%) | 1.30 (-1.01 to 3.61) | 2.21 (-0.14 to 4.56)      | -0.12 (-2.47 to 2.24)                           | 2.63 (-4.07 to 9.34)  |

| End point values                             | Linagliptin 5 mg - DINAMO Mono | Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |  |  |
|----------------------------------------------|--------------------------------|------------------------------------------------------|--|--|
| Subject group type                           | Subject analysis set           | Subject analysis set                                 |  |  |
| Number of subjects analysed                  | 6                              | 4                                                    |  |  |
| Units: millimeters of mercury (mmHg)         |                                |                                                      |  |  |
| least squares mean (confidence interval 95%) | 5.16 (-0.74 to 11.06)          | 2.63 (-4.86 to 10.12)                                |  |  |

**Statistical analyses**

|                            |                         |
|----------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 20 |
|----------------------------|-------------------------|

## Statistical analysis description:

Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the

continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements.

|                                         |                                                                    |
|-----------------------------------------|--------------------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO v Empagliflozin pooled (10 mg and 25 mg) - DINAMO |
| Number of subjects included in analysis | 98                                                                 |
| Analysis specification                  | Pre-specified                                                      |
| Analysis type                           |                                                                    |
| P-value                                 | = 0.3967                                                           |
| Method                                  | Mixed models analysis                                              |
| Parameter estimate                      | Mean difference (final values)                                     |
| Point estimate                          | -1.42                                                              |
| Confidence interval                     |                                                                    |
| level                                   | 95 %                                                               |
| sides                                   | 2-sided                                                            |
| lower limit                             | -4.72                                                              |
| upper limit                             | 1.88                                                               |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 19 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements.

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| Comparison groups                       | Placebo - DINAMO v Linagliptin 5 mg - DINAMO |
| Number of subjects included in analysis | 99                                           |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           |                                              |
| P-value                                 | = 0.587                                      |
| Method                                  | Mixed models analysis                        |
| Parameter estimate                      | Mean difference (final values)               |
| Point estimate                          | 0.91                                         |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -2.4                                         |
| upper limit                             | 4.22                                         |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 22 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements.

|                   |                                                                              |
|-------------------|------------------------------------------------------------------------------|
| Comparison groups | Placebo - DINAMO Mono v Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |
|-------------------|------------------------------------------------------------------------------|

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 8                              |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           |                                |
| P-value                                 | = 0.9995                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0                              |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -10.13                         |
| upper limit                             | 10.13                          |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 21 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements.

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Linagliptin 5 mg - DINAMO Mono v Placebo - DINAMO Mono |
| Number of subjects included in analysis | 10                                                     |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| P-value                                 | = 0.5414                                               |
| Method                                  | Mixed models analysis                                  |
| Parameter estimate                      | Mean difference (final values)                         |
| Point estimate                          | 2.53                                                   |
| Confidence interval                     |                                                        |
| level                                   | 95 %                                                   |
| sides                                   | 2-sided                                                |
| lower limit                             | -6.42                                                  |
| upper limit                             | 11.47                                                  |

## Secondary: Change in diastolic blood pressure (DBP, mmHg) from baseline to the end of 26 weeks

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Change in diastolic blood pressure (DBP, mmHg) from baseline to the end of 26 weeks |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

Change in diastolic blood pressure (DBP, millimeters of mercury (mmHg)) from baseline to the end of 26 weeks. Adjusted values taken from mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements. The modified intention-to-treat set (mITT) included all patients treated with at least 1 dose of trial medication who had a baseline HbA1c measurement. All available data as observed were included. Any values after start of rescue medication and any on- and post-treatment values were kept. Only patients with non-missing data were included.

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

End point timeframe:

Baseline (Day 1) and week 26.

| End point values                                | Placebo -<br>DINAMO     | Linagliptin 5<br>mg - DINAMO | Empagliflozin<br>pooled (10 mg<br>and 25 mg) -<br>DINAMO | Placebo -<br>DINAMO Mono |
|-------------------------------------------------|-------------------------|------------------------------|----------------------------------------------------------|--------------------------|
| Subject group type                              | Subject analysis set    | Subject analysis set         | Subject analysis set                                     | Subject analysis set     |
| Number of subjects analysed                     | 50                      | 49                           | 48                                                       | 4                        |
| Units: millimeters of mercury (mmHg)            |                         |                              |                                                          |                          |
| least squares mean (confidence interval<br>95%) | 0.76 (-1.01 to<br>2.53) | 2.26 (0.46 to<br>4.05)       | 0.78 (-1.04 to<br>2.60)                                  | 3.42 (-4.92 to<br>11.75) |

| End point values                                | Linagliptin 5<br>mg - DINAMO<br>Mono | Empagliflozin<br>pooled (10 mg<br>and 25 mg) -<br>DINAMO Mono |  |  |
|-------------------------------------------------|--------------------------------------|---------------------------------------------------------------|--|--|
| Subject group type                              | Subject analysis set                 | Subject analysis set                                          |  |  |
| Number of subjects analysed                     | 6                                    | 4                                                             |  |  |
| Units: millimeters of mercury (mmHg)            |                                      |                                                               |  |  |
| least squares mean (confidence interval<br>95%) | 6.75 (0.14 to<br>13.35)              | -3.20 (-10.10<br>to 3.69)                                     |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Statistical analysis 23                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                              |
| Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements. |                                              |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Placebo - DINAMO v Linagliptin 5 mg - DINAMO |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                                                                           | 99                                           |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Pre-specified                                |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                              |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | = 0.2433                                     |
| Method                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Mixed models analysis                        |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Mean difference (final values)               |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1.5                                          |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                              |
| level                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 95 %                                         |
| sides                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2-sided                                      |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | -1.03                                        |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 4.02                                         |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Statistical analysis 26                                                      |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                              |
| Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements. |                                                                              |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Placebo - DINAMO Mono v Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                                                                           | 8                                                                            |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Pre-specified                                                                |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                              |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | = 0.2348                                                                     |
| Method                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Mixed models analysis                                                        |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Mean difference (final values)                                               |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -6.62                                                                        |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                              |
| level                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 95 %                                                                         |
| sides                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2-sided                                                                      |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | -18.19                                                                       |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 4.95                                                                         |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Statistical analysis 25                                |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                        |
| Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements. |                                                        |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Linagliptin 5 mg - DINAMO Mono v Placebo - DINAMO Mono |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                                                                           | 10                                                     |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Pre-specified                                          |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                        |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | = 0.567                                                |
| Method                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Mixed models analysis                                  |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Mean difference (final values)                         |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 3.33                                                   |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                        |
| level                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 95 %                                                   |
| sides                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2-sided                                                |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | -9                                                     |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 15.65                                                  |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 24 |
|-----------------------------------|-------------------------|

**Statistical analysis description:**

Mixed model for repeated measures (MMRM) with the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit was treated as repeated measure with an unstructured covariance structure used to model the within-patient measurements.

|                                         |                                                                    |
|-----------------------------------------|--------------------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO v Empagliflozin pooled (10 mg and 25 mg) - DINAMO |
| Number of subjects included in analysis | 98                                                                 |
| Analysis specification                  | Pre-specified                                                      |
| Analysis type                           |                                                                    |
| P-value                                 | = 0.9878                                                           |
| Method                                  | Mixed models analysis                                              |
| Parameter estimate                      | Mean difference (final values)                                     |
| Point estimate                          | 0.02                                                               |
| Confidence interval                     |                                                                    |
| level                                   | 95 %                                                               |
| sides                                   | 2-sided                                                            |
| lower limit                             | -2.52                                                              |
| upper limit                             | 2.56                                                               |

**Secondary: Percentage of patients who achieve HbA1c <6.5% at the end of 26 weeks**

|                        |                                                                                                                                                                                                                                                                            |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Percentage of patients who achieve HbA1c <6.5% at the end of 26 weeks                                                                                                                                                                                                      |
| End point description: | Percentage of patients who achieve HbA1c <6.5% at the end of 26 weeks. The modified intention-to-treat set (mITT) included all patients treated with at least 1 dose of trial medication who had a baseline HbA1c measurement. Missing values were regarded as 'failures'. |
| End point type         | Secondary                                                                                                                                                                                                                                                                  |
| End point timeframe:   | Baseline (Day 1) and week 26.                                                                                                                                                                                                                                              |

| <b>End point values</b>       | Placebo - DINAMO     | Linagliptin 5 mg - DINAMO | Empagliflozin pooled (10 mg and 25 mg) - DINAMO | Placebo - DINAMO Mono |
|-------------------------------|----------------------|---------------------------|-------------------------------------------------|-----------------------|
| Subject group type            | Subject analysis set | Subject analysis set      | Subject analysis set                            | Subject analysis set  |
| Number of subjects analysed   | 5                    | 8                         | 11                                              | 2                     |
| Units: Percentage of subjects |                      |                           |                                                 |                       |
| number (not applicable)       | 9.4                  | 15.4                      | 21.2                                            | 40.0                  |

| <b>End point values</b> | Linagliptin 5 mg - DINAMO Mono | Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |  |  |
|-------------------------|--------------------------------|------------------------------------------------------|--|--|
|-------------------------|--------------------------------|------------------------------------------------------|--|--|

|                               |                      |                      |  |  |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type            | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed   | 1                    | 1                    |  |  |
| Units: Percentage of subjects |                      |                      |  |  |
| number (not applicable)       | 16.7                 | 16.7                 |  |  |

## Statistical analyses

|                                                                                                                                                                                                      |                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                    | Statistical analysis 27                      |
| Statistical analysis description:                                                                                                                                                                    |                                              |
| The risk difference of active treatments versus placebo was determined and assessed by an exact 2-sided 95% confidence interval. Exact 95% CI by Chan and Zhang. Asymptotic and two-sided Wald test. |                                              |
| Comparison groups                                                                                                                                                                                    | Placebo - DINAMO v Linagliptin 5 mg - DINAMO |
| Number of subjects included in analysis                                                                                                                                                              | 13                                           |
| Analysis specification                                                                                                                                                                               | Pre-specified                                |
| Analysis type                                                                                                                                                                                        |                                              |
| P-value                                                                                                                                                                                              | = 0.3536                                     |
| Method                                                                                                                                                                                               | Wald test                                    |
| Parameter estimate                                                                                                                                                                                   | Rate difference (percentage)                 |
| Point estimate                                                                                                                                                                                       | 6                                            |
| Confidence interval                                                                                                                                                                                  |                                              |
| level                                                                                                                                                                                                | 95 %                                         |
| sides                                                                                                                                                                                                | 2-sided                                      |
| lower limit                                                                                                                                                                                          | -7.7                                         |
| upper limit                                                                                                                                                                                          | 19.9                                         |

|                                                                                                                                                                                                      |                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                    | Statistical analysis 30                                                      |
| Statistical analysis description:                                                                                                                                                                    |                                                                              |
| The risk difference of active treatments versus placebo was determined and assessed by an exact 2-sided 95% confidence interval. Exact 95% CI by Chan and Zhang. Asymptotic and Fisher's exact test. |                                                                              |
| Comparison groups                                                                                                                                                                                    | Placebo - DINAMO Mono v Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |
| Number of subjects included in analysis                                                                                                                                                              | 3                                                                            |
| Analysis specification                                                                                                                                                                               | Pre-specified                                                                |
| Analysis type                                                                                                                                                                                        |                                                                              |
| P-value                                                                                                                                                                                              | = 0.5455                                                                     |
| Method                                                                                                                                                                                               | Fisher exact                                                                 |
| Parameter estimate                                                                                                                                                                                   | Rate difference (percentage)                                                 |
| Point estimate                                                                                                                                                                                       | -23.3                                                                        |
| Confidence interval                                                                                                                                                                                  |                                                                              |
| level                                                                                                                                                                                                | 90 %                                                                         |
| sides                                                                                                                                                                                                | 2-sided                                                                      |
| lower limit                                                                                                                                                                                          | -67.9                                                                        |
| upper limit                                                                                                                                                                                          | 27.1                                                                         |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 29 |
|-----------------------------------|-------------------------|

**Statistical analysis description:**

The risk difference of active treatments versus placebo was determined and assessed by an exact 2-sided 95% confidence interval. Exact 95% CI by Chan and Zhang. Asymptotic and Fisher's exact test.

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO Mono v Linagliptin 5 mg - DINAMO Mono |
| Number of subjects included in analysis | 3                                                      |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| P-value                                 | = 0.5455                                               |
| Method                                  | Fisher exact                                           |
| Parameter estimate                      | Rate difference (percentage)                           |
| Point estimate                          | -23.3                                                  |
| Confidence interval                     |                                                        |
| level                                   | 90 %                                                   |
| sides                                   | 2-sided                                                |
| lower limit                             | -67.9                                                  |
| upper limit                             | 27.1                                                   |

**Statistical analysis title**

Statistical analysis 28

**Statistical analysis description:**

The risk difference of active treatments versus placebo was determined and assessed by an exact 2-sided 95% confidence interval. Exact 95% CI by Chan and Zhang. Asymptotic and two-sided Wald test.

|                                         |                                                                    |
|-----------------------------------------|--------------------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO v Empagliflozin pooled (10 mg and 25 mg) - DINAMO |
| Number of subjects included in analysis | 16                                                                 |
| Analysis specification                  | Pre-specified                                                      |
| Analysis type                           |                                                                    |
| P-value                                 | = 0.0914                                                           |
| Method                                  | Wald test                                                          |
| Parameter estimate                      | Rate difference (percentage)                                       |
| Point estimate                          | 11.7                                                               |
| Confidence interval                     |                                                                    |
| level                                   | 95 %                                                               |
| sides                                   | 2-sided                                                            |
| lower limit                             | -2.4                                                               |
| upper limit                             | 26.3                                                               |

**Secondary: Percentage of patients who achieve HbA1c <7.0% at the end of 26 weeks**

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | Percentage of patients who achieve HbA1c <7.0% at the end of 26 weeks |
|-----------------|-----------------------------------------------------------------------|

**End point description:**

Percentage of patients who achieve HbA1c <7.0% at the end of 26 weeks.

The modified intention-to-treat set (mITT) included all patients treated with at least 1 dose of trial medication who had a baseline HbA1c measurement. Missing values were regarded as 'failures'.

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

**End point timeframe:**

Baseline (Day 1) and week 26.

| End point values              | Placebo -<br>DINAMO  | Linagliptin 5<br>mg - DINAMO | Empagliflozin<br>pooled (10 mg<br>and 25 mg) -<br>DINAMO | Placebo -<br>DINAMO Mono |
|-------------------------------|----------------------|------------------------------|----------------------------------------------------------|--------------------------|
| Subject group type            | Subject analysis set | Subject analysis set         | Subject analysis set                                     | Subject analysis set     |
| Number of subjects analysed   | 13                   | 14                           | 18                                                       | 2                        |
| Units: Percentage of subjects |                      |                              |                                                          |                          |
| number (not applicable)       | 24.5                 | 26.9                         | 34.6                                                     | 40.0                     |

| End point values              | Linagliptin 5<br>mg - DINAMO<br>Mono | Empagliflozin<br>pooled (10 mg<br>and 25 mg) -<br>DINAMO Mono |  |  |
|-------------------------------|--------------------------------------|---------------------------------------------------------------|--|--|
| Subject group type            | Subject analysis set                 | Subject analysis set                                          |  |  |
| Number of subjects analysed   | 1                                    | 4                                                             |  |  |
| Units: Percentage of subjects |                                      |                                                               |  |  |
| number (not applicable)       | 16.7                                 | 66.7                                                          |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                           | Statistical analysis 31                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Statistical analysis description:                                                                                                                                                                    |                                              |
| The risk difference of active treatments versus placebo was determined and assessed by an exact 2-sided 95% confidence interval. Exact 95% CI by Chan and Zhang. Asymptotic and two-sided Wald test. |                                              |
| Comparison groups                                                                                                                                                                                    | Placebo - DINAMO v Linagliptin 5 mg - DINAMO |
| Number of subjects included in analysis                                                                                                                                                              | 27                                           |
| Analysis specification                                                                                                                                                                               | Pre-specified                                |
| Analysis type                                                                                                                                                                                        |                                              |
| P-value                                                                                                                                                                                              | = 0.7789                                     |
| Method                                                                                                                                                                                               | Wald test                                    |
| Parameter estimate                                                                                                                                                                                   | Rate difference (percentage)                 |
| Point estimate                                                                                                                                                                                       | 2.4                                          |
| Confidence interval                                                                                                                                                                                  |                                              |
| level                                                                                                                                                                                                | 95 %                                         |
| sides                                                                                                                                                                                                | 2-sided                                      |
| lower limit                                                                                                                                                                                          | -15.2                                        |
| upper limit                                                                                                                                                                                          | 19.5                                         |

| Statistical analysis title | Statistical analysis 32 |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

The risk difference of active treatments versus placebo was determined and assessed by an exact 2-sided 95% confidence interval. Exact 95% CI by Chan and Zhang. Asymptotic and two-sided Wald test.

|                                         |                                                                    |
|-----------------------------------------|--------------------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO v Empagliflozin pooled (10 mg and 25 mg) - DINAMO |
| Number of subjects included in analysis | 31                                                                 |
| Analysis specification                  | Pre-specified                                                      |
| Analysis type                           |                                                                    |
| P-value                                 | = 0.2548                                                           |
| Method                                  | Wald test                                                          |
| Parameter estimate                      | Rate difference (percentage)                                       |
| Point estimate                          | 10.1                                                               |
| Confidence interval                     |                                                                    |
| level                                   | 95 %                                                               |
| sides                                   | 2-sided                                                            |
| lower limit                             | -7.7                                                               |
| upper limit                             | 28.1                                                               |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 33 |
|-----------------------------------|-------------------------|

Statistical analysis description:

The risk difference of active treatments versus placebo was determined and assessed by an exact 2-sided 95% confidence interval. Exact 95% CI by Chan and Zhang. Asymptotic and Fisher's exact test.

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO Mono v Linagliptin 5 mg - DINAMO Mono |
| Number of subjects included in analysis | 3                                                      |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| P-value                                 | = 0.5455                                               |
| Method                                  | Fisher exact                                           |
| Parameter estimate                      | Rate difference (percentage)                           |
| Point estimate                          | -23.3                                                  |
| Confidence interval                     |                                                        |
| level                                   | 90 %                                                   |
| sides                                   | 2-sided                                                |
| lower limit                             | -67.9                                                  |
| upper limit                             | 27.1                                                   |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 34 |
|-----------------------------------|-------------------------|

Statistical analysis description:

The risk difference of active treatments versus placebo was determined and assessed by an exact 2-sided 95% confidence interval. Exact 95% CI by Chan and Zhang. Asymptotic and Fisher's exact test.

|                                         |                                                                              |
|-----------------------------------------|------------------------------------------------------------------------------|
| Comparison groups                       | Placebo - DINAMO Mono v Empagliflozin pooled (10 mg and 25 mg) - DINAMO Mono |
| Number of subjects included in analysis | 6                                                                            |
| Analysis specification                  | Pre-specified                                                                |
| Analysis type                           |                                                                              |
| P-value                                 | = 0.5671                                                                     |
| Method                                  | Fisher exact                                                                 |
| Parameter estimate                      | Rate difference (percentage)                                                 |
| Point estimate                          | 26.7                                                                         |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | -30.8   |
| upper limit         | 70.8    |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Date of first study drug intake until date of last active study drug intake + residual effect period (7 days), up to 402 days.

Adverse event reporting additional description:

The treated set (TS) included all patients treated with at least 1 dose of randomised trial medication.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

### Reporting groups

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Placebo pooled - DINAMO & DINAMO Mono |
|-----------------------|---------------------------------------|

Reporting group description:

Patients from either DINAMO or DINAMO Mono randomized to Placebo.

|                       |                                                   |
|-----------------------|---------------------------------------------------|
| Reporting group title | Empagliflozin 25 mg pooled - DINAMO & DINAMO Mono |
|-----------------------|---------------------------------------------------|

Reporting group description:

Patients from either DINAMO or DINAMO Mono who were on Placebo and switched to 25 mg Empagliflozin following re-randomisation at week 26 or who were on 10 mg Empagliflozin and switched to 25 mg Empagliflozin following re-randomisation at week 14. 1 film-coated tablet of 25 mg empagliflozin, taken once daily, until end of treatment.

|                       |                                                   |
|-----------------------|---------------------------------------------------|
| Reporting group title | Empagliflozin 10 mg pooled - DINAMO & DINAMO Mono |
|-----------------------|---------------------------------------------------|

Reporting group description:

Patients from either DINAMO or DINAMO Mono who either started on 10 mg Empagliflozin or switched to 10 mg Empagliflozin from Placebo at week 26. 1 film-coated tablet of 10 milligram (mg) Empagliflozin once daily.

|                       |                                                |
|-----------------------|------------------------------------------------|
| Reporting group title | Linagliptin 5 mg pooled - DINAMO & DINAMO Mono |
|-----------------------|------------------------------------------------|

Reporting group description:

Patients from either DINAMO or DINAMO Mono who either started on Linagliptin or who switched to Linagliptin from Placebo at week 26. 1 film-coated tablet of 5 milligram (mg) Linagliptin once daily.

| Serious adverse events                               | Placebo pooled -<br>DINAMO & DINAMO<br>Mono | Empagliflozin 25 mg<br>pooled - DINAMO &<br>DINAMO Mono | Empagliflozin 10 mg<br>pooled - DINAMO &<br>DINAMO Mono |
|------------------------------------------------------|---------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|
| Total subjects affected by serious<br>adverse events |                                             |                                                         |                                                         |
| subjects affected / exposed                          | 2 / 58 (3.45%)                              | 0 / 29 (0.00%)                                          | 4 / 74 (5.41%)                                          |
| number of deaths (all causes)                        | 0                                           | 0                                                       | 0                                                       |
| number of deaths resulting from<br>adverse events    | 0                                           | 0                                                       | 0                                                       |
| Investigations                                       |                                             |                                                         |                                                         |
| Blood glucose increased                              |                                             |                                                         |                                                         |
| subjects affected / exposed                          | 0 / 58 (0.00%)                              | 0 / 29 (0.00%)                                          | 0 / 74 (0.00%)                                          |
| occurrences causally related to<br>treatment / all   | 0 / 0                                       | 0 / 0                                                   | 0 / 0                                                   |
| deaths causally related to<br>treatment / all        | 0 / 0                                       | 0 / 0                                                   | 0 / 0                                                   |
| Injury, poisoning and procedural<br>complications    |                                             |                                                         |                                                         |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| Road traffic accident                                |                |                |                |
| subjects affected / exposed                          | 0 / 58 (0.00%) | 0 / 29 (0.00%) | 1 / 74 (1.35%) |
| 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                                   |                |                |                |
| Hypovolaemic shock                                   |                |                |                |
| subjects affected / exposed                          | 1 / 58 (1.72%) | 0 / 29 (0.00%) | 0 / 74 (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          |
| Peripheral ischaemia                                 |                |                |                |
| subjects affected / exposed                          | 0 / 58 (0.00%) | 0 / 29 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders                 |                |                |                |
| Splenic vein thrombosis                              |                |                |                |
| subjects affected / exposed                          | 1 / 58 (1.72%) | 0 / 29 (0.00%) | 0 / 74 (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          |
| General disorders and administration site conditions |                |                |                |
| Systemic inflammatory response syndrome              |                |                |                |
| subjects affected / exposed                          | 1 / 58 (1.72%) | 0 / 29 (0.00%) | 0 / 74 (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                           |                |                |                |
| Colitis                                              |                |                |                |
| subjects affected / exposed                          | 0 / 58 (0.00%) | 0 / 29 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Pancreatitis acute                                   |                |                |                |
| subjects affected / exposed                          | 1 / 58 (1.72%) | 0 / 29 (0.00%) | 0 / 74 (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          |
| Respiratory, thoracic and mediastinal disorders      |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Acute respiratory failure                       |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 29 (0.00%) | 0 / 74 (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          |
| Asthma                                          |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 29 (0.00%) | 0 / 74 (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          |
| Pneumomediastinum                               |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 29 (0.00%) | 0 / 74 (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 / 58 (0.00%) | 0 / 29 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Suicidal ideation                               |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 29 (0.00%) | 1 / 74 (1.35%) |
| 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 and urinary disorders                     |                |                |                |
| Acute kidney injury                             |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 29 (0.00%) | 0 / 74 (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          |
| Tubulointerstitial nephritis                    |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 29 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Chorioretinitis                                 |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 29 (0.00%) | 0 / 74 (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          |
| Skin candida                                    |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 29 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Breast abscess                                  |                |                |                |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 0 / 29 (0.00%) | 0 / 74 (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              |                |                |                |
| Diabetic ketoacidosis                           |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 29 (0.00%) | 0 / 74 (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          |
| Hyperglycaemia                                  |                |                |                |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 29 (0.00%) | 0 / 74 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                   |                                                |  |  |
|---------------------------------------------------|------------------------------------------------|--|--|
| <b>Serious adverse events</b>                     | Linagliptin 5 mg pooled - DINAMO & DINAMO Mono |  |  |
| Total subjects affected by serious adverse events |                                                |  |  |
| subjects affected / exposed                       | 8 / 77 (10.39%)                                |  |  |
| number of deaths (all causes)                     | 0                                              |  |  |
| number of deaths resulting from adverse events    | 0                                              |  |  |
| Investigations                                    |                                                |  |  |
| Blood glucose increased                           |                                                |  |  |
| subjects affected / exposed                       | 1 / 77 (1.30%)                                 |  |  |
| occurrences causally related to treatment / all   | 1 / 1                                          |  |  |
| deaths causally related to treatment / all        | 0 / 0                                          |  |  |
| Injury, poisoning and procedural complications    |                                                |  |  |
| Road traffic accident                             |                                                |  |  |

|                                                      |                |  |  |
|------------------------------------------------------|----------------|--|--|
| subjects affected / exposed                          | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Vascular disorders                                   |                |  |  |
| Hypovolaemic shock                                   |                |  |  |
| subjects affected / exposed                          | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Peripheral ischaemia                                 |                |  |  |
| subjects affected / exposed                          | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Blood and lymphatic system disorders                 |                |  |  |
| Splenic vein thrombosis                              |                |  |  |
| subjects affected / exposed                          | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Systemic inflammatory response syndrome              |                |  |  |
| subjects affected / exposed                          | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Gastrointestinal disorders                           |                |  |  |
| Colitis                                              |                |  |  |
| subjects affected / exposed                          | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pancreatitis acute                                   |                |  |  |
| subjects affected / exposed                          | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders      |                |  |  |
| Acute respiratory failure                            |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Asthma                                          |                |  |  |
| subjects affected / exposed                     | 1 / 77 (1.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumomediastinum                               |                |  |  |
| subjects affected / exposed                     | 1 / 77 (1.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary embolism                              |                |  |  |
| subjects affected / exposed                     | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| Suicidal ideation                               |                |  |  |
| subjects affected / exposed                     | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Acute kidney injury                             |                |  |  |
| subjects affected / exposed                     | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tubulointerstitial nephritis                    |                |  |  |
| subjects affected / exposed                     | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Chorioretinitis                                 |                |  |  |
| subjects affected / exposed                     | 1 / 77 (1.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Skin candida                                    |                |  |  |
| subjects affected / exposed                     | 0 / 77 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Breast abscess                                  |                |  |  |
| subjects affected / exposed                     | 1 / 77 (1.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Diabetic ketoacidosis                           |                |  |  |
| subjects affected / exposed                     | 2 / 77 (2.60%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hyperglycaemia                                  |                |  |  |
| subjects affected / exposed                     | 1 / 77 (1.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Placebo pooled -<br>DINAMO & DINAMO<br>Mono | Empagliflozin 25 mg<br>pooled - DINAMO &<br>DINAMO Mono | Empagliflozin 10 mg<br>pooled - DINAMO &<br>DINAMO Mono |
|-------------------------------------------------------|---------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|
| Total subjects affected by non-serious adverse events |                                             |                                                         |                                                         |
| subjects affected / exposed                           | 30 / 58 (51.72%)                            | 14 / 29 (48.28%)                                        | 47 / 74 (63.51%)                                        |
| Investigations                                        |                                             |                                                         |                                                         |
| Blood ketone body increased                           |                                             |                                                         |                                                         |
| subjects affected / exposed                           | 2 / 58 (3.45%)                              | 3 / 29 (10.34%)                                         | 5 / 74 (6.76%)                                          |
| occurrences (all)                                     | 3                                           | 5                                                       | 5                                                       |
| Urine albumin/creatinine ratio increased              |                                             |                                                         |                                                         |
| subjects affected / exposed                           | 2 / 58 (3.45%)                              | 1 / 29 (3.45%)                                          | 1 / 74 (1.35%)                                          |
| occurrences (all)                                     | 2                                           | 1                                                       | 1                                                       |
| Nervous system disorders                              |                                             |                                                         |                                                         |
| Dizziness                                             |                                             |                                                         |                                                         |
| subjects affected / exposed                           | 3 / 58 (5.17%)                              | 0 / 29 (0.00%)                                          | 4 / 74 (5.41%)                                          |
| occurrences (all)                                     | 3                                           | 0                                                       | 4                                                       |

|                                                                                                               |                       |                      |                        |
|---------------------------------------------------------------------------------------------------------------|-----------------------|----------------------|------------------------|
| Headache<br>subjects affected / exposed<br>occurrences (all)                                                  | 9 / 58 (15.52%)<br>12 | 3 / 29 (10.34%)<br>4 | 12 / 74 (16.22%)<br>21 |
| Immune system disorders<br>Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)               | 0 / 58 (0.00%)<br>0   | 0 / 29 (0.00%)<br>0  | 4 / 74 (5.41%)<br>4    |
| Gastrointestinal disorders<br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)        | 2 / 58 (3.45%)<br>2   | 2 / 29 (6.90%)<br>2  | 2 / 74 (2.70%)<br>2    |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                            | 4 / 58 (6.90%)<br>7   | 1 / 29 (3.45%)<br>1  | 4 / 74 (5.41%)<br>4    |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                                    | 3 / 58 (5.17%)<br>4   | 0 / 29 (0.00%)<br>0  | 3 / 74 (4.05%)<br>4    |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                                 | 5 / 58 (8.62%)<br>9   | 2 / 29 (6.90%)<br>2  | 3 / 74 (4.05%)<br>4    |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                  | 2 / 58 (3.45%)<br>2   | 2 / 29 (6.90%)<br>2  | 5 / 74 (6.76%)<br>6    |
| Reproductive system and breast disorders<br>Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all) | 0 / 58 (0.00%)<br>0   | 1 / 29 (3.45%)<br>1  | 6 / 74 (8.11%)<br>8    |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)  | 5 / 58 (8.62%)<br>5   | 1 / 29 (3.45%)<br>1  | 4 / 74 (5.41%)<br>4    |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                        | 1 / 58 (1.72%)<br>1   | 0 / 29 (0.00%)<br>0  | 5 / 74 (6.76%)<br>5    |
| Musculoskeletal and connective tissue disorders                                                               |                       |                      |                        |

|                                                                                       |                       |                       |                        |
|---------------------------------------------------------------------------------------|-----------------------|-----------------------|------------------------|
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 58 (1.72%)<br>1   | 0 / 29 (0.00%)<br>0   | 2 / 74 (2.70%)<br>2    |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 58 (3.45%)<br>2   | 0 / 29 (0.00%)<br>0   | 4 / 74 (5.41%)<br>4    |
| Infections and infestations                                                           |                       |                       |                        |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 58 (0.00%)<br>0   | 1 / 29 (3.45%)<br>1   | 5 / 74 (6.76%)<br>5    |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 1 / 58 (1.72%)<br>1   | 2 / 29 (6.90%)<br>2   | 5 / 74 (6.76%)<br>5    |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 58 (5.17%)<br>3   | 1 / 29 (3.45%)<br>1   | 3 / 74 (4.05%)<br>3    |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 58 (0.00%)<br>0   | 0 / 29 (0.00%)<br>0   | 3 / 74 (4.05%)<br>3    |
| Metabolism and nutrition disorders                                                    |                       |                       |                        |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 58 (3.45%)<br>3   | 0 / 29 (0.00%)<br>0   | 3 / 74 (4.05%)<br>4    |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)                     | 7 / 58 (12.07%)<br>22 | 5 / 29 (17.24%)<br>52 | 12 / 74 (16.22%)<br>66 |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all)              | 8 / 58 (13.79%)<br>8  | 2 / 29 (6.90%)<br>2   | 10 / 74 (13.51%)<br>10 |

|                                                                                         |                                                      |  |  |
|-----------------------------------------------------------------------------------------|------------------------------------------------------|--|--|
| <b>Non-serious adverse events</b>                                                       | Linagliptin 5 mg<br>pooled - DINAMO &<br>DINAMO Mono |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 45 / 77 (58.44%)                                     |  |  |
| Investigations<br>Blood ketone body increased                                           |                                                      |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>8 / 77 (10.39%)</p> <p>12</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| <p>Urine albumin/creatinine ratio increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>5 / 77 (6.49%)</p> <p>6</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |
| <p>Nervous system disorders</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 77 (1.30%)</p> <p>2</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>12 / 77 (15.58%)</p> <p>24</p>                                                                                                                                                                                                                                                                                                                                                  |  |  |  |
| <p>Immune system disorders</p> <p>Seasonal allergy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>0 / 77 (0.00%)</p> <p>0</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |  |  |
| <p>Gastrointestinal disorders</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 77 (2.60%)</p> <p>2</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>5 / 77 (6.49%)</p> <p>8</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>4 / 77 (5.19%)</p> <p>8</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>7 / 77 (9.09%)</p> <p>8</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>8 / 77 (10.39%)</p> <p>9</p> |  |  |  |
| <p>Reproductive system and breast disorders</p> <p>Dysmenorrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 77 (2.60%)</p> <p>2</p>                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Cough                                           |                  |  |  |
| subjects affected / exposed                     | 6 / 77 (7.79%)   |  |  |
| occurrences (all)                               | 6                |  |  |
| Oropharyngeal pain                              |                  |  |  |
| subjects affected / exposed                     | 3 / 77 (3.90%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |
| Arthralgia                                      |                  |  |  |
| subjects affected / exposed                     | 4 / 77 (5.19%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Back pain                                       |                  |  |  |
| subjects affected / exposed                     | 4 / 77 (5.19%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Infections and infestations                     |                  |  |  |
| Upper respiratory tract infection               |                  |  |  |
| subjects affected / exposed                     | 3 / 77 (3.90%)   |  |  |
| occurrences (all)                               | 7                |  |  |
| Urinary tract infection                         |                  |  |  |
| subjects affected / exposed                     | 1 / 77 (1.30%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Nasopharyngitis                                 |                  |  |  |
| subjects affected / exposed                     | 6 / 77 (7.79%)   |  |  |
| occurrences (all)                               | 7                |  |  |
| Influenza                                       |                  |  |  |
| subjects affected / exposed                     | 4 / 77 (5.19%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Metabolism and nutrition disorders              |                  |  |  |
| Hyperglycaemia                                  |                  |  |  |
| subjects affected / exposed                     | 5 / 77 (6.49%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| Hypoglycaemia                                   |                  |  |  |
| subjects affected / exposed                     | 16 / 77 (20.78%) |  |  |
| occurrences (all)                               | 77               |  |  |
| Vitamin D deficiency                            |                  |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 6 / 77 (7.79%) |  |  |
| occurrences (all)           | 6              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 03 October 2019   | <p>Streamlining and clarification of wording and inclusion of authority feedback (Food and Drug Administration (FDA) proposed pediatric study request, European Medicines Agency (EMA) paediatric investigational plan, and Medicine and Healthcare products Regulatory Agency in the United Kingdom (UK)) as follows:</p> <ul style="list-style-type: none"><li>- Statistical method for primary endpoint changed from MMRM to pattern mixture model (jump-to-placebo and inverse probability weighting approach). The previous Mixed model for repeated measures (MMRM) became a sensitivity analysis</li><li>- Number of patients increased in DINAMO</li><li>- Trial part with DINAMO Mono added</li><li>- Minor adaptations to the flow chart including additional interactions between patient and site</li><li>- Exclusion criterion specified (acute metabolic decompensation)</li><li>- Addition of further efficacy endpoint (proportion of patients who achieve HbA1c reduction of &gt;0.5% at the end of 26 and 52 weeks)</li><li>- Frequency for blood ketone bodies measurement adapted</li><li>- Addition of Adverse event of special interest (AESIs) arthralgia, bullous pemphigoid, AEs related to reduced intravascular volume</li><li>- Removal of hospitalisation for unstable angina and of pancreatic events from the adjudication process</li><li>- New recommendations on diet and exercise for the patients by the site</li><li>- Addition of Body mass index (BMI) as new subgroup</li></ul> |
| 28 September 2020 | <p>Streamlining and clarification of wording, inclusion of authority feedback (FDA and EMA), and addition of measures related to the COVID-19 pandemic as follows:</p> <ul style="list-style-type: none"><li>- Updated inclusion criteria: reduction in length of diagnosis of Type 2 diabetes mellitus (T2DM) from 12 to 8 weeks and addition of minimum daily metformin dosage</li><li>- Change in primary endpoint analysis from pattern mixture model ('jump-to-placebo' and 'inverse probability weighting' approach) to 'wash-out' and 'inverse probability weighting' approach for primary and secondary hypotheses</li><li>- Addition of measures related to the COVID-19 pandemic</li><li>- Addition of remote visits</li><li>- Guidance added for patients stopping prematurely (also related to Diabetic ketoacidosis (DKA))</li><li>- Addition of local instead of central laboratory testing</li><li>- Shipment of trial medication directly to the patients</li><li>- Possibility added to replace patients to keep a certain sample size despite the pandemic</li><li>- Addition of alternative method for SAE report transmission in certain countries</li><li>- Addition of sensitivity analysis for the primary endpoint</li><li>- Rules implemented for remote source data verification during restricted on-site monitoring visits</li></ul>                                                                                                                                                        |
| 14 December 2020  | <p>Administrative changes, streamlining of wording, and addition of further measures related to the COVID-19 pandemic as follows:</p> <ul style="list-style-type: none"><li>- Reconsent could be done remotely due to the COVID-19 pandemic</li><li>- Serum pregnancy test could be done at a local laboratory due to the COVID-19 pandemic</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

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| 14 July 2021      | <p>This version was only submitted to the FDA and never implemented due to the requested changes. It included administrative changes, clarified wording, and incorporated feedback from the FDA on the previous global amendment.</p> <ul style="list-style-type: none"> <li>- Time reduced between rescreening visits (from 12 to 8 weeks) to allow earlier inclusion of patients</li> <li>- Clarification of maintaining the blinded conditions while the bioanalyst required access to the data when migrating from the main trial to the ancillary trial</li> <li>- If a centrally analysed, National Glycohemoglobin Standardization Program (NGSP)-certified Glycated haemoglobin (HbA1c) assay was unavailable (e.g. due to the COVID-19 pandemic), an HbA1c assay performed at a local laboratory was acceptable. Text added to specify the corresponding sensitivity analyses</li> <li>- Addition of an alternative means to measure blood glucose concentration</li> <li>- Clarification of the secondary hypotheses for the Analysis of covariance (ANCOVA)</li> </ul> |
| 28 September 2021 | <p>This amendment included administrative changes and incorporated feedback from the FDA:</p> <ul style="list-style-type: none"> <li>- Clarification that patients with a Continuous glucose monitoring (CGM) device could use relevant readings from that device to avoid additional finger pricks</li> <li>- Further clarification on secondary hypotheses for the ANCOVA</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 23 May 2022       | <p>This amendment mainly impacted the ancillary trial DINAMO Mono which is still ongoing. Changes regarding DINAMO included addition of bone fracture as further safety endpoint; bone fracture was already introduced via the initial Trial statistical analysis plan (TSAP) version.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date          | Interruption                                                                                                                                                                                | Restart date |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 17 March 2020 | Due to the COVID-19 pandemic, the enrolment of new patients and the initiation of new sites were temporarily put on hold on 17 March 2020 and resumed on a per country level in April 2020. | -            |

Notes:

## Limitations and caveats

None reported