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, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127 x 001, clintriage.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)	EMEA-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:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	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
Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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[1]	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[1]	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[1]	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:

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:

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:

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:

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:

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:

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:

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 - Empagliflozin 25 mg - DINAMO & DINAMO Mono	Linagliptin 5 mg - DINAMO & DINAMO Mono	Empagliflozin 10 mg - DINAMO & 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

Reporting group values	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:

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:

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:

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:

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:

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:

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:

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:

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:

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[1]	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 α 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 α 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 α 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

Statistical analysis title	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 α 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:
- Use of rescue medication at any time up to Week 26
- Increase from baseline in HbA1c by 0.5% at Week 26
. Increase from baseline in HbA1c to above 7.0% at Week 26 in patients with baseline HbA1c <7.0%.

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 - 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	3	3	3	
Units: Percentage of subjects				
number (confidence interval 90%)	60.0 (18.9 to 92.4)	50.0 (15.3 to 84.7)	50.0 (15.3 to 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

Statistical analysis title	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.

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	3	4	3	
Units: Days				
arithmetic mean (standard error)	65.600 (± 19.941)	72.167 (± 20.280)	167.333 (± 26.711)	

Statistical analyses

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

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

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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.

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: 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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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 - 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%)	0.76 (-1.01 to 2.53)	2.26 (0.46 to 4.05)	0.78 (-1.04 to 2.60)	3.42 (-4.92 to 11.75)

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%)	6.75 (0.14 to 13.35)	-3.20 (-10.10 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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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.

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	5	8	11	2
Units: Percentage of subjects				
number (not applicable)	9.4	15.4	21.2	40.0

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	1	1		
Units: Percentage of subjects				
number (not applicable)	16.7	16.7		

Statistical analyses

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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 - 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	13	14	18	2
Units: Percentage of subjects				
number (not applicable)	24.5	26.9	34.6	40.0

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	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

Statistical analysis title	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

Statistical analysis title	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 - DINAMO & DINAMO Mono	Empagliflozin 25 mg pooled - DINAMO & DINAMO Mono	Empagliflozin 10 mg pooled - DINAMO & DINAMO Mono
Total subjects affected by serious 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 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 treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

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

Serious adverse events	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 %

Non-serious adverse events	Placebo pooled - DINAMO & DINAMO Mono	Empagliflozin 25 mg pooled - DINAMO & DINAMO Mono	Empagliflozin 10 mg pooled - DINAMO & 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			
subjects affected / exposed	9 / 58 (15.52%)	3 / 29 (10.34%)	12 / 74 (16.22%)
occurrences (all)	12	4	21
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 58 (0.00%)	0 / 29 (0.00%)	4 / 74 (5.41%)
occurrences (all)	0	0	4
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 58 (3.45%)	2 / 29 (6.90%)	2 / 74 (2.70%)
occurrences (all)	2	2	2
Abdominal pain			
subjects affected / exposed	4 / 58 (6.90%)	1 / 29 (3.45%)	4 / 74 (5.41%)
occurrences (all)	7	1	4
Nausea			
subjects affected / exposed	3 / 58 (5.17%)	0 / 29 (0.00%)	3 / 74 (4.05%)
occurrences (all)	4	0	4
Diarrhoea			
subjects affected / exposed	5 / 58 (8.62%)	2 / 29 (6.90%)	3 / 74 (4.05%)
occurrences (all)	9	2	4
Vomiting			
subjects affected / exposed	2 / 58 (3.45%)	2 / 29 (6.90%)	5 / 74 (6.76%)
occurrences (all)	2	2	6
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 58 (0.00%)	1 / 29 (3.45%)	6 / 74 (8.11%)
occurrences (all)	0	1	8
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 58 (8.62%)	1 / 29 (3.45%)	4 / 74 (5.41%)
occurrences (all)	5	1	4
Oropharyngeal pain			
subjects affected / exposed	1 / 58 (1.72%)	0 / 29 (0.00%)	5 / 74 (6.76%)
occurrences (all)	1	0	5
Musculoskeletal and connective tissue disorders			

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

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

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

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 occurrences (all)	6 / 77 (7.79%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2019	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: - 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 - Number of patients increased in DINAMO - Trial part with DINAMO Mono added - Minor adaptions to the flow chart including additional interactions between patient and site - Exclusion criterion specified (acute metabolic decompensation) - Addition of further efficacy endpoint (proportion of patients who achieve HbA1c reduction of >0.5% at the end of 26 and 52 weeks) - Frequency for blood ketone bodies measurement adapted - Addition of Adverse event of special interest (AESIs) arthralgia, bullous pemphigoid, AEs related to reduced intravascular volume - Removal of hospitalisation for unstable angina and of pancreatic events from the adjudication process - New recommendations on diet and exercise for the patients by the site - Addition of Body mass index (BMI) as new subgroup
28 September 2020	Streamlining and clarification of wording, inclusion of authority feedback (FDA and EMA), and addition of measures related to the COVID-19 pandemic as follows: - 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 - 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 - Addition of measures related to the COVID-19 pandemic - Addition of remote visits - Guidance added for patients stopping prematurely (also related to Diabetic ketoacidosis (DKA)) - Addition of local instead of central laboratory testing - Shipment of trial medication directly to the patients - Possibility added to replace patients to keep a certain sample size despite the pandemic - Addition of alternative method for SAE report transmission in certain countries - Addition of sensitivity analysis for the primary endpoint - Rules implemented for remote source data verification during restricted on-site monitoring visits
14 December 2020	Administrative changes, streamlining of wording, and addition of further measures related to the COVID-19 pandemic as follows: - Reconsent could be done remotely due to the COVID-19 pandemic - Serum pregnancy test could be done at a local laboratory due to the COVID-19 pandemic

14 July 2021	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. - Time reduced between rescreening visits (from 12 to 8 weeks) to allow earlier inclusion of patients - Clarification of maintaining the blinded conditions while the bioanalyst required access to the data when migrating from the main trial to the ancillary trial - 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 - Addition of an alternative means to measure blood glucose concentration - Clarification of the secondary hypotheses for the Analysis of covariance (ANCOVA)
28 September 2021	This amendment included administrative changes and incorporated feedback from the FDA: - Clarification that patients with a Continuous glucose monitoring (CGM) device could use relevant readings from that device to avoid additional finger pricks - Further clarification on secondary hypotheses for the ANCOVA
23 May 2022	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.

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