



Clinical trial results:

Efficacy and Safety of Oral Semaglutide versus Empagliflozin in Subjects with Type 2 Diabetes Mellitus. A 52-week Randomised, Open-label, Active-controlled Trial

Summary

EudraCT number	2015-005209-36
Trial protocol	HU GR PL ES HR IT
Global end of trial date	08 March 2018

Results information

Result version number	v1 (current)
This version publication date	24 March 2019
First version publication date	24 March 2019

Trial information

Trial identification

Sponsor protocol code	NN9924-4223
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02863328
WHO universal trial number (UTN)	U1111-1176-6006

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 August 2017
Global end of trial reached?	Yes
Global end of trial date	08 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, on glycaemic control in subjects with type 2 diabetes mellitus.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013), ICH Good Clinical Practice, including archiving of essential documents, (1996) and 21 CFR 312.120.

Background therapy:

Subjects continued on a stable daily dose of anti-diabetic background metformin (≥ 1500 mg or maximum tolerated dose as documented in the subject medical record) throughout the trial.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	10 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 52
Country: Number of subjects enrolled	Brazil: 61
Country: Number of subjects enrolled	Spain: 70
Country: Number of subjects enrolled	Greece: 51
Country: Number of subjects enrolled	Croatia: 36
Country: Number of subjects enrolled	Hungary: 46
Country: Number of subjects enrolled	Italy: 46
Country: Number of subjects enrolled	Poland: 65
Country: Number of subjects enrolled	Russian Federation: 60
Country: Number of subjects enrolled	Serbia: 51
Country: Number of subjects enrolled	Thailand: 41
Country: Number of subjects enrolled	United States: 242
Worldwide total number of subjects	821
EEA total number of subjects	314

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	606
From 65 to 84 years	215
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 108 sites in 12 countries as follows: Argentina (4), Brazil (3), Croatia (4), Greece (7), Hungary (7), Italy (5), Poland (6), Russian Federation (6), Serbia (5), Spain (8), Thailand (3), United States (46). 1 site each in Croatia and Italy, and 2 sites in the United States screened, but didn't randomise any subjects.

Pre-assignment

Screening details:

Not applicable.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The trial was an open label study. Only the clinical study group remained blinded throughout the conduct of the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Oral semaglutide 14 mg

Arm description:

Subjects received once-daily oral semaglutide tablets for 52 weeks. Subjects started oral semaglutide at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52).

Arm type	Experimental
Investigational medicinal product name	Semaglutide 3 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral semaglutide 3 mg was administered from week 0 to week 4, as part of dose escalation regimen. The tablet was taken once-daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The tablet was taken with up to a half a glass of water (approximately 120 mL/4 fluid oz) and was swallowed whole and not broken or chewed. Oral medication other than trial product could be taken 30 minutes after administration of trial product.

Investigational medicinal product name	Semglutide 7 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral semaglutide 7 mg was administered from week 4 to week 8, as part of dose escalation regimen. The tablet was taken once-daily in the morning in a fasting state and at least 30 minutes before the first meal of the day. The tablet was taken with up to a half a glass of water (approximately 120 mL/4 fluid oz) and was swallowed whole and not broken or chewed. Oral medication other than trial product could be taken 30 minutes after administration of trial product.

Investigational medicinal product name	Semglutide 14 mg
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral semaglutide 14 mg was administered from week 8 to week 52, once-daily in the morning. The tablet was taken in a fasting state and at least 30 minutes before the first meal of the day. The tablet was taken with up to a half a glass of water (approximately 120 mL/4 fluid oz) and was swallowed whole and not broken or chewed. Oral medication other than trial product could be taken 30 minutes after administration of trial product.

Arm title	Empagliflozin 25 mg
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Arm description:

Subjects received once-daily empagliflozin tablets for 52 weeks. Subjects started empagliflozin at 10 mg for 8 weeks. The subjects were treated with empagliflozin 25 mg from week 8 until week 52.

Arm type	Active comparator
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	Jardiance 10 mg
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin 10 mg tablet was to be taken once-daily in the morning from week 0 to week 8, as part of dose escalation regimen. The tablet was to be swallowed whole with water and it could be taken with or without food.

Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	Jardiance 25 mg
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin 25 mg tablet was to be taken once-daily in the morning from week 8 to week 52. The tablet was to be swallowed whole with water and it could be taken with or without food.

Number of subjects in period 1	Oral semaglutide 14 mg	Empagliflozin 25 mg
Started	411	410
Completed	400	387
Not completed	11	23
Consent withdrawn by subject	7	12
Lost to follow-up	4	10
Died	-	1

Baseline characteristics

Reporting groups

Reporting group title	Oral semaglutide 14 mg
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Reporting group description:

Subjects received once-daily oral semaglutide tablets for 52 weeks. Subjects started oral semaglutide at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52).

Reporting group title	Empagliflozin 25 mg
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Reporting group description:

Subjects received once-daily empagliflozin tablets for 52 weeks. Subjects started empagliflozin at 10 mg for 8 weeks. The subjects were treated with empagliflozin 25 mg from week 8 until week 52.

Reporting group values	Oral semaglutide 14 mg	Empagliflozin 25 mg	Total
Number of subjects	411	410	821
Age Categorical Units: Subjects			
Adults (18-65 years)	306	300	606
From 65-75 years	92	98	190
From 75-85 years	13	12	25
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	57	58	-
standard deviation	± 10	± 10	-
Gender Categorical Units: Subjects			
Female	205	201	406
Male	206	209	415
HbA1c Units: percent			
arithmetic mean	8.1	8.1	-
standard deviation	± 0.9	± 0.9	-
Body weight Units: kg			
arithmetic mean	91.9	91.3	-
standard deviation	± 20.5	± 20.1	-

End points

End points reporting groups

Reporting group title	Oral semaglutide 14 mg
Reporting group description: Subjects received once-daily oral semaglutide tablets for 52 weeks. Subjects started oral semaglutide at 3 mg and were dose escalated in 4-week increments until the final maintenance dose of 14 mg once-daily was reached (i.e. 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to week 52).	
Reporting group title	Empagliflozin 25 mg
Reporting group description: Subjects received once-daily empagliflozin tablets for 52 weeks. Subjects started empagliflozin at 10 mg for 8 weeks. The subjects were treated with empagliflozin 25 mg from week 8 until week 52.	

Primary: Change in HbA1c (in-trial observation period)

End point title	Change in HbA1c (in-trial observation period)
End point description: Observed mean change from baseline (week 0) to week 26 in glycosylated haemoglobin (HbA1c). The endpoint was evaluated based on data from the in-trial observation period. In trial observation period: the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of rescue medication or premature discontinuation of trial product. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data at week 26.	
End point type	Primary
End point timeframe: From baseline to week 26	

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392	395		
Units: %-point				
arithmetic mean (standard deviation)	-1.3 (± 1.1)	-0.9 (± 0.9)		

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg vs. Empagliflozin
Statistical analysis description: Analysed using an ANCOVA model with treatment and region as categorical fixed effects and baseline value as covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference. Hypothesis: H0: $\mu \geq 0.4\%$ -points against Ha: $\mu < 0.4\%$ -points. (μ denotes mean treatment difference). HbA1c non-inferiority, using a non-inferiority margin of 0.4%-points. A value of 0.4% was added to imputed values at week 26 for the oral semaglutide treatment arms only.	
Comparison groups	Oral semaglutide 14 mg v Empagliflozin 25 mg

Number of subjects included in analysis	787
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	< 0.0001 ^[2]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.3

Notes:

[1] - The analysis was for the treatment policy estimand based on data from in-trial observation period. "Subjects in this analysis"=number of subjects with available data at week 26; all subjects in the FAS (N=821) contributed to the analysis.

[2] - Unadjusted two-sided p-value for test of no difference from the non-inferiority margin.

Statistical analysis title	Oral semaglutide 14 mg vs. empagliflozin 25 mg
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Statistical analysis description:

Change from baseline was analysed using an ANCOVA model with treatment and region as categorical fixed effects and baseline value as covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference. Hypothesis: H0: $\mu \geq 0.0\%$ -points against Ha: $\mu < 0.0\%$ -points (μ denotes mean treatment difference).

Comparison groups	Oral semaglutide 14 mg v Empagliflozin 25 mg
Number of subjects included in analysis	787
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.0001 ^[4]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.3

Notes:

[3] - The analysis was for the treatment policy estimand based on data from in-trial observation period. "Subjects in this analysis"=number of subjects with available data at week 26; all subjects in the FAS (N=821) contributed to the analysis.

[4] - Unadjusted two-sided p-value for test of no difference from 0.

Primary: Change in HbA1c (on-treatment observation period)

End point title	Change in HbA1c (on-treatment observation period)
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End point description:

Observed mean change from baseline (week 0) to week 26 in HbA1c. The endpoint was analysed based on data from the on-treatment without rescue medication observation period. On-treatment without rescue medication observation period: the time period when a subject was on treatment with trial product, excluding any period after initiation of rescue medication. The results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

End point type	Primary
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End point timeframe:

From baseline to week 26

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	378		
Units: %-points				
arithmetic mean (standard deviation)	-1.5 (\pm 1.1)	-0.9 (\pm 0.9)		

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg vs. empagliflozin 25 mg
Statistical analysis description:	
Changes from baseline were analysed using a mixed model for repeated measurements model with treatment and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. Hypothesis: H0: $\mu \geq 0.4\%$ -points against Ha: $\mu < 0.4\%$ -points. (μ denotes mean treatment difference). HbA1c non-inferiority, using a non-inferiority margin of 0.4%-points.	
Comparison groups	Oral semaglutide 14 mg v Empagliflozin 25 mg
Number of subjects included in analysis	725
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[5]
P-value	< 0.0001 ^[6]
Method	Mixed model for repeated measurements
Parameter estimate	Treatment difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.4

Notes:

[5] - The analysis was for the hypothetical estimand based on data from on-treatment observation period. "Subjects in this analysis"=number of subjects with available data at week 26; all subjects in the FAS (N=821) contributed to the analysis.

[6] - Unadjusted two-sided p-value for test of no difference from the non-inferiority margin.

Statistical analysis title	Oral semaglutide 14 mg vs. empagliflozin 25 mg
Statistical analysis description:	
Changes from baseline were analysed using a mixed model for repeated measurements model with treatment and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix.	
The null hypothesis (H0) and the alternate hypothesis (HA) were: H0: $\mu \geq 0.0\%$ -points against HA: $\mu < 0.0\%$. (μ denotes mean treatment difference).	
Comparison groups	Oral semaglutide 14 mg v Empagliflozin 25 mg

Number of subjects included in analysis	725
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	< 0.0001 ^[8]
Method	Treatment difference
Parameter estimate	Treatment difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.4

Notes:

[7] - The analysis was for the hypothetical estimand based on data from on-treatment observation period. "Subjects in this analysis"=number of subjects with available data; all subjects in the FAS (N=821) contributed to the analysis.

[8] - Unadjusted two-sided p-value for test of no difference from 0.

Secondary: Change in body weight (in-trial observation period)

End point title	Change in body weight (in-trial observation period)
End point description:	
Observed mean change from baseline (week 0) to week 26 in body weight. The endpoint was evaluated based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.	
End point type	Secondary
End point timeframe:	
From baseline to week 26	

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	396		
Units: kg				
arithmetic mean (standard deviation)	-3.9 (± 4.4)	-3.8 (± 3.8)		

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg vs. empagliflozin 25 mg
Statistical analysis description:	
Change from baseline was analysed using an ANCOVA model with treatment and region as categorical fixed effects and baseline value as covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference. Hypothesis tested: H0: $\mu \geq 0.0$ kg against Ha: $\mu < 0.0$ kg (μ denotes mean treatment difference).	
Comparison groups	Oral semaglutide 14 mg v Empagliflozin 25 mg

Number of subjects included in analysis	789
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.7593 ^[10]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.5

Notes:

[9] - Analysis was for the treatment policy estimand based on data from in-trial observation period. "Subjects in this analysis"=number of subjects with available data at week 26; all subjects in the FAS (N=821) contributed to the analysis.

[10] - Unadjusted two-sided p-value for test of no difference from 0.

Secondary: Change in body weight (on-treatment observation period)

End point title	Change in body weight (on-treatment observation period)
End point description:	
Observed mean change from baseline (week 0) to week 26 in body weight. The endpoint was analysed based on data from the on-treatment without rescue medication observation period. Full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.	
End point type	Secondary
End point timeframe:	
From baseline to week 26	

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	348	378		
Units: kg				
arithmetic mean (standard deviation)	-4.3 (± 4.4)	-3.9 (± 3.8)		

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg vs. empagliflozin
Statistical analysis description:	
Changes from baseline were analysed using a mixed model for repeated measurements model with treatment and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix.	
Comparison groups	Oral semaglutide 14 mg v Empagliflozin 25 mg

Number of subjects included in analysis	726
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.1358 ^[12]
Method	Mixed model for repeated measurements
Parameter estimate	Treatment difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.1

Notes:

[11] - Analysis was for the treatment policy estimand based on data from on-treatment observation period. "Subjects in this analysis"=number of subjects with available data at week 26; all subjects in the FAS (N=821) contributed to the analysis.

[12] - Unadjusted two-sided p-value for test of no difference from 0.

Secondary: Change in HbA1c (52 weeks)

End point title	Change in HbA1c (52 weeks)
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End point description:

Observed mean change from baseline (week 0) to week 52 in HbA1c. The endpoint was evaluated for the treatment policy estimand based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data. The endpoint was evaluated for the treatment policy estimand based on data from the in-trial observation period.

End point type	Secondary
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End point timeframe:

From baseline to week 52

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	382		
Units: percentage				
arithmetic mean (standard deviation)	-1.3 (± 1.2)	-0.9 (± 1.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight (52 weeks)

End point title	Change in body weight (52 weeks)
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End point description:

Observed mean change from baseline (week 0) to week 52 in body weight. The endpoint was evaluated for the treatment policy estimand based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

End point type	Secondary
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End point timeframe:
From baseline to week 52

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	386	383		
Units: kg				
arithmetic mean (standard deviation)	-4.0 (\pm 5.5)	-3.7 (\pm 4.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (week 26)

End point title	Change in fasting plasma glucose (week 26)
End point description: Observed mean change from baseline (week 0) to week 26 in fasting plasma glucose. The endpoint was evaluated for the treatment policy estimand based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.	
End point type	Secondary
End point timeframe: From baseline to week 26	

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	391		
Units: mmol/L				
arithmetic mean (standard deviation)	-2.01 (\pm 2.56)	-2.08 (\pm 2.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (week 52)

End point title	Change in fasting plasma glucose (week 52)
End point description: Observed mean change from baseline (week 0) to week 52 in fasting plasma glucose. The endpoint was evaluated for the treatment policy estimand based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"	

=subjects with available data.

End point type	Secondary
End point timeframe:	
From baseline to week 52	

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	380	378		
Units: mmol/L				
arithmetic mean (standard deviation)	-2.04 (± 2.50)	-2.14 (± 2.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Achieved HbA1c <7.0 % (53 mmol/mol) American Diabetes Association (ADA) target (yes/no) (week 26)

End point title	Achieved HbA1c <7.0 % (53 mmol/mol) American Diabetes Association (ADA) target (yes/no) (week 26)
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End point description:

Percentage of subjects achieving HbA1c less than 7.0% (53 mmol/mol) American Diabetes Association (ADA) target at week 26. The endpoint was evaluated for the treatment policy estimand based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

End point type	Secondary
End point timeframe:	
After week 26	

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392	395		
Units: Percentage of subjects				
number (not applicable)				
Yes	66.8	40.0		
No	33.2	60.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Achieved HbA1c < 7.0 % (53 mmol/mol) American Diabetes Association target (yes/no) (week 52)

End point title	Achieved HbA1c < 7.0 % (53 mmol/mol) American Diabetes Association target (yes/no) (week 52)
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End point description:

Percentage of subjects achieving HbA1c less than 7.0% (53 mmol/mol) American Diabetes Association (ADA) target at week 52. The endpoint was evaluated for the treatment policy estimand based on data from the in-trial observation period. Results are based on full analysis set comprised of all randomised subjects. "Number of subjects analysed"=subjects with available data.

End point type	Secondary
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End point timeframe:

After week 52

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	382		
Units: percentage of subjects				
number (not applicable)				
Yes	66.1	43.2		
No	33.9	56.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent adverse events (TEAE)

End point title	Number of treatment-emergent adverse events (TEAE)
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End point description:

A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset in the on-treatment observation period (the time period where subjects are considered treated with trial product). The safety analysis set (SAS) included all randomised subjects who received at least one dose of trial product. "Number of subjects analysed"=subjects with available data.

End point type	Secondary
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End point timeframe:

Weeks 0-57

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	409		
Units: Event				
number (not applicable)	1022	948		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks

End point title	Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 57 weeks
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End point description:

Hypoglycaemic episodes defined as treatment-emergent if the onset of the episode occurs within the on-treatment observation period. Severe or BG-confirmed symptomatic hypoglycaemia is an episode that is severe according to the American Diabetes Association classification or blood glucose-confirmed by a plasma glucose value <3.1 mmol/L (56mg/dL) with symptoms consistent with hypoglycaemia. The safety analysis set (SAS) included all randomised subjects who received at least one dose of trial product. "Number of subjects analysed"=subjects with available data.

End point type	Secondary
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End point timeframe:

Weeks 0-57

End point values	Oral semaglutide 14 mg	Empagliflozin 25 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	409		
Units: Episode				
number (not applicable)	10	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first trial-related activity after the subject had signed the informed consent until the end of the post-treatment follow-up period (week 52+ 5 weeks of follow-up; until week 57), or until the end of trial for discontinued subjects.

Adverse event reporting additional description:

A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset in the on-treatment observation period (the time period where subjects are considered treated with trial product). The results are based on the safety analysis set.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Empagliflozin 25 mg
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Reporting group description:

N/A

Reporting group title	Oral semaglutide 14 mg
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Reporting group description:

N/A

Serious adverse events	Empagliflozin 25 mg	Oral semaglutide 14 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 409 (9.05%)	27 / 410 (6.59%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			

subjects affected / exposed	1 / 409 (0.24%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 409 (0.49%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary arterial stent insertion			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			

subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Arteriogram coronary			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis postoperative			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 409 (0.24%)	2 / 410 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 409 (0.73%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			

subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 409 (0.24%)	2 / 410 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CANVAS syndrome			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			

subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 409 (0.49%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 409 (0.00%)	2 / 410 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 409 (0.49%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hypocoagulable state			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Ear haemorrhage			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cholecystitis			
subjects affected / exposed	0 / 409 (0.00%)	2 / 410 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 409 (0.24%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 409 (0.24%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head deformity			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoarthritis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perichondritis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 409 (0.24%)	2 / 410 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubo-ovarian abscess			
subjects affected / exposed	0 / 409 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 409 (0.24%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Empagliflozin 25 mg	Oral semaglutide 14 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 409 (10.76%)	128 / 410 (31.22%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 409 (3.18%)	38 / 410 (9.27%)	
occurrences (all)	17	48	
Nausea			
subjects affected / exposed	10 / 409 (2.44%)	81 / 410 (19.76%)	
occurrences (all)	12	106	
Vomiting			
subjects affected / exposed	7 / 409 (1.71%)	30 / 410 (7.32%)	
occurrences (all)	7	40	
Infections and infestations			
Influenza			
subjects affected / exposed	21 / 409 (5.13%)	8 / 410 (1.95%)	
occurrences (all)	23	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 409 (0.49%)	21 / 410 (5.12%)	
occurrences (all)	2	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2016	<ol style="list-style-type: none">1. Introduction of additional eye examinations and additional data collection on diabetic retinopathy.2. Added text to highlight the investigator's responsibility in ensuring evaluation and management of certain risk factors and complications.3. Clarification of the criteria for completion, withdrawal and lost to follow-up.4. Other minor corrections and clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported