Clinical trial results:
Efficacy and safety of once-daily oral semaglutide 25 mg and 50 mg compared with 14 mg in subjects with type 2 diabetes

Summary

EudraCT number	2020-000299-39
Trial protocol	CZ DE SK HU BG SI PL HR EE
Global end of trial date	06 March 2023

Results information

Result version number	v1 (current)
This version publication date	23 March 2024
First version publication date	23 March 2024

Trial information

Trial identification

Sponsor protocol code	NN9924-4635

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04707469
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Alle, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (2834), 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	21 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm superiority of oral semaglutide 25 mg and 50 mg once daily versus oral semaglutide 14 mg once daily on glycated haemoglobin (HbA1c) reduction in subjects with type 2 diabetes (T2D) on stable dose of 1-3 oral anti-diabetic drugs (OADs).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th World Medical Association [WMA] general assembly, Oct 2013) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, including archiving of essential documents (Current step 4 version, Nov 2016), and 21 US Code of Federal Regulations (CFR) 312.120.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	15 January 2021
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	Australia: 37
Country: Number of subjects enrolled	Bulgaria: 153
Country: Number of subjects enrolled	Canada: 87
Country: Number of subjects enrolled	Croatia: 52
Country: Number of subjects enrolled	Czechia: 42
Country: Number of subjects enrolled	Estonia: 27
Country: Number of subjects enrolled	Germany: 89
Country: Number of subjects enrolled	Hungary: 97
Country: Number of subjects enrolled	India: 214
Country: Number of subjects enrolled	Poland: 289
Country: Number of subjects enrolled	Slovakia: 114
Country: Number of subjects enrolled	Slovenia: 48
Country: Number of subjects enrolled	Taiwan: 26
Country: Number of subjects enrolled	United States: 331
Worldwide total number of subjects	1606
EEA total number of subjects	911

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)	1110
From 65 to 84 years	494
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 14 countries (184 sites screened/177 randomised subjects) as follows: Australia: 7/6; Bulgaria: 15/15; Canada: 13/13; Croatia: 5/5; Czech Republic: 5/5; Estonia: 6/5; Germany: 8/8; Hungary: 9/9; India: 20/20; Poland: 18/18; Slovakia: 9/9; Slovenia: 5/5; Taiwan: 2/2; United States: 62/57.

Pre-assignment

Screening details:

Subjects were randomised in 1:1:1 ratio to receive either 14 mg, 25 mg or 50 mg oral semaglutide once daily. The trial had a 68-week treatment period (8-16 weeks of dose escalation period and 52-60 weeks of maintenance period), followed by a 5-week follow-up period.

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

Arms

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

Arm description:

Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8 and 14 mg from week 8 to week 68.

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

Dosage and administration details:

Subjects received 14 mg semaglutide tablet orally once daily in a dose escalation manner for 68 weeks.

Arm title	Oral semaglutide 25 mg

Arm description:

Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to 12 and 25 mg from week 12 to week 68.

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

Dosage and administration details:

Subjects received 25 mg semaglutide tablet orally once daily in a dose escalation manner for 68 weeks.

Arm title	Oral semaglutide 50 mg

Arm description:

Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to 12, 25 mg

from week 12 to week 16 and 50 mg from week 16 to week 68.

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

Dosage and administration details:

Subjects received 50 mg semaglutide tablet orally once daily in a dose escalation manner for 68 weeks.

Number of subjects in period 1	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg
Started	536	535	535
Treated	534	534	534
Full analysis set (FAS)	536	535	535
Safety analysis set (SAS)	534	534	534
Completed	507	490	505
Not completed	29	45	30
Adverse event, serious fatal	1	6	2
Physician decision	2	2	2
Consent withdrawn by subject	17	16	12
Lost to follow-up	9	19	14
Site closure	-	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8 and 14 mg from week 8 to week 68.	
Reporting group title	Oral semaglutide 25 mg
Reporting group description:	
Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to 12 and 25 mg from week 12 to week 68.	
Reporting group title	Oral semaglutide 50 mg
Reporting group description:	
Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to 12, 25 mg from week 12 to week 16 and 50 mg from week 16 to week 68.	

Reporting group values	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg
Number of subjects	536	535	535
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 58.4 ± 10.4	 58.8 ± 10.7	 57.6 ± 11.2
Gender Categorical Units: Subjects			
Female	211	231	228
Male	325	304	307

Reporting group values	Total		
Number of subjects	1606		
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 -		
Gender Categorical Units: Subjects			
Female Male	670 936		

End points

End points reporting groups

Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8 and 14 mg from week 8 to week 68.	
Reporting group title	Oral semaglutide 25 mg
Reporting group description:	
Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to 12 and 25 mg from week 12 to week 68.	
Reporting group title	Oral semaglutide 50 mg
Reporting group description:	
Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to 12, 25 mg from week 12 to week 16 and 50 mg from week 16 to week 68.	

Primary: Change in glycated haemoglobin (HbA1c)

End point title	Change in glycated haemoglobin (HbA1c)
End point description:	
Change from baseline (week 0) in glycosylated haemoglobin (HbA1c) was evaluated at week 52. Results are based on the data from the in-trial observation period, which was the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of additional anti-diabetic medication or discontinuation of trial treatment. Percentage point refers to arithmetic difference between two percentages. Full Analysis Set (FAS) which comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this endpoint.	
End point type	Primary
End point timeframe:	
From baseline (week 0) to week 52	

End point values	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	497	475	492	
Units: Percentage point of HbA1c				
arithmetic mean (standard deviation)	-1.5 (± 1.3)	-1.9 (± 1.3)	-2.1 (± 1.4)	

Statistical analyses

Statistical analysis title	Oral semaglutide 14 mg vs Oral semaglutide 25 mg
Statistical analysis description:	
Change from baseline was analyzed using an ANCOVA model with treatment, strata 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.	

Comparison groups	Oral semaglutide 14 mg v Oral semaglutide 25 mg
Number of subjects included in analysis	972
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [1]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	-0.12

Notes:

[1] - Unadjusted two-sided p-value for test of no difference.

Statistical analysis title	Oral semaglutide 14 mg vs Oral semaglutide 50 mg

Statistical analysis description:

Change from baseline was analyzed using an ANCOVA model with treatment, strata 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.

Comparison groups	Oral semaglutide 14 mg v Oral semaglutide 50 mg
Number of subjects included in analysis	989
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	-0.38

Notes:

[2] - Unadjusted two-sided p-value for test of no difference.

Secondary: Change in body weight

End point title	Change in body weight

End point description:

Change from baseline (week 0) in body weight was evaluated at week 52. Results are based on the data from the in-trial observation period, which was the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of additional anti-diabetic medication or discontinuation of trial treatment. FAS which comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 52

End point values	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	503	480	495	
Units: Kilogram (Kg)				
arithmetic mean (standard deviation)	-4.4 (± 5.2)	-7.1 (± 6.8)	-8.3 (± 7.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (FPG)

End point title	Change in fasting plasma glucose (FPG)

End point description:

Change from baseline (week 0) in fasting plasma glucose (FPG) was evaluated at week 52. Results are based on the data from the in-trial observation period, which was the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of additional anti-diabetic medication or discontinuation of trial treatment. FAS which comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this outcome measure.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 52

End point values	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	494	460	482	
Units: millimole per litre (mmol/L)				
arithmetic mean (standard deviation)	-2.4 (± 3.4)	-3.0 (± 3.5)	-3.2 (± 3.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Achievement of HbA1c below 7%

End point title	Achievement of HbA1c below 7%

End point description:

Percentage of subjects who achieved HbA1c <7.0 % at week 52 are presented. Results are based on the data from the in-trial observation period, which was the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of additional anti-diabetic medication or discontinuation of trial treatment.

End point type	Secondary

End point timeframe:

At week 52

End point values	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	536	535	535	
Units: Percentage of subjects				
number (not applicable)	39	50.5	63	

Statistical analyses

No statistical analyses for this end point

Secondary: Achievement of HbA1c equal to or below 6.5%

End point title	Achievement of HbA1c equal to or below 6.5%

End point description:

Percentage of subjects who achieved HbA1c <=6.5 % at week 52 are presented. Results are based on the data from the in-trial observation period, which was the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of additional anti-diabetic medication or discontinuation of trial treatment.

End point type	Secondary

End point timeframe:

At week 52

End point values	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	536	535	535	
Units: Percentage of subjects				
number (not applicable)	25.8	39.6	51.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Relative change in body weight

End point title	Relative change in body weight

End point description:

Relative change from baseline (week 0) in body weight was evaluated at week 52. Results are based on the data from the in-trial observation period, which was the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of additional anti-diabetic medication or discontinuation of trial treatment. FAS which comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this outcome measure.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 52

End point values	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	503	480	495	
Units: Percentage change in body weight				
arithmetic mean (standard deviation)	-4.7 (± 5.4)	-7.3 (± 6.6)	-8.5 (± 7.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in waist circumference

End point title	Change in waist circumference

End point description:

Change from baseline (week 0) in waist circumference was evaluated at week 52. Results are based on the data from the in-trial observation period, which was the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of additional anti-diabetic medication or discontinuation of trial treatment. FAS which comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this outcome measure.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 52

End point values	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	502	479	494	
Units: centimetre (cm)				
arithmetic mean (standard deviation)	-4 (± 7)	-5 (± 7)	-6 (± 7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Achievement of weight loss equal to or above 5%

End point title	Achievement of weight loss equal to or above 5%

End point description:

Percentage of subjects who achieved weight loss >= 5 % at week 52 are presented. Results are based on the data from the in-trial observation period, which was the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of additional anti-diabetic medication or discontinuation of trial treatment.

End point type	Secondary

End point timeframe:

At week 52

End point values	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	536	535	535	
Units: Percentage of subjects				
number (not applicable)	41	60	67.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events

End point title	Number of adverse events

End point description:

An adverse event (AE) defined as any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an investigational medicinal products (IMP). Results are based on the data from the on-treatment observation period, which was the time period when a subject was on trial treatment, including any period after initiation of rescue medication. Safety Analysis Set (SAS) which comprised all randomised subjects who received at least 1 dose of trial treatment. Overall number of subjects analyzed = subjects with available data for this outcome measure.

End point type	Secondary

End point timeframe:

From baseline (week 0) to follow-up visit (week 73)

End point values	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	534	534	534	
Units: Events	1641	2055	2115	

Statistical analyses

No statistical analyses for this end point

Secondary: Achievement of weight loss equal to or above 10%

End point title	Achievement of weight loss equal to or above 10%

End point description:

Percentage of subjects who achieved weight loss >= 10 % at week 52 are presented. Results are based on the data from the in-trial observation period, which was the time period from when a subject was randomised until the final scheduled visit, including any period after initiation of additional anti-diabetic medication or discontinuation of trial treatment.

End point type	Secondary

End point timeframe:

At week 52

End point values	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	536	535	535	
Units: Percentage of subjects				
number (not applicable)	13.9	29	37.2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Week 0 to week 73	
Adverse event reporting additional description:	
Results are based on the safety analysis set which comprised all randomised subjects who received at least 1 dose of trial treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	Oral semaglutide 14 mg
Reporting group description:	
Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8 and 14 mg from week 8 to week 68.	
Reporting group title	Oral semaglutide 25 mg
Reporting group description:	
Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to 12 and 25 mg from week 12 to week 68.	
Reporting group title	Oral semaglutide 50 mg
Reporting group description:	
Subjects were to take oral semaglutide tablets once daily in a dose escalation manner from week 0 to week 68: 3 mg from week 0 to week 4, 7 mg from week 4 to week 8, 14 mg from week 8 to 12, 25 mg from week 12 to week 16 and 50 mg from week 16 to week 68.	

Serious adverse events	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 534 (9.93%)	57 / 534 (10.67%)	44 / 534 (8.24%)
number of deaths (all causes)	1	6	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chronic myelomonocytic leukaemia			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon neoplasm			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Hepatic cancer			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Lung cancer metastatic			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lymphoma			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
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			
Circulatory collapse			
subjects affected / exposed	0 / 534 (0.00%)	2 / 534 (0.37%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Iliac artery stenosis			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 534 (0.37%)	0 / 534 (0.00%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Hip arthroplasty			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Keratoplasty			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Chest pain			
subjects affected / exposed	1 / 534 (0.19%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Swelling face			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Cystocele			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Endometrial hyperplasia			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gynaecomastia			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Dyspnoea			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal turbinate hypertrophy			

subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 534 (0.19%)	1 / 534 (0.19%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary mass			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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 failure			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Somatic symptom disorder			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Anaemia postoperative			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Brachial plexus injury			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Clavicle fracture			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc injury			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Rib fracture			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			

subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic injury			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
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 graft occlusion			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve disease			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	4 / 534 (0.75%)	3 / 534 (0.56%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 4	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			

subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Atrial flutter			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Atrial fibrillation			
subjects affected / exposed	2 / 534 (0.37%)	1 / 534 (0.19%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	1 / 534 (0.19%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chronic coronary syndrome			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conduction disorder			

subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	2 / 534 (0.37%)	1 / 534 (0.19%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 534 (0.37%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Nervous system disorders			
Carotid artery occlusion			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 534 (0.19%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system lesion			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Dizziness			

subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Hemiparesis			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 534 (0.19%)	2 / 534 (0.37%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelopathy			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Speech disorder			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract subcapsular			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiretinal membrane			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papilloedema			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Abdominal pain			
subjects affected / exposed	1 / 534 (0.19%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocele			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Food poisoning			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal pseudo-obstruction			

subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Nausea			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Pancreatitis acute			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 534 (0.37%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 534 (0.19%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 534 (0.19%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			

subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder disorder			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Non-alcoholic steatohepatitis			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Ischaemic skin ulcer			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus bladder			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			

subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
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 hypertension			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Cervical spinal stenosis			
subjects affected / exposed	2 / 534 (0.37%)	0 / 534 (0.00%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Greater trochanteric pain syndrome			

subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Intervertebral disc disorder			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon disorder			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Infections and infestations			
Abscess oral			

subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess intestinal			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	3 / 534 (0.56%)	0 / 534 (0.00%)	3 / 534 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cellulitis			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	2 / 534 (0.37%)	2 / 534 (0.37%)	2 / 534 (0.37%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis pharyngeal			

subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic gangrene			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Erysipelas			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 534 (0.37%)	0 / 534 (0.00%)	2 / 534 (0.37%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 534 (0.00%)	0 / 534 (0.00%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Urosepsis			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 534 (0.19%)	0 / 534 (0.00%)	0 / 534 (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
Dehydration			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	1 / 534 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	1 / 534 (0.19%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 534 (0.00%)	2 / 534 (0.37%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	0 / 534 (0.00%)	1 / 534 (0.19%)	0 / 534 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Oral semaglutide 14 mg	Oral semaglutide 25 mg	Oral semaglutide 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	277 / 534 (51.87%)	294 / 534 (55.06%)	314 / 534 (58.80%)
Nervous system disorders			
Headache			
subjects affected / exposed	34 / 534 (6.37%)	28 / 534 (5.24%)	38 / 534 (7.12%)
occurrences (all)	63	81	81
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	41 / 534 (7.68%)	26 / 534 (4.87%)	35 / 534 (6.55%)
occurrences (all)	44	30	40
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 534 (2.62%)	27 / 534 (5.06%)	21 / 534 (3.93%)
occurrences (all)	25	34	27
Abdominal pain upper			
subjects affected / exposed	14 / 534 (2.62%)	32 / 534 (5.99%)	22 / 534 (4.12%)
occurrences (all)	17	52	55
Constipation			
subjects affected / exposed	40 / 534 (7.49%)	35 / 534 (6.55%)	33 / 534 (6.18%)
occurrences (all)	46	41	39
Diarrhoea			
subjects affected / exposed	66 / 534 (12.36%)	69 / 534 (12.92%)	76 / 534 (14.23%)
occurrences (all)	84	108	150
Dyspepsia			
subjects affected / exposed	28 / 534 (5.24%)	29 / 534 (5.43%)	30 / 534 (5.62%)
occurrences (all)	32	47	50
Nausea			
subjects affected / exposed	96 / 534 (17.98%)	145 / 534 (27.15%)	146 / 534 (27.34%)
occurrences (all)	119	222	218

Vomiting			
subjects affected / exposed	52 / 534 (9.74%)	91 / 534 (17.04%)	97 / 534 (18.16%)
occurrences (all)	69	155	184
Infections and infestations			
COVID-19			
subjects affected / exposed	63 / 534 (11.80%)	64 / 534 (11.99%)	66 / 534 (12.36%)
occurrences (all)	65	68	68
Nasopharyngitis			
subjects affected / exposed	24 / 534 (4.49%)	22 / 534 (4.12%)	27 / 534 (5.06%)
occurrences (all)	28	27	30
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	38 / 534 (7.12%)	39 / 534 (7.30%)	58 / 534 (10.86%)
occurrences (all)	43	42	61

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2020	This protocol is amended for the following reasons: 1) The exclusion and discontinuation criteria have been amended to allow simultaneous participation in trials with the primary objective of evaluating an approved or non-approved investigational medicinal product for prevention or treatment of COVID-19 disease or COVID-19 postinfectious conditions. 2) Clarifications for missed doses and treatment compliance, as well as administrative changes were also addressed.
04 March 2021	This protocol is amended for the following reasons: 1) The exposure-response modelling have been updated based on data available after the completion of the first version of the protocol. 2) Few additional changes such as third-party responsibility and user credentials for IT systems were also addressed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported