Clinical trial results:
Effect of Empagliflozin and Semaglutide on Cardio-Renal Target Organ Damage in patients with type 2 diabetes – A randomized Trial

Summary

EudraCT number	2019-000781-38
Trial protocol	DK
Global end of trial date	04 April 2022

Results information

Result version number	v1 (current)
This version publication date	23 February 2023
First version publication date	23 February 2023

Trial information

Trial identification

Sponsor protocol code	sempa1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital, Diabetes og Hormonsygdomme
Sponsor organisation address	Palle Juul Jensens Boulevard 165, Aarhus, Denmark, 8200
Public contact	Esben Laugesen, Aarhus University Hospital, 0045 23886954, auh.doh.sempa@rm.dk
Scientific contact	Esben Laugesen, Aarhus University Hospital, 0045 30283068, esben.laugesen@clin.au.dk

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	10 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2022
Global end of trial reached?	Yes
Global end of trial date	04 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study has two co-primary aims:
Aim 1:
To test the hypothesis that treatment with empagliflozin, semaglutide or the combination vs. placebo improves arterial function in T2DM patients. Further, we aim to compare the different treatment modalities with each other (empagliflozin vs semaglutide, combination vs semaglutide, combination vs empagliflozin).
The main outcome is change in arterial stiffness assessed as carotid-femoral PWV.

Aim 2:
To test the hypothesis that treatment with empagliflozin, semaglutide or the combination vs. placebo improves renal oxygenation in T2DM patients. Further, we aim to compare the different treatment modalities with each other (empagliflozin vs semaglutide, combination vs semaglutide, combination vs empagliflozin).
The main outcome is change in renal oxygenation assesed by magnetic resonance imaging (MRI).

Protection of trial subjects:

Participants were contacted by phone and/or email every fourth week to ensure well-being. If needed and by the discretion of the investigator, additional contact was facilitated. The addition of supplementary therapy including anti-hyperglycemic drugs and antihypertensive medication was furthermore handled by study investigators.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2019
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	Denmark: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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)	32
From 65 to 84 years	88
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were primarily recruited through "e-Boks". If they responded, we sent written information about the trial.

Pre-assignment

Screening details:

Participants were invited to a screening meeting, at which the potential for in- or exclusion was evaluated through interview, physical examination and medical records.

Period 1

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

Blinding implementation details:

The emapgliflozin and the tablet placebo was double-blinded. The semaglutide was open-label. The combination was open-label with respect to semaglutide, whereas empagliflozin was double-blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Empagliflozin

Arm description:

Participants receiving Empagliflozin

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

Dosage and administration details:

10 mg once daily

Arm title	Placebo

Arm description:

Participants receiving tablet placebo

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

Dosage and administration details:

Matching placebo; One tablet once-daily

Arm title	Semaglutide

Arm description:

Participants receiving semaglutide

Arm type	Active comparator

Investigational medicinal product name	Ozempic
Investigational medicinal product code	
Other name	Semaglutide
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.25 -> 0.5 mg -> 1.0 mg. Uptitration according to regular schedule.

Arm title	Combination

Arm description:

Participants receiving semaglutide and empagliflozin

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

Dosage and administration details:

10 mg once daily

Investigational medicinal product name	Ozempic
Investigational medicinal product code	
Other name	Semaglutide
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.25 -> 0.5 mg -> 1.0 mg. Uptitration according to regular schedule.

Number of subjects in period 1	Empagliflozin	Placebo	Semaglutide
Started	30	30	30
Completed	28	27	27
Not completed	2	3	3
Did not want to take the treatment	1	-	-
Adverse event, non-fatal	1	2	1
Gave no reason	-	1	-
Side effects	-	-	2

Number of subjects in period 1	Combination
Started	30
Completed	26
Not completed	4
Did not want to take the treatment	-
Adverse event, non-fatal	4
Gave no reason	-
Side effects	-

Baseline characteristics

Reporting groups	
Reporting group title	Empagliflozin
Reporting group description:	
Participants receiving Empagliflozin	
Reporting group title	Placebo
Reporting group description:	
Participants receiving tablet placebo	
Reporting group title	Semaglutide
Reporting group description:	
Participants receiving semaglutide	
Reporting group title	Combination
Reporting group description:	
Participants receiving semaglutide and empagliflozin	

Reporting group values	Empagliflozin	Placebo	Semaglutide
Number of subjects	30	30	30
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	70.4	66.7	69.7
standard deviation	± 6.6	± 6.8	± 6.6
Gender categorical Units: Subjects			
Female	8	6	4
Male	22	24	26
History of Cardiovascular Disease Units: Subjects			
Yes	22	15	19
No	8	15	11
Metformin Units: Subjects			
Yes	26	26	27
No	4	4	3
Insulin therapy Units: Subjects			

Yes	9	7	7
No	21	23	23
Renin-Angiotension-Aldosteron-Inhibitor Units: Subjects			
Yes	23	25	24
No	7	5	6
Calciumantagonist Units: Subjects			
Yes	12	16	14
No	18	14	16
Beta blocker Units: Subjects			
Yes	10	8	16
No	20	22	14
Thiazide/Loop diuretics Units: Subjects			
Yes	13	9	13
No	17	21	17
BMI Units: kg/m2			
arithmetic mean	27.6	27.7	27.9
standard deviation	± 5.1	± 4.3	± 5.3
Duration of diabetes Units: year			
median	11	9.5	10.5
inter-quartile range (Q1-Q3)	5 to 19	5 to 12	4 to 17
HbA1c Units: mmol/mol			
median	57	59	59
inter-quartile range (Q1-Q3)	52 to 63	51 to 68	51 to 63
Glomerular Filtration Rate Units: ml/min/1.73 m2			
arithmetic mean	84	91	87
standard deviation	± 19	± 22	± 19
Urine albumin/creatinine ratio Units: mg/g			
median	13.5	13.5	16
inter-quartile range (Q1-Q3)	9 to 31	5 to 91	8 to 70
Office systolic blood pressure Units: mmHg			
arithmetic mean	142	144	139
standard deviation	± 14	± 25	± 17
Office diastolic blood pressure Units: mmHg			
arithmetic mean	78	82	78
standard deviation	± 9	± 11	± 8
24 h systolic blood pressure Units: mmHg			
arithmetic mean	132	134	126
standard deviation	± 11	± 15	± 14
24 h diastolic blood pressure			

Units: mmHg			
arithmetic mean	77	82	76
standard deviation	± 8	± 7	± 8
Cf-PWV			
Units: m/s			
arithmetic mean	9.7	10.1	9.3
standard deviation	± 1.8	± 1.5	± 2.0

Reporting group values	Combination	Total	
Number of subjects	30	120	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	69.5		
standard deviation	± 6.8	-	
Gender categorical			
Units: Subjects			
Female	5	23	
Male	25	97	
History of Cardiovascular Disease			
Units: Subjects			
Yes	24	80	
No	6	40	
Metformin			
Units: Subjects			
Yes	29	108	
No	1	12	
Insulin therapy			
Units: Subjects			
Yes	3	26	
No	27	94	
Renin-Angiotension-Aldosteron-Inhibitor			
Units: Subjects			
Yes	27	99	
No	3	21	
Calciumantagonist			
Units: Subjects			
Yes	13	55	
No	17	65	
Beta blocker			

Units: Subjects			
Yes	13	47	
No	17	73	
Thiazide/Loop diuretics Units: Subjects			
Yes	7	42	
No	23	78	
BMI Units: kg/m2			
arithmetic mean	26.4		
standard deviation	± 4.0	-	
Duration of diabetes Units: year			
median	9.5		
inter-quartile range (Q1-Q3)	4.5 to 12.5	-	
HbA1c Units: mmol/mol			
median	57		
inter-quartile range (Q1-Q3)	51 to 68	-	
Glomerular Filtration Rate Units: ml/min/1.73 m2			
arithmetic mean	79		
standard deviation	± 23	-	
Urine albumin/creatinine ratio Units: mg/g			
median	21		
inter-quartile range (Q1-Q3)	7 to 78	-	
Office systolic blood pressure Units: mmHg			
arithmetic mean	138		
standard deviation	± 16	-	
Office diastolic blood pressure Units: mmHg			
arithmetic mean	76		
standard deviation	± 9	-	
24 h systolic blood pressure Units: mmHg			
arithmetic mean	130		
standard deviation	± 12	-	
24 h diastolic blood pressure Units: mmHg			
arithmetic mean	77		
standard deviation	± 8	-	
Cf-PWV Units: m/s			
arithmetic mean	9.5		
standard deviation	± 1.8	-	

End points

End points reporting groups	
Reporting group title	Empagliflozin
Reporting group description: Participants receiving Empagliflozin	
Reporting group title	Placebo
Reporting group description: Participants receiving tablet placebo	
Reporting group title	Semaglutide
Reporting group description: Participants receiving semaglutide	
Reporting group title	Combination
Reporting group description: Participants receiving semaglutide and empagliflozin	

Primary: Kidney cortical oxygenation	
End point title	Kidney cortical oxygenation
End point description:	
End point type	Primary
End point timeframe: Week 32	

End point values	Empagliflozin	Placebo	Semaglutide	Combination
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	16
Units: Hz				
number (confidence interval 95%)	23.3 (22.5 to 24.0)	23.5 (22.7 to 24.2)	23.5 (22.8 to 24.2)	23.5 (22.8 to 24.3)

Statistical analyses

Statistical analysis title	Empagliflozin vs placebo
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.653
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.6

Statistical analysis title	Semaglutide vs placebo
Comparison groups	Semaglutide v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.869
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.8

Statistical analysis title	Combination vs placebo
Comparison groups	Placebo v Combination
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.811
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.8

Primary: Kidney medullary oxygenation	
End point title	Kidney medullary oxygenation
End point description:	

End point type	Primary
End point timeframe:	
Week 32	

End point values	Empagliflozin	Placebo	Semaglutide	Combination
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	16
Units: Hz				
number (confidence interval 95%)	25.4 (24.7 to 26.2)	24.5 (23.9 to 25.1)	24.4 (23.7 to 25.0)	25.4 (24.7 to 26.2)

Statistical analyses

Statistical analysis title	Empagliflozin vs placebo
Comparison groups	Empagliflozin v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.016
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.7

Statistical analysis title	Semaglutide vs placebo
Comparison groups	Placebo v Semaglutide
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.734
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.6

Statistical analysis title	Combination vs placebo

Comparison groups	Placebo v Combination
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.6

Primary: Cf-PWV

End point title	Cf-PWV

End point description:

End point type	Primary

End point timeframe:

32 weeks

End point values	Empagliflozin	Placebo	Semaglutide	Combination
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	26	26	26
Units: m/s				
number (confidence interval 95%)	9.6 (9.2 to 10.1)	9.3 (8.9 to 9.8)	9.9 (9.5 to 10.4)	9.5 (9.0 to 9.9)

Statistical analyses

Statistical analysis title	Empagliflozin vs placebo
Comparison groups	Placebo v Empagliflozin
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.8

Statistical analysis title	Semaglutide vs placebo
Comparison groups	Placebo v Semaglutide
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	1.1

Statistical analysis title	Combination vs placebo
Comparison groups	Placebo v Combination
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.7

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 01-08-2019 -> 04-04-2022	
Assessment type	Systematic
Dictionary used	
Dictionary name	None
Dictionary version	0
Reporting groups	
Reporting group title	Empagliflozin
Reporting group description: Participants receiving Empagliflozin	
Reporting group title	Placebo
Reporting group description: Participants receiving tablet placebo	
Reporting group title	Semaglutide
Reporting group description: Participants receiving semaglutide	
Reporting group title	Combination
Reporting group description: Participants receiving semaglutide and empagliflozin	

Serious adverse events	Empagliflozin	Placebo	Semaglutide
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 30 (10.00%)	3 / 30 (10.00%)	4 / 30 (13.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer obs pro			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	4 / 30 (13.33%)
occurrences causally related to treatment / all	0 / 8	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
TCI/Stroke obs pro			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACS/AFLI obs. pro			

subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Vascular occlusion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Blood in faeces/Ileus			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bladder/Lungs			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Combination		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 30 (23.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer obs pro			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
TCI/Stroke obs pro			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

ACS/AFLI obs. pro			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Vascular occlusion			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Blood in faeces/Ileus			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bladder/Lungs			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Empagliflozin	Placebo	Semaglutide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)	23 / 30 (76.67%)	26 / 30 (86.67%)
Nervous system disorders			
Headache/Dizziness			
subjects affected / exposed	3 / 30 (10.00%)	3 / 30 (10.00%)	1 / 30 (3.33%)
occurrences (all)	9	9	9
Eye disorders			
Eye disease			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	5	5	5
Gastrointestinal disorders			
Gastrointestinal symptoms			

subjects affected / exposed	4 / 30 (13.33%)	8 / 30 (26.67%)	23 / 30 (76.67%)
occurrences (all)	58	58	58
Respiratory, thoracic and mediastinal disorders			
Airways			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	1 / 30 (3.33%)
occurrences (all)	8	8	8
Skin and subcutaneous tissue disorders			
Skin			
subjects affected / exposed	3 / 30 (10.00%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	9	9	9
Renal and urinary disorders			
Urinary diseases			
subjects affected / exposed	14 / 30 (46.67%)	5 / 30 (16.67%)	3 / 30 (10.00%)
occurrences (all)	32	32	32
Endocrine disorders			
Metabolism/Glucose			
subjects affected / exposed	4 / 30 (13.33%)	5 / 30 (16.67%)	4 / 30 (13.33%)
occurrences (all)	14	14	14
Musculoskeletal and connective tissue disorders			
Musculoskeletal symptoms			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	2 / 30 (6.67%)
occurrences (all)	5	5	5
Infections and infestations			
Infections			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	5 / 30 (16.67%)
occurrences (all)	13	13	13

Non-serious adverse events	Combination		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 30 (90.00%)		
Nervous system disorders			
Headache/Dizziness			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	9		
Eye disorders			
Eye disease			

subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 5		
Gastrointestinal disorders Gastrointestinal symptoms subjects affected / exposed occurrences (all)	 23 / 30 (76.67%) 58		
Respiratory, thoracic and mediastinal disorders Airways subjects affected / exposed occurrences (all)	 3 / 30 (10.00%) 8		
Skin and subcutaneous tissue disorders Skin subjects affected / exposed occurrences (all)	 2 / 30 (6.67%) 9		
Renal and urinary disorders Urinary diseases subjects affected / exposed occurrences (all)	 10 / 30 (33.33%) 32		
Endocrine disorders Metabolism/Glucose subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 14		
Musculoskeletal and connective tissue disorders Musculoskeletal symptoms subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 5		
Infections and infestations Infections subjects affected / exposed occurrences (all)	 4 / 30 (13.33%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2019	Inclusion criterion HbA1c was lowered from 55 mmol/mol to 48 mmol/mol. Inclusion criterion: 50 years or older with eGFR below 60 ml/min/1.73 m2 was added. Inclusion criterion: 60 years or older with persistent hypertension was added Exclusion criterion eGFR was lowered to be below 45 ml/min/1.73 m2
05 October 2020	Change of secondary endpoints regarding insulin sensitivity and glucose measurements Removal of the Oral Minimal Model

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 March 2020	Due to the COVID.19 Pandemic, the trial inclusion and planned outcome assessments halted, however participants already enrolled continued the take the allocated intervention.	11 May 2020

Notes:

Limitations and caveats

None reported