Clinical trial results:
A randomized, double-blind, three arm, three treatment period, cross-over trial to investi-gate the effect of a SGLT-2 inhibitor, a DPP-4 inhibitor and a SGLT-2 inhibitor + DPP-4 inhibitor on glucagon levels, endogenous glucose production and lipolysis during hyper-, normo- and hypoglycaemia in subjects with type 2 diabetes using stable tracer technique.

Summary

EudraCT number	2015-004637-27
Trial protocol	AT
Global end of trial date	06 October 2016

Results information

Result version number	v1 (current)
This version publication date	02 December 2020
First version publication date	02 December 2020

Trial information

Trial identification

Sponsor protocol code	AZ-01_SGLT-2

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University of Graz, Department of Internal Medicine Division of Endocrinology and Metabolism
Sponsor organisation address	Auenbruggerplatz 15, Graz, Austria,
Public contact	Study Coordinator , Medical University of Graz, +43 31638572835, stefanie.sach-friedl@medunigraz.at
Scientific contact	Principal Investigator and Sponsor , Medical University of Graz, Univ. Prof. Dr. Thomas R. Pieber, +43 316 385 12383, thomas.pieber@medunigraz.at

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	23 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 October 2016
Global end of trial reached?	Yes
Global end of trial date	06 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the glucagon response of a treatment with metformin monotherapy (baseline), a SGLT-2 inhibitor, a DPP-4 inhibitor and a combination of a SGLT-2 inhibitor and a DPP-4 inhibitor during normo-, hyper- and hypoglycaemia in a controlled clamp setting under stable metformin therapy.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 January 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	Austria: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	19

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Single-Center Study - 1 site in Austria

Pre-assignment

Screening details:

33 Patients have been screened and in total 19 randomizations were performed. 17 subjects completed the study. There have been 2 drop-outs – not drug related

Period 1

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

Blinding implementation details:

The allocation of a treatment arm to a randomisation nr has been provided by an unblinded trial staff. The documentation on the allocation of the treatment arm sequences to the randomisation nr has beenstored only accessible for the unblinded trial staff. Dapaglifllozin, Saxagliptin, Placebo Dapaglifllozin orPlacebo Saxagliptin were packed and labelled to fulfil the requirements for double-blind procedures.Blinding was maintained for the whole study period

Arms

Are arms mutually exclusive?	No
Arm title	Dapagliflozin and Placebo Saxagliptin

Arm description:

Each randomized subject was allocated to one of the three treatment sequences (seven days once daily dosing of either Dapagliflozin+placebo Saxagliptin, or Saxagliptin + placebo Dapagliflozin or the combination of Saxagliptin + Dapagliflozin). A wash-out period of 56-84 days between the first period and second period and one of 7-42 days between the second and third period has been carried out.
1 tablet of Dapagliflozin 10 mg and 1 tablet of matching placebo for Saxagliptin 5 mg has been administrated once daily in the morning for 7 days

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin 10 mg
Investigational medicinal product code	
Other name	Forxiga™
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of Dapagliflozin 10 mg together with 1 tablet of matching placebo for Saxagliptin 5 mg has been administrated once daily in the morning for 7 days

Investigational medicinal product name	Matching placebo for Saxagliptin 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of matching placebo for Saxagliptin 5 mg together with 1 tablet of Dapagliflozin 10 mg has been administrated once daily in the morning for 7 days

Arm title	Saxagliptin and Placebo Dapagliflozin

Arm description:

Each randomized subject was allocated to one of the three treatment sequences (seven days once daily dosing of either Dapagliflozin+placebo Saxagliptin, or Saxagliptin + placebo Dapagliflozin or the

combination of Saxagliptin + Dapagliflozin). A wash-out period of 56-84 days between the first period and second period and one of 7-42 days between the second and third period has been carried out. In this sequence 1 tablet of Saxagliptin 5 mg and 1 tablet of matching placebo for Dapagliflozin 10 mg has been administrated once daily in the morning for 7 days.

Arm type	Experimental
Investigational medicinal product name	Saxagliptin 5 mg
Investigational medicinal product code	
Other name	Onglyza®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of Saxagliptin 5 mg together with 1 tablet of matching placebo for Dapagliflozin 10 mg has been administrated once daily in the morning for 7 days

Investigational medicinal product name	Matching placebo for Dapagliflozin 10 mg
Investigational medicinal product code	o
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of matching placebo for Dapagliflozin 10 mg and 1 tablet of Saxagliptin 5 mg has been administrated once daily in the morning for 7 days

Arm title	Saxagliptin and Dapagliflozin

Arm description:

Each randomized subject was allocated to one of the three treatment sequences (seven days once daily dosing of either Dapagliflozin+placebo Saxagliptin, or Saxagliptin + placebo Dapagliflozin or the combination of Saxagliptin + Dapagliflozin).A wash-out period of 56-84 days between the first period and second period and one of 7-42 days between the second and third period has been carried out. In this seuence 1 tablet of Saxagliptin 5 mg and 1 tablet of Dapagliflozin 10 mg has been administrated ce daily in the morning for 7 days

Arm type	Experimental
Investigational medicinal product name	Dapagliflozin 10 mg
Investigational medicinal product code	
Other name	Forxiga™
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of Dapagliflozin 10 mg together with 1 tablet of Saxagliptin 5 mg has been administrated once daily in the morning for 7 days

Investigational medicinal product name	Saxagliptin 5 mg
Investigational medicinal product code	
Other name	Onglyza®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of Saxagliptin 5 mg together with 1 tablet of Dapagliflozin 10 mg has been administrated once daily in the morning for 7 days

Arm title	Pre - treatment

Arm description:

All the results from all arms have been compared to the values before starting the treatment.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Dapagliflozin and Placebo Saxagliptin	Saxagliptin and Placebo Dapagliflozin	Saxagliptin and Dapagliflozin
Started	17	17	17
Completed	17	17	17

Number of subjects in period 1	Pre - treatment
Started	17
Completed	17

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study (overall period)

Reporting group description: -

Reporting group values	Overall Study (overall period)	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	19	19	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	53		
standard deviation	± 6	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	18	18	
Diabetes duration Units: years			
arithmetic mean	7.6		
standard deviation	± 5.8	-	
BMI Units: kg/m²			
arithmetic mean	29.4		
standard deviation	± 3.5	-	
HbA1c Units: mmol/mol			
arithmetic mean	60.6		
standard deviation	± 10.3	-	

End points

End points reporting groups

Reporting group title	Dapagliflozin and Placebo Saxagliptin
Reporting group description:	
Each randomized subject was allocated to one of the three treatment sequences (seven days once daily dosing of either Dapagliflozin+placebo Saxagliptin, or Saxagliptin + placebo Dapagliflozin or the combination of Saxagliptin + Dapagliflozin). A wash-out period of 56-84 days between the first period and second period and one of 7-42 days between the second and third period has been carried out. 1 tablet of Dapagliflozin 10 mg and 1 tablet of matching placebo for Saxagliptin 5 mg has been administrated once daily in the morning for 7 days	

Reporting group title	Saxagliptin and Placebo Dapagliflozin
Reporting group description:	
Each randomized subject was allocated to one of the three treatment sequences (seven days once daily dosing of either Dapagliflozin+placebo Saxagliptin, or Saxagliptin + placebo Dapagliflozin or the combination of Saxagliptin + Dapagliflozin). A wash-out period of 56-84 days between the first period and second period and one of 7-42 days between the second and third period has been carried out. In this sequence 1 tablet of Saxagliptin 5 mg and 1 tablet of matching placebo for Dapagliflozin 10 mg has been administrated once daily in the morning for 7 days.	

Reporting group title	Saxagliptin and Dapagliflozin
Reporting group description:	
Each randomized subject was allocated to one of the three treatment sequences (seven days once daily dosing of either Dapagliflozin+placebo Saxagliptin, or Saxagliptin + placebo Dapagliflozin or the combination of Saxagliptin + Dapagliflozin).A wash-out period of 56-84 days between the first period and second period and one of 7-42 days between the second and third period has been carried out. In this seuence 1 tablet of Saxagliptin 5 mg and 1 tablet of Dapagliflozin 10 mg has been administrated ce daily in the morning for 7 days	

Reporting group title	Pre - treatment
Reporting group description:	
All the results from all arms have been compared to the values before starting the treatment.	

Primary: Change in glucagon concentration from 5.5 mmol/L low insulin to 11.1 mmol/L: Glucagon11.1-Glucagon5.5.

End point title	Change in glucagon concentration from 5.5 mmol/L low insulin to 11.1 mmol/L: Glucagon11.1-Glucagon5.5.
End point description:	
Dapagliflozin (+/- saxagliptin) did not increase glucagon during eu-, hyper-, and hypoglycaemia compared to no treatment (see attachment)	
End point type	Primary
End point timeframe:	
During Clamp Procedure - comparison between treatments	

End point values	Dapagliflozin and Placebo Saxagliptin	Saxagliptin and Placebo Dapagliflozin	Saxagliptin and Dapagliflozin	Pre - treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: pmol/L				
arithmetic mean (standard deviation)				
5.5 mmol/L low insulin	11.5 (± 6.0)	11.1 (± 6.2)	11.6 (± 5.3)	9.4 (± 4.1)
11.1 mmol/L	7.0 (± 4.8)	6.3 (± 4.8)	5.9 (± 4.9)	6.2 (± 3.6)

5.5 mmol/L high insulin	4.4 (± 3.6)	4.4 (± 4.1)	4.1 (± 3.2)	3.3 (± 3.4)
3.5 mmol/L	6.5 (± 4.5)	7.2 (± 7.3)	7.9 (± 10.3)	6.6 (± 5.0)
2.5 mmol/L	21.2 (± 12.6)	24.5 (± 18.9)	16.5 (± 12.0)	18.9 (± 14.0)

Attachments (see zip file)	Trial design.PNG Clamp Design.PNG

Statistical analyses

Statistical analysis title	Mixed effects model

Statistical analysis description:

Mixed effects model, using treatment (No treatment; SGLT-2; DPP-4; SGLT-2+DPP-4), sequence (No treatment -> SGLT-2 -> DPP-4 -> SGLT-2+DPP-4; No treatment -> SGLT-2 -> SGLT-2+DPP-4 -> DPP-4;…), and period (Baseline Period; Treatment Peri-od 1; Treatment period 2; Treatment Period 3) as fixed effects and patient (PATIENT) as random effect.

Comparison groups	Dapagliflozin and Placebo Saxagliptin v Saxagliptin and Placebo Dapagliflozin v Saxagliptin and Dapagliflozin
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Mixed models analysis

Notes:

[1] - Not applicable

Secondary: Ketone bodies during euglycaemia at ambient insulin levels and hyperglycaemia

End point title	Ketone bodies during euglycaemia at ambient insulin levels and hyperglycaemia

End point description:

Dapagliflozin did not significantly increase ketone bodies during euglycaemia at ambient insulin levels and hyperglycaemia compared to no treatment. Saxagliptin significantly decreased ketone body concentrations compared to no treatment during hyperglycaemia and compared to dapagliflozin and the combination of saxagliptin and dapagliflozin during eu- and hypoglycaemia at high insulin levels

End point type	Secondary

End point timeframe:

During Clamp Procedure - comparison between treatments

End point values	Dapagliflozin and Placebo Saxagliptin	Saxagliptin and Placebo Dapagliflozin	Saxagliptin and Dapagliflozin	Pre - treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: µmol/L				
arithmetic mean (standard deviation)				
5.5 mmol/L low insulin	51.8 (± 25.0)	37.6 (± 28.1)	157 (± 268)	63.8 (± 64.6)
11.1 mmol/L	125 (± 156)	35.1 (± 26.1)	111 (± 152)	119 (± 142)
5.5 mmol/L high insulin	12.2 (± 7.9)	8.2 (± 4.2)	11.1 (± 6.7)	9.6 (± 5.8)

3.5 mmol/L	10.4 (± 5.2)	7.4 (± 3.7)	9.5 (± 5.4)	8.0 (± 4.2)
2.5 mmol/L	13.3 (± 7.6)	9.3 (± 5.9)	0.1 (± 0.2)	13.3 (± 15.1)

Statistical analyses

No statistical analyses for this end point

Secondary: NEFA concentrations

End point title	NEFA concentrations

End point description:

NEFA concentrations were significantly reduced during hyperglycaemia in saxagliptin and dapagliflozin + saxagliptin treatment compared to no treatment

End point type	Secondary

End point timeframe:

During Clamp Procedure - comparison between treatments

End point values	Dapagliflozin and Placebo Saxagliptin	Saxagliptin and Placebo Dapagliflozin	Saxagliptin and Dapagliflozin	Pre - treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: mmol/L				
arithmetic mean (standard deviation)				
5.5 mmol/L low insulin	0.4 (± 0.2)	0.3 (± 0.2)	0.4 (± 0.3)	0.4 (± 0.2)
11.1 mmol/L	0.5 (± 0.3)	0.4 (± 0.2)	0.4 (± 0.2)	0.5 (± 0.3)
5.5 mmol/L high insulin	0.02 (± 0.03)	0.02 (± 0.03)	0.01 (± 0.03)	0.02 (± 0.04)
3.5 mmol/L	0.02 (± 0.05)	0.02 (± 0.03)	0.02 (± 0.04)	0.02 (± 0.1)
2.5 mmol/L	0.1 (± 0.1)	0.1 (± 0.2)	0.1 (± 0.1)	0.1 (± 0.2)

Statistical analyses

No statistical analyses for this end point

Secondary: C-Peptide

End point title	C-Peptide

End point description:

C-Peptide was significantly higher during hyper- and hypoglycaemia for dapagliflozin + saxagliptin compared to no treatment

End point type	Secondary

End point timeframe:

During Clamp Procedure - comparison between treatments

End point values	Dapagliflozin and Placebo Saxagliptin	Saxagliptin and Placebo Dapagliflozin	Saxagliptin and Dapagliflozin	Pre - treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: ng/mL				
arithmetic mean (standard deviation)				
5.5 mmol/L low insulin	0.8 (± 0.5)	0.9 (± 0.4)	1.0 (± 0.5)	0.8 (± 0.5)
11.1 mmol/L	2.7 (± 1.4)	2.5 (± 1.0)	3.2 (± 1.3)	2.3 (± 1.3)
5.5 mmol/L high insulin	1.5 (± 0.9)	1.4 (± 0.6)	1.9 (± 1.1)	1.3 (± 0.9)
3.5 mmol/L	1.0 (± 6.0)	1.0 (± 0.4)	1.3 (± 0.7)	0.9 (± 0.6)
2.5 mmol/L	0.6 (± 0.3)	0.6 (± 0.3)	0.8 (± 0.4)	0.6 (± 0.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Noradrenalin concentration

End point title	Noradrenalin concentration

End point description:

Saxagliptin reduced noradrenalin concentration significantly during euglycaemia at ambient insulin levels compared to no treatment and dapagliflozin and euglycaemia at high insulin levels compared to dapagliflozin

End point type	Secondary

End point timeframe:

During Clamp Procedure - comparison between treatments

End point values	Dapagliflozin and Placebo Saxagliptin	Saxagliptin and Placebo Dapagliflozin	Saxagliptin and Dapagliflozin	Pre - treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: pg/mL				
arithmetic mean (standard deviation)				
5.5 mmol/L low insulin	143 (± 89)	79 (± 70)	132 (± 77)	127 (± 64)
11.1 mmol/L	131 (± 81)	95 (± 81)	132 (± 88)	150 (± 184)
5.5 mmol/L high insulin	169 (± 99)	117 (± 84)	141 (± 73)	115 (± 63)
3.5 mmol/L	185 (± 111)	122 (± 94)	160 (± 100)	155 (± 81)
2.5 mmol/L	283 (± 206)	202 (± 167)	276 (± 164)	246 (± 97)

Statistical analyses

No statistical analyses for this end point

Secondary: Endogenous Glucose Production

End point title	Endogenous Glucose Production

End point description:

All three treatments significantly reduced EGP during hyper-, but not during hypoglycaemia (see Figure)

End point type	Secondary

End point timeframe:

During Clamp Procedure - comparison between treatments

End point values	Dapagliflozin and Placebo Saxagliptin	Saxagliptin and Placebo Dapagliflozin	Saxagliptin and Dapagliflozin	Pre - treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: mg/kg/min				
arithmetic mean (standard deviation)				
5.5 mmol/L low insulin	2.23 (± 0.46)	2.46 (± 0.47)	2.36 (± 0.42)	2.25 (± 0.46)
11.1 mmol/L	1.46 (± 0.41)	1.55 (± 0.62)	1.43 (± 0.55)	1.77 (± 0.45)
5.5 mmol/L high insulin	0.57 (± 0.42)	0.42 (± 0.39)	0.41 (± 0.33)	0.79 (± 0.77)
3.5 mmol/L	0.64 (± 0.22)	0.59 (± 0.33)	0.48 (± 0.33)	0.80 (± 0.48)
2.5 mmol/L	0.91 (± 0.25)	0.89 (± 0.36)	0.76 (± 0.32)	0.94 (± 0.40)

Attachments (see zip file)	Endogenous Glucose Production.PNG

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin

End point title	Insulin

End point description:

Insulin level was comparable for all treatment groups

End point type	Secondary

End point timeframe:

During Clamp Procedure - comparison between treatments

End point values	Dapagliflozin and Placebo Saxagliptin	Saxagliptin and Placebo Dapagliflozin	Saxagliptin and Dapagliflozin	Pre - treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: mU/L				
arithmetic mean (standard deviation)				
5.5 mmol/L low insulin	14.2 (± 5.6)	18.5 (± 7.1)	15.0 (± 7.6)	28.7 (± 48.3)
11.1 mmol/L	20.8 (± 18.6)	20.3 (± 14.8)	27.3 (± 19.5)	30.8 (± 38.4)
5.5 mmol/L high insulin	230.2 (± 43.9)	237.8 (± 44.4)	238.8 (± 51.9)	230.2 (± 43.6)
3.5 mmol/L	224.7 (± 40.1)	235.1 (± 45.0)	236.9 (± 49.2)	228.5 (± 42.0)
2.5 mmol/L	201.8 (± 60.4)	201.0 (± 67.2)	195.0 (± 67.1)	204.0 (± 53.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Ra Glycerol

End point title	Ra Glycerol

End point description:

End point type	Secondary

End point timeframe:

During Clamp Procedure - comparison between treatments

End point values	Dapagliflozin and Placebo Saxagliptin	Saxagliptin and Placebo Dapagliflozin	Saxagliptin and Dapagliflozin	Pre - treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: µmol/kg/min				
arithmetic mean (standard deviation)				
5.5 mmol/L low insulin	1.36 (± 0.43)	1.69 (± 0.55)	1.71 (± 0.71)	2.01 (± 0.93)
11.1 mmol/L	1.56 (± 0.61)	1.78 (± 0.85)	1.60 (± 0.52)	2.23 (± 0.85)
5.5 mmol/L high insulin	0.70 (± 0.24)	0.80 (± 0.33)	0.81 (± 0.40)	1.21 (± 0.41)
3.5 mmol/L	0.66 (± 0.23)	0.80 (± 0.38)	0.79 (± 0.37)	1.28 (± 0.44)
2.5 mmol/L	1.10 (± 0.46)	1.40 (± 0.92)	1.40 (± 1.02)	1.83 (± 0.81)

Attachments (see zip file)	Ra Glycerol.PNG

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall period of study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	Saxagliptin
Reporting group description: -	
Reporting group title	Dapagliflozin
Reporting group description: -	
Reporting group title	Dapagliflozin and Saxagliptin
Reporting group description: -	
Reporting group title	Before first treatment
Reporting group description: -	
Reporting group title	After last treatment
Reporting group description: -	

Serious adverse events	Saxagliptin	Dapagliflozin	Dapagliflozin and Saxagliptin
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Before first treatment	After last treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Saxagliptin	Dapagliflozin	Dapagliflozin and Saxagliptin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)	2 / 17 (11.76%)	4 / 17 (23.53%)
Investigations			
Maculopapular, pruritic rash on both lower arms			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	1	1
Cardiac disorders			
Common Cold			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	1	1
Palpitations			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	2	2
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	5	5	5
Pain in the left jaw			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	1	1
Increased neuropathic pain in the feet			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	1	1	1
Retrograde amnesia	Additional description: Retrogade amnesia on the time of hypoglycaemic clamp		
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	1	1
Dizzyness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	1	1
Eye disorders			
Fever			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	1	1
Gastrointestinal disorders			

Diarrhea	Additional description: 1 Diarrhea was bright colored		
subjects affected / exposed	2 / 17 (11.76%)	1 / 17 (5.88%)	1 / 17 (5.88%)
occurrences (all)	6	6	6
Nausea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	1 / 17 (5.88%)
occurrences (all)	2	2	2
Hepatobiliary disorders			
Hypertensive episodes	Additional description: Multiple not clinically significant hypertensive episodes during the clamp visit		
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	0 / 17 (0.00%)
occurrences (all)	1	1	1
Renal and urinary disorders			
Urinary retention (temporary)			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	1	1
Endocrine disorders			
Pain in the epigastric region			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Lower back pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	1	1

Non-serious adverse events	Before first treatment	After last treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 17 (17.65%)	2 / 17 (11.76%)	
Investigations			
Maculopapular, pruritic rash on both lower arms			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	1	1	
Cardiac disorders			
Common Cold			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	1	1	
Palpitations			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	2	2	

Nervous system disorders			
Headache			
subjects affected / exposed	2 / 17 (11.76%)	1 / 17 (5.88%)	
occurrences (all)	5	5	
Pain in the left jaw			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	1	1	
Increased neuropathic pain in the feet			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	1	1	
Retrograde amnesia	Additional description: Retrogade amnesia on the time of hypoglycaemic clamp		
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	
occurrences (all)	1	1	
Dizzyness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	1	1	
Eye disorders			
Fever			
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Diarrhea	Additional description: 1 Diarrhea was bright colored		
subjects affected / exposed	1 / 17 (5.88%)	1 / 17 (5.88%)	
occurrences (all)	6	6	
Nausea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	
occurrences (all)	2	2	
Hepatobiliary disorders			
Hypertensive episodes	Additional description: Multiple not clinically significant hypertensive episodes during the clamp visit		
subjects affected / exposed	0 / 17 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Urinary retention (temporary)			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	
occurrences (all)	1	1	
Endocrine disorders			

Pain in the epigastric region subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 1	1 / 17 (5.88%) 1	
Musculoskeletal and connective tissue disorders Lower back pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 17 (0.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2016	The study protocol was amended regarding Primary Objective, Primary and Secondary Endpoints and Study Duration per patient

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported