Clinical trial results:
A single-dose cross-over study to assess direct and indirect effects of dapagliflozin on pancreatic alpha and beta cells in patients with type 2 diabetes

Summary

EudraCT number	2015-005549-30
Trial protocol	SE
Global end of trial date	01 December 2016

Results information

Result version number	v1 (current)
This version publication date	07 August 2020
First version publication date	07 August 2020
Summary attachment (see zip file)	A single-dose cross-over study to assess direct and indirect effects of dapagliflozin on pancreatic alpha and beta cells in patients with type 2 diabetes (DG CSR 3.0_20180503_CLEAN.docx)

Trial information

Trial identification

Sponsor protocol code	ESR-15-11421

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02765204
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Uppsala University
Sponsor organisation address	Sjukhusvägen 1, Uppsala, Sweden, 75185
Public contact	Jan Eriksson, Dept of Medical Sciences, Clinical Diabetes and Metabolism, Uppsala University, 46 186114419, jan.eriksson@medsci.uu.se
Scientific contact	Jan Eriksson, Dept of Medical Sciences, Clinical Diabetes and Metabolism, Uppsala University, 46 186114419, jan.eriksson@medsci.uu.se

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	15 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2016
Global end of trial reached?	Yes
Global end of trial date	01 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if Dapagliflozin has direct effect on alpha cell glucagon release.

Protection of trial subjects:

Heartrate, bloodpressure, bloodsamples taken as a standard procedure as in ordinary healthcare

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	4
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Advertisment, studycenter patientlist

Pre-assignment

Screening details:

Age 18-75 years, BMI 20-35, diagnosis at least 6 months of T2D, Metformin treatment with stable dos for at least 1 month, HbA1c range 55-86mmol/mol

Period 1

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

Blinding implementation details:

Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dapa

Arm description:

D=Dapagliflozin 10mg and Salin infusion

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

Dosage and administration details:

10 mg dapagliflozin

Arm title	Dapa+Iso

Arm description:

Dapagliflozin 10mg and isoglycemiclamp

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

Dosage and administration details:

10 mg Dapagliflozin

Arm title	Dapa + Saxa

Arm description:

Dapagliflozin 10mg and saxagliptin 5mg and salininfusion

Arm type	Active comparator

Investigational medicinal product name	Dapagliflozin and saxagluptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10mg Dapagliflozin
5mg saxagliptin

Number of subjects in period 1	Dapa	Dapa+Iso	Dapa + Saxa
Started	5	5	5
Completed	3	5	4
Not completed	2	0	1
Consent withdrawn by subject	1	-	1
Adverse event, non-fatal	1	-	-

Baseline characteristics

End points

End points reporting groups

Reporting group title	Dapa
Reporting group description: D=Dapagliflozin 10mg and Salin infusion	
Reporting group title	Dapa+Iso
Reporting group description: Dapagliflozin 10mg and isoglycemiclamp	
Reporting group title	Dapa + Saxa
Reporting group description: Dapagliflozin 10mg and saxagliptin 5mg and salininfusion	

Primary: Plasma glucose and glucagon levels during experimental periods. Comparing experiments with spontaneous glycemia and isoglycemia respectively.

End point title	Plasma glucose and glucagon levels during experimental periods. Comparing experiments with spontaneous glycemia and isoglycemia respectively.

End point description:

This study will provide insight into SGLT2 action in beta and alpha cells, in particular with respect to direct and
indirect effects on glucagon secretion. Furthermore, it explores the mechanisms of glucose control when combining SGLT2- and DPP4 inhibitors.

End point type	Primary
End point timeframe: 10 month	

End point values	Dapa	Dapa+Iso	Dapa + Saxa	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	5	4	
Units: mmol/mol				
number (not applicable)	3	5	4	

Attachments (see zip file)	2019 PL Dapa glucagon JCEM.pdf

Statistical analyses

Statistical analysis title	Primary comparison: Effect of Dapagliflozin on glu
Comparison groups	Dapa v Dapa+Iso v Dapa + Saxa

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.001 [2]
Method	Mixed models analysis
Parameter estimate	Hazard ratio (HR)

Notes:

[1] - The study had 90% power to detect a 15% difference in the primary end point between the two conditions in the primary comparison. Based on previous work, this difference was judged to be clinically relevant and calculated to be 3 pmol/L (baseline level of about 20 pmol/L; SD, 3 pmol/L) (11). Thus, the sample size required for analysis of the primary end point was 12 evaluable patients. A maximum of three patients who did not complete the study (premature withdrawals) was expected. Thus, 15 patie

[2] - The study had 90% power to detect a 15% difference in the primary end point between the two conditions in the primary comparison. Based on previous work, this difference was judged to be clinically relevant and calculated to be 3 pmol/L (baseline lev

Adverse events

Adverse events information

Timeframe for reporting adverse events:

10 month

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Tiredness

Reporting group description:

Safety Ingeneral,thestudytreatmentswerewelltolerated;19 AEs were reported in six patients. No new and unexpected AEs were observed. The most commonly reportedeventswereheadache(sixeventsinthreepatients) andtiredness(fiveeventsinthreepatients).Fifteenevents were mild and two (ureteral stone and urticaria) were moderateinintensity.Oneevent,deepveinthrombosisof thearm,wasdeemedsevereinintensityandresultedinthe patient withdrawing from the study. The moderate and severe AEs required medication but none required hospitalization. Only one event (dizziness) was

Serious adverse events	Tiredness		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Tiredness		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)		
General disorders and administration site conditions			
Head banging	Additional description: Safety Ingeneral,thestudytreatmentswerewelltolerated; 19 AEs were reported in six patients. No new and unexpected AEs were observed. The most commonly reportedeventswereheadache (sixeventsinthreepatients) andtiredness(fiveeventsinthreepatients).Fifteen		
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported