Clinical trial results:
The Effect of an SGLT2 inhibitor on Glucose Flux, Lipolysis and Ketogenesis following insulin withdrawal in people with absolute or relative endogenous insulin deficiency

Summary

EudraCT number	2015-002094-38
Trial protocol	GB
Global end of trial date	02 August 2019

Results information

Result version number	v1 (current)
This version publication date	12 May 2021
First version publication date	12 May 2021
Summary attachment (see zip file)	Abstract (Abstract.docx)

Trial information

Trial identification

Sponsor protocol code	0584

Additional study identifiers

ISRCTN number	ISRCTN16404006
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leicester
Sponsor organisation address	Research Governance Office, Academic Department, Leicester General Hospital, Leicester, United Kingdom, LE5 4PW
Public contact	Roselle Herring, Royal Surrey County Hospital, 0044 07777621085, roselle.herring@nhs.net
Scientific contact	Roselle Herring, Royal Surrey County Hospital, 0044 07777621085, roselle.herring@nhs.net

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	28 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 March 2019
Global end of trial reached?	Yes
Global end of trial date	02 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the difference in glucose concentration of Dapagliflozin when compared with placebo treatment following insulin withdrawal.

Protection of trial subjects:

Participants received dapagliflozin (10 mg daily) or placebo in random order for 7 days. During the intake of the trial medication, that is, 6 days prior to the study visit, they were made aware of potential changes in glycaemic control and were asked to record trial medication administration, any concomitant medication (to include insulin), hypoglycaemia frequency (capillary glucose level <4mmol/L), fasting ketone levels and any adverse events.
During the study visit 2 and 3, the metabolic study was terminated at 600 minutes (10 hours) or in the event of blood glucose of 18mmol/L, bicarbonate <15mmol/L or venous pH <7.35 or point of care capillary ketone level of >5.0 mmol/L the metabolic study and participants commenced on rescue intravenous insulin infusion and 5% dextrose until blood glucose levels stabilised.

Background therapy:

Allowable concomitant type 1 and type 3c diabetes therapy: Insulin
Patients with type 1 diabetes were on pump therapy.
Permitted concomitant therapy: statins, antihypertensives..

Evidence for comparator:

Investigational product: Dapagliflozin 10 mg Dosage form and strength: Green, plain, diamond shaped, film-coated 10 mg tablet
Manufacturer: AstraZeneca Ltd
Investigational product: Matching placebo for Dapagliflozin 10 mg. Dosage form and strength: Green, plain, diamond shaped, film-coated tablet

Dapagliflozin is a SGLT2 inhibitors are highly potent, selective and reversible orally active inhibitors of renal SGLT2 the major transporter responsible for renal glucose reabsorption.
Therapeutic indications
o Forxiga is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:
o Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.
o Add-on combination therapy in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control
o Estimated cumulative exposure of clinical study participants: 7 days
In this trial, the incidence of adverse events was minimal and their severity was mild or moderate and self-limiting. Should the data suggest that Dapagliflozin was effective, then it could be said that it has a favourable risk-benefit profile.

There are no important or significant risks associated with taking Dapagliflozin. This conclusion is based on the available data at the time of creation of this document.
Comparator- a matching placebo tablet.

Actual start date of recruitment	01 February 2018
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	United Kingdom: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	14
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment: From Diabetes Clinics at Cedar centre, Royal Surrey County Hospital Surrey, UK- between 30/01/2018 and 17/03/2018.
Identification: Diabetes Consultants, from diabetes clinics at the Cedar centre, Royal Surrey County Hospital, will identify Participants with type 1 diabetes or type3c diabetes.

Pre-assignment

Screening details:

No washout or pre assignment periods for this study. 14 patients were recruited, 13 patients with type 1 diabetes and 1 with type 3c diabetes. 1 patient with T1D was withdrawn due to inability to be cannulated while attending VISIT 2 at the end of the first dosing of either Dapagliflozin or placebo. 1 patient with T3cD was not included in analysis.

Period 1

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

Blinding implementation details:

This is a double blind crossover study. Subjects were randomised into 2 groups. One group received once daily one tablet of dapagliflozin taken orally for 7 days followed by a 4 week washout then once daily one tablet of placebo taken orally for 7 days. The other group received once daily one tablet of placebo taken orally for 7 days followed by a 4 week washout then once daily one tablet of dapagliflozin taken orally for 7 days. The placebo and dapagliflozin tablets are indistinguishable.

Arms

Are arms mutually exclusive?	No
Arm title	Dapagliflozin

Arm description:

Dapagliflozin and placebo are considered as investigational medicinal product (IMP). insulin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly.
Identity of investigational products(s)
Dapagliflozin was supplied as 10 mg Dosage form and strength: Green, plain, diamond shaped, film-coated 10 mg tablet once daily for 7 days.
Dapagliflozin and its matching placebo will be supplied in bottles. The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals

Arm type	cross over
Investigational medicinal product name	Dapagliflozin
Investigational medicinal product code	461432-26-8, Cayman Chemical
Other name	Farxiga,
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Investigational product: Dapagliflozin 10 mg Dosage form and strength: Green, plain, diamond shaped, film-coated 10 mg tablet
Manufacturer: AstraZeneca Ltd

Dapagliflozin and its matching placebo will be supplied in bottles. The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals.

Used once daily

Investigational medicinal product name	Comparator to Dapagliflozin
Investigational medicinal product code	PL1
Other name	Placebo
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Investigational product: Matching placebo for Dapagliflozin 10 mg. Dosage form and strength: Green, plain, diamond shaped, film-coated tablet
Dapagliflozin and its matching placebo will be supplied in bottles. The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals.

Once daily

Arm title	placebo

Arm description:

Dapagliflozin and placebo are considered as investigational medicinal product (IMP). Insulin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly.
Identity of investigational products(s)
Dapagliflozin 10 mg Dosage form and strength: Green, plain, diamond shaped, film-coated 10 mg tablet
Manufacturer: AstraZeneca Ltd

Matching placebo for Dapagliflozin 10 mg. Dosage form and strength: Green, plain, diamond shaped, film-coated tablet
Dapagliflozin and its matching placebo were supplied in bottles. The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals.

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

Dosage and administration details:

Matching placebo for Dapagliflozin 10 mg. Dosage form and strength: Green, plain, diamond shaped, film-coated tablet
Dapagliflozin and its matching placebo were supplied in bottles. The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals.

Number of subjects in period 1	Dapagliflozin	placebo
Started	13	12
Completed	12	12
Not completed	1	0
Physician decision	1	-

Baseline characteristics

Reporting groups[1]	
Reporting group title	Overall period
Reporting group description:	
Overall trial n=12	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The study was designed to investigate the effects of dapagliflozin versus placebo in two cohorts of patients with type 1 and type 3C diabetes. 13 T1D were recruited of which 12 completed the study. We failed to recruit the full quota for T3c D.
one subject was recruited to the T3cD cohort who received both dapagliflozin and placebo with no adverse event.
Baseline characteristics reported here are for those participants who completed the study that is T1D cohort of n=12.

Reporting group values	Overall period	Total	
Number of subjects	13	13	
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	40.7		
standard deviation	± 13.4	-	
Gender categorical			
Female			
Units: Subjects			
Female	9	9	
Male	4	4	
HbA1C			
Haemoglobin A1C			
Units: mmol/mol			
arithmetic mean	59.9		
standard deviation	± 7.9	-	
Body weight			
Body weight at baseline			
Units: Kg			
arithmetic mean	81.7		
standard deviation	± 18.9	-	
BMI			
Body mass index			

Units: kg/m2			
arithmetic mean	26.8		
standard deviation	± 5.0	-	
Systolic BP			
Systolic blood pressure			
Units: mmHg			
arithmetic mean	126		
standard deviation	± 7	-	
Diastolic BP			
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	74		
standard deviation	± 8	-	

End points

End points reporting groups

Reporting group title	Dapagliflozin

Reporting group description:

Dapagliflozin and placebo are considered as investigational medicinal product (IMP). insulin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly.
Identity of investigational products(s)
Dapagliflozin was supplied as 10 mg Dosage form and strength: Green, plain, diamond shaped, film-coated 10 mg tablet once daily for 7 days.
Dapagliflozin and its matching placebo will be supplied in bottles. The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals

Reporting group title	placebo

Reporting group description:

Dapagliflozin and placebo are considered as investigational medicinal product (IMP). Insulin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly.
Identity of investigational products(s)
Dapagliflozin 10 mg Dosage form and strength: Green, plain, diamond shaped, film-coated 10 mg tablet
Manufacturer: AstraZeneca Ltd

Matching placebo for Dapagliflozin 10 mg. Dosage form and strength: Green, plain, diamond shaped, film-coated tablet
Dapagliflozin and its matching placebo were supplied in bottles. The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals.

Primary: Plasma glucose concentration

End point title	Plasma glucose concentration

End point description:

Glucose concentration (mmol/L) at 600 minutes following insulin cessation at the end of 7 days treatment with dapagliflozin or placebo (visits V2 or V3 depending on the randomisation). Dapagliflozin or placebo was administered at 0 min. Study was terminated when one of the rescue parameters was reached. Results are mean ± SEM.

End point type	Primary

End point timeframe:

Plasma glucose concentration at 600 minutes following insulin cessation or at the time of glycaemic rescue, whichever occurs first

End point values	Dapagliflozin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[1]	12		
Units: mmol/L				
arithmetic mean (standard error)	8.5 (± 0.7)	14.3 (± 1.1)		

Notes:

[1] - One subject was withdrawn due to inability to insert a cannula for venous sampling.

Statistical analyses

Statistical analysis title	Superiority testing

Statistical analysis description:

The primary end point was glucose concentration at 600 min. Final glucose concentration was statistically analysed as the response variable in a general linear mixed model (using PROC MIXED procedure in SAS software), with treatment, period, treatment by period interaction, as fixed effects, and the baseline glucose concentration as a covariate. The participant was a random effect in the model. The denominator degrees of freedom were adjusted using the Kenward-Roger approximations.

Comparison groups	Dapagliflozin v placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	≤ 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	6.1865
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4573
upper limit	8.9157
Variability estimate	Standard error of the mean

Notes:

[2] - Statistical analysis was performed using R version 3.5.1 and SAS version 9.4 or above. All hypothesis tests were two sided and evaluated at a significance level of 5%.

General linear mixed model , with treatment, period, treatment by period interaction, as fixed effects, and the baseline glucose concentration as a covariate. The participant was a random effect in the model. The denominator degrees of freedom were adjusted using the Kenward-Roger approximations.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

This includes events from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol.

Adverse event reporting additional description:

The following criteria were used to identify adverse events: Any unfavourable or unintended sign or symptom, Any deterioration in laboratory data, vital signs or found on physical examination.
All concomitant medications taken during the study were recorded.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Dapagliflozin

Reporting group description:

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Identity of investigational products(s)
Dapagliflozin was supplied as 10 mg Dosage form and strength: Green, plain, diamond shaped, film-coated 10 mg tablet once daily for 7 days.
Dapagliflozin and its matching placebo will be supplied in bottles. The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals

Reporting group title	placebo

Reporting group description:

Dapagliflozin and placebo are considered as investigational medicinal product (IMP). Insulin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly.
Identity of investigational products(s)
Dapagliflozin 10 mg Dosage form and strength: Green, plain, diamond shaped, film-coated 10 mg tablet
Manufacturer: AstraZeneca Ltd

Matching placebo for Dapagliflozin 10 mg. Dosage form and strength: Green, plain, diamond shaped, film-coated tablet
Dapagliflozin and its matching placebo were supplied in bottles. The tablets contain lactose, which may cause discomfort in lactose-intolerant individuals.

Serious adverse events	Dapagliflozin	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Dapagliflozin	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	2 / 13 (15.38%)	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	2 / 14 (14.29%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2017	Change of site for Final Quality Person (QP) release and certification of the IMP: Dapagliflozin and its matching placebo tablet and its randomisation
02 June 2017	Administrative change and overnight insulin requirements.
01 April 2019	To improve Type 3c recruitment and extend the recruitment period to the 3rd August 2019.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

1- Urinary ketone excretion was not measured.
2- We were unable to recruit patients with Type 3c diabetes.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32641376