



Clinical trial results:

The Effect of a SGLT2 inhibitor on Glucose flux, Lipolysis and Exercise in type 2 Diabetes

Summary

EudraCT number	2016-004878-17
Trial protocol	GB
Global end of trial date	08 January 2020

Results information

Result version number	v1 (current)
This version publication date	15 May 2021
First version publication date	15 May 2021
Summary attachment (see zip file)	Abstract (Summary for EudraCT.docx)

Trial information

Trial identification

Sponsor protocol code	0585
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04219124
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, +44 (0) 777621085, roselle.herring@nhs.net
Scientific contact	Roselle Herring, Royal Surrey County Hospital, +44 (0) 777621085, 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	Interim
Date of interim/final analysis	26 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 January 2020
Global end of trial reached?	Yes
Global end of trial date	08 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the differences in mean concentration of 3-hydroxybutyrate between 420-480 mins and the AUC of 3-hydroxybutyrate concentration time curve between 0-240 mins and 0-480 mins following 4 week treatment with dapagliflozin compared to placebo in Visit 4 and visit 6 where the IMP was given at 0 mins.

Protection of trial subjects:

This was not an efficacy study. All safety assessments were standard.

The study personnel were all trained on managing safety information according to agreed procedures. During the study adverse events were collected and documented at every visit, regardless of relationship to study medication. these events were coded using MedDRA (medical Dictionary for Regulatory Activities) dictionary version 18.1 September 2015 checked by the study physician. 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.

Background therapy:

Allowable concomitant diabetes therapy: Metformin

Evidence for comparator:

The type of control group: as it was a cross-over trial the participants acted as their own controls. The placebo and Dapagliflozin tablets were indistinguishable and provided in similar containers.

Rationale behind design: A randomised double-blind placebo controlled study design was chosen to study the effect of dapagliflozin against a placebo treatment where both the participant and the research group were blinded to the order of the treatment received.

Known or potential problems with design or control groups chosen in relation to the study: Using a cross-over trial can mean that a carry-over effect occurs from the first period to the second period of the trial. This was minimised by using a double blinded approach and by the presence of a four-week washout period between the treatment arms. Statistical analyses were conducted to determine whether a period effect was present. In this eventuality, comparisons between treatments were made solely at data from period one.

Actual start date of recruitment	20 September 2018
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	United Kingdom: 13
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Worldwide total number of subjects	13
EEA total number of subjects	13

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)	6
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

recruitment: From Diabetes Clinics at Cedar centre, Royal Surrey County Hospital and additional locations: local GP practices, other healthcare settings including but not limited to outpatient clinics, retinal screening, podiatry, diabetes patient groups, University of Surrey staff.
Recruitment was between September 2018 and January 2020.

Pre-assignment

Screening details:

There were no washout or pre assignment periods for screening. Interested patients with type 2 diabetes inadequately controlled by metformin were interviewed on the phone to confirm the inclusion criteria, 13 patients were recruited 4 patients were withdrawn.

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	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

This is a double blind cross study. Subjects were randomised into 2 groups. One group received a once daily oral tablet of dapagliflozin for 4 weeks followed by a 4 week washout then once daily oral tablet of placebo for 4 weeks. The other group received a once daily oral tablet of placebo for 4 weeks followed by a 4 week washout then once daily oral intake of tablet of dapagliflozin for 4 week. the placebo and dapagliflozin tablets were indistinguishable.

Arms

Are arms mutually exclusive?	No
Arm title	Dapagliflozin

Arm description:

Dapagliflozin or placebo are considered as investigational medical product (IMP). Metformin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly.

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, and 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.

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: Matching placebo for Dapagliflozin 10 mg. Dosage form and strength: Green, plain, diamond shaped, and 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.

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, and 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.

Arm title	placebo
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Arm description:

Dapagliflozin and placebo are considered as investigational medicinal product (IMP). Metformon is not considered an investigational medicinal product. 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, and 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.

Arm type	cross over
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: 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, and 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.

Used once daily

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

Investigational product: Matching placebo for Dapagliflozin 10 mg. Dosage form and strength: Green, plain, diamond shaped, and 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.

Number of subjects in period 1	Dapagliflozin	placebo
Started	9	9
Completed	9	9

Baseline characteristics

Reporting groups^[1]

Reporting group title	Overall period
Reporting group description:	
Participants with type 2 diabetes completed both arm of the trial in the cross over study.	
Four participants were withdrawn from the study, two participants while receiving dapagliflozin and two participants while receiving placebo.	

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: Justification- Baseline characteristics reported here are for those participants who completed the study that is n=9.

Reporting group values	Overall period	Total	
Number of subjects	9	9	
Age categorical			
Overall-			
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.			
Baseline characteristics reported here are for those participants who completed the study n=9.			
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)	3	3	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	61.7		
standard deviation	± 11.1	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	6	6	
BMI			
Body mass index			
Units: kg/m2			
arithmetic mean	28.9		
standard deviation	± 2.9	-	
HbA1c			
HeamoglobinA1c			
Units: mmol/mol			
arithmetic mean	60.2		
standard deviation	± 7.6	-	
SBP			
Systolic blood pressure			
Units: mmHg			

arithmetic mean	136.3		
standard deviation	± 11.8	-	
DBP			
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	81.7		
standard deviation	± 10.7	-	

End points

End points reporting groups

Reporting group title	Dapagliflozin
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Reporting group description:

Dapagliflozin or placebo are considered as investigational medical product (IMP). Metformin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly.

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, and 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.

Reporting group title	placebo
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Reporting group description:

Dapagliflozin and placebo are considered as investigational medicinal product (IMP). Metformin is not considered an investigational medicinal product. 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, and 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.

Primary: Plasma concentration of 3-hydroxybutyrate Mean (420-480 min)

End point title	Plasma concentration of 3-hydroxybutyrate Mean (420-480 min)
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End point description:

Mean plasma concentration of 3-hydroxybutyrate measured at (420-480 min) following 4 weeks treatment with either dapagliflozin or Placebo (Visit 4 or Visit 6, depending on the randomisation) dapagliflozin was administered at 0 min.

End point type	Primary
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End point timeframe:

4 week once daily oral intake of dapagliflozin or Placebo tablets, blood samples obtained at 4 weeks (Visit 4 or Visit 6).

End point values	Dapagliflozin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: mmol/L				
arithmetic mean (standard deviation)	0.39 (± 0.08)	0.15 (± 0.04)		

Attachments (see zip file)	BOHB concentration after a fat meal at 0min.
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Statistical analyses

Statistical analysis title	Superiority testing
Statistical analysis description:	
This was a double blind cross-over study. BOHB concentration mean value for 420-480min 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 BOHB concentration as a covariate. The subject will be the random effects in the model. The denominator degrees of freedom will be adjusted using Kenward-Roger approximations.	
Comparison groups	Dapagliflozin v placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.015 ^[2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.234
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.052
upper limit	0.415
Variability estimate	Standard error of the mean
Dispersion value	0.084

Notes:

[1] - This was a double blind cross-over study. BOHB concentration mean value for 420-480min 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 BOHB concentration as a covariate. The subject will be the random effects in the model. The denominator degrees of freedom will be adjusted using Kenward-Roger approximations.

[2] - significant at p <0.05

Primary: the AUC of 3-hydroxybutyrate concentration time curve between 0-240 mins

End point title	the AUC of 3-hydroxybutyrate concentration time curve between 0-240 mins
End point description:	
Area under the curve for 3-hydroxybutyrate concentration (mmol/L *min) for period 0-240 mins, after an intake of 30 ml of olive oil containing 200 mg U labelled ¹³ C Palmitic acid at 0 min, at the end of 4 weeks treatment with either dapagliflozin or placebo (visits V4 or V6, depending on randomisation). Dapagliflozin or Placebo was taken orally at 0 min.	
End point type	Primary

End point timeframe:

4 week once daily oral in take of dapagliflozin or placebo, blood samples obtained at 4 weeks

End point values	Dapagliflozin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: mmol/L *min				
arithmetic mean (standard error)	41.1 (± 7.8)	23.5 (± 3.8)		

Statistical analyses

Statistical analysis title	Superiority testing
Statistical analysis description:	
This was a double blind cross-over study. BOHB concentration AUC 0-240 min 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 BOHB concentration as a covariate. The subject will be the random effects in the model. The denominator degrees of freedom will be adjusted using Kenward-Roger approximations.	
Comparison groups	Dapagliflozin v placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.081 ^[4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	8.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.518
upper limit	36.003
Variability estimate	Standard error of the mean

Notes:

[3] - This was a double blind cross-over study. BOHB concentration AUC 0-240 min 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 BOHB concentration as a covariate. The subject will be the random effects in the model. The denominator degrees of freedom will be adjusted using Kenward-Roger approximations.

[4] - not significant

Primary: Plasma concentration of 3-hydroxybutyrate AUC(0-480 min)

End point title	Plasma concentration of 3-hydroxybutyrate AUC(0-480 min)
End point description:	
Area under the curve for 3-hydroxybutyrate concentration (mmol/L *min) for period 0-480 mins, after an intake of 30 ml of olive oil containing 200 mg U labelled ¹³ C Palmitic acid at 0 min, at the end of 4 weeks treatment with either dapagliflozin or placebo (visits V4 or V6, depending on randomisation). Dapagliflozin or Placebo was taken orally at 0 min.	
End point type	Primary
End point timeframe:	
4 week once daily oral intake of dapagliflozin or Placebo tablets, blood samples obtained at 4 weeks (Visit 4 or Visit 6).	

End point values	Dapagliflozin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: mmol/L *min				
arithmetic mean (standard error)	116.4 (± 17.7)	56.6 (± 8.9)		

Statistical analyses

Statistical analysis title	Superiority testing
Statistical analysis description:	
This was a double blind cross-over study. BOHB concentration AUC 0-480 min 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 BOHB concentration as a covariate. The subject will be the random effects in the model. The denominator degrees of freedom will be adjusted using Kenward-Roger approximations.	
Comparison groups	Dapagliflozin v placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.012 ^[6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	57.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.95
upper limit	100.41
Variability estimate	Standard error of the mean
Dispersion value	19.92

Notes:

[5] - This was a double blind cross-over study. BOHB concentration AUC 0-480 min 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 BOHB concentration as a covariate. The subject will be the random effects in the model. The denominator degrees of freedom will be adjusted using Kenward-Roger approximations.

[6] - Significant at p<0.05

Adverse events

Adverse events information

Timeframe for reporting adverse events:

This includes events from the first trial activity after the subject has signed the informed consent and until post treatment follow

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 physical examination.

All concomitant medications taken during the study were recorded.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Dapagliflozin
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Reporting group description:

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, and 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.

Reporting group title	placebo
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Reporting group description:

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, and 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.

Serious adverse events	Dapagliflozin	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	2 / 12 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm	Additional description: New diagnosis of Glioma		
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Infection	Additional description: Developed skin infection that required hospital admission		

subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	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	6 / 11 (54.55%)	8 / 12 (66.67%)	
Injury, poisoning and procedural complications			
Drug dispensed to wrong patient	Additional description: Patient received wrong IMP for 2 days. Removed from trial		
subjects affected / exposed	1 / 11 (9.09%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Cardiac disorders			
Hypotension	Additional description: Postural		
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Immune system disorders			
Allergy test positive	Additional description: Skin reaction		
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Eye disorders			
Photophobia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Crohn's flare			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Colonoscopy subjects affected / exposed occurrences (all)	Additional description: benign polyps		
	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0	
Renal and urinary disorders			
Balanitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Renal colic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Sciatica			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2017	1- Change of site for Final QP release and randomisation 2- updating of the protocol to reflect the source data will be entered into workbooks and then entered into CRFs.
19 December 2017	- Change of isotope and definition of primary and secondary end point - due to the National shortage of IV palmitodionate the study methodology had to be changed. This has resulted in a change in the statistical analysis.
01 June 2018	Notification to MHRA and HRA- We have been informed Renascience, the company which was providing the randomised, paired, kit numbers bottles containing 28 tablets of either placebo or active and shipping to Royal Surrey County Hospital research pharmacy for dispensing is restructuring. Renascience clinical trials service was also organising the randomisation and proving emergency randomisation codes. As a result of restructuring, Renaclical Ltd has been created, MHRA authorisations held by Renascience have been realigned via a change of ownership process. MIA (IMP) 44696 has been transferred to Renaclical as MIA(IMP)49160.
31 October 2018	1- Owing to difficulties in recruitment we would like to broaden our recruitment to allow us to approach patients in additional locations. 2- requesting permission to analyse blood taken during the metabolic study day for additional biomarkers of heart failure. 3- Extension of the study to 31/08/2019 as the green light was only received in August 2018.
25 September 2019	Extension of the study until 31/04/2020. owing to early recruitment difficulties and 4 people withdrawn from the study, some patients have been enrolled late and will be unable to complete the second arm of the study until December 2019. This will not incur any additional cost but means the lab analysis is delayed until early next year.

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 the whole quota for the patient group. This may have an impact on the level of significance on the metabolomics findings carried out on visit 4 and V6.

Notes: