Clinical trial results:
The effect of empagliflozin versus metformin on hormonal, metabolic and cardiovascular risk factors in patients with polycystic ovary syndrome (PCOS) – a randomised open-label parallel study.

Summary

EudraCT number	2016-004435-20
Trial protocol	GB
Global end of trial date	16 March 2018

Results information

Result version number	v1 (current)
This version publication date	15 May 2019
First version publication date	15 May 2019
Summary attachment (see zip file)	Publication (EMMET_RESUBMISSION2_CE_FINAL.pdf)

Trial information

Trial identification

Sponsor protocol code	Version 3, 23.05.17

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hull and East Yorkshire Hospitals NHS Trust
Sponsor organisation address	Anlaby Road, Hull, United Kingdom, HU3 2JZ
Public contact	Professor Thozhukat Sathyapalan, University of Hull, 01482 675312, thozhukat.sathyapalan@hyms.ac.uk
Scientific contact	Professor Thozhukat Sathyapalan, University of Hull, 01482 675312, thozhukat.sathyapalan@hyms.ac.uk

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	31 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does empagliflozin at a dose of 25mg improve enothelial function (cardiovascular risk marker) in women with PCOS?

Protection of trial subjects:

All women will be instructed to maintain their usual dietary habits and physical activity during the study. No vulnerable subjects or non-English speakers will be recruited. All subjects will be Caucasian as PCOS may differ among ethnic groups.
Adverse events will be reported in accordance with HEY R&D department's Safety Reporting standard operating procedure (R&D GCP SOP 07) to ensure compliance with UK Clinical Trial Regulations; ICH GCP and the Research Governance Framework 2005. The AE reporting period for this trial begins as soon as patients have consented to the
trial and ends 30 days after the patients final study medication visit.

Black triangle scheme for empagliflozin:
All suspected ADRs for empagliflozin will be reported using the Yellow Card scheme
These can be reported through the Yellow Card website, https://yellowcard.mhra.gov.uk/
Or, by emailing yellowcard@mhra.gsi.gov.uk
Or, by using a yellow card found in the back of the BNF.

Development safety update report (DSUR):
The PI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor.
The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) or the MHRA clinical trial authorisation of the trial each year until the trial is declared ended.
Due to the seriousness of the disease in this study, the following expected SAEs will not require reporting within 24hrs to R&D on the initial and follow-up SAE forms, but will still need to be recorded on R&D's AE report form.

Background therapy: -

Evidence for comparator:

The comparator to empagliflozin will be metformin that is used widely to improve insulin sensitivity, reduce androgen levels, may reduce diastolic blood pressure,
dyslipidaemia and body mass index (BMI) in patients with PCOS.

Actual start date of recruitment	03 April 2017
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: 39

Worldwide total number of subjects	39
EEA total number of subjects	39

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)	39
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with PCOS will be identified from endocrine clinics and will be contacted by a clinician responsible for the patient. Participants, who have agreed to be contacted for potential research opportunities, will also be recruited from a departmental PCOS biobank.

Pre-assignment

Screening details:

Patients with PCOS will be identified from endocrine clinics and will be contacted by a clinician responsible for the patient.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Empaglifozin

Arm description:

Experimental medicine

Arm type	Experimental
Investigational medicinal product name	Jardiance
Investigational medicinal product code	SUB35915
Other name	Empaglifozin
Pharmaceutical forms	Coated tablet
Routes of administration	Buccal use

Dosage and administration details:

12 weeks; 25mg per day; oral use

Arm title	Metformin

Arm description:

Comparator

Arm type	Active comparator
Investigational medicinal product name	Glucophage
Investigational medicinal product code	SUB03200MIG
Other name	Metformin
Pharmaceutical forms	Coated tablet
Routes of administration	Buccal use

Dosage and administration details:

1500mg per day for 12 weeks.

Number of subjects in period 1	Empaglifozin	Metformin
Started	19	20
Completed	19	20

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	39	39	
Age categorical			
Women, aged 18-45 years (inclusive), with confirmed diagnosis of PCOS based on Rotterdam criteria.			
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)	39	39	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	39	39	
Male	0	0	
Ethnic group			
Caucasion only accepted due to nature of study.			
Units: Subjects			
Caucasian	39	39	

Subject analysis sets

Subject analysis set title	Full analysis
Subject analysis set type	Full analysis

Subject analysis set description:

The trial will be reported according to CONSORT guidelines [20]. Between-group comparisons will be summarized as a series of 'effect sizes' for primary and secondary outcomes, from which numbers needed to plan for a larger trial can be estimated. No subgroup analysis are planned. The Stata statistical computer package will be used to analyse the data.

Reporting group values	Full analysis		
Number of subjects	39		
Age categorical			
Women, aged 18-45 years (inclusive), with confirmed diagnosis of PCOS based on Rotterdam criteria.			
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)	39		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	39		
Male	0		
Ethnic group			
Caucasion only accepted due to nature of study.			
Units: Subjects			
Caucasian			

End points

End points reporting groups

Reporting group title	Empaglifozin
Reporting group description:	
Experimental medicine	
Reporting group title	Metformin
Reporting group description:	
Comparator	
Subject analysis set title	Full analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
The trial will be reported according to CONSORT guidelines [20]. Between-group comparisons will be summarized as a series of 'effect sizes' for primary and secondary outcomes, from which numbers needed to plan for a larger trial can be estimated. No subgroup analysis are planned. The Stata statistical computer package will be used to analyse the data.	

Primary: RHI

End point title	RHI
End point description:	
Measured by reactive hyperamia index	
End point type	Primary
End point timeframe:	
12 weeks (recruitment to end of trial visit for patient)	

End point values	Empaglifozin	Metformin	Full analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	19	20	39	
Units: percent	19	20	39	

Statistical analyses

Statistical analysis title	Statistical analysis plane
Statistical analysis description:	
The trial will be reported according to CONSORT guidelines [20]. Between-group comparisons will be summarized as a series of 'effect sizes' for primary and secondary outcomes, from which numbers needed to plan for a larger trial can be estimated. No subgroup analysis are planned. The Stata statistical computer package will be used to analyse the data	
Comparison groups	Empaglifozin v Metformin v Full analysis
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	
P-value	≥ 0.05
Method	ANOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from consent to 30 days after final visit	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21
Reporting groups	
Reporting group title	non serious AE
Reporting group description: Headache seen in one patient	

Serious adverse events	non serious AE		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	non serious AE		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
General disorders and administration site conditions			
Headache	Additional description: Headache		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

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