Clinical trial results:
Liraglutide in PCOS (LIPOS) Study: Evaluation of the Efficacy of Liraglutide on Menstrual Cyclicity in Women with PCOS - a prospective randomised double-blind placebo-controlled study

Summary

EudraCT number	2012-002073-60
Trial protocol	GB
Global end of trial date	15 October 2016

Results information

Result version number	v1 (current)
This version publication date	27 October 2017
First version publication date	27 October 2017

Trial information

Trial identification

Sponsor protocol code	REGO-2012-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1126-3292

Notes:

Sponsors

Sponsor organisation name	Warwick Medical School
Sponsor organisation address	Gibbet Hill Road, Coventry, United Kingdom, CV4 7AL
Public contact	LIPOS study team, Warwick Medical School, LIPOS@warwick.ac.uk
Scientific contact	LIPOS study team, Warwick Medical School, LIPOS@warwick.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	24 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2016
Global end of trial reached?	Yes
Global end of trial date	15 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to investigate whether adding liraglutide (at a maximum dose of 1.8 mg once daily) to metformin (at a maximum dose of 1000 mg twice daily) for 48 weeks of treatment has a significant benefit in improving the regularity of periods (menstruation) in PCOS women.

Protection of trial subjects:

The study was approved by a Research Ethics Committee and received authorisation from the Medicines and Healthcare Products Regulatory Authority. Patients received verbal and written information prior to consenting to the trial and had the time to consider their participation and opportunity to ask questions. Patient data were anonymised to ensure information was kept confidential. Identifiable information was kept separately in a secure location

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
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: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	80
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from local PCOS clinics

Pre-assignment

Screening details:

496 patients were screened for eligibility, with 105 patients consented and registered with the study. Registered patients were prescribed metformin and followed up for four weeks before being randomized into the study.

Period 1

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

Blinding implementation details:

Placebo injections were used to blind medication use. The participant, clinical team and data analyst were blinded to treatment arm. A remote randomisation service independent from the trial management team was used to conceal allocation. Data which could un-blind treatment arm was not analysed until data collection was complete

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide arm

Arm description:

Liraglutide and metformin

Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Starting dose for liraglutide is 0.6 mg once daily. Daily dose of liraglutide is increased by a dose level increment of 0.6 mg every 7 days, until maintenance dose of 1.8 mg once daily has been achieved. Dose remains at 1.2mg if maintenance level not tolerated.

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose of Glucophage SR was 500mg once daily, titrated weekly over four weeks to a maintenance dose of 1,000mg twice daily.
If 1,000mg twice daily was not tolerated, then the maximum dosage tolerated was maintained.

Arm title	Control arm

Arm description:

Placebo injection and metformin

Arm type	Placebo

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The usual starting dose is one tablet of Glucophage SR 1,000 mg twice daily.
If 1,000mg twice daily was not tolerated, then the maximum dosage tolerated was maintained.

Number of subjects in period 1	Liraglutide arm	Control arm
Started	39	41
Completed	24	27
Not completed	15	14
Consent withdrawn by subject	6	2
Pregnancy	2	5
Lost to follow-up	6	7
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Liraglutide arm
Reporting group description: Liraglutide and metformin	
Reporting group title	Control arm
Reporting group description: Placebo injection and metformin	

Reporting group values	Liraglutide arm	Control arm	Total
Number of subjects	39	41	80
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	39	41	80
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Participant age at randomization			
Units: years			
arithmetic mean	29.8	31	
standard deviation	± 6.7	± 7.5	-
Gender categorical			
Participant gender			
Units: Subjects			
Female	39	41	80
Male	0	0	0

End points

End points reporting groups

Reporting group title	Liraglutide arm
Reporting group description: Liraglutide and metformin	
Reporting group title	Control arm
Reporting group description: Placebo injection and metformin	
Subject analysis set title	Completed follow up - liraglutide arm
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who were randomized to the liraglutide arm, completed all 48 weeks of follow up and returned at least one month of diary data.	
Subject analysis set title	Completed follow up - control arm
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who were randomized to the control arm, completed all 48 weeks of follow up and returned at least one month of diary data.	

Primary: Median number of menstrual cycles per participant during intervention

End point title	Median number of menstrual cycles per participant during intervention

End point description:

Median number of menstrual cycles per participant during study follow up:
A menstrual cycle is defined as at least two consecutive days of bleeding separated by 14 or more days. At least one day of bleeding must be heavier than spotting. Women who withdraw from the trial due to pregnancy will have experienced ovulation and hence have a "masked" period during follow up. This will be estimated by assigning day 0 of the pregnancy (as approximated by the pregnancy dating scan) as the last observed period.

To be entered into the analysis, participants must also have returned at least one month of diary data.

End point type	Primary

End point timeframe:

48 weeks after randomization

End point values	Liraglutide arm	Control arm	Completed follow up - liraglutide arm	Completed follow up - control arm
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	30[1]	37[2]	20[3]	27[4]
Units: Menstrual periods	7	4	8	7

Notes:

[1] - No. of women who returned diary data

[2] - No. of women who returned diary data

[3] - No. of women who returned diary data

[4] - No. of women who returned diary data

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The number of menstrual cycles will be modelled by a Poisson regression model with the addition of a single binary variable denoting treatment group and an offset term denoting time in follow up.

Comparison groups	Liraglutide arm v Control arm
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Poisson regression model
Parameter estimate	Rate ratio
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.71

Statistical analysis title	Completed follow-up
Comparison groups	Completed follow up - control arm v Completed follow up - liraglutide arm
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	superiority[5]
P-value	= 0.01
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	1.91

Notes:

[5] - Sensitivity analysis of the primary analysis, restricting the data to those 47 women who completed follow-up

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From randomisation to end of follow up (56 weeks)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	Liraglutide arm
Reporting group description: Liraglutide and metformin	
Reporting group title	Control arm
Reporting group description: Placebo injection and metformin	

Serious adverse events	Liraglutide arm	Control arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 39 (5.13%)	2 / 41 (4.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Gallbladder enlargement			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Tonsillitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Liraglutide arm	Control arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2013	Diagnosis criteria changed to PCOS based 2/3 of Rotterdam criteria, instead of 3/3.
07 October 2013	1) R&D/SSI: Expansion of recruitment sites to include local GP practices. 2) Design and display of a poster for display at PCOS clinics and GP surgeries. 3) Inclusion criteria amended: - Upper age limitation removed; replaced with 'pre-menopausal' - Upper BMI limitation removed - Non-smoking requirement removed - Restrictions based on IGT testing removed
25 February 2014	Condensed Patient Information Sheet
13 August 2014	Reduced number of women to be recruited; amended visit schedule to be fewer visits and to allow home pregnancy testing
14 November 2014	1) Amendment to protocol (section on power calculation amended, inclusion of Bodpod assessments for body composition) 2) Changes to Patient Information Scheet (to include Bodpod, undesirable effects, minor corrections) 3) Extension of end date to 31/03/16
17 July 2015	1) New document: end-of-study letter (thanking participants; stating what happens to their care and how to access study results. Enclosing shopping voucher) 2) Approval for use of shopping vouchers as reward for patients who have completed the study
11 August 2016	1) Amendment to protocol (clarifications withdrawal process, EudraCT number included, updated statistical analysis plan and changed study windows). 2) New documents: follow up letter template, template text messages, email to participants and letter to employer.

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.

84% of the participants returned evaluable primary outcome data. There were participants who did not return data for the whole of the follow up. There was a higher than expected rate of loss to follow up. The initial targeted power was not achieved.

Notes: