Clinical trial results:
A randomized, subject- and investigator-blinded, placebo controlled pharmacodynamic study of oral LIK066 in overweight and obese women with polycystic ovary syndrome

Summary

EudraCT number	2017-001373-16
Trial protocol	DE
Global end of trial date	25 June 2018

Results information

Result version number	v1 (current)
This version publication date	13 April 2019
First version publication date	13 April 2019

Trial information

Trial identification

Sponsor protocol code	CLIK066X2205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03152591
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

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	25 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2018
Global end of trial reached?	Yes
Global end of trial date	25 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the treatment effect of LIK066 on hyperandrogenism at Day 15 in overweight and obese subjects with polycystic ovary syndrome (PCOS).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 July 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	Germany: 26
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	29
EEA total number of subjects	26

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)	29
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 5 centers in 2 countries: Germany (3), and USA (2).

Pre-assignment

Screening details:

Participants were randomized in the ratio of 1:1 to receive either LIK066 50 mg tid or placebo for 14 days and morning dose on Day 15.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LIK066

Arm description:

LIK066 tablets received three times daily; before breakfast, lunch and dinner for 14 days and once on day 15 morning before meal test

Arm type	Experimental
Investigational medicinal product name	LIK066
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects administered orally LIK066 50 mg tablets tid for 14 days and only one dose in the morning on Day 15.

Arm title	Placebo

Arm description:

Placebo tablets received three times daily; before breakfast, lunch and dinner for 14 days and once on day 15 morning before meal test

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

Dosage and administration details:

Subjects administered orally matching placebo tablets tid for 14 days and only one dose in the morning on Day 15.

Number of subjects in period 1	LIK066	Placebo
Started	15	14
Pharmacokinetic (PK) analysis set	14 [1]	0 [2]
Pharmacodynamic (PD) analysis set	15	14
Completed	15	14

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 15 patients were enrolled into the LIK066 Treatment Arm; 14 of them were part of the PK analysis set; all 15 of them were included in the PD analysis set

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: PK analysis only performed in the LIK066 Treatment Arm

Baseline characteristics

Reporting groups	
Reporting group title	LIK066
Reporting group description:	
LIK066 tablets received three times daily; before breakfast, lunch and dinner for 14 days and once on day 15 morning before meal test	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets received three times daily; before breakfast, lunch and dinner for 14 days and once on day 15 morning before meal test	

Reporting group values	LIK066	Placebo	Total
Number of subjects	15	14	29
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)	15	14	29
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	26.1	29.1	
standard deviation	± 4.76	± 5.66	-
Sex/Gender, Customized			
Units: Subjects			
Female	15	14	29
Race/Ethnicity, Customized			
Units: Subjects			
White	15	14	29
Average fasting total testosterone			
Units: nmol/L			
arithmetic mean	1.98	2.07	
standard deviation	± 0.841	± 0.608	-
Average fasting free testosterone			
Units: nmol/L			
arithmetic mean	0.037	0.032	
standard deviation	± 0.0163	± 0.0086	-
Sex hormone binding globulin (SHBG)			
Units: nmol/L			
arithmetic mean	18.3	24.6	
standard deviation	± 7.72	± 10.51	-
Free androgen Index			

Units: ratio			
arithmetic mean	12.4	9.0	
standard deviation	± 6.65	± 2.77	-

End points

End points reporting groups

Reporting group title	LIK066
Reporting group description: LIK066 tablets received three times daily; before breakfast, lunch and dinner for 14 days and once on day 15 morning before meal test	
Reporting group title	Placebo
Reporting group description: Placebo tablets received three times daily; before breakfast, lunch and dinner for 14 days and once on day 15 morning before meal test	

Primary: Change in average morning fasting free testosterone blood concentrations from baseline

End point title	Change in average morning fasting free testosterone blood concentrations from baseline
End point description:	
End point type	Primary
End point timeframe: Baseline, Day 15	

End point values	LIK066	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: nmol/L				
geometric mean (confidence interval 90%)	0.91 (0.77 to 1.07)	1.03 (0.88 to 1.21)		

Statistical analyses

Statistical analysis title	Fasting free testosterone blood concentrations
Comparison groups	LIK066 v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.353
Method	t-test, 2-sided
Parameter estimate	Ratio LIK066/Placebo
Point estimate	0.88

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	1.11

Secondary: Change from baseline in Luteinizing Hormone (LH) at Day 15

End point title	Change from baseline in Luteinizing Hormone (LH) at Day 15
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Day 15	

End point values	LIK066	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: U/L				
geometric mean (confidence interval 90%)	1.37 (1.11 to 1.69)	1.10 (0.89 to 1.36)		

Statistical analyses

Statistical analysis title	Luteinizing Hormone (LH) at Day 15
Comparison groups	LIK066 v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.218
Method	t-test, 2-sided
Parameter estimate	Ratio LIK066/Placebo
Point estimate	1.25
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.92
upper limit	1.68

Secondary: Change from baseline in follicle stimulating hormone (FSH) at Day 15

End point title	Change from baseline in follicle stimulating hormone (FSH) at Day 15

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 15

End point values	LIK066	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: U/L				
geometric mean (confidence interval 90%)	1.13 (0.89 to 1.43)	0.89 (0.70 to 1.13)		

Statistical analyses

Statistical analysis title	Follicle stimulating hormone (FSH) at Day 15
Comparison groups	LIK066 v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.249
Method	t-test, 2-sided
Parameter estimate	Ratio LIK066/Placebo
Point estimate	1.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9
upper limit	1.78

Secondary: Change from baseline in sex hormone binding globulin (SHBG) at Day 15

End point title	Change from baseline in sex hormone binding globulin (SHBG) at Day 15

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 15

End point values	LIK066	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: nmol/L				
geometric mean (confidence interval 90%)	1.06 (0.95 to 1.20)	0.93 (0.83 to 1.03)		

Statistical analyses

Statistical analysis title	Sex hormone binding globulin (SHBG) at Day 15
Comparison groups	LIK066 v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.173
Method	t-test, 2-sided
Parameter estimate	Ratio LIK066/Placebo
Point estimate	1.15
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.97
upper limit	1.36

Secondary: Change from baseline in androstenedione at Day 15

End point title	Change from baseline in androstenedione at Day 15

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 15

End point values	LIK066	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: nmol/L				
geometric mean (confidence interval 90%)	0.85 (0.74 to 0.97)	1.03 (0.91 to 1.17)		

Statistical analyses

Statistical analysis title	Androstenedione at Day 15
Comparison groups	LIK066 v Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.089
Method	t-test, 2-sided
Parameter estimate	Ratio LIK066/Placebo
Point estimate	0.82
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.68
upper limit	0.99

Secondary: Change from baseline in dehydroepiandrostenedione (DHEA) at Day 15

End point title	Change from baseline in dehydroepiandrostenedione (DHEA) at Day 15

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 15

End point values	LIK066	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: nmol/L				
geometric mean (confidence interval 90%)	0.75 (0.58 to 0.98)	1.09 (0.85 to 1.39)		

Statistical analyses

Statistical analysis title	Dehydroepiandrostenedione (DHEA) at Day 15
Comparison groups	LIK066 v Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.109
Method	t-test, 2-sided
Parameter estimate	Ration LIK066/Placebo
Point estimate	0.69

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.48
upper limit	1.01

Secondary: Change from baseline in dehydroepiandrostenedione sulfate (DHEAS) at Day 15

End point title	Change from baseline in dehydroepiandrostenedione sulfate (DHEAS) at Day 15
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Day 15	

End point values	LIK066	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: umol/L				
geometric mean (confidence interval 90%)	0.84 (0.75 to 0.94)	1.10 (0.99 to 1.23)		

Statistical analyses

Statistical analysis title	DHEAS at Day 15
Comparison groups	LIK066 v Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.008
Method	t-test, 2-sided
Parameter estimate	Ration LIK066/Placebo
Point estimate	0.76
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.65
upper limit	0.89

Secondary: Change from baseline in total testosterone at Day 15

End point title	Change from baseline in total testosterone at Day 15

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 15

End point values	LIK066	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: nmol/L				
geometric mean (confidence interval 90%)	0.95 (0.84 to 1.06)	1.04 (0.92 to 1.17)		

Statistical analyses

Statistical analysis title	Total testosterone at Day 15
Comparison groups	LIK066 v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.34
Method	t-test, 2-sided
Parameter estimate	Ratio LIK066/Placebo
Point estimate	0.91
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.77
upper limit	1.07

Secondary: Change from baseline in Free Androgen Index (FAI) at Day 15

End point title	Change from baseline in Free Androgen Index (FAI) at Day 15

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 15

End point values	LIK066	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: 100x total testosterone/SHBG				
geometric mean (confidence interval 90%)	0.85 (0.69 to 1.05)	1.07 (0.88 to 1.31)		

Statistical analyses

Statistical analysis title	Free Androgen Index (FAI) at Day 15
Comparison groups	LIK066 v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.204
Method	t-test, 2-sided
Parameter estimate	Ratio LIK066/Placebo
Point estimate	0.79
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.58
upper limit	1.08

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events were collected for the maximum duration of participants' treatment exposure plus any follow up period, approximately 2 months.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	LIK066 50mg t.i.d.
Reporting group description:	
LIK066 50mg t.i.d.	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	LIK066 50mg t.i.d.	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (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: 0 %

Non-serious adverse events	LIK066 50mg t.i.d.	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	10 / 14 (71.43%)	
Investigations			
MENSTRUATION NORMAL			
subjects affected / exposed	4 / 15 (26.67%)	2 / 14 (14.29%)	
occurrences (all)	4	2	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	4 / 15 (26.67%)	1 / 14 (7.14%)	
occurrences (all)	4	2	
MIGRAINE			

subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
THIRST			
subjects affected / exposed	4 / 15 (26.67%)	1 / 14 (7.14%)	
occurrences (all)	4	1	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	2 / 15 (13.33%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
ABDOMINAL PAIN			
subjects affected / exposed	2 / 15 (13.33%)	0 / 14 (0.00%)	
occurrences (all)	4	0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
DIARRHOEA			
subjects affected / exposed	15 / 15 (100.00%)	3 / 14 (21.43%)	
occurrences (all)	16	3	
DYSPEPSIA			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
FLATULENCE			
subjects affected / exposed	6 / 15 (40.00%)	0 / 14 (0.00%)	
occurrences (all)	6	0	
GASTROINTESTINAL TRACT IRRITATION			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
NAUSEA			
subjects affected / exposed	5 / 15 (33.33%)	2 / 14 (14.29%)	
occurrences (all)	5	2	
VOMITING			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			

HYPOMENORRHOEA			
subjects affected / exposed	2 / 15 (13.33%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
MENSTRUAL DISORDER			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
DRY THROAT			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
MOOD ALTERED			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
POLYURIA			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL DISCOMFORT			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	2 / 15 (13.33%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
RHINITIS			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
VAGINAL INFECTION			

subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
VULVOVAGINAL MYCOTIC INFECTION			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2017	Amendment 1 was issued to address comments received from the German Federal Institute for Drugs and Medical Devices (BfArM) and the Ethics Committee (EC) in the advice/information request letter following review of the clinical trial application (CTA). It • added text advising investigators to instruct the study subjects to watch for symptoms of ketoacidosis, hypoglycemia and hypotension • added risk of lower limb amputation • changed study treatment discontinuation criteria related to hypoglycemia and ketoacidosis • Changed stopping criteria related to hypoglycemia and ketoacidosis.
29 September 2017	Amendment 2 was issued to enable recruitment of the intended PCOS population with hyperandrogenism. The definition of hyperandrogenism was adjusted and the BMI cut off was removed. It included the following changes: • Biochemical hyperandrogenism was defined as free testosterone level that was approximately equal to or > 1.75× the ULN range of the assay used. • Overweight/obese subjects with BMI equal to or > 27 kg/m2, and stable weight ± 3 kg over previous 3 month (by history) were allowed to participate in the study. • The exclusion criterion for TSH was specified as, TSH levels > 10 uUI/ml and clinical symptoms of hypothyroidism. Subjects with sub clinical hypothyroidism need not be excluded. Subjects with well controlled on thyroid medication could be enrolled.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported