Sponsor

Novartis

Generic Drug Name

LIK066

Trial Indication(s)

Polycystic ovary syndrome

Protocol Number

CLIK066X2205

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: July 2017 (Actual)
Primary Completion Date: June 2018 (Actual)
Study Completion Date: June 2018 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a randomized, subject- and investigator-blinded, placebo-controlled, parallel group, non-confirmatory study in overweight and obese PCOS subjects. Subjects 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.

A total of 29 subjects were randomized and analyzed in the study.

Centers

5 centers in 2 countries: United States(2), Germany(3)

Objectives:

- The primary objective was to assess the treatment effect of LIK066 on hyperandrogenism at Day 15 in overweight and obese subjects with PCOS.
- Secondary objectives were to assess the safety and tolerability of LIK066 in overweight and obese subjects with PCOS throughout the study and to evaluate the treatment effect of LIK066 on gonadotropins and sex steroid levels on Day 15.

The study completed as planned.

Test Product (s), Dose(s), and Mode(s) of Administration

The treatment period was 2 weeks, with oral dosing just before meals, 50 mg of LIK066 or matching placebo tid for 14 days and only one dose in the morning on Day 15.

Subjects administered orally LIK066 50 mg tablets or matching placebo tablets.

Statistical Methods

The primary analysis assessed the treatment effect of LIK066 on free T at Day 15. The ratio of Day 15 to baseline free T were analyzed in an analysis of covariance model with treatment as a categorical factor, baseline weight and baseline free T as a covariate. The logarithm of the ratio and of baseline free T were applied prior to the analysis.

The geometric mean of the ratio to baseline for free T were estimated from the model for LIK066 and placebo, along with the treatment ratio and the associated p-value and two-sided 90% confidence interval (CI). From these quantities, the following criteria were assessed:

1. the upper confidence limit of the 90% CI is less than 1, and
2. the estimated treatment ratio is less than 0.75.

The ratio of Day 15 to baseline for secondary variables were analyzed in an analysis of covariance model with treatment as a categorical factor and baseline as a covariate. The logarithm of the ratio and of baseline will be applied prior to the analysis.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
- PCOS (diagnosed as clinical or biochemical hyperandrogenism, amenorrhea or oligomenorrhea and exclusion of other causes of hyperandrogenism.
- Overweight/obese female subjects with BMI of 28 – 45 kg/m^2, inclusive, and stable weight +/- 3 kg over previous 3 months
- Subjects must use non-hormonal methods of contraception during the study.

Key Exclusion Criteria:
- Subjects with exogenous causes of hirsutism
- Menstruation in the 30 days prior to screening or treatment
- Pregnant or nursing (lactating) women
- Use of prohibited medications
- Preexisting medical condition which may significantly alter the absorption, metabolism, or excretion of the study drug, or which may jeopardize the subject in case of participation in the study

Participant Flow Table

Overall Study

	LIK066	Placebo
Started	15	14
Pharmacokinetic (PK) analysis set	14	0
Pharmacodynamic (PD) analysis set	15	14
Completed	15	14
Not Completed	0	0

Baseline Characteristics

	LIK066	Placebo	Total
Number of Participants [units: participants]	15	14	29
Age Continuous (units: Years) Mean ± Standard Deviation			
	26.1±4.76	29.1±5.66	27.6±5.34
Race/Ethnicity, Customized (units: Participants)			
White	15	14	29
Sex/Gender, Customized (units: Participants)			
Female	15	14	29

Average fasting total testosterone (units: nmol/L) Mean ± Standard Deviation			
	1.98±0.841	2.07±0.608	2.02±0.724
Average fasting free testosterone (units: nmol/L) Mean ± Standard Deviation			
	0.037±0.0163	0.032±0.0086	0.034±0.0132
Sex hormone binding globulin (SHBG) (units: nmol/L) Mean ± Standard Deviation			
	18.3±7.72	24.6±10.51	21.4±9.58
Free androgen Index (units: ratio) Mean ± Standard Deviation			
	12.4±6.65	9.0±2.77	10.7±5.27

Summary of Efficacy

Primary Outcome Result(s)

Change in average morning fasting free testosterone blood concentrations from baseline

	LIK066	Placebo
Number of Participants Analyzed [units: participants]	15	14
Change in average morning fasting free testosterone blood		

concentrations from baseline (units: nmol/L) Geometric Mean (90% Confidence Interval)		
(n= 10, 10)	0.91 (0.77 to 1.07)	1.03 (0.88 to 1.21)

Statistical Analysis

Groups	LIK066, Placebo	
P Value	0.353	
Method	t-test, 2 sided	Two-sided test at the 0.1 significance level
Other Ratio LIK066/Placebo	0.88	
90 % Confidence Interval 2-Sided	0.70 to 1.11	

Secondary Outcome Result(s)

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

	LIK066	**Placebo**
Number of Participants Analyzed [units: participants]	15	14
Change from baseline in Luteinizing Hormone (LH) at Day 15 (units: U/L)		

Geometric Mean (90% Confidence Interval)		
(n= 10, 10)	1.37 (1.11 to 1.69)	1.10 (0.89 to 1.36)

Statistical Analysis

Groups	LIK066, Placebo	
P Value	0.218	
Method	t-test, 2 sided	Two-sided test at the 0.1 significance level
Other Ratio LIK066/Placebo	1.25	
90 % Confidence Interval 2-Sided	0.92 to 1.68	

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

	LIK066	**Placebo**
Number of Participants Analyzed [units: participants]	15	14
Change from baseline in follicle stimulating hormone (FSH) at Day 15 (units: U/L) Geometric Mean (90% Confidence Interval)		
(n= 10, 10)	1.13 (0.89 to 1.43)	0.89 (0.70 to 1.13)

Statistical Analysis

Groups	LIK066, Placebo	
P Value	0.249	
Method	t-test, 2 sided	Two-sided test at the 0.1 significance level
Other Ratio LIK066/Placebo	1.27	
90 % Confidence Interval 2-Sided	0.90 to 1.78	

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

	LIK066	Placebo
Number of Participants Analyzed [units: participants]	15	14
Change from baseline in sex hormone binding globulin (SHBG) at Day 15 (units: nmol/L) Geometric Mean (90% Confidence Interval)		
(n= 9, 10)	1.06 (0.95 to 1.20)	0.93 (0.83 to 1.03)

Statistical Analysis

Groups	LIK066, Placebo	
P Value	0.173	
Method	t-test, 2 sided	Two-sided test at the 0.1 significance level

Other Ratio LIK066/Placebo	1.15	Values < LLOQ and values > ULOQ are imputed as LLOQ/2 and ULOQ respectively.
90 % Confidence Interval 2-Sided	0.97 to 1.36	

Change from baseline in androstenedione at Day 15

	LIK066	Placebo
Number of Participants Analyzed [units: participants]	15	14
Change from baseline in androstenedione at Day 15 (units: nmol/L) Geometric Mean (90% Confidence Interval)		
(n= 11, 12)	0.85 (0.74 to 0.97)	1.03 (0.91 to 1.17)

Statistical Analysis

Groups	LIK066, Placebo	
P Value	0.089	
Method	t-test, 2 sided	Two-sided test at the 0.1 significance level
Other Ratio LIK066/Placebo	0.82	Values < LLOQ and values > ULOQ are imputed as LLOQ/2 and ULOQ respectively

90 % Confidence Interval 2-Sided	0.68 to 0.99

Change from baseline in dehydroepiandrostenedione (DHEA) at Day 15

	LIK066	Placebo
Number of Participants Analyzed [units: participants]	15	14
Change from baseline in dehydroepiandrostenedione (DHEA) at Day 15 (units: nmol/L) Geometric Mean (90% Confidence Interval)		
(n= 11, 12)	0.75 (0.58 to 0.98)	1.09 (0.85 to 1.39)

Statistical Analysis

Groups	LIK066, Placebo	
P Value	0.109	
Method	t-test, 2 sided	Two-sided test at the 0.1 significance level
Other Ration LIK066/Placebo	0.69	Values < LLOQ and values > ULOQ are imputed as LLOQ/2 and ULOQ respectively.
90 % Confidence Interval 2-Sided	0.48 to 1.01	

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

	LIK066	Placebo
Number of Participants Analyzed [units: participants]	15	14
Change from baseline in dehydroepiandrostenedione sulfate (DHEAS) at Day 15 (units: umol/L) Geometric Mean (90% Confidence Interval)		
(n= 11, 12)	0.84 (0.75 to 0.94)	1.10 (0.99 to 1.23)

Statistical Analysis

Groups	LIK066, Placebo	
P Value	0.008	
Method	t-test, 2 sided	Two-sided test at the 0.1 significance level
Other Ration LIK066/Placebo	0.76	Values < LLOQ and values > ULOQ are imputed as LLOQ/2 and ULOQ respectively.
90 % Confidence Interval 2-Sided	0.65 to 0.89	

Change from baseline in total testosterone, at Day 15

	LIK066	Placebo
Number of Participants Analyzed [units: participants]	15	14

Change from baseline in total testosterone, at Day 15 (units: nmol/L) Geometric Mean (90% Confidence Interval)		
(n= 10, 10)	0.95 (0.84 to 1.06)	1.04 (0.92 to 1.17)

Statistical Analysis

Groups	LIK066, Placebo	
P Value	0.340	
Method	t-test, 2 sided	Two-sided test at the 0.1 significance level
Other Ratio LIK066/Placebo	0.91	
90 % Confidence Interval 2-Sided	0.77 to 1.07	

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

	LIK066	**Placebo**
Number of Participants Analyzed [units: participants]	15	14
Change from baseline in Free Androgen Index (FAI), at Day 15 (units: 100x total testosterone/SHBG) Geometric Mean (90% Confidence Interval)		

(n= 9, 10)	0.85 (0.69 to 1.05)	1.07 (0.88 to 1.31)

Statistical Analysis

Groups	LIK066, Placebo	
P Value	0.204	
Method	t-test, 2 sided	Two-sided test at the 0.1 significance level
Other Ratio LIK066/Placebo	0.79	Values < LLOQ and values > ULOQ are imputed as LLOQ/2 and ULOQ respectively.
90 % Confidence Interval 2-Sided	0.58 to 1.08	

Summary of Safety

Safety Results

All-Cause Mortality

	LIK066 N = 15	**Placebo N = 14**
Total participants affected	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Other Adverse Events by System Organ Class

Time Frame	Adverse Events were collected for the maximum duration of participants' treatment exposure plus any follow up period, approximately 2 months.
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	LIK066 N = 15	Placebo N = 14
Total participants affected	15 (100.00%)	10 (71.43%)
GASTROINTESTINAL DISORDERS		
ABDOMINAL DISTENSION	2 (13.33%)	0 (0.00%)
ABDOMINAL PAIN	2 (13.33%)	0 (0.00%)
ABDOMINAL PAIN UPPER	1 (6.67%)	0 (0.00%)
DIARRHOEA	15 (100.00%)	3 (21.43%)
DYSPEPSIA	1 (6.67%)	0 (0.00%)
FLATULENCE	6 (40.00%)	0 (0.00%)
GASTROINTESTINAL TRACT IRRITATION	0 (0.00%)	1 (7.14%)
NAUSEA	5 (33.33%)	2 (14.29%)
VOMITING	0 (0.00%)	1 (7.14%)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
THIRST	4 (26.67%)	1 (7.14%)
INFECTIONS AND INFESTATIONS		
NASOPHARYNGITIS	2 (13.33%)	1 (7.14%)
RHINITIS	1 (6.67%)	0 (0.00%)
VAGINAL INFECTION	1 (6.67%)	0 (0.00%)
VULVOVAGINAL MYCOTIC INFECTION	1 (6.67%)	0 (0.00%)
INVESTIGATIONS		
MENSTRUATION NORMAL	4 (26.67%)	2 (14.29%)
METABOLISM AND NUTRITION DISORDERS		
DECREASED APPETITE	1 (6.67%)	0 (0.00%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
MUSCULOSKELETAL DISCOMFORT	0 (0.00%)	1 (7.14%)
NERVOUS SYSTEM DISORDERS		
HEADACHE	4 (26.67%)	1 (7.14%)
MIGRAINE	0 (0.00%)	1 (7.14%)
PSYCHIATRIC DISORDERS		
INSOMNIA	1 (6.67%)	0 (0.00%)

MOOD ALTERED	1 (6.67%)	0 (0.00%)
RENAL AND URINARY DISORDERS		
POLYURIA	0 (0.00%)	1 (7.14%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
HYPOMENORRHOEA	2 (13.33%)	1 (7.14%)
MENSTRUAL DISORDER	0 (0.00%)	1 (7.14%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
DRY THROAT	0 (0.00%)	1 (7.14%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
RASH	1 (6.67%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

In patients with polycystic ovary syndrome (PCOS), 15 days of treatment with LIK066 demonstrated numerical improvements in free testosterone compared to Placebo. The size of the effect was too small to reach statistical significance. The fact that additional biomarkers of antiandrogenic effects also trended in the direction of an improvement of the hyperandrogenic situation in PCOS patients support LIK066`s mode of action and the basic pathophysiological concept. Diarrhea was the most common reported AE in subjects treated with LIK066. The study did not reveal any new safety and tolerability findings.

Date of Clinical Trial Report

06-Dec-2018