CLINICAL STUDY PROTOCOL

PRODUCT NAME: MLE4901

STUDY NUMBER: MLE4901-101

A Double-blind, Randomized, Parallel-group, Placebo-controlled Study of MLE4901 for the Treatment of Polycystic Ovary Syndrome (PCOS)

Study Phase: 2b
Product Name: MLE4901
IND Number: 116350
EudraCT Number: 2016-002179-91

Indication: Polycystic Ovary Syndrome (PCOS)

Sponsor: Millendo Therapeutics, Inc.

Sponsor Medical Contact: Vivian H. Lin, M.D.

Original Protocol: Version 0.0 – 19 May 2016
Country-specific Protocol Amendment 1/UK: 18 October 2016
Global Protocol Amendment 1: 16 February 2017
Global Protocol Amendment 2: 08 March 2017

INVESTIGATOR'S AGREEMENT

Study Title: A Double-blind, Randomized, Parallel-group, Placebo-controlled Study of MLE4901 for the Treatment of Polycystic Ovary Syndrome (PCOS)

This protocol is provided for use by you, your staff and the Institutional Review Board or Ethics Committee. The information contained in this document is confidential and belongs to Millendo Therapeutics, Inc. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law) nor use it for unauthorized purposes. In the event of actual or suspected breach of this obligation, Millendo Therapeutics, Inc. must be promptly notified.

STUDY INVESTIGATOR SIGNATURE

By my signature below, I agree to conduct this clinical study in accordance with applicable government regulations or laws and institutional/ethical review and informed consent practices. I have read the Investigator's Brochure and protocol. I agree to ensure the confidentiality of my subjects; however, I agree to make available to Millendo Therapeutics, Inc. or designee the subject's medical and/or research chart specifically for the purposes of this clinical study. I am fully conversant with Good Clinical Practices (GCP) and agree to conduct the clinical study in accordance with these principles and the procedures described in this protocol. I am aware of my responsibilities as an Investigator.

Name: _____
Please print

Title: _____

Signature: _____

Date: _____

Address: _____

_____

_____

SPONSOR SIGNATURE

Study Title: A Double-blind, Randomized, Parallel-group, Placebo-controlled Study of MLE4901 for the Treatment of Polycystic Ovary Syndrome (PCOS)

SPONSOR SIGNATURE

I have read and approve the protocol and appendices. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the study will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the International Conference on Harmonisation (ICH) Guidelines for GCP, the US Code of Federal Regulations (CFR) and the ethical principles that have their origins in the Declaration of Helsinki, as well as all applicable privacy laws.

Name: Pharis Mohideen, MD
Please print

Title: Chief Medical Officer

Signature: P Mohideen

Date: MARCH 9, 2017

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SYNOPSIS

Name of Sponsor/Company:
Millendo Therapeutics, Inc.

Name of Investigational Product:
MLE4901

Title of Study:
A Double-blind, Randomized, Parallel-group, Placebo-controlled Study of MLE4901 for the Treatment of Polycystic Ovary Syndrome (PCOS)

Study Center(s): approximately 30 sites in the United States

Principal Investigator: TBD

Studied Period:	**Phase of Development:**
Estimated date first subject screened: 01AUG2016 Estimated date last subject completed: 01MAY2018	2b

Objectives:

Primary: To evaluate the efficacy of MLE4901 compared to placebo in improving menstrual regularity in women with oligo-/amenorrhea due to PCOS

Secondary:

- To evaluate the efficacy of MLE4901 compared to placebo during the 28-week Treatment Period in improving:
  - ovulation regularity
  - the Most Bothersome Symptom of PCOS
  - hormone levels (including testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), LH/FSH, estradiol, progesterone and anti-Müllerian hormone (AMH))
  - clinical signs of hyperandrogenism (hirsutism, acne and alopecia)
  - metabolic syndrome-related parameters (including fasting glucose, insulin, lipid panel, blood pressure and body mass index (BMI))
- To determine the durability of MLE4901 effects during the 8-week Follow-up Period
- To explore the impact of MLE4901 on measures of health-related quality of life and work productivity
- To assess the safety and tolerability of MLE4901
- To determine the pharmacokinetic (PK) parameters of MLE4901 and its major metabolite
- To evaluate the PK/PD relationships of MLE4901

Methodology:

This is a Phase 2b double-blind, randomized, parallel-group, placebo-controlled study of MLE4901 versus placebo in women with PCOS. Following a Screening/Wash-out Period of up to 12 weeks, an 8-week Lead-in Period (starting with a progestin challenge) will be used to better characterize the study population. A Treatment Period of 28 weeks' duration will follow the Lead-in Period. Then, an 8-week Follow-up Period (i.e., no study drug) will be used to assess the durability of effects of MLE4901. The study duration will be approximately 48 weeks (11 months) per subject. A study schematic is shown in Figure 1 below. A detailed schedule of study assessments is presented in Appendix 1.

The Screening Visit will assess the subjects' preliminary eligibility for the study based on the inclusion and exclusion criteria. In addition, pertinent information will be collected such as past medical history, demographic data and prior and current medications. The Screening Visit will also assess laboratory tests as part of study eligibility. If needed, subjects will undergo a wash-out of medications used to treat symptoms of PCOS. Subjects who meet all of the inclusion criteria and none of the exclusion criteria that are assessable

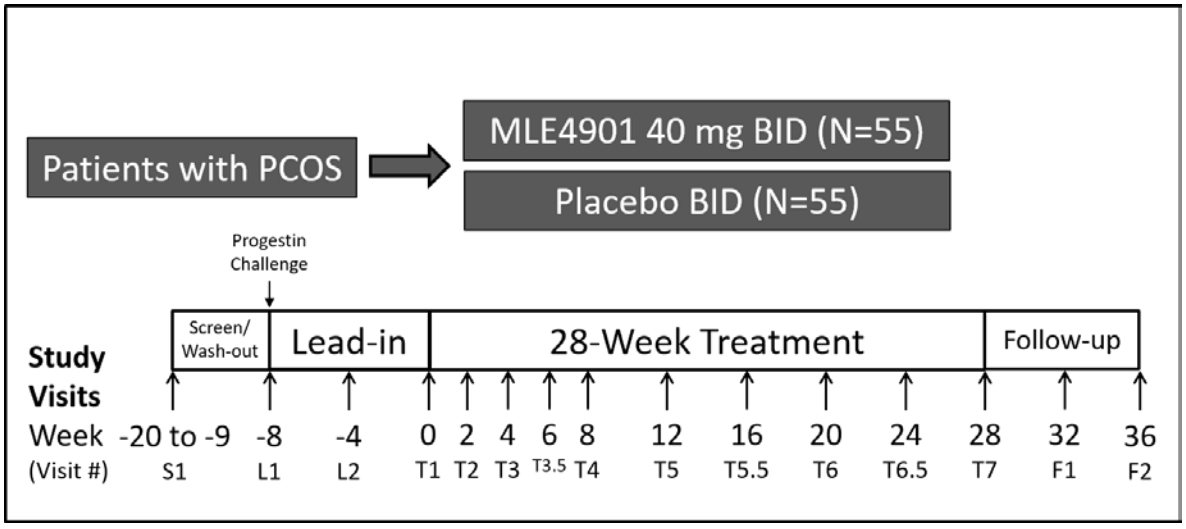
during Screening will undergo a transvaginal ultrasound and enter into the Lead-in Period. Note: Subjects do not need to wait for Screening/Wash-out hormone results prior to proceeding with the TVU and the Lead-in Period.

The Lead-in Period will last for 8 weeks, with visits every 4 weeks. At the beginning of the Lead-in Period, all subjects will undergo a progestin challenge with medroxyprogesterone acetate (MPA) 10 mg orally daily (QD) for 5 days. During the Lead-in Period, subjects will use an electronic self-reported daily diary to report menstrual bleeding. In addition, ovulation status will be assessed by having subjects collect urine for pregnenediol-3-glucuronide three times per week. Instructions on proper use of the diary and collection of urine samples will be provided at the study site. Continued study eligibility (including frequency of menstrual periods) will be assessed during the Lead-in Period, prior to randomization into the Treatment Period.

Eligible subjects will enter the 28-week Treatment Period. At Visit T1, additional information will be obtained to further characterize each subject's baseline status (e.g., Most Bothersome Symptom associated with PCOS, Polycystic Ovary Syndrome Questionnaire (PCOSQ) domain scores, PCOS Acne Questionnaire, EQ-5D-5L™ score, Patient Health Questionnaire-4 (PHQ-4) score, Work Productivity and Activity Impairment: General Health (WPAI:GH) domain scores, Ferriman-Gallwey score, Investigator's Static Global Assessment (ISGA) of acne, Savin score, laboratory tests, etc.). Subjects will be stratified by frequency of self-reported menstrual periods (<4/year vs 4-6/year) and by baseline BMI (22 to <35 kg/m^2 vs 35 to 45 kg/m^2) and randomized 1:1 into one of two study arms: MLE4901 40 mg twice daily (BID) or placebo BID. All tablets used in the study will be identical in appearance to maintain double-blind status. Study drug will be administered orally beginning on Day 1 of the Treatment Period. The first dose of study drug will be given at the study site. During the Treatment Period, subjects will continue to self-report menstrual bleeding and collect thrice-weekly urine samples for assessment of ovulation status. Additional study visits will take place 2, 4, 6, 8, 12, 16, 20, 24 and 28 weeks after initiation of study drug.

An 8-week Follow-up Period will occur immediately after the Treatment Period, with visits every 4 weeks. No study drug will be administered during this period. However, subjects will continue to self-report menstrual bleeding and collect thrice-weekly urine samples for assessment of ovulation status. This period will be used to assess the durability of effects of MLE4901.

Figure 1: Study Schematic



Number of Subjects (planned):

Approximately 110 women with PCOS and oligo-/amenorrhea with hyperandrogenism (clinical or biochemical) and/or polycystic ovaries

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Provision of signed and dated informed consent prior to any study-specific procedures
2. Women 18 to 45 years of age (inclusive) at Screening
3. Oligo-/amenorrhea defined as ≤6 menstrual cycles per year off of any hormone therapy (may be based on subject historical recall)
4. At least one of the following during Screening:
   - Clinical signs of hyperandrogenism, where clinical hyperandrogenism may include hirsutism (defined as excessive terminal hair that appears in a male pattern), acne, or androgenic alopecia
   - Biochemical hyperandrogenism refers to an elevated serum androgen level (i.e., total, bioavailable or free testosterone level ≥ULN)
   - Polycystic ovarian morphology, defined as the presence of 12 or more follicles 2-9 mm in diameter and/or an increased ovarian volume >10 mL (without a cyst or dominant follicle) in either ovary
5. Body mass index (BMI) 22 to 45 kg/m^2, inclusive
6. Must be willing to avoid use of all hair removal procedures (e.g., electrolysis, laser hair removal, plucking/tweezing, waxing, threading, etc.) and products (e.g., Vaniqa®, Nair™, etc.) during study participation in the areas of the scalp, upper lip, chin, chest, back, abdomen, upper arms and thighs
   Note: Shaving is allowed; however, subjects must not shave within 72 hours prior to visits S1, T1 and T7 to permit assessment of hair growth
7. Must be willing to avoid all prescription treatments for acne and not increase the dose or frequency of their current non-prescription acne treatment regimen during study participation
8. Must be willing to avoid the use of all hair growth procedures (e.g., hair transplant) and products (e.g., minoxidil (Rogaine®)) during study participation
9. Must be willing to avoid the use of all of the other prohibited medications (including metformin, oral contraceptives, clomiphene, letrozole, spironolactone, finasteride and flutamide) and procedures during study participation (Sections 5.12, 5.13 and 5.14)
10. Permanently surgically sterilized (bilateral salpingectomy or tubal occlusion) >2 years **or** male partner(s) has had a vasectomy >2 years **or** must consent to use two permitted medically-acceptable methods of contraception throughout the study during any sexual intercourse with a male partner. Permitted medically-acceptable methods of birth control for this study are defined as use of a male condom plus one of the following: spermicide, diaphragm with spermicide, or an intrauterine device that does not contain steroid hormones.
11. Must agree to not attempt to conceive during participation in the study

Exclusion Criteria:

1. Menopausal or peri-menopausal, defined for this study as FSH >10 IU/L
2. Irregular vaginal/menstrual bleeding caused by conditions other than PCOS (e.g., uterine polyps or submucosal uterine fibroids)
3. For women ≥21 years of age, abnormal Papanicolaou (Pap) test during Screening requiring follow-up sooner than 1 year after the test (Notes: Results from a Pap test performed within 1 year prior to Screening may be used. Women under 21 years of age at Screening do not require a Pap.)
4. Uncontrolled hypo- or hyperthyroidism, defined as having an abnormal TSH during Screening or Lead-in and/or change in thyroid medication dose within the month prior to Screening
5. Any suspected cause of hirsutism, acne, or alopecia other than PCOS
6. Post-hysterectomy or endometrial ablation
7. Post-oophorectomy (unilateral or bilateral) or other ovarian surgery
8. No menstrual periods during Lead-in (i.e., failed progestin challenge)
9. Two or more menstrual periods during Lead-in
10. Use of any of the following medications within 28 days prior to the wash-out visit (for those requiring wash-out; See Section 5.12 for additional prohibited medications):
    - Metformin or other insulin-sensitizing medications (e.g., rosiglitazone, pioglitazone, etc.)
    - Hormonal contraceptives (e.g., birth control pills, hormone-releasing implants, etc. Depo-Provera needs to be washed out for 16 weeks.)
    - Hormone-releasing intrauterine device
    - Anti-androgens (e.g., spironolactone, flutamide, finasteride, etc.)

- Clomiphene citrate or estrogen modulators such as letrozole
- GnRH modulators such as leuprolide

Note: Women who received every-3-month progestin challenge and no other hormonal therapy during the year prior to Screening and who did not have any menstrual bleeding other than that due to withdrawal from progestin challenge may be randomized (if they meet all other inclusion/exclusion criteria) into the <4 menstrual cycles per year stratum.

11. Medical requirement for any of the prohibited concomitant medications
12. Medical history of type 1 or type 2 diabetes mellitus
13. Uncontrolled hypertension, defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥90 mmHg
14. Any history of gastric or small intestinal surgery or any current disease that causes malabsorption
15. Alcohol or substance abuse (cocaine, amphetamines and/or opioids) within the year prior to Screening
16. Abnormal laboratory values as per the guidelines listed below or any other clinically significant, unexplained laboratory abnormality according to the Investigator:
    - ALT or AST >2 times ULN
    - Total bilirubin >1.5 times ULN
    - Creatinine >1.5 times ULN
    - Fasting glucose >126 mg/dL (6.99 mmol/L)
    - Hemoglobin A1c >6.5%
    - Prolactin >ULN
    - 17-hydroxyprogesterone >200 ng/dL (6 nmol/L)
    - Total testosterone >150 ng/dL (5.21 nmol/L)
    - DHEA-S >800 µg/dL (21.6 µmol/L)
    - TSH >ULN or <LLN
17. Currently pregnant or breastfeeding or having conceived or given birth within the 3 months prior to Screening
18. QTc >470 msec on electrocardiogram at Screening or at Visit T1 (subjects with a single QTc >470 msec may have 2 additional ECGs taken and the QTcs averaged; if the average QTc is >470 msec then the subject is excluded)
19. History of Gilbert's syndrome or autoimmune hepatitis
20. HIV, hepatitis B, or hepatitis C positivity
21. Any malignancy within the previous 10 years, other than curatively resected basal or squamous cell skin cancer
22. Previous receipt of any amount of MLE4901, AZD4901 or AZD2624
23. Participation in any study of an investigational drug or device or investigational biological agent within 30 days (or 5 half-lives of the investigational agent, whichever is longer) prior to Screening
24. Any other medical or psychiatric condition (e.g., uncontrolled sleep apnea, severe depression, etc.) that, in the opinion of the Investigator, is likely to confound the interpretation of the study results or prevent the subject from understanding the requirements of or successfully completing the study

Investigational Product, Dosage and Mode of Administration:

MLE4901 40 mg tablets for oral administration, twice per day.

Duration of Treatment:

Approximately 28 weeks

Reference Therapy, Dosage and Mode of Administration:

Placebo matching tablets for oral administration, twice per day.

Study Endpoints:

Primary Efficacy Endpoint:

- The change in the duration of menstrual cycles from Baseline to End-of-Treatment (EoT).

Note: The Baseline menstrual cycle duration will be measured as the time from the start of the first menstrual period after the progestin challenge to the start of the next consecutive menstrual period. The EoT menstrual cycle duration will be the duration between the last two menstrual period start dates during the Treatment Period.

Key Secondary Efficacy Endpoint:

- The number of menstrual periods during the Treatment Period

Additional Efficacy Endpoints:

- The duration of menstrual cycles over the Treatment Period
- The change from Baseline in the duration of each menstrual cycle over the Treatment Period
- The change in the ovulation interval from Baseline to EoT
- The number of ovulations during the Treatment Period
- The duration of ovulation intervals over the Treatment Period
- The change from Baseline in the ovulation interval for each ovulation over the Treatment Period
- The time from the start of the last menstrual period prior to randomization to the first menstrual period after randomization
- The time to the first normal menstrual cycle duration
- The number of consecutive menstrual cycles of 21-35 days' duration over the Treatment Period
- The time from the last ovulation prior to randomization (or first dose of MPA, if no ovulation during Lead-in) to the first ovulation after randomization
- The time to the first normal ovulation interval
- The number of consecutive ovulation intervals of 21-35 days' duration over the Treatment Period
- The proportion of subjects with at least 4 self-reported menstrual periods over the Treatment Period
- The proportion of subjects having menstrual cycles of 21-35 days' duration for a continuous 6-month period during the Treatment Period
- The proportion of subjects having menstrual bleeding of 2-7 days' duration for a continuous 6-month period during the Treatment Period
- The proportion of subjects with normal menstrual cycles for a continuous 6-month period during the Treatment Period
- The change from Baseline in the severity of the subjects' self-identified Most Bothersome Symptom of PCOS
- The change from Baseline in the severity of each symptom of PCOS (oligo-/amenorrhea, hirsutism, acne and alopecia)
- The change from Baseline in testosterone (total, free and bioavailable), LH, FSH, LH/FSH, estradiol, progesterone and AMH
- The change from Baseline in the modified Ferriman-Gallwey score for hirsutism
- The change from Baseline in the Investigator's Static Global Assessment of acne score
- The change from Baseline in the Savin score for androgenic alopecia
- The change from Baseline in fasting glucose, insulin, total cholesterol, LDL, HDL and triglycerides
- The change from Baseline in systolic blood pressure, diastolic blood pressure and body mass index
- The duration of menstrual cycles over the Follow-up Period
- The duration of ovulation intervals over the Follow-up Period
- The change from Baseline in the frequency of removal of unwanted hair from the upper lip and chin
- The change from Baseline in the domain scores on the PCOSQ and the PCOS Acne Questionnaire
- The change from Baseline in the score on the EQ-5D-5L health state survey
- The change from Baseline in the domain scores on the Work Productivity and Activity Impairment: General Health Questionnaire (WPAI:GH)

- The change from Baseline in the mean total score, anxiety subscale score and depression subscale score on the PHQ-4

Safety Endpoints: Safety endpoints will include the incidence of treatment-emergent adverse events and serious adverse events, as well as changes from baseline in clinical laboratory tests, vital signs, physical examinations and ECG parameters.

Pharmacokinetic Endpoints:

- The C_{max}, T_{max}, AUC, $t_{1/2}$ and other PK parameters of MLE4901 and its major metabolite (as appropriate and as the data allow)
- The relationship between C_{max} and AUC vs. the change in the duration of menstrual cycles from Baseline to EoT; other PK/PD relationships may be explored as appropriate and as data allow

Statistical Methods:

A Statistical Analysis Plan that includes a more technical and detailed description of the planned statistical analyses will be prepared prior to study unblinding.

Populations:

Efficacy – The primary efficacy analyses will include all randomized subjects (Intent-to-Treat; ITT). For efficacy analyses, subjects will be included in the treatment group to which they were randomized. Additional efficacy analyses will be performed on all subjects who complete at least 16 weeks of treatment (Evaluable Population).

Safety – The Safety Population will include all treated subjects. Safety analyses will be based on the Safety Population. For the safety analyses, subjects randomized to the placebo group who receive MLE4901 will be included in the treatment group of the study drug that they received.

Pharmacokinetic – The PK Population will include all subjects with measurable drug concentrations. PK analyses will be based on the PK Population.

Sample size considerations:

Assuming a study dropout rate of approximately 10-20%, a total of 110 subjects will be randomized in the study so that each dose group will have 50 subjects at a 1:1 allocation.

Sample size considerations were based on a multiple comparison Dunnett intersection test and a 1-sided alpha of 0.025. The standard deviation of change in days between start of menstruation was assumed to be 15 days. If the mean change in days between onset of menstruation was assumed to be 0 for the placebo group and 10 days for at least one active dose group, the study has a power of approximately 80-90% as demonstrated in simulations.

Analysis Methodology:

Primary endpoint – The change in the duration of menstrual cycles from Baseline to EoT will be analyzed with an ANOVA model including treatment and stratification factors following the Dunnett intersection test procedure to control for multiple comparison testing. Should the primary endpoint distribution depart from an approximate normal distribution, an appropriate non-parametric test will be utilized such as the Wilcoxon rank-sum test.

Key secondary endpoint – The number of menstrual periods during the Treatment Period will be analyzed with an ANOVA model including treatment and stratification factors following the Dunnett intersection test procedure to control for multiple comparison testing. Should this key secondary endpoint distribution depart from an approximate normal distribution, an appropriate non-parametric test will be utilized such as the Wilcoxon rank-sum test.

Additional efficacy endpoints – No further adjustments for multiple group comparisons, multiple additional endpoints or multiple subgroups of interest are planned.

The ovulation interval duration will be analyzed in a similar manner as the menstrual cycle duration, with the exception that the analysis of this endpoint will utilize an ANOVA, instead of an ANCOVA model. Other continuous endpoints will utilize similar ANCOVA or ANOVA model methodology, as appropriate. Responder analyses and other categorical analyses will be based on the Cochran-Mantel-Haenszel (CMH) test or Fisher's exact test, as appropriate. Time-to-event endpoints will be summarized using Kaplan-Meier estimates and compared using the log-rank test.

Exploratory endpoints – Additional efficacy endpoints will be pre-specified in the Statistical Analysis Plan, including sensitivity analyses associated with drug compliance and missing data issues.

Safety endpoints – Adverse events counts (overall, as well as by severity, causality and seriousness) will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Descriptive statistics and shift tables will be used to summarize continuous laboratory parameters. Counts and shift tables will be used for categorical lab parameters.

PK endpoints – Individual PK parameters will be derived using the WinNonlin software and table summaries will be provided using descriptive summary statistics.

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Table 1: Abbreviations

Abbreviation	Explanation
17-OHP	17-hydroxyprogesterone
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AMH	anti-Müllerian hormone
AST	aspartate aminotransferase
aPTT	activated partial thromboplastin time
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration-time curve
AUC_{0-4h}	area under the plasma concentration-time curve from time zero to 4 hours postdose
AUC_{0-4h}/D	dose-normalized AUC_{0-4h}
AUC_{0-8h}	area under the plasma concentration-time curve from time zero to 8 hours postdose
AUC_{0-24h}	area under the plasma concentration-time curve from time zero to 24 hours postdose
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve up to the last quantifiable concentration time point (t)
$AUC_{\%extrap}$	the percentage of $AUC_{0-\infty}$ extrapolated
βhCG	beta human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BUN	blood urea nitrogen
C_{avg}	average concentration
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CL	clearance
CL/F	oral clearance calculated as dose/$AUC_{0-\infty}$
C_{last}	last quantifiable plasma concentration
C_{max}	maximum observed plasma concentration
C_{max}/D	dose-normalized C_{max}
CMH	Cochran-Mantel-Haenszel
CQA	clinical quality assurance
CRA	clinical research associate
CRO	clinical research organization
CSR	clinical study report
CYP	cytochrome P450

Abbreviation	Explanation
DBP	diastolic blood pressure
DHEA-S	dehydroepiandrosterone sulfate
DSMB	Data Safety Monitoring Board
E2	estradiol
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EoS	End-of-Study
EoT	End-of-Treatment
ET	Early Termination
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels Survey
FSH	follicle-stimulating hormone
FT	free testosterone
GCP	Good Clinical Practices
GnRH	gonadotropin-releasing hormone
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose and throat
hERG	human ether-à-go-go-related gene
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HPG	hypothalamic-pituitary-gonadal
HRQ	Hair Removal Questionnaire
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ISGA	Investigator's Static Global Assessment (of acne)
ITT	intent-to-treat
IRB	institutional review board
IWRS	interactive web response system
KNDy	kisspeptin-neurokinin-dynorphin neuron system
λz	plasma terminal phase rate constant
LDL	low density lipoprotein
LFTs	liver function tests
LH	luteinizing hormone
LLN	lower limit of normal
MBSQ	PCOS Most Bothersome Symptom Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MPA	medroxyprogesterone acetate

Abbreviation	Explanation
NK3	neurokinin-3
NKB	neurokinin B
P	progesterone
Pap	Papanicolaou
PCOM	polycystic ovarian morphology
PCOS	polycystic ovary syndrome
PCOSQ	PCOS Questionnaire
PD	pharmacodynamic
PE	physical examination
PGIC	Patient's Global Impression of Change
PHQ-4	Patient's Health Questionnaire-4
PK	pharmacokinetic
PT	prothrombin time
QD	once daily
QT interval	the time from the start of the Q wave and the end of the T wave
QTc	corrected QT interval
QTcF	QT interval corrected using the Fridericia method
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvate transaminase
SHBG	sex hormone-binding globulin
SOC	system organ class
T	testosterone
$t_{1/2}$	terminal phase half-life
T4	thyroxine
TBD	to be determined
T_{max}	time of maximum plasma concentration
TMF	trial master file
TSH	thyroid-stimulating hormone
TT	total testosterone
TVU	transvaginal ultrasound
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

1. INTRODUCTION

1.1. Background

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women, affecting approximately 5% to 10% of women overall (March 2010). It is a heterogeneous disorder of which the principal clinical features are hyperandrogenism, disturbances of menstruation, infertility, metabolic derangement and polycystic ovaries. Patients exhibit excessive amounts or effects of androgenic hormones, resulting in acne, hirsutism and insulin resistance, often associated with obesity, type 2 diabetes mellitus and high cholesterol levels. The symptoms and severity of the syndrome vary greatly among affected women. Long-term risks in such patients include coronary artery disease and cerebrovascular disease, as well as the risk of unopposed estrogen and chronic anovulation: endometrial hyperplasia, dysfunctional uterine bleeding and possibly endometrial cancer.

Expression of the PCOS phenotype appears to be dependent on both genetic and environmental factors. Potential etiologies include ovarian hyperresponsiveness to LH and selective insulin resistance; reflecting the heterogeneity of the condition, linkage studies have shown possible associations with a wide variety of genes, ranging from those encoding proopiomelanocortin to steroidogenic enzymes to genes involved in regulation of cell growth. Polycystic ovary syndrome (PCOS) is known to be associated with gonadotropin releasing hormone (GnRH) hyperpulsatility along with increased luteinizing hormone (LH) pulse amplitude and pulse frequency. While gonadotropin-releasing hormone (GnRH) pulsatile release cannot be assessed directly in humans, it is believed that peripheral LH pulses are directly related to hypothalamic GnRH. In healthy premenopausal women, GnRH pulses occur approximately once every 90 to 100 minutes during the follicular stage, with a gradual increase in GnRH pulsatility at mid-cycle causing an LH surge and thus ovulation. In contrast, women with PCOS have GnRH pulses approximately once every 60 minutes. This results in an excess of pituitary LH secretion and frequently a lack of an LH surge, leading to failure of ovulation. In addition, the excess LH results in increased ovarian testosterone production (Clarke 1982, Hall 1998, Knobil 2006, Levine 1982, Waldstreicher 1988).

The symptoms usually related to PCOS, including menstrual irregularities, hirsutism, anovulation and acne, can lead to a significant decrease in quality of life, mood disorders including depression, marital and social maladjustment and sexual dysfunction (Bazarganipour 2015, Barnard 2007). Self-ratings of hirsutism have been shown to be significantly associated with depression ($r=0.14$, $p<0.05$) (Pasch 2016). Given that the population of women with PCOS is relatively young, since depression is a co-morbidity, PCOS could also impact work productivity and limit activities.

There are no treatments indicated specifically for PCOS as those available treat only the symptoms. Current symptom-based treatments for PCOS address the effects of the disease, e.g., spironolactone, cyproterone acetate and GnRH modulators as anti-androgen therapy; metformin for the metabolic derangement; oral contraceptives for normalization of menstruation; and the selective estrogen receptor modulator, clomiphene, to induce ovulation. All of these treatments address symptomatology but not pathophysiology and have significant side effects, such as menopausal-like adverse events, prevention of pregnancy, inducement of multiple/multi-fetal

pregnancies, ovarian hyperstimulation syndrome, gastrointestinal complaints, or lactic acidosis. None modify the underlying GnRH pulse generator to modify the disease.

The GnRH pulse generator is controlled by the kisspeptin-neurokinin-dynorphin (KNDy) neuron system. Kisspeptin and neurokinin have stimulatory effects on the GnRH pulse generator, while dynorphin has inhibitory effects (Maeda 2010). MLE4901 is a high-affinity NK3 receptor antagonist. In both clinical pharmacology studies in healthy volunteers and in a study of schizophrenia (mainly in men), a reduction in testosterone and to some degree LH, has been observed, suggesting that MLE4901 regulates pituitary LH and gonadal testosterone via modulation of GnRH pulsatility. Based on the clinical endocrine changes observed and an understanding of its mechanism of action, MLE4901 is now being evaluated for the treatment of PCOS. A treatment that could modulate the GnRH axis could potentially control the symptoms of PCOS and restore regular menses and ovulation.

1.1.1. Preclinical Studies

MLE4901 binds with high affinity to human NK3 receptors, with a dissociation constant of an inhibitor of 2 nM versus [^{125}I]His, MePhe7 NKB agonist. MLE4901 completely blocked agonist (senktide)-induced calcium flux in Chinese hamster ovary (CHO) cells stably expressing human NK3 receptors with a concentration of drug causing half-maximal inhibitory concentration (IC_{50}) of 2.57 nM. M12 (also referred to as AZ12592232), a metabolite of MLE4901, completely blocked agonist (senktide)-induced calcium flux in CHO cells stably expressing human NK3 receptors with an IC_{50} value of 9.05 nM.

The preclinical safety evaluation of MLE4901 includes repeat dose toxicity studies of up to 6 months in rats and 9 months in dogs, embryofetal development studies in rats and rabbits, an assessment of fertility in female rats and *in vitro* and *in vivo* genetic toxicology studies. MLE4901 was generally well tolerated following repeated oral administration of doses up to 2000 mg/kg/day in rats for up to 6 months, doses up to 1000 mg/kg/day in dogs for up to 3 months and doses up to 750 mg/kg/day in dogs for 9 months. At ~1000 times the clinical dose (rats) and ~70 times the clinical dose (dogs), reversible increases in liver weights occurred. This was found to be associated with diffuse hepatocellular hypertrophy and was judged to be an adaptive response. At 100 times the clinical dose, rats showed minimal epithelial hypertrophy of the thyroid gland along with changes in T4 and TSH. At 500 times the clinical dose (dogs), reversible increases in thyroid gland weights were observed with no histopathological correlates. Finally, at 100 times the clinical dose, a 25% inhibition of the human ether-à-go-go-related gene (hERG) channel was observed.

1.1.2. Clinical Studies

The early clinical program conducted with MLE4901 (previously referred to as AZD2624 and AZD4901) for the indication of schizophrenia was comprised of 2 single ascending dose studies (1 in Japanese volunteers) and 2 multiple ascending dose studies (1 in Japanese volunteers) in healthy male volunteers, a relative bioavailability study in healthy male and female volunteers and a Phase 2a study in patients with schizophrenia. One hundred and sixty subjects (6 of whom were women) received MLE4901 at doses ranging between 1 and 80 mg (single doses), 30 mg twice daily (BID) (multiple dose study), or for up to 28 days at 40 mg once daily (QD). Both suspension and tablets (20-mg strength) were utilized.

The early clinical program conducted with MLE4901 for the indication of polycystic ovary syndrome was comprised of a double-blinded, randomized, parallel-group Phase 2a study of 3 doses of MLE4901 (20 mg QD, 20 mg BID and 40 mg BID) and placebo for 28 days in 65 women with PCOS. 20-mg MLE4901 tablets were utilized.

Data obtained from the clinical studies to date did not identify any safety or tolerability concerns that preclude development of MLE4901 in patients with PCOS.

Pharmacokinetic (PK) properties have been well investigated in healthy male volunteers. MLE4901 was quickly absorbed following oral dosing. T_{max} was approximately 2 hours. The elimination half-life for MLE4901 was approximately 7 hours. Both the area under the concentration-time curve (AUC) and maximum observed concentration (C_{max}) appeared to be dose-proportional for both MLE4901 and its major metabolite, M12. Renal elimination of MLE4901 and M12 was negligible.

Following multiple dose administration, PK steady state was achieved within 4 days, at which the exposure to M12 was approximately 66% of the parent; the accumulation of MLE4901 in the plasma was minimal following QD dosing and was greater following BID dosing. MLE4901 PK appeared to be time-independent. Limited exposure observed in women suggests no difference in PK properties between women and men. Based on limited observations, oral administration of MLE4901 suspension or tablets with food (a high fat meal) increased the rate of absorption (suspension: 25% increase in C_{max}; tablet: 75% increase in C_{max}). To date, there has been no clear demonstration of C_{max}-related toxicity in humans receiving up to 80 mg of the suspension.

Cytochrome P450 (CYP) enzymes *CYP2C9*, *CYP3A4* and *CYP3A5 in vitro* appeared to be involved in the metabolism of MLE4901. MLE4901 exhibited a weak to moderate inhibitory effect on *CYP3A4/5* with an apparent IC_{50} of 7.1 and 19.8 μM in midazolam and testosterone assays, respectively. MLE4901 may also have the potential to induce *CYP3A4/5* enzymes. Clinical drug-drug interaction studies have not yet been performed.

MLE4901 Treatment of Patients with Schizophrenia

This was a double-blind, randomized, parallel-group, placebo-controlled, multicenter study conducted in adult subjects who were diagnosed with schizophrenia and were symptomatic at admission. A total of 106 subjects, 18 to 65 years of age, were randomized to treatment once daily for 28 days with MLE4901 40 mg (N=43; 40 male and 3 female), placebo (N=41; 39 male and 2 female), or olanzapine 15 mg (N=22; all male). Eighty-one subjects completed treatment. MLE4901 was administered in the morning as an oral suspension in an oral suspending vehicle.

A comparison of baseline to end-of-treatment (EoT) values of total testosterone revealed that 6 subjects in the MLE4901 group, 3 subjects in the olanzapine group and 2 subjects in the placebo group had shifted from normal testosterone at baseline to low testosterone below the normal range. The decrease was greater in the MLE4901 and olanzapine groups. Two male subjects in the MLE4901 treatment group had total testosterone values less than 150 ng/dL; no male subjects in either the olanzapine or placebo groups had testosterone values less than 150 ng/dL. No female subjects in the study had total testosterone values below the normal range of 20 to 76 ng/dL.

A total of 6 SAEs were reported in this study population of adult patients with symptomatic schizophrenia at admission. All SAEs were reported as psychotic disorder; 4 events were in the

MLE4901 group (9%; all moderate intensity) and 2 events were in the placebo group (5%; 1 moderate and 1 severe intensity). Discontinuations due to an AE with onset during treatment occurred in both the MLE4901 and placebo groups. Psychotic disorder led to the discontinuation of 3 (7.0%) subjects in the MLE4901 group and 2 (5%) subjects in the placebo group. There were no other significant AEs reported in the study. The overall incidence of AEs was highest in the olanzapine group (82%), followed by the MLE4901 and placebo groups (67% and 66%, respectively). Most AEs were mild to moderate in severity. The most common AEs reported in patients with schizophrenia administered MLE4901 were headache, vomiting, nausea, psychotic disorder (i.e., failure of efficacy as MLE4901 did not differentiate from placebo in this study), sedation, decreased appetite, somnolence and stomach discomfort.

MLE4901 Treatment of Women with PCOS

This was a double-blind, randomized, parallel-group, placebo-controlled Phase 2a study that assessed the effects of MLE4901 in women with PCOS. The study's 28-day treatment and intensive blood sampling regimen (baseline, Day 7 and Day 28) were designed to evaluate the onset of action of MLE4901 and to provide preliminary information concerning the durability of those effects with daily administration of MLE4901 (20 mg QD, 20 mg BID and 40 mg BID) and placebo. A total of 67 women diagnosed with PCOS were randomized into the study across 9 study sites. Of the 65 subjects who received the investigational product, 49 subjects were randomized to receive MLE4901 and 16 to receive placebo.

The study showed that MLE4901 at the 40 mg BID dose decreased LH and free testosterone levels and reduced LH pulse frequency, as follows:

- LH: mean $AUC_{0\text{-}8h}$ fell by ~52% (95% CI, 32.73 to 70.36%) between baseline and Day 7 in subjects treated with the highest tested dose of MLE4901 (40 mg BID) compared to placebo. Less marked reductions were also observed at the lower tested doses, but their 90% CIs did not conclusively demonstrate a reduction compared to placebo. Post-hoc subset analysis of subjects lacking strong biochemical evidence of recent ovulation (progesterone <6 ng/mL throughout the study) further revealed marked reduction of LH $AUC_{0\text{-}8}$ on Day 28 of treatment (95% CI, 45.43 to 93.38%).
- Free testosterone: mean $AUC_{0\text{-}8h}$ decreased between baseline and Day 7 by 19% (90% CI, 67.75 to 96.59%) in subjects treated with the highest tested dose of MLE4901 (40 mg BID) compared to placebo. Free testosterone also remained lower on Day 28 in this group (16% from baseline versus placebo), but its 90% CI (69.60, 100.38%) did not conclusively establish a reduction compared to placebo. Similar results were obtained for C_{avg}. Post-hoc subset analysis of subjects lacking strong biochemical evidence of recent ovulation (progesterone <6 ng/mL throughout the study) clearly showed a reduction of free testosterone $AUC_{0\text{-}8h}$ on Day 7 and Day 28 (~23%) of treatment with the highest dose of MLE4901 in comparison to subjects receiving placebo (90% CI: 66.10 to 90.49% for Day 7 and 64.95 to 90.04% for Day 28). For the subset analysis of C_{avg}, similar results were obtained.
- LH pulsatility: a reduction by 3.55 pulses/8 hours (90% CI: -4.85 to -2.25; 95% CI: -5.10, to -2.00] on Day 7 was observed in subjects receiving the highest dose of MLE4901 (40 mg BID) compared to placebo. This decrease was less pronounced in subjects receiving lower drug doses, where the 90% CI did not clearly establish a

reduction. At Day 28, a reduction in pulse frequency (decrease by 1.19 pulses/8 hours) was still apparent at the highest dose, but was not conclusively (90% CI: -2.58 to 0.19) different from placebo. Determination of mean differences in LH pulse number in subjects lacking clear biochemical evidence of ovulation (progesterone <6 ng/mL) more plainly demonstrated a reduction at both 7 (decrease by 3.90 pulses/8 hours) and 28 days (decrease by 1.89 pulses/8 hours) [90% CI, -5.14 to -2.66 on Day 7 and -3.22 to -0.56 on Day 28].

The underlying mechanism of action predicted for NK3 pathway blockade was confirmed, with MLE4901 decreasing LH pulsatility. Lower doses of MLE4901 showed less marked changes from placebo.

The safety profile of multiple-dose administration of MLE4901 in female patients with PCOS in this study did not raise any safety concerns. Of the 49 subjects who received MLE4901, 32 subjects (65.3%) reported at least 1 AE during the study, compared to 50.0% of subjects who received placebo. Adverse events by system organ class are shown in Table 2.

Table 2: Number (%) of Subjects Who Had at least 1 Adverse Event, by System Organ Class (Safety Analysis Set)

	Number (%) of Subjects				
		MLE4901			
System Organ Class:	**Placebo (N=16)**	**20 mg QD (N=15)**	**20 mg BID (N=17)**	**40 mg BID (N=17)**	**Total MLE4901 (N=49)**
Subjects with any AE	8 (50.0%)	8 (53.3%)	14 (82.4%)	10 (58.8%)	32 (65.3%)
Nervous System Disorders	5 (31.3%)	3 (20.0%)	5 (29.4%)	5 (29.4%)	13 (26.5%)
Gastrointestinal Disorders	1 (6.3%)	4 (26.7%)	4 (23.5%)	1 (5.9%)	9 (18.4%)
Infections and Infestations	2 (12.5%)	4 (26.7%)	3 (17.6%)	1 (5.9%)	8 (16.3%)
Skin and Subcutaneous Tissue Disorders	0 (0.0%)	0 (0.0%)	3 (17.6%)	1 (5.9%)	4 (8.2%)
General Disorders and Administration Site Conditions	1 (6.3%)	0 (0.0%)	1 (5.9%)	2 (11.8%)	3 (6.1%)
Injury, Poisoning and Procedural Complications	0 (0.0%)	1 (6.7%)	2 (11.8%)	0 (0.0%)	3 (6.1%)
Investigations	0 (0.0%)	2 (13.3%)	0 (0.0%)	1 (5.9%)	3 (6.1%)
Reproductive System and Breast Disorders	2 (12.5%)	1 (6.7%)	1 (5.9%)	0 (0.0%)	2 (4.1%)
Musculoskeletal and Connective Tissue Disorders	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (5.9%)	2 (4.1%)
Respiratory, Thoracic and Mediastinal Disorders	0 (0.0%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	2 (4.1%)
Ear and Labyrinth Disorders	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (2.0%)
Eye Disorders	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (2.0%)

	Number (%) of Subjects				
Renal and Urinary Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (2.0%)
Vascular Disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (2.0%)

AE: Adverse event; MedDRA: Medical Dictionary for Regulatory Activities; N: Number of subjects; PT: Preferred Term; SOC: System Organ Class

Number (%) of subjects with AEs, sorted by SOC in decreasing order of frequency (sorted by total number on MLE4901). A subject could have had 1 or more PTs reported under a given SOC. MedDRA version 16.1.

The most commonly reported AEs in the MLE4901 treatment groups in the study were in the system organ classes (SOCs) of nervous system disorders, gastrointestinal disorders and infections and infestations. Headache was the most commonly reported AE in both of the MLE4901 and the placebo treatment groups (18.4% and 31.3%, respectively). Most of the AEs observed in this study were mild in intensity, resolved by the end of the study and were deemed by the Investigators unrelated to MLE4901.

Additional information may be found in the Investigator's Brochure.

1.2. Research Hypothesis

The study will evaluate the hypothesis that treatment with MLE4901 will result in improvements in symptoms associated with PCOS such as menstrual irregularity, hirsutism, acne and alopecia.

1.3. Rationale for Conducting This Study

The use of MLE4901 in PCOS is based on established literature on the hypothalamic kisspeptin, neurokinin B and dynorphin (KNDy) neurons. An NK3 receptor antagonist, MLE4901 is expected to decrease LH hyperpulsatility via modulation of GnRH, thereby improving symptoms associated with PCOS. *In vitro* and *in vivo* data indicate that NKB, the ligand for the NK3 receptor, is 1 of 3 generators of GnRH pulsatility (Lehman 2010, Maeda 2010).

In the previous Phase 2a schizophrenia study, conducted primarily in men, MLE4901 did not meet the psychiatric endpoints, but was associated with decreases in testosterone. It was hypothesized that this was due to blockade of the effect of NKB through NK3 receptor antagonism, decreasing GnRH pulse activity, with the consequent observed effects on LH and downstream gonadal hormones. In patients with PCOS, the clinical effect of MLE4901 would be to reduce the 'over-activity' of the GnRH pulse generator in patients with PCOS, thereby normalizing the hormonal axis.

Based on these results, the 28-day Phase 2a study in PCOS was conducted. In this study, MLE4901 at doses of 40 mg BID showed decreases in testosterone, LH and LH pulsatility after 7 and 28 days of treatment, establishing proof-of-mechanism. Lower doses of MLE4901 showed lesser effects on testosterone and LH.

The current study, with a 28-week Treatment Period and an 8-week Follow-up Period, will be conducted to evaluate the efficacy of MLE4901 in improving symptoms of PCOS such as menstrual irregularity, hirsutism, acne and alopecia.

1.4. Benefit/Risk and Ethical Assessment

In preclinical and clinical studies to date, MLE4901 has been well tolerated. At very high doses, preclinical data indicate potential adaptive change effects on the liver and thyroid, as well as on QT interval prolongation. However, these effects occurred at 70-1000 times the clinical dose. None of these effects have been observed in the clinical program to date; and subjects' liver function tests (LFTs), ECGs and TSH will be monitored during the study.

As a disease of premenopausal women, the subjects in the study are necessarily of childbearing potential, although PCOS often impairs fertility. Subjects will be required to use reliable contraception throughout the study and must not seek to become pregnant while participating. Hormonal contraception is disallowed as it could impact the primary efficacy measurements.

Polycystic ovary syndrome can result in disruption of menstruation, infertility, virilization, and, in the longer term, serious metabolic consequences. Treatments are available, but only suppress symptoms of PCOS with variable effectiveness and do not address the underlying pathophysiology. MLE4901 addresses the underlying biology of PCOS and the previous 28-day study of MLE4901 demonstrated improvements in LH pulse frequency and decreases in androgen levels. The dose of MLE4901 to be tested in the current study will be 40 mg BID, the efficacious dose in the previous Phase 2a study. Notably, the highest dose of 40 mg BID is 140-2000 times less than the doses tolerated in the long-term rat and dog toxicity studies, providing for a significant margin of safety. The current study will help to determine the efficacy of MLE4901 in ameliorating symptoms of PCOS. Based on the currently available data, the benefit:risk is reasonable and administration of MLE4901 to additional women with PCOS is justified.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To evaluate the efficacy of MLE4901 compared to placebo in improving menstrual regularity in women with oligo-/amenorrhea due to PCOS

2.2. Secondary Objectives

- To evaluate the efficacy of MLE4901 compared to placebo during the 28-week Treatment Period in improving:
  - ovulation regularity
  - the Most Bothersome Symptom of PCOS
  - hormone levels (including testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), LH/FSH, estradiol, progesterone and anti-Müllerian hormone (AMH))
  - clinical signs of hyperandrogenism (hirsutism, acne and alopecia)
  - metabolic syndrome-related parameters (including fasting glucose, insulin, lipid panel, blood pressure and body mass index (BMI))
- To determine the durability of MLE4901 effects during the 8-week Follow-up Period
- To explore the impact of MLE4901 on measures of health-related quality of life and work productivity
- To assess the safety and tolerability of MLE4901
- To determine the pharmacokinetic (PK) parameters of MLE4901 and its major metabolite
- To evaluate the PK/PD relationships of MLE4901

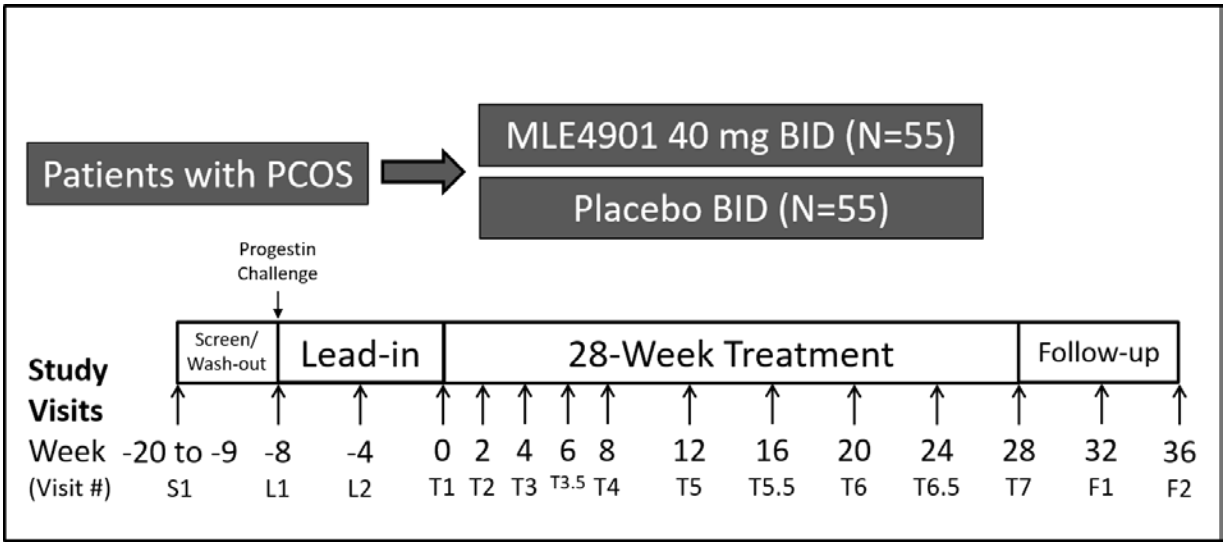
3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 2b double-blind, randomized, parallel-group, placebo-controlled study of MLE4901 versus placebo in women with PCOS. The study will be conducted at approximately 30 sites in the US.

Following a Screening Period of up to 12 weeks, an 8-week Lead-in Period (starting with a progestin challenge) will be used to better characterize the study population. A Treatment Period of 28 weeks' duration will follow the Lead-in Period. Then, an 8-week Follow-up Period (i.e., no study drug) will be used to assess the durability of effects of MLE4901. The study duration will be approximately 48 weeks (11 months) per subject. A schematic of the study design is presented in Figure 2. A detailed schedule of study assessments is presented in Appendix 1.

Figure 2: Study Schematic



3.1.1. Screening Period

The Screening Visit will assess the subjects' preliminary eligibility for the study based on the inclusion and exclusion criteria. In addition, pertinent information will be collected such as past medical history, demographic data and prior and current medications. The Screening Visit will also assess laboratory tests as part of study eligibility. If needed, subjects will undergo a wash-out of medications used to treat symptoms of PCOS. Subjects who meet all of the inclusion criteria and none of the exclusion criteria that are assessable during Screening will undergo a transvaginal ultrasound (TVU) and enter into the Lead-in Period. Note: Subjects do not need to wait for Screening/Wash-out hormone results prior to proceeding with the TVU and the Lead-in Period. All Screening/Wash-out hormone results should be reviewed and confirmed to be inclusionary prior to Randomization.

3.1.2. Lead-in Period

The Lead-in Period will last for 8 weeks, with visits every 4 weeks. At the beginning of the Lead-in Period, all subjects will undergo a progestin challenge with medroxyprogesterone

acetate (MPA) 10 mg orally QD for 5 days. During the Lead-in Period, subjects will use an electronic self-reported daily diary to report menstrual bleeding. In addition, ovulation status will be assessed by having subjects collect urine for pregnenediol-3-glucuronide three times per week. Instructions on proper use of the diary and collection of urine samples will be provided at the study site. Continued study eligibility (including frequency of menstrual periods) will be assessed during the Lead-in Period, prior to randomization into the Treatment Period.

3.1.3. Treatment Period

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria will enter the 28-week Treatment Period. At Visit T1, additional information will be obtained to further characterize each subject's baseline status (e.g., Most Bothersome Symptom associated with PCOS, Polycystic Ovary Syndrome Questionnaire (PCOSQ) domain scores, PCOS Acne Questionnaire, EQ-5D-5L score, Patient Health Questionnaire-4 (PHQ-4) score, Work Productivity and Activity Impairment: General Health (WPAI:GH) domain scores, Ferriman-Gallwey score, Investigator's Static Global Assessment (ISGA) of acne, Savin score, laboratory tests, etc.). Subjects will be stratified by frequency of self-reported menstrual periods (<4/year vs 4-6/year) and by baseline BMI (22 to <35 kg/m^2 vs 35 to 45 kg/m^2) and randomized 1:1 into one of two study arms: MLE4901 40 mg BID or placebo BID.

Note: for subjects not on any hormone therapy during the past year, the number of menstrual periods over the past year should be used for stratification. For subjects who were on hormone therapy such as oral contraceptive medications during the past year, the number of menstrual periods per year prior to commencing hormone therapy should be used for stratification. Women who received every-3-month progestin challenge and no other hormonal therapy during the year prior to Screening and who did not have any menstrual bleeding other than that due to withdrawal from progestin challenge may be randomized (if they meet all other inclusion/exclusion criteria) into the <4 menstrual cycles per year stratum.

All tablets used in the study will be identical in appearance to maintain double-blind status. Study drug will be administered orally beginning on Day 1 of the Treatment Period. The first dose of study drug will be given at the study site. During the Treatment Period, subjects will continue to self-report menstrual bleeding and collect thrice-weekly urine samples for assessment of ovulation status. Additional study visits will take place 2, 4, 6, 8, 12, 16, 20, 24 and 28 weeks after initiation of study drug to evaluate the subjects for changes in questionnaire responses; Investigator assessments of hirsutism, acne and alopecia; and hormone levels.

3.1.4. Follow-up Period

An 8-week Follow-up Period will occur immediately after the Treatment Period, with visits every 4 weeks. No study drug will be administered during this period. However, subjects will continue to self-report menstrual bleeding and collect thrice-weekly urine samples for assessment of ovulation status. This period will be used to assess the durability of effects of MLE4901.

Throughout the course of the study, safety evaluations will include assessment of AEs, concomitant medications, clinical laboratory tests, vital signs, physical examinations and 12-lead ECGs.

3.2. Rationale for Study Design and Dose Levels

MLE4901 is an NK3 receptor antagonist that has shown to decrease LH and testosterone levels in women with PCOS. This Phase 2b study will assess the ability of MLE4901 at various dose levels to restore regularity of menses and correct other symptoms of PCOS in women with oligo-/amenorrhea due to PCOS.

The study is randomized in order to minimize any bias in determining which subject receives which dose level of MLE4901 or placebo. The study is double blinded so there is no bias introduced by knowledge of the treatment identity received by a subject in reporting the clinical findings. Double blinding also minimizes the bias in assessing treatment response measures that could be introduced by the Investigators had they known the treatment identity. The study is placebo-controlled in order to have a comparison group to help determine whether safety findings during the study are related to the study drug and also to provide a true control rate for the assessment of efficacy. The 8-week Lead-in Period will allow establishment of baseline data on PCOS symptoms. Previous studies of various treatments for PCOS have been limited by their short term treatment duration. The 28-week Treatment Period will allow adequate time to determine the onset and consistency of changes in monthly menstrual cycles, PCOS symptoms, hormonal levels and quality of life. Stratification of randomized subjects as having <4 or 4-6 menstrual cycles/year and as having BMI 22 to <35 or 35 to 45 kg/m^2 is based on findings from a previous PCOS study (Azziz 2001) that demonstrated that subjects in the highest ovulatory rate tertile had a higher baseline menstrual period frequency (5.3 menses/year) than those in the lowest tertile (3.3 menses/year); also, the highest ovulatory rate tertile had a mean BMI of 33.3 kg/m^2 compared to 38.7 kg/m^2 for the lowest tertile. In addition, 4 menses/year is the benchmark for minimizing endometrial hyperplasia and risks associated with endometrial cancer.

Based on toxicity investigations in preclinical species, previous clinical observations in PK and PD responses, expected bioavailability, continuous suppression of testosterone and LH pulse frequency and safety demonstrated in a previous MLE4901 study in women with PCOS, the dose of 40 mg BID has been selected to evaluate the clinical effects of MLE4901 in women with PCOS.

3.3. Criteria for Study Termination

An unblinded Data Safety Monitoring Board (DSMB) will review pooled and individual subject data during the course of the study. In addition, a single occurrence of the following safety events will trigger an expedited, *ad hoc* DSMB meeting to review individual cases in an unblinded manner:

- Hepatic toxicity such as marked elevations in transaminases or simultaneous elevations in hepatic transaminases and bilirubin (i.e., Hy's Law)
- Severe renal impairment
- Severe cardiovascular dysfunction such as arrhythmia or valvular dysfunction

If the DSMB determines that the event is drug-related and a clear safety signal has been identified, early termination of the study may occur.

4. STUDY POPULATION SELECTION

4.1. Study Population

Approximately 110 subjects (55 per study arm) are planned to participate in this study. The subject population will consist of adult pre-menopausal women with oligo-amenorrhea who meet criteria for a diagnosis of PCOS by also having 1) clinical signs of hyperandrogenism and/or 2) biochemical hyperandrogenism and/or 3) polycystic ovaries on screening transvaginal ultrasound (TVU).

4.2. Inclusion Criteria

Each subject must meet all of the following criteria to be randomized into this study:

1. Provision of signed and dated informed consent prior to any study-specific procedures
2. Women 18 to 45 years of age (inclusive) at Screening
3. Oligo-/amenorrhea defined as ≤6 menstrual cycles per year off of any hormone therapy (may be based on subject historical recall)
4. At least one of the following during Screening:
   - Clinical signs of hyperandrogenism, where clinical hyperandrogenism may include hirsutism (defined as excessive terminal hair that appears in a male pattern), acne, or androgenic alopecia
   - Biochemical hyperandrogenism defined as an elevated serum androgen level (i.e., total, bioavailable or free testosterone level ≥ULN)
   - Polycystic ovarian morphology, defined as the presence of 12 or more follicles 2-9 mm in diameter and/or an increased ovarian volume >10 mL (without a cyst or dominant follicle) in either ovary
5. Body mass index (BMI) 22 to 45 kg/m^2, inclusive
6. Must be willing to avoid use of all hair removal procedures (e.g., electrolysis, laser hair removal, plucking/tweezing, waxing, threading, etc.) and products (e.g., Vaniqa®, Nair™, etc.) during study participation in the areas of the scalp, upper lip, chin, chest, back, abdomen, upper arms and thighs
   Note: Shaving is allowed; however, subjects must not shave within 72 hours prior to visits S1, T1 and T7 to permit assessment of hair growth
7. Must be willing to avoid all prescription treatments for acne and not increase the dose or frequency of their current non-prescription acne treatment regimen during study participation
8. Must be willing to avoid the use of all hair growth procedures (e.g., hair transplant) and products (e.g., minoxidil (Rogaine®)) during study participation
9. Must be willing to avoid the use of all of the other prohibited medications (including metformin, oral contraceptives, clomiphene, letrozole, spironolactone, finasteride and flutamide) and procedures during study participation (Sections 5.12 , 5.13 and 5.14)
10. Permanently surgically sterilized (bilateral salpingectomy or tubal occlusion) >2 years **or** male partner(s) has had a vasectomy >2 years **or** must consent to use two permitted medically-acceptable methods of contraception throughout the study during any sexual intercourse with a male partner. Permitted medically-acceptable methods of birth control for

this study are defined as use of a male condom plus one of the following: spermicide, diaphragm with spermicide, or an intrauterine device that does not contain steroid hormones.
11. Must agree to not attempt to conceive during participation in the study

4.3. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Menopausal or peri-menopausal, defined for this study as FSH >10 IU/L
2. Irregular vaginal/menstrual bleeding caused by conditions other than PCOS (e.g., uterine polyps or submucosal uterine fibroids)
3. For women ≥21 years of age, abnormal Papanicolaou (Pap) test during Screening requiring follow-up sooner than 1 year after the test (Notes: Results from a Pap test performed within 1 year prior to Screening may be used. Women under 21 years of age at Screening do not require a Pap.)
4. Uncontrolled hypo- or hyperthyroidism, defined as having an abnormal TSH during Screening or Lead-in and/or change in thyroid medication dose within the month prior to Screening
5. Any suspected cause of hirsutism, acne, or alopecia other than PCOS
6. Post-hysterectomy or endometrial ablation
7. Post-oophorectomy (unilateral or bilateral) or other ovarian surgery
8. No menstrual periods during Lead-in (i.e., failed progestin challenge)
9. Two or more menstrual periods during Lead-in
10. Use of any of the following medications within 28 days prior to the wash-out visit (for those requiring wash-out; see Section 5.12 for additional prohibited medications):
    - Metformin or other insulin-sensitizing medications (e.g., rosiglitazone, pioglitazone, etc.)
    - Hormonal contraceptives (e.g., birth control pills, hormone-releasing implants, etc. Depo-Provera needs to be washed out for 16 weeks.)
    - Hormone-releasing intrauterine device
    - Anti-androgens (e.g., spironolactone, flutamide, finasteride, etc.)
    - Clomiphene citrate or estrogen modulators such as letrozole
    - GnRH modulators such as leuprolide

    Note: Women who received every-3-month progestin challenge and no other hormonal therapy during the year prior to Screening and who did not have any menstrual bleeding other than that due to withdrawal from progestin challenge, may be randomized (if they meet all other inclusion/exclusion criteria) into the <4 menstrual cycles per year stratum.
11. Medical requirement for any of the prohibited concomitant medications
12. Medical history of type 1 or type 2 diabetes mellitus
13. Uncontrolled hypertension, defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥90 mmHg
14. Any history of gastric or small intestinal surgery or any current disease that causes malabsorption
15. Alcohol or substance abuse (cocaine, amphetamines and/or opioids) within the year prior to Screening
16. Abnormal laboratory values as per the guidelines listed below or any other clinically significant, unexplained laboratory abnormality according to the Investigator:
    - ALT or AST >2 times ULN

- Total bilirubin >1.5 times ULN
- Creatinine >1.5 times ULN
- Fasting glucose >126 mg/dL (6.99 mmol/L)
- Hemoglobin A1c >6.5%
- Prolactin >ULN
- 17-hydroxyprogesterone >200 ng/dL (6 nmol/L)
- Total testosterone >150 ng/dL (5.21 nmol/L)
- DHEA-S >800 µg/dL (21.6 µmol/L)
- TSH >ULN or <LLN

17. Currently pregnant or breastfeeding or having conceived or given birth within the 3 months prior to Screening
18. QTc >470 msec on electrocardiogram at Screening or at Visit T1 (subjects with a single QTc >470 msec may have 2 additional ECGs taken and the QTcs averaged; if the average QTc is >470 msec then the subject is excluded)
19. History of Gilbert's syndrome or autoimmune hepatitis
20. HIV, hepatitis B, or hepatitis C positivity
21. Any malignancy within the previous 10 years, other than curatively resected basal or squamous cell skin cancer
22. Previous receipt of any amount of MLE4901, AZD4901 or AZD2624
23. Participation in any study of an investigational drug or device or investigational biological agent within 30 days (or 5 half-lives of the investigational agent, whichever is longer) prior to Screening
24. Any other medical or psychiatric condition (e.g., uncontrolled sleep apnea, severe depression, etc.) that, in the opinion of the Investigator, is likely to confound the interpretation of the study results or prevent the subject from understanding the requirements of or successfully completing the study

5. STUDY TREATMENT

5.1. Assignment of Subject Identification Numbers

Once the subject has signed the ICF at Screening, site personnel will assign a subject identification number (ID). The subject ID will include the site number (3 digits) and 3 digit subject number, assigned sequentially starting with 001. This number will be utilized to identify the subject throughout the study period. Each subject ID will only be assigned to one subject, e.g., if a subject is withdrawn from the study early, their subject ID will not be used for a new subject.

5.2. Description of Study Drug

The drug product consists of a white, round, immediate release tablet of MLE4901 40 mg (free base) for oral administration. A placebo tablet has been developed to match the appearance of the active tablet in size, shape, color and weight.

Study drug will be supplied as 40 mg tablets that are identical in appearance to the placebo as described in Table 3.

Table 3: Investigational Product

	Investigational Product	
Product Name:	MLE4901	Placebo
Dosage Form:	tablet	tablet
Unit Dose	40 mg	0 mg
Route of Administration	Oral	Oral
Physical Description	Plain, round, biconvex, white film-coated tablets	Plain, round, biconvex, white film-coated tablets that appear identical to MLE4901 tablets
Manufacturer	Patheon	Patheon

Tests for identity, activity, purity and safety will be performed for the MLE4901 formulation. A certificate of analysis will be provided to the Sponsor prior to drug product shipment. For more information regarding the manufacturer and fill/finish, refer to the most recent version of the Investigator's Brochure.

5.3. Study Drug Packaging and Labeling

The formulation and bulk packaging of MLE4901 will be conducted according to standard procedures. The drug product will be packaged and labeled by Millendo Therapeutics, Inc.'s designated contract packager and labeled according to regulatory requirements.

5.4. Study Drug Storage and Accountability

Study drug must be kept in a secure location and stored at controlled room temperature at the study site within its original container and protected from light. A daily temperature log for monitoring of proper storage conditions must be maintained by the site.

Access to study drug must be restricted to designated study personnel only. Under no circumstances should the Investigator or other site personnel supply study product to other Investigators or clinics, or allow the supplies to be used other than as directed by this protocol without written authorization from Millendo Therapeutics, Inc. The Investigator (or designee) must maintain records of the delivery of the study drug to the study site, the inventory at the study site, use for each subject and return of the study drug to a designee of the Sponsor or destruction. Total study site accountability will be conducted at the end of the study and the Investigator must explain all discrepancies. A Site Drug Accountability Log will be supplied by Millendo Therapeutics, Inc. or designated CRO. This log must be kept current and will contain information such as:

- Identification (subject ID) of the subject to whom the study drug was dispensed
- The dates and lot numbers for the dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor. Additional details on the storage and handling of MLE4901 are provided in the Pharmacy Manual.

5.5. Medroxyprogesterone Acetate

Medroxyprogesterone acetate (MPA), 10 mg orally once per day for 5 days, will be used at the beginning of the Lead-in Period for the progestin challenge. MPA tablets must be kept in a secure location and stored at the study site under conditions consistent with the label for MPA. For further details, see the Pharmacy Manual.

5.6. Study Drug Administration

Subjects will be randomized to be treated with MLE4901 40 mg BID or placebo BID. Each treatment will consist of one tablet (MLE4901 40 mg or placebo) taken orally BID. Each study dose will be self-administered by the subject with a nonalcoholic beverage (except grapefruit juice). At each Treatment Period visit except T3.5, T5.5, T6.5, and T7, the morning study drug dose will be taken at the study site. Plasma for PK analysis will be drawn at Visits T1, T3, T5 and T7.

If a subject forgets to take a dose on a given day (e.g., the AM dose was not taken), a “make up” dose should not be taken. Study drug may be withheld if needed if, for example, the subject has a temporary medical need for a prohibited medication. The Investigator should discuss potential events of this nature with the study Medical Monitor and Sponsor prior to the event if at all possible.

5.7. Dose Adjustment Criteria

Study drug doses will not be adjusted during the study.

5.8. Study Drug Compliance

The investigational product is to be dispensed by qualified personnel at the study site and only to subjects randomized into the study. Subject compliance with therapy will be assessed by reviewing the collected study drug at scheduled study visits and documenting the review on the eCRF. If subject compliance with study drug administration is outside of the range of 80-120%, then the subject will receive additional instruction on compliance.

5.9. Randomization and Blinding

All tablets used in the study will be identical in appearance to maintain double-blind status. Subjects will administer MLE4901 and/or placebo tablets BID as described in Section 5.6.

Study drug will be packaged as described in Section 5.3.

The following personnel will be unblinded as to the exact content of investigational treatments (i.e., the randomization code):

- Personnel analyzing the PK samples
- CRO statistician and programmers preparing tables for DSMB review
- DSMB members

Subjects will be stratified by frequency of self-reported menstrual periods (<4/year vs 4-6/year) and by baseline BMI (22 to <35 kg/m^2 vs 35 to 45 kg/m^2) and randomized 1:1 into one of two study arms: MLE4901 40 mg BID or placebo BID. The randomization list will be kept in a secure location until after database lock at the end of the study; however, the treatment assignment for an individual subject will be provided if unblinding is necessary for a related SAE. The procedures for emergency unblinding are provided in Appendix 14.

5.10. Study Drug Retention at Study Site

At the time of study close-out, Millendo Therapeutics, Inc. will direct the site regarding the disposition of any unused study drug, i.e., whether it is to be destroyed or be returned to the Sponsor's designated location. See Pharmacy Manual.

5.11. Concomitant Medications

Use of concomitant medications should be kept to a minimum during the study. However, if concomitant medications are considered necessary for the subject's welfare and are unlikely to interfere with the investigational product, they may be given at the discretion of the Investigator. During the study, any medication given other than the study drug (including blood transfusions, parenteral fluids and premedications) is to be considered a concomitant medication and must be documented on the electronic case report form (eCRF).

5.12. Prohibited Medications

The following medications are prohibited from 28 days prior to the wash-out visit (for those requiring wash-out) through the end of the study (including the 8-week Follow-up Period):

- Metformin, rosiglitazone, or pioglitazone

- Hormonal contraceptives (e.g., birth control pills, hormone-releasing implants, etc. Depo-Provera needs to be washed out for 16 weeks.)
- Hormone-releasing intrauterine devices
- Anti-androgens (e.g., spironolactone, flutamide, finasteride (Propecia®), etc.)
- Clomiphene citrate or estrogen modulators such as letrozole
- GnRH modulators such as leuprolide

The following medications are prohibited from Screening through the end of the study (including the 8-week Follow-up Period):

- Minoxidil (Rogaine®) and any other hair growth products
- Eflornithine (Vaniqa®) and other depilatory creams (e.g., Nair™) may not be used in the areas of the upper lip, chin, chest, back, abdomen, upper arms and thighs
- Prescription treatments for acne
- New medications or over-the-counter supplements/therapies used with the intent to induce or cause weight loss. Subjects entering the study on a stable regimen of weight loss medications, whose weight is documented to have been stable for at least 3 months, should continue their maintenance medications at the same dose and frequency.
- Moderate to strong inducers of CYP3A4, including bosentan, carbamazepine, modafinil, nafcillin, phenytoin, rifampin, St. John's wort

5.13. Prohibited Procedures

The following procedures are prohibited during the study:

- Elective hysterectomy, endometrial ablation, or ovarian surgery
- Any form of intentional weight loss including weight-loss diets or bariatric surgery
- Hair removal procedures (e.g., electrolysis, laser hair removal, plucking/tweezing, waxing, threading, etc.) are prohibited in the areas of the scalp, upper lip, chin, chest, back, abdomen, upper arms and thighs. Note: shaving is allowed; however, subjects must not shave within 72 hours prior to visits S1 (Screening), T1 (Randomization) and T7 (End-of-Treatment) to permit assessment of hair growth.
- Hair growth procedures (e.g., hair transplant)

5.14. Restricted Medications

The use of the following medications is restricted as follows:

- Subjects should not increase the dose or frequency of their Screening non-prescription acne treatment regimen during the study. Starting a new anti-acne therapy or restarting a previously used anti-acne therapy is not allowed.

- Anti-lipid medications should remain at the same dose and frequency of use as at Screening during the study
- The following medications are allowed but should be used with caution:
  - Moderate to strong inhibitors of CYP3A4, including: clarithromycin, conivaptan, grapefruit juice, itraconazole, aprepitant, ciprofloxacin, crizotinib, diltiazem, erythromycin, fluconazole, imatinib, verapamil, ketoconazole (systemic exposure only), nefazodone, posaconazole, telithromycin, voriconazole
  - Sensitive CYP3A4 substrates, including: alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, fluticasone (systemic exposure only), lovastatin, lurasidone, midazolam, nisoldipine, quetiapine, simvastatin, sirolimus, tolvaptan, triazolam, ticagrelor
- Anti-diabetic medications other than metformin, rosiglitazone, or pioglitazone should be limited only to those that are medically necessary

6. STUDY PROCEDURES

6.1. Allowable Variation in Study Visits

Visit time points are intended as targets and variations may be made to allow for logistical considerations and to accommodate scheduling conflicts. Unless otherwise specified in this protocol, assessments are to be completed within ±3 days of the planned visit date. The medical monitor should be contacted to discuss any visits that will occur greater than ±3 days outside of the planned visit schedule.

6.2. Informed Consent

Prior to any study specific screening evaluations and study participation, written informed consent will be obtained from each subject to be involved in the study by using the Institutional Review Board or Ethics Committee (IRB/EC)-approved Informed Consent Form (ICF). Potential subjects will be informed in detail about the study drug and the nature of the clinical investigation with the risks and discomforts to be expected. The subjects will also be instructed that they are free to withdraw their consent and discontinue their participation in the clinical study at any time. The Investigator or qualified designee will verify that the subject has granted consent. Each subject will be given a copy of the signed ICF. Certified translated ICFs will be provided by the Sponsor in those languages required or requested by investigational sites.

6.3. Eligibility

Review of relevant study inclusion/exclusion criteria will be done at/after the Screening Visit and at the start of the Lead-in Period; and a comprehensive review of all inclusion/exclusion criteria will be done prior to randomization into the Treatment Period.

6.4. Medical History

A complete medical history will be obtained at the Screening visit (Visit S1). The following systems will be reviewed: head, eyes, ears, nose and throat (HEENT), respiratory, cardiovascular, gastrointestinal/hepatobiliary (specifically, a history of liver dysfunction or the presence of hepatomegaly or splenomegaly), genitourinary/ reproductive, musculoskeletal, neurological, psychiatric, endocrine/metabolic, blood/lymphatic, dermatologic and immunologic. Past surgeries will also be recorded.

6.5. Prior and/or Concomitant Medication Assessments

Prior and concomitant medications include any treatments taken from Screening (Visit S1) until the end of the study (Visit F2). In addition, any treatments for symptoms of PCOS taken during the year prior to Screening should be recorded. Any treatments given during the study other than MLE4901, including blood transfusions, parental fluids and herbal preparations, are considered concomitant therapy and must be recorded on the eCRF. All prior and concomitant medications will be coded using the latest version of the World Health Organization (WHO) Drug Dictionary, categorizing them by WHO Anatomical Therapeutic Chemical (ATC) levels 1-4 and drug name.

6.6. Vital Signs, Height, Weight and Body Mass Index

Vital signs (oral temperature, systolic and diastolic blood pressure, pulse and respiratory rate) and weight will be measured at each study visit.

Systolic and diastolic blood pressure should be taken in the same arm per subject at each study visit after the subject has been sitting for at least 5 minutes. Any clinically necessary deviations to this will be documented but do not need to be confirmed with the medical monitor prior to occurrence or documented as a protocol deviation.

Body weight will be obtained at each study visit, using a calibrated scale, after voiding and without shoes or outerwear (i.e., coats). Height will be assessed only at Screening. Body mass index will be calculated based on body weight and Screening height.

6.7. Physical Examination

A complete physical examination (PE) will be obtained at Visits S1, T1 and T7. A brief PE will be performed at Visits T5 and F2. At all other visits, targeted PEs may be performed as needed based on adverse events and positives from review of systems.

The following systems will be examined for a complete physical examination: HEENT, respiratory, cardiovascular, gastrointestinal/hepatobiliary (specifically the presence of hepatomegaly or splenomegaly will be assessed), musculoskeletal, neurological and dermatologic. On a brief physical examination, the following systems will be examined: respiratory, cardiovascular, gastrointestinal/hepatobiliary and any areas pertinent to any adverse events and positives from review of systems.

A Pap test may be performed as part of the physical examination at Visit S1 if the subject has not had one done within the past year.

6.8. Electrocardiography and Determination of QTc

All subjects will have 12-lead ECGs performed at Visits S1, T1, T5 and T7, prior to study drug dosing. The ECG test tracings will be interpreted by usual clinic procedures and ECG findings will be recorded on the eCRF. ECGs will be stored for later analysis if needed.

If the QTc is greater than 470 msec on the Screening (Visit S1) ECG, three consecutive ECGs will be obtained and the QTc values corrected by the Fridericia method will be averaged. If the average is greater than 470 msec, the subject will be ineligible for the study.

For all ECGs, the QT interval will be corrected using the Fridericia method ($QTcF = QT/RR^{0.33}$). During the study, if the QTcF is greater than 470 msec, a repeat 12-lead ECG will be obtained as soon as practicable.

In the event of an abnormal ECG (especially in the setting of an intraventricular conduction delay) that makes QTc determination unreliable by standard means, the QT interval will be corrected by the method of Rautaharju et al.

6.9. Transvaginal Ultrasound

TVU will be performed by a trained ultrasonographer during the Screening Period and at Visit T7. The number and size of ovarian cysts, ovarian size and endometrial thickness will be

assessed. In addition, the ovaries, uterus and adnexae will be assessed for pathology such as the presence and size of uterine polyps as well as the presence, size and location of uterine fibroids.

6.10. Menstrual Bleeding Diary

Subjects will be instructed in the use of the daily electronic diary for recording menstrual bleeding at Visit L1. Review of diary entries and reinforcement of instructions if needed will occur at each scheduled study visit. From Visit L1 to Visit F2, subjects should enter information into the diary every day. The diary entries will be used to evaluate the number and duration of menstrual cycles and menstrual bleeding. (Appendix 9)

6.11. PCOS Most Bothersome Symptom Questionnaire (MBSQ)

The MBSQ will be administered at all study visits to evaluate the subjects' Most Bothersome Symptom of PCOS (Appendix 2). At Visits S1, L1, L2 and T1, subjects will indicate their Most Bothersome Symptom of PCOS (oligo-/amenorrhea, hirsutism, acne, alopecia and other) prior to study entry. At all scheduled study visits, subjects will indicate the severity of each symptom of PCOS (hirsutism, acne, alopecia, irregular menses and other) using a Likert scale. Changes in the questionnaire results will be used to assess the efficacy of MLE4901 in improving symptoms of PCOS.

6.12. Hair Removal Questionnaire (HRQ)

The self-administered HRQ at Visits S1, L1, T1, T5, T6, T7 and F2 will assess how often subjects remove unwanted hair from their upper lip and chin. (Appendix 3)

6.13. Polycystic Ovary Syndrome Questionnaire (PCOSQ) and PCOS Acne Questionnaire

The PCOSQ (Appendix 4) is a self-administered questionnaire for measuring health-related quality of life in women with PCOS. The PCOSQ has 5 domains: emotions, body hair, weight, infertility, and menstrual problems. (Cronin 1998)

The PCOS Acne Questionnaire (Appendix 4) consists of 4 questions that assess health-related quality of life related to acne, scored on a 7-point Likert scale. (Barnard 2007)

The PCOSQ and the PCOS Acne Questionnaire will be administered to subjects at Visits T1, T5, T7 and F2 and used to compare changes in health-related quality of life between treatment groups.

6.14. EuroQol-5 Dimensions-5 Levels Survey (EQ-5D-5L)

The EQ-5D-5L (an example of the English version for the US is provided in Appendix 5) is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which can take one of five responses. The responses record five levels of severity within a particular EQ-5D dimension. (http://www.euroqol.org/about-eq-5d/eq-5d-nomenclature.html) The validated EQ-5D-5L survey will be administered to subjects at Visits T1, T5, T7 and F2 and used to compare changes in health status between treatment groups. (http://www.euroqol.org/eq-5d-products/eq-5d-5l.html)

6.15. Patient Health Questionnaire-4 (PHQ-4)

The PHQ-4 (Appendix 6) is a validated 4-item self-reporting tool that allows for a brief assessment of depression and anxiety. The validated PHQ-4 will be administered to subjects at Visits T1, T5, T7 and F2 and used to compare severity of depression and anxiety between treatment groups. (Kroenke 2009, Löwe 2010)

6.16. Work Productivity and Activity Impairment: General Health Questionnaire (WPAI:GH)

The WPAI:GH (Appendix 7) is a well-validated instrument to measure impairments in work and activities. It measures absenteeism, presenteeism, as well as impairments in unpaid activity because of health problems during the past seven days.

The validated WPAI:GH questionnaire will be administered to subjects at Visits T1, T5, T7 and F2 and used to compare changes in work productivity and activity impairment between treatment groups. (http://www.reillyassociates.net/WPAI_GH.html)

6.17. Patient's Global Impression of Change (PGIC)

The PGIC is administered to subjects at Visit T7 and used to compare assessments of overall changes in acne, unwanted hair and PCOS between treatment groups. (Appendix 8)

6.18. Modified Ferriman-Gallwey Score for Hirsutism

The Primary Investigator (or designee) will assess each subject's degree of hirsutism using the modified Ferriman-Gallwey scale at Visits S1, T1 and T7. The clinician (MD, DO, NP, RN, or PA) performing this evaluation should be the same per subject during the course of the study. (Appendix 10; Ferriman 1961)

6.19. Investigator's Static Global Assessment (ISGA) of Acne Score

The Primary Investigator (or designee) will assess each subject's degree of acne according to the ISGA scale in Appendix 11 at Visits S1, T1 and every subsequent scheduled study visit. The clinician (MD, DO, NP, RN, or PA) performing this evaluation should be the same per subject during the course of the study.

Appendix 11 also lists the photographic equivalents for each level of the ISGA scale from the Leeds Revised Acne Grading System shown in Appendix 12. (US Food and Drug Administration Guidance for Industry: Acne Vulgaris: Developing Drugs for Treatment. September 2005; Tazorac® Medical Review 2012, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202428Orig1s000MedR.pdf. Table 8, p 20; Appendix 12; O'Brien 1998)

6.20. Savin Scale for Alopecia

The Primary Investigator (or designee) will assess each subject's degree of alopecia using the Savin scale at Visits S1, T1 and T7. The clinician (MD, DO, NP, RN, or PA) performing this evaluation should be the same per subject during the course of the study. (Appendix 13; Savin 1994)

6.21. Pharmacokinetic Assessments

Approximately 5 mL of blood will be drawn at each PK sampling time point:

Table 4: Pharmacokinetic Sampling Time Points

Visit	Sampling Time Points (Morning Dose Only)
T1	0 (within 30 min predose), 1 hr (± 5 min), 2 hr (± 10 min), 2.5 hr (± 10 min), 3 hr(± 10 min) and 4 hr (± 10 min)
T3	0 hr (trough, within 30 min predose)
T5	0 hr (trough, within 30 min predose)
T7	0 hr (trough)

Logistic considerations may dictate a deviation from the specified time point; therefore, a window is permitted around each sampling time point, as shown in Table 4: sampling times up to and including 1 hour postdose have a window of ± 5 min and subsequent time points have a window of ± 10 min. Actual times of sampling and actual dosing times of MLE4901 must be recorded on the eCRF. Specific collection and shipment procedures for PK samples are provided in the Laboratory Manual. All samples will be analyzed using a validated assay at a central laboratory.

PK parameters will be derived using non-compartmental methods employing WinNonlin® Phoenix version 6.3 or later (Pharsight Corp., Mountain View, CA). The following PK parameters will be estimated for MLE4901 and its major metabolite M12 for T1 as data permit and as appropriate:

Table 5: Pharmacokinetic Parameters

C_{last}	The last quantifiable drug concentration in plasma determined directly from individual concentration-time data
C_{max}	The maximum drug concentration in plasma determined directly from individual concentration-time data
C_{max}/D	Dose-normalized C_{max}, calculated as the ratio of C_{max} to dose
T_{max}	The observed time to reach maximum concentration
AUC_{0-t}	The area under the plasma concentration-time curve from time zero to the time of the last quantified concentration, calculated using the linear-up/log-down trapezoidal rule
AUC_{0-4h}	The area under the concentration-time curve from time zero to 4 h after dosing, calculated using the linear-up/log-down trapezoidal rule
AUC_{0-4h}/D	Dose-normalized AUC_{0-4h}, calculated as the ratio of AUC_{0-4h} to dose
λz	The terminal phase rate constant, estimated by linear regression through the terminal phase of the log concentration-time profile

$t_{½}$	The terminal phase half-life, calculated as: $t½ = \frac{\ln(2)}{\lambda z}$
$AUC_{0-\infty}$	The area under the concentration versus time curve from time 0 to infinity (first dose only), calculated as $AUC_{0-4h} + C_{last}/\lambda_z$
$AUC_{\%extrap}$	Percentage of $AUC_{0-\infty}$ extrapolated, represented as $(1 - AUC_{0-t}/AUC_{0-\infty})*100$ (Day 1 only)
CL/F	Oral clearance calculated as: $Dose/AUC_{0-\infty}$ (Day 1 only)

6.22. Pharmacodynamic Assessments

The relationship between C_{max}, AUC and other PK parameters with efficacy assessments will be explored as appropriate.

6.23. Adverse Events, Serious Adverse Events, Pregnancies and Reporting

6.23.1. Definition of Adverse Event, Adverse Drug Reaction and Unexpected Adverse Drug Reaction

Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

- All AEs, regardless of relationship to study drug, should be collected beginning from the time the subject signs the study consent until the early termination/final visit or 30 days after the last dose of study drug, whichever is longer. (Any SAE judged by the investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion.) AEs in study subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes.
- Wherever possible, a specific disease or syndrome, rather than individual associated signs and symptoms should be identified by the Investigator and recorded. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure. Any medical condition already present at screening should not be reported as an AE unless the medical condition or signs or symptoms present at baseline worsens in severity or seriousness at any time during the study. Clinically significant examination (e.g. electrocardiogram) findings that are detected during the study or are present at screening and worsen during the study should be reported as an AE.
- An abnormal laboratory value may be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not. It is up to the Investigator to determine whether an abnormal laboratory value

constitutes an AE. If an abnormal laboratory value is caused by a disease process, the disease process and not the laboratory abnormality should be listed as the AE (e.g., if new onset viral hepatitis is causing elevated alanine aminotransferase (ALT), hepatitis and not the elevated ALT should be listed as the AE).

- Examples of laboratory abnormalities that should be considered AEs include those that result in withdrawal of the study treatment, withholding study treatment pending some investigational outcome, or additional concomitant treatment. All laboratory abnormalities considered to constitute an AE should be recorded on the appropriate AE page of the eCRF. Laboratory abnormalities do not need to be listed as separate AEs if they are considered to be part of a clinical syndrome that is being reported as an AE. It is the responsibility of the Investigator to review all safety laboratory findings in all subjects. Abnormal values should be commented upon as to clinical relevance or importance on the eCRF or the laboratory report as appropriate. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.
- Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to study drug.
- Subjects who develop toxicity on study will be followed until the event resolves, stabilizes or returns to baseline.

Adverse Reaction: All noxious and unintended responses to study drug at any dose should be considered to be adverse reactions. “Responses to study drug” means that there is a causal relationship between the study drug and the responses. “Suspected adverse reaction” implies a lesser degree of certainty about causality than “adverse reaction.”

Unexpected Adverse Reaction: An unexpected adverse reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For the study drug, the reference safety information is included in the version of the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

6.23.2. Assessing Severity of Adverse Events

The assessment of severity must be provided by the Investigator and based on the Investigator’s clinical judgment. Maximum severity should be assigned to one of the following categories:

- **Mild**: An AE that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An AE that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: An AE that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with a serious AE (SAE). Refer to Section 6.23.4.1 for the definition of an SAE.

6.23.3. Assessing Relationship to Study Treatment

The Investigator will categorize each AE as to its potential relationship to study drug: **unrelated**, **unlikely related**, **possibly related**, **probably related** and **definitely related**. Items to be considered when assessing the relationship of an AE to the study treatment are as follows:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, considering especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study treatment-related factors that are known to be associated with the occurrence of the event

The relationship categories of unrelated and unlikely related will be summarized for reporting purposes as **Not Related**. For Not Related events, the time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship with study drug and another cause of the AE (concomitant drugs, therapies, complications, etc.) is suspected.

The relationship categories of possibly, probably and definitely related will be summarized for reporting purposes as **Related**. Only AEs thought to be caused by the study drug should be classified as "related to study drug." For Related events, the time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified. The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

6.23.4. Serious Adverse Events

6.23.4.1. Definition of Serious Adverse Event

A serious adverse event (experience; SAE) or reaction is any untoward medical occurrence that:

- Results in death
- Is life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which, in view of either the investigator or sponsor, the subject was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of an existing hospitalization

NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a serious adverse event (SAE) under this criterion, nor will hospitalization for a

procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness.

The following hospitalizations are not considered to be SAEs because there is no "AE" (i.e., no untoward medical occurrence) associated with the hospitalization:

– Hospitalizations for respite/hospice care

– Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration)

- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect, or
- Is determined to be an important medical event (at the discretion of the Investigator)

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.23.4.2. Reporting Serious Adverse Events (SAEs) – Procedure for Investigators

Initial Reports

SAEs, regardless of causality assessment, must be collected beginning from the time the subject signs the study consent until the early termination/final visit or 30 days after the last dose of study drug, whichever is longer. All SAEs must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned seriousness criteria). Any SAE judged by the investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets seriousness criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below) and fax or email the completed paper SAE form to Medpace (fax number/email address listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

It is very important that the SAE electronic case report form be filled out as completely as possible at the time of the initial report, including if possible the investigator's assessment of causality. The minimum information needed for making a preliminary SAE report is the protocol number, the subject ID, an adverse event term and the name of the person reporting the

information to the Sponsor. Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports and other documents requested by the Sponsor (see Follow-up Reports, below).

The Investigator should notify the IRB/EC of the occurrence of the SAE, in writing, in accordance with local requirements. A copy of this communication must be forwarded to the clinical research associate (CRA) and filed in the trial master file (TMF).

Medpace Clinical Safety Contact Information:

Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, ext. 2999 **or** +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 **or** +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

Medpace SAE hotline – Europe:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
e-mail: medpace-safetynotification@medpace.com

Follow-Up Reports

All AEs and SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

6.23.5. Pregnancy Reporting

Any pregnancy following study drug dosing where the estimated date of conception occurred either prior to the study termination visit or within 30 days of last study treatment must be reported. The investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure *In Utero* form to the Investigator for completion. **The contact information for reporting pregnancies is the same as for reporting SAEs** (Section 6.23.4.2).

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The subject should be followed by the Investigator until completion of the pregnancy. During the pregnancy, fetal growth parameters should be obtained regularly. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the fetus has a congenital anomaly, the Investigator should follow the procedures for reporting an SAE. If the pregnancy results in a live birth, regular reports should be submitted regarding the child's development from birth to three years of age.

6.23.6. Regulatory Reporting of Adverse Events

AEs will be reported to the regulatory authorities in compliance with local and regional law and established guidance by the Sponsor or by a third party acting on behalf of the Sponsor. The format of these reports will be dictated by the local and regional requirements.

6.24. Clinical Laboratory Tests

Blood samples for hematology, chemistry, insulin, HbA1c, lipid panel, coagulation, TSH, viral screen, hormones and βhCG and urine samples for pregnancy tests and urinalysis, will be obtained as shown in the study schedule in Appendix 1. Approximately 3 mL of blood will be collected for hematology, 7 mL for chemistry, 3 mL for coagulation and 4 mL for the viral screen. Testing will be carried out by the central laboratory and will include the laboratory tests listed in Table 6. Subjects need to fast prior to visits S1, T1 and T7 as fasting insulin, glucose and/or a lipid panel are to be collected at those visits. Subjects may be in a seated or supine position during blood collection.

For subjects who are not surgically sterile, a serum pregnancy test will be performed via the central laboratory at Screening (Visit S1) and a urine pregnancy test will be performed at the study site at all subsequent study visits.

Abnormal, clinically significant results may be verified to rule out laboratory error. Persistent relevant abnormal values must be followed up until the cause is determined or until they return to the previous values. Abnormal laboratory findings that are considered clinically significant by the Investigator should be recorded as AEs (Section 6.23.1).

Further details on sample collection and handling are provided in the Laboratory Manual.

Table 6: List of Clinical Laboratory Tests

Hematology	hematocrit (Hct), hemoglobin (Hgb), platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential
Chemistry	albumin (ALB), alkaline phosphatase (ALK-P), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), blood urea nitrogen (BUN), calcium (Ca), creatinine, glucose, total bilirubin, total protein, electrolytes (magnesium, sodium, potassium, chloride, bicarbonate); direct and indirect bilirubin will be performed if total bilirubin is elevated
Metabolic	insulin, HbA1c, lipid panel (total cholesterol, triglycerides, HDL, LDL)
Coagulation	PT, aPTT
Viral Screen	HBsAg, HCV, HIV
Serum Hormone Levels	SHBG, total testosterone, free testosterone, bioavailable testosterone, LH, FSH, estradiol, progesterone, AMH, 17-hydroxyprogesterone (Screening only), prolactin (Screening only), DHEA-S (Screening only)
Urinalysis	appearance, bilirubin, color, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, urobilinogen; microscopic examination will be performed if leukocyte esterase, nitrite, and/or occult blood are positive
Ovulation	urinary pregnanediol-3-glucuronide

Hematology	hematocrit (Hct), hemoglobin (Hgb), platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential
Other	serum and urine pregnancy tests, TSH, urine drug screen

6.24.1. Efficacy Laboratory Tests

Note: From Visit T1 to Visit F2, study site personnel (including Investigators) will be blinded to all efficacy laboratory tests listed below, except for fasting glucose, HbA1c and the fasting lipid panel.

6.24.1.1. Urinary Pregnanediol-3-Glucuronide

Urine will be self-collected by each subject thrice weekly from Visit L1 to Visit F2 for evaluation of ovulation during the study via assessment of pregnanediol-3-glucuronide at the central laboratory (Kassam 1996). The pregnanediol-3-glucuronide levels will be used to estimate the number of ovulations and the ovulation interval during the study.

6.24.1.2. Serum Hormone Levels

SHBG, testosterone (total, bioavailable and free), LH, FSH, estradiol, progesterone and AMH will be measured at the central laboratory using validated methods at L2, T1, T3, and all subsequent study visits except T3.5, T5.5, and T6.5. At Visit S1 (or W1, if wash-out is required), SHBG, testosterone, and FSH will be assessed. Screening levels will be used to assess potential subjects for eligibility (e.g., elevated androgen levels). Changes in hormone levels during the study will be used to assess the efficacy of MLE4901.

17-hydroxyprogesterone, prolactin and DHEA-S levels will be measured at the central laboratory using validated methods at Visit S1 (or W1, if wash-out is required) only to assess whether potential subjects meet the inclusion/exclusion criteria associated with these parameters.

6.24.1.3. Fasting Glucose, Insulin and HbA1c

Fasting glucose and HbA1c will be measured at Visit S1 and subjects with results suggestive of diabetes mellitus will be excluded based on the parameters defined in exclusion criterion #16. Fasting glucose, insulin and HbA1c will be measured at the central laboratory using validated methods at Visits T1 and T7 and used for evaluations of insulin sensitivity.

6.24.1.4. Fasting Lipid Panel

A fasting lipid panel (total cholesterol, LDL, HDL and triglycerides) will be measured at the central laboratory using validated methods at Visits S1, T1 and T7 to evaluate for improvements in these metabolic syndrome parameters.

6.24.2. Safety Laboratory Tests

As shown in Appendix 1, hematology and chemistry will be obtained at Screening and at Weeks -4, 0 (baseline), 2, 4, 8, 12, 20, 28 (EoT), and 32 (F1). PT, PTT, and TSH will be obtained at Screening, Week -4, and Week 28. Subjects on thyroid hormone replacement who require a wash-out of medications that affect hormone levels should also have an additional TSH level done at the wash-out (W1) visit. Urinalysis will be obtained at Screening, Week 0, and Week 28. A serum pregnancy test will be done at Screening, and a urine pregnancy test will be done at all other visits.

6.24.2.1. Liver Function Tests

Liver function tests (LFTs: AST, ALT, alkaline phosphatase, and total bilirubin) will be collected at Screening and at Weeks -4, 0 (baseline), 2, 4, 6, 8, 12, 16, 20, 24, 28 (EoT), and 32 (F1). Direct and indirect bilirubin will be obtained if total bilirubin is elevated.

Elevated AST or ALT >3x ULN occurring after baseline should be managed according to the guidance in Appendix 15.

6.24.3. Sample Collection, Storage and Shipping

Sample collection, storage and shipment procedures for the clinical laboratory samples will be provided in the laboratory manual.

6.25. Blood Sample Collection

In total, approximately 1¼ cup (300 mL) of blood will be collected from each subject randomized into the study.

6.26. Removal of Subjects from the Study

In accordance with the Declaration of Helsinki and subsequent conferences, subjects have the right to withdraw from the study at any time for any reason. The Investigator and the Sponsor also have the right to withdraw subjects from the study. Subjects may be removed from the study for the following reasons:

1. In the Investigator's judgment, administration of study drug would be detrimental to the subject's health.
2. The subject withdraws consent for continued participation or refuses further treatment with the investigational product.
3. The subject is noncompliant with the protocol.
4. The subject becomes pregnant.
5. The subject dies.
6. The subjects experiences an SAE or medically important event that would preclude further treatment with study drug.
7. The subject requires long-term therapy with a prohibited medication.
8. The subject experiences persistent and/or significant increases in LFTs and is required to be withdrawn per the guidance in Appendix 15.

Subjects should return to the investigational site for an Early Termination (ET) Visit after withdrawal/removal from the study.

- If the subject is to be withdrawn from the study prior to Visit T7, the ET visit will consist of the Visit T7 procedures (Section 7.3.9), including the TVU.
- If the subject is to be withdrawn from the study after Visit T7 but before Visit F2, the ET visit will consist of the Visit F2 procedures (Section 7.4.2).

The reason for and date of withdrawal/removal from the study will be documented in the subject's medical records. Investigational site personnel must attempt to determine whether the reason for withdrawal was an AE and if so, this must be reported in accordance with the

procedures provided in Section 6.23. For all subjects who do not complete the study, regardless of the duration of treatment, all relevant information related to the withdrawal/removal will be entered into the eCRF.

Subjects who withdraw or are removed from the study after randomization will not be replaced. All randomized subjects will be fully accounted for and documented in the final clinical study report (CSR).

7. STUDY ACTIVITIES

7.1. Screening/Wash-out Period

7.1.1. Screening/Wash-out Period, Visit S1 (Screening)

The Screening Visit should be conducted within 12 weeks prior to the beginning of the Lead-in Period. The date of Screening is considered to be the date that the first study-related screening assessment is performed. The subject needs to be fasting after 10 PM (water and maintenance medications allowed) the evening prior to the Screening Visit. Blood samples for the Screening Visit need to be collected as close to 8 AM as practicable and between 6-10 AM.

At Screening, appropriate study site personnel should:

- Obtain and document informed consent from the subject prior to any study procedures being performed.
- Assign a study-specific subject identification number (subject ID).
- Obtain and record medical history, demographic data, prior and current medications and the subject's self-reported number of menstrual periods/12 months (off of any hormone therapy).
- Administer the MBSQ and the HRQ.
- Record vital signs, height and weight.
- Perform and document a complete physical examination (PE).
- Perform or confirm a Papanicolaou test (Notes: results from 1 year prior to Screening are acceptable. Women under 21 years of age at Screening do not require a Pap.)
- Record the subject's modified Ferriman-Gallwey score, ISGA score and Savin score.
- Obtain a 12-lead ECG.
- Collect fasting blood samples (as close to 8 AM as practicable and between 6-10 AM) for hematology, chemistry, HbA1c, lipid panel, PT, aPTT, TSH, HBsAg, hepatitis C antibody, HIV test, SHBG, total testosterone, free testosterone, bioavailable testosterone, FSH, 17-hydroxyprogesterone, prolactin, DHEA-S and a serum pregnancy test.

NOTE: Subjects who require wash-out of medications that affect hormone levels should NOT have their hormone levels (SHBG, total testosterone, free testosterone, bioavailable testosterone, FSH, 17-hydroxyprogesterone, prolactin, DHEA-S) drawn at S1. Instead, they should complete the required wash-out and return to the site for these hormone levels at a wash-out visit (Visit W1). Subjects who do not require wash-out should not undergo a wash-out visit.

- Collect a urine sample for urinalysis and urine drug screen.
- Review and assess relevant inclusion and exclusion criteria.

- Obtain a transvaginal ultrasound (TVU) on subjects who meet all of the inclusion criteria and none of the exclusion criteria assessable based on the Screening procedures (Note: Subjects do not need to wait for Screening/Wash-out hormone results prior to proceeding with the TVU and the Lead-in Period.). The TVU results should be reviewed prior to Visit L1 to ensure that there are no exclusionary abnormalities.

Note: For subjects who require a wash-out, the transvaginal ultrasound should occur after completion of the wash-out and prior to or at Visit L1. Subjects who require a wash-out should have hormones drawn after wash-out.

In addition, if a subject requires the TVU to show polycystic ovarian morphology (PCOM) in order to qualify for the study, please note that more than 4 weeks' wash-out from some medications (such as clomiphene and letrozole) may be needed to re-develop PCOM.

- If the subject requires wash-out, schedule the subject for a wash-out visit (Visit W1) so that blood sample collection for that visit will occur as close to 8 AM as practicable and between 6-10 AM. Inform the subject that she does not need to be fasting for Visit W1.
- If the subject does not require wash-out, schedule the subject for Visit L1. Inform the subject that she does not need to be fasting at Visit L1.

7.1.2. Screening/Wash-out Period, Visit W1 (Wash-out)

At Wash-out, appropriate study site personnel should:

- Record adverse events and update medications.
- Collect blood samples (as close to 8 AM as practicable and between 6-10 AM) for SHBG, total testosterone, free testosterone, bioavailable testosterone, FSH, 17-hydroxyprogesterone, prolactin, and DHEA-S. Subjects on thyroid hormone replacement who require wash-out should also have an additional TSH level done.
- Collect a urine sample for and perform a urine pregnancy test.

7.2. Lead-in Period

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria assessable during the Screening Period, including TVU findings, should enter the 8-week Lead-in Period. Note: Subjects do not need to wait for Screening/Wash-out hormone results prior to proceeding with the TVU and the Lead-in Period. All Screening/Wash-out hormone results should be reviewed and confirmed to be inclusionary prior to Randomization. During the Lead-in Period, subjects are trained on the use of the daily electronic diary and on collection and storage of thrice-weekly urine samples for assessment of ovulation. Additionally, at the beginning of the Lead-in Period, all subjects will undergo a progestin challenge with MPA 10 mg daily for 5 days.

7.2.1. Lead-in Period, Visit L1

At Visit L1, appropriate study site personnel should:

- Record adverse events and update medications.

- Administer the MBSQ and the HRQ.
- Record vital signs and weight.
- Collect a urine sample for and perform a urine pregnancy test.
- Review and assess relevant inclusion and exclusion criteria.
- Instruct the subject on the use of the daily menstrual bleeding electronic diary.
- Instruct the subject on the collection and storage of thrice-weekly urine samples for assessment of ovulation and provide the subject with sufficient collection and storage materials to last until the subject's next study visit. Urine should be collected as first void samples on non-consecutive days when possible.
- Instruct the subject on MPA dosing, provide the subject with 5 tablets of MPA 10 mg and have the subject self-administer the first dose of MPA with a nonalcoholic beverage (except grapefruit juice) while at the study site. Record the time of MPA administration.
- Schedule the subject for the next study visit (Visit L2) so that blood sample collection for that visit will occur as close to 8 AM as practicable and between 6-10 AM.
- Inform the subject that she does not need to be fasting at Visit L2.

7.2.2. Lead-in Period, Visit L2

Prior to Visit L2, appropriate study site personnel should review the subject's menstrual diary entries. If the subject did not experience a menstrual period following the progestin challenge, or has experienced more than one menstrual period following the progestin challenge, the subject should be screen-failed from the study. In addition, subjects may be lead-in failed if the number of menstrual periods that occurred during the Lead-in Period is unclear due to poor diary compliance. Subjects who fail during the Lead-in Period should return any provisioned devices back to the site; stored urine samples may be defrosted with the urine discarded into the toilet, and any urine collection materials and kits may be discarded into household trash or recycled as appropriate. A menstrual period is defined as 2 or more consecutive days of bleeding, excluding spotting.

At Visit L2, appropriate study site personnel should:

- Record adverse events and update medications.
- Administer the MBSQ.
- Record vital signs and weight.
- Collect blood samples (as close to 8 AM as practicable and between 6-10 AM) for hematology, chemistry, PT, aPTT, TSH, SHBG, total testosterone, free testosterone, bioavailable testosterone, LH, FSH, estradiol, progesterone and AMH.
- Collect a urine sample for and perform a urine pregnancy test.
- Review the subject's electronic diary entries and reinforce instruction on the use of the diary as needed.

- Review the subject's collection and storage of thrice-weekly urine samples and reinforce instruction on the collection and storage of these samples as needed. Urine should be collected as first void samples on non-consecutive days when possible. Provide the subject with sufficient collection and storage materials to last until the subject's next study visit.
- Schedule the next study visit (Visit T1) so that blood sample collection for hormones for that visit will occur as close to 8 AM as practicable and between 6-10 AM.
- Instruct the subject that she needs to be fasting after 10 PM (water and maintenance medications allowed) the evening prior to Visit T1.

7.3. Treatment Period

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria should enter the 28-week Treatment Period. Please note that subjects who have no menstrual periods during the 8-week Lead-in Period and those with two or more menstrual periods during the 8-week Lead-in Period should be excluded from the study, as should any subjects with significant findings on TVU other than findings related to PCOS. A menstrual period is defined as 2 or more consecutive days of bleeding, excluding spotting.

During the Treatment Period, subjects will take their assigned study drug and undergo assessments to evaluate pharmacokinetics, efficacy, safety and tolerability of study drug. Blood samples for hormones for all of the Treatment Period visits (Note: hormones are not scheduled to be collected at Visits T2, T3.5, T5.5, or T6.5) need to be collected as close to 8 AM as practicable and between 6-10 AM. The subject needs to be fasting after 10 PM (water and maintenance medications allowed) the evening prior to Visits T1 and T7. In the evening prior to study visits, subjects should take their evening dose of study drug (and also note the date and exact time of the last dose prior to Visits T3, T5 and T7). On the morning of study visits, subjects should wait to take their morning dose of study drug until directed by site personnel at the study site.

7.3.1. Treatment Period, Study Day 1, Visit T1

At Visit T1, appropriate study site personnel should:

- Record adverse events and update medications.
- Review the subject's electronic diary entries and reinforce instruction on the use of the daily diary as needed. Confirm that the subject has had one and only one menstrual period during the Lead-in Period.
- Record vital signs and weight.
- Perform a complete PE.
- Collect a urine sample for urinalysis and perform a urine pregnancy test.
- Obtain a 12-lead ECG.
- Review inclusion and exclusion criteria to confirm that the subject is eligible for the study.

- Randomize the subject.
- Administer the MBSQ, the HRQ, the PCOSQ, the PCOS Acne Questionnaire, the EQ-5D-5L, the PHQ-4 and the WPAI:GH.
- Record the subject's modified Ferriman-Gallwey hirsutism score, ISGA score and Savin score.
- Collect fasting blood samples (as close to 8 AM as practicable and between 6-10 AM) for hematology, chemistry, insulin, HbA1c, lipid panel, SHBG, total testosterone, free testosterone, bioavailable testosterone, LH, FSH, estradiol, progesterone and AMH prior to administration of study drug.
- Collect a plasma PK sample within 30 minutes prior to administration of study drug. Record the exact time of each PK sample collection.
- Review the subject's collection and storage of thrice-weekly urine samples and reinforce instruction on the collection and storage of these samples as needed. Urine should be collected as first void samples on non-consecutive days when possible. Provide the subject with sufficient collection and storage materials to last until the subject's next study visit.
- Dispense study drug and instruct the subject on self-administration of study drug orally twice per day.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site. Record the exact time of study drug administration.
- Collect plasma PK samples at 1, 2, 2.5, 3 and 4 hours after administration of study drug. Record the exact time of each PK sample collection.
- Schedule the next study visit (Treatment Period, Visit T2).
- Instruct the subject that on the morning of Visit T2, she should not take her morning dose of study drug at home, but rather will take it at the study site as directed by site personnel.
- Inform the subject that she does not need to be fasting at Visit T2.

7.3.2. Treatment Period, Visit T2

At Visit T2, appropriate study site personnel should:

- Record adverse events and update medications.
- Administer the MBSQ.
- Record vital signs and weight.
- Record the subject's ISGA score.
- Collect blood samples for hematology and chemistry prior to administration of study drug.

- Collect a urine sample for and perform a urine pregnancy test.
- Review the subject's electronic diary entries and reinforce instruction on the use of the daily diary as needed.
- Review the subject's collection and storage of thrice-weekly urine samples and reinforce instruction on the collection and storage of these samples as needed. Urine should be collected as first void samples on non-consecutive days when possible. Provide the subject with sufficient collection and storage materials to last until the subject's next study visit.
- Collect study drug and assess compliance.
- Reinforce self-administration of study drug orally twice per day.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site.
- Schedule the next study visit (Visit T3) so that blood sample collection will occur as close to 8 AM as practicable and between 6-10 AM.
- Instruct the subject that the evening prior to Visit T3, she should note the date and exact time of her evening dose of study drug.
- Instruct the subject that on the morning of Visit T3, she should not take her morning dose of study drug at home but rather will take it at the study site as directed by site personnel.
- Inform the subject that she does not need to be fasting at Visit T3.

7.3.3. Treatment Period, Visit T3

At Visit T3, appropriate study site personnel should:

- Record adverse events and update medications.
- Record the date and time of the subject's last dose of study drug prior to the visit.
- Administer the MBSQ.
- Record vital signs and weight.
- Record the subject's ISGA score.
- Collect blood samples (as close to 8 AM as practicable and between 6-10 AM) for hematology, chemistry, SHBG, total testosterone, free testosterone, bioavailable testosterone, LH, FSH, estradiol, progesterone and AMH prior to administration of study drug.
- Collect a plasma PK sample within 30 minutes prior to administration of study drug. Record the exact time of each PK sample collection.
- Collect a urine sample for and perform a urine pregnancy test.
- Review the subject's electronic diary entries and reinforce instruction on the use of the daily diary as needed.

- Review the subject's collection and storage of thrice-weekly urine samples and reinforce instruction on the collection and storage of these samples as needed. Urine should be collected as first void samples on non-consecutive days when possible. Provide the subject with sufficient collection and storage materials to last until Visit T4.
- Collect study drug and assess compliance.
- Dispense study drug and instruct the subject on self-administration of study drug orally twice per day.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site.
- Schedule the next two study visits (Visits T3.5 and T4). Blood sample collection at Visit T4 should occur as close to 8 AM as practicable and between 6-10 AM.
- Instruct the subject that on the morning of Visit T3.5, she should go ahead and take her morning dose of study drug at home. Instruct the subject that on the morning of Visit T4, she should NOT take her morning dose of study drug at home but rather will take it at the study site as directed by site personnel.
- Inform the subject that she does not need to be fasting at Visits T3.5 or T4.

7.3.4. Treatment Period, Visit T3.5

At Visit T3.5, appropriate study site personnel should:

- Collect a blood sample for AST, ALT, alkaline phosphatase, and total bilirubin.

7.3.5. Treatment Period, Visit T4

At Visit T4, appropriate study site personnel should:

- Record adverse events and update medications.
- Administer the MBSQ.
- Record vital signs and weight.
- Record the subject's ISGA score.
- Collect blood samples (as close to 8 AM as practicable and between 6-10 AM) for hematology, chemistry, SHBG, total testosterone, free testosterone, bioavailable testosterone, LH, FSH, estradiol, progesterone and AMH prior to administration of study drug.
- Collect a urine sample for and perform a urine pregnancy test.
- Review the subject's electronic diary entries and reinforce instruction on the use of the daily diary as needed.
- Review the subject's collection and storage of thrice-weekly urine samples and reinforce instruction on the collection and storage of these samples as needed. Urine should be collected as first void samples on non-consecutive days when possible.

Provide the subject with sufficient collection and storage materials to last until the subject's next study visit.

- Collect study drug and assess compliance.
- Dispense study drug and instruct the subject on self-administration of study drug orally twice per day.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site.
- Schedule the next study visit (Visit T5) so that blood sample collection will occur as close to 8 AM as practicable and between 6-10 AM.
- Instruct the subject that the evening prior to Visit T5, she should note the date and exact time of her evening dose of study drug.
- Instruct the subject that on the morning of Visit T5, she should not take her morning dose of study drug at home but rather will take it at the study site as directed by site personnel.
- Inform the subject that she does not need to be fasting at Visit T5.

7.3.6. Treatment Period, Visit T5

At Visit T5, appropriate study site personnel should:

- Record adverse events and update medications.
- Record the date and time of the subject's last dose of study drug prior to the visit.
- Administer the MBSQ, the HRQ, the PCOSQ, the PCOS Acne Questionnaire, the EQ-5D-5L, the PHQ-4 and the WPAI:GH.
- Record vital signs and weight.
- Perform a brief PE.
- Record the subject's ISGA score.
- Obtain a 12-lead ECG.
- Collect blood samples (as close to 8 AM as practicable and between 6-10 AM) for hematology, chemistry, SHBG, total testosterone, free testosterone, bioavailable testosterone, LH, FSH, estradiol, progesterone and AMH prior to administration of study drug.
- Collect a plasma PK sample within 30 minutes prior to administration of study drug. Record the exact time of each PK sample collection.
- Collect a urine sample for and perform a urine pregnancy test.
- Review the subject's electronic diary entries and reinforce instruction on the use of the daily diary as needed.

- Review the subject's collection and storage of thrice-weekly urine samples and reinforce instruction on the collection and storage of these samples as needed. Urine should be collected as first void samples on non-consecutive days when possible. Provide the subject with sufficient collection and storage materials to last until Visit T6.
- Collect study drug and assess compliance.
- Dispense study drug and reinforce self-administration of study drug orally twice per day.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site (all Treatment Period visits).
- Schedule the next two study visits (Visits T5.5 and T6). Blood sample collection at Visit T6 should occur as close to 8 AM as practicable and between 6-10 AM.
- Instruct the subject that on the morning of Visit T5.5, she should go ahead and take her morning dose of study drug at home. Instruct the subject that on the morning of Visit T6, she should NOT take her morning dose of study drug at home but rather will take it at the study site as directed by site personnel.
- Inform the subject that she does not need to be fasting at Visits T5.5 or T6.

7.3.7. Treatment Period, Visit T5.5

At Visit T5.5, appropriate study site personnel should:

- Collect a blood sample for AST, ALT, alkaline phosphatase, and total bilirubin.

7.3.8. Treatment Period, Visit T6

At Visit T6, appropriate study site personnel should:

- Record adverse events and update medications.
- Administer the MBSQ and the HRQ.
- Record vital signs and weight.
- Record the subject's ISGA score.
- Collect blood samples (as close to 8 AM as practicable and between 6-10 AM) for hematology, chemistry, SHBG, total testosterone, free testosterone, bioavailable testosterone, LH, FSH, estradiol, progesterone and AMH prior to administration of study drug.
- Collect a urine sample for and perform a urine pregnancy test.
- Review the subject's electronic diary entries and reinforce instruction on the use of the daily diary as needed.
- Review the subject's collection and storage of thrice-weekly urine samples and reinforce instruction on the collection and storage of these samples as needed. Urine should be collected as first void samples on non-consecutive days when possible.

Provide the subject with sufficient collection and storage materials to last until Visit T7.

- Collect study drug and assess compliance.
- Dispense study drug and reinforce self-administration of study drug orally twice per day.
- Ask the subject to self-administer study drug with a nonalcoholic beverage (except grapefruit juice) while at the study site.
- Schedule the next two study visits (Visits T6.5 and T7). Blood sample collection at Visit T7 should occur as close to 8 AM as practicable and between 6-10 AM.
- Schedule a TVU to be performed within 2 weeks prior to Visit T7.
- Instruct the subject that on the morning of Visit T6.5, she should go ahead and take her morning dose of study drug at home. Inform the subject that she does not need to be fasting at Visit T6.5.
- Instruct the subject that the evening prior to Visit T7, she should note the date and exact time of her evening dose of study drug.
- Instruct the subject that on the morning of Visit T7, she should NOT take her morning dose of study drug.
- Instruct the subject that she needs to be fasting after 10 PM (water and maintenance medications allowed) the evening prior to Visit T7.

7.3.9. Treatment Period, Visit T6.5

At Visit T6.5, appropriate study site personnel should:

- Collect a blood sample for AST, ALT, alkaline phosphatase and total bilirubin.

7.3.10. Treatment Period, Visit T7

At Visit T7, appropriate study site personnel should:

- Record adverse events and update medications.
- Record the date and time of the subject's last dose of study drug prior to the visit.
- Administer the MBSQ, the HRQ, the PCOSQ, the PCOS Acne Questionnaire, the EQ-5D-5L, the PHQ-4, the WPAI:GH and the PGIC.
- Record vital signs and weight.
- Perform a complete PE.
- Record the subject's modified Ferriman-Gallwey score, ISGA score and Savin score.
- Obtain a 12-lead ECG.
- Collect fasting blood samples (as close to 8 AM as practicable and between 6-10 AM) for hematology, chemistry, insulin, HbA1c, lipid panel, PT, aPTT, TSH, SHBG, total

testosterone, free testosterone, bioavailable testosterone, LH, FSH, estradiol, progesterone and AMH.

- Collect a plasma PK sample. Record the exact time of each PK sample collection.
- Collect a urine sample for urinalysis and perform a urine pregnancy test.
- Perform a TVU (this may be performed within 2 weeks prior to Visit T7).
- Review the subject's electronic diary entries and reinforce instruction on the use of the daily diary as needed.
- Review the subject's collection and storage of thrice-weekly urine samples and reinforce instruction on the collection and storage of these samples as needed. Urine should be collected as first void samples on non-consecutive days when possible. Provide the subject with sufficient collection and storage materials to last until the subject's next study visit.
- Collect study drug and assess compliance.
- Schedule the next study visit (Visit F1) so that blood sample collection will occur as close to 8 AM as practicable and between 6-10 AM.
- Inform the subject that she does not need to be fasting at Visit F1.

7.4. Follow-up Period

During the 8-week Follow-up Period, the durability of study drug effects after discontinuation of study drug will be assessed. Blood samples for all of the Follow-up Period visits need to be collected as close to 8 AM as practicable and between 6-10 AM. The subject does not need to be fasting at any of the visits during the Follow-up Period.

7.4.1. Follow-up Period, Visit F1

At Visit F1, appropriate study site personnel should:

- Record adverse events and update medications.
- Administer the MBSQ.
- Record vital signs and weight.
- Record the subject's ISGA score.
- Collect blood samples (as close to 8 AM as practicable and between 6-10 AM) for hematology, chemistry, SHBG, total testosterone, free testosterone, bioavailable testosterone, LH, FSH, estradiol, progesterone and AMH.
- Collect a urine sample for and perform a urine pregnancy test.
- Review the subject's electronic diary entries and reinforce instruction on the use of the daily diary as needed.
- Review the subject's collection and storage of thrice-weekly urine samples and reinforce instruction on the collection and storage of these samples as needed. Urine

should be collected as first void samples on non-consecutive days when possible. Provide the subject with sufficient collection and storage materials to last until the subject's next study visit.

- Schedule the next study visit (Visit F2) so that blood sample collection will occur as close to 8 AM as practicable and between 6-10 AM.
- Inform the subject that she does not need to be fasting at Visit F2.

7.4.2. Follow-up Period, Visit F2

At Visit F2, appropriate study site personnel should:

- Record adverse events and update medications.
- Administer the MBSQ, the HRQ, the PCOSQ, the PCOS Acne Questionnaire, the EQ-5D-5L, the PHQ-4, and the WPAI:GH.
- Record vital signs and weight.
- Perform a brief PE.
- Record the subject's ISGA score.
- Collect blood samples (as close to 8 AM as practicable and between 6-10 AM) for SHBG, total testosterone, free testosterone, bioavailable testosterone, LH, FSH, estradiol, progesterone and AMH.
- Collect a urine sample for and perform a urine pregnancy test.
- Review the subject's electronic diary entries.
- At the completion of Visit F2, discharge the subject from the study.

7.5. Early Termination Visit

The Early Termination (ET) Visit will occur if a randomized subject is not able to complete the study procedures as detailed in the protocol for any reason.

- If the subject is to be withdrawn from the study prior to Visit T7, the ET visit will consist of the Visit T7 procedures (Section 7.3.9), including the TVU.
- If the subject is to be withdrawn from the study after Visit T7 but before Visit F2, the ET visit will consist of the Visit F2 procedures (Section 7.4.2).
- At the completion of the ET visit, discharge the subject from the study.

8. QUALITY CONTROL AND ASSURANCE

Before any subjects can be consented at an investigational site and prior to the conduct of any protocol-specific procedures, formal training of investigational site personnel will be conducted. The Investigator and all relevant investigational site staff are to be trained on all aspects of the study for which they are responsible. Site personnel may be trained at a formal initiation visit, at an Investigator's Meeting, or by another means as necessary. Monitoring and auditing procedures will be conducted in compliance with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP). Onsite verification of the eCRFs for completeness and clarity, crosschecking with source documents and clarification of administrative matters will be performed on a regular basis. Monitoring visits will occur at regular intervals as noted in the monitoring plan. Through frequent communications with the investigational site, the CRA will ensure that the investigation is conducted according to protocol design and all applicable regulatory requirements. Additional details on the monitoring of this study are provided in Section 10.5. During the course of the study, investigational sites, the study database and all associated study documentation may be subject to quality assurance audits by the Sponsor, or their appointed representatives, on a planned or as-needed basis. In addition, representatives of associated regulatory bodies may conduct inspections at their discretion. The Investigator is responsible for ensuring direct access to all protocol-specific materials for the purpose of these activities.

9. PLANNED STATISTICAL METHODS

A Statistical Analysis Plan that includes a more technical and detailed description of the planned statistical analyses will be prepared prior to study unblinding.

9.1. General Considerations

9.1.1. Sample Size

Assuming a study dropout rate of approximately 10-20%, a total of 110 subjects will be randomized in the study so that each dose group will have 50 subjects at a 1:1 allocation.

Sample size considerations were based on a multiple comparison Dunnett intersection test and a 1-sided alpha of 0.025. The standard deviation of change in days between start of menstruation was assumed to be 15 days. If the mean change in days between onset of menstruation was assumed to be 0 for the placebo group and 10 days for at least one active dose group, the study has a power of approximately 80-90% as demonstrated in simulations.

9.1.2. Randomization and Stratification

Patients who are confirmed as having met all study eligibility requirements will be randomized in a 1:1 ratio into the placebo and the MLE4901 40 mg BID dose groups. There are two stratification factors;

1) Baseline self-reported menstrual period frequency: a) <4/year and b) 4-6/year.

2) BMI: a) 22 to <35 kg/m^2 (mid-normal to obesity class I) and b) 35-45 kg/m^2 (obesity classes II/ III).

This is a double blind study in which subjects will be randomized by a web-based system by stratum using central randomization and a variable block design.

9.2. Analysis Populations

Efficacy – The primary efficacy analyses will include all randomized subjects (Intent-to-Treat; ITT). For efficacy analyses, subjects will be included in the treatment group to which they were randomized. Additional efficacy analyses will be performed on all subjects who complete at least 16 weeks of treatment (Evaluable Population).

Safety – The Safety Population will include all treated subjects. Safety analyses will be based on the Safety Population. For the safety analyses, subjects randomized to the placebo group who receive MLE4901 will be included in the treatment group of the study drug that they received.

Pharmacokinetic – The PK Population will include all subjects with measurable drug concentrations. PK analyses will be based on the PK population.

9.3. Demographics and Baseline Characteristics

Demographic and clinical characteristics of subjects randomized into this study will be summarized. For categorical variables, frequencies and percentages will be provided. Means with standard deviations or medians/percentiles will summarize non-categorical variables.

9.4. Efficacy

9.4.1. Efficacy Endpoints

9.4.1.1. Primary Efficacy Endpoint

- The change in the duration of menstrual cycles from Baseline to End-of-Treatment (EoT).

9.4.1.2. Key Secondary Efficacy Endpoint

- The number of menstrual periods during the Treatment Period

9.4.1.3. Additional Efficacy Endpoints

- The duration of menstrual cycles over the Treatment Period
- The change from Baseline in the duration of each menstrual cycle over the Treatment Period
- The change in the ovulation interval from Baseline to EoT
- The number of ovulations during the Treatment Period
- The duration of ovulation intervals over the Treatment Period
- The change from Baseline in the ovulation interval for each ovulation over the Treatment Period
- The time from the start of the last menstrual period prior to randomization to the first menstrual period after randomization
- The time to the first normal menstrual cycle duration
- The number of consecutive menstrual cycles of 21-35 days' duration over the Treatment Period
- The time from the last ovulation prior to randomization (or first dose of MPA, if no ovulation during Lead-in) to the first ovulation after randomization
- The time to the first normal ovulation interval
- The number of consecutive ovulation intervals of 21-35 days' duration over the Treatment Period
- The proportion of subjects with at least 4 self-reported menstrual periods over the Treatment Period
- The proportion of subjects having menstrual cycles of 21-35 days' duration for a continuous 6-month period during the Treatment Period
- The proportion of subjects having menstrual bleeding of 2-7 days' duration for a continuous 6-month period during the Treatment Period
- The proportion of subjects with normal menstrual cycles for a continuous 6-month period during the Treatment Period
- The change from Baseline in the severity of the subjects' self-identified Most Bothersome Symptom of PCOS
- The change from Baseline in the severity of each symptom of PCOS (oligo-/amenorrhea, hirsutism, acne and alopecia)
- The change from Baseline in testosterone (total, free and bioavailable), LH, FSH, LH/FSH, estradiol, progesterone and AMH
- The change from Baseline in the modified Ferriman-Gallwey score for hirsutism
- The change from Baseline in the Investigator's Static Global Assessment of acne score
- The change from Baseline in the Savin score for androgenic alopecia

- The change from Baseline in fasting glucose, insulin, total cholesterol, LDL, HDL and triglycerides
- The change from Baseline in systolic blood pressure, diastolic blood pressure and body mass index
- The duration of menstrual cycles over the Follow-up Period
- The duration of ovulation intervals over the Follow-up Period
- The change from Baseline in the frequency of removal of unwanted hair from the upper lip and chin
- The change from Baseline in the domain scores on the PCOSQ and the PCOS Acne Questionnaire
- The change from Baseline in the score on the EQ-5D-5L health state survey
- The change from Baseline in the domain scores on the Work Productivity and Activity Impairment: General Health Questionnaire (WPAI:GH)
- The change from Baseline in the mean total score, anxiety subscale score and depression subscale score on the PHQ-4

9.4.2. Efficacy Analysis Methodology

9.4.2.1. Primary Efficacy Endpoint

The Baseline menstrual cycle duration will be measured as the time from the start of the first menstrual period after the progestin challenge to the start of the next consecutive menstrual period. The EoT menstrual cycle duration will be the duration between the last two menstrual period start dates during the Treatment Period.

The change in the duration of menstrual cycles from Baseline to EoT will be analyzed with an ANOVA model including treatment and stratification factors following the Dunnett intersection test procedure to control for multiple comparison testing. Should the primary endpoint distribution depart from an approximate normal distribution, an appropriate non-parametric test will be utilized such as the Wilcoxon rank-sum test.

9.4.2.2. Key Secondary Efficacy Endpoint

The number of menstrual periods during the Treatment Period will be analyzed with an ANOVA model including treatment and stratification factors following the Dunnett intersection test procedure to control for multiple comparison testing. Should this key secondary endpoint distribution depart from an approximate normal distribution, an appropriate non-parametric test will be utilized such as the Wilcoxon rank-sum test.

9.4.2.3. Additional Efficacy Endpoints

No further adjustments for multiple group comparisons, multiple additional endpoints or multiple subgroups of interest are planned.

The ovulation interval duration will be analyzed in a similar manner as the menstrual cycle duration, with the exception that the analysis of this endpoint will utilize an ANOVA, instead of an ANCOVA model. Other continuous endpoints will utilize similar ANCOVA or ANOVA model methodology, as appropriate. Responder analyses and other categorical analyses will be based on the Cochran-Mantel-Haenszel (CMH) test or Fisher's exact test, as appropriate. Time-

to-event endpoints will be summarized using Kaplan-Meier estimates and compared using the log-rank test.

9.4.2.4. Exploratory Endpoints

Additional efficacy endpoints will be pre-specified in the Statistical Analysis Plan, including sensitivity analyses associated with drug compliance and missing data issues.

9.5. Safety

9.5.1. Safety Endpoints

Safety endpoints will include the incidence of treatment-emergent adverse events and serious adverse events, as well as changes from baseline in clinical laboratory tests, vital signs, physical examinations and ECG parameters.

9.5.2. Safety Analyses

Adverse events counts (overall, as well as by severity, causality and seriousness) will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Descriptive statistics and shift tables will be used to summarize continuous laboratory, blood pressure and ECG parameters. Counts and shift tables will be used for categorical lab parameters.

9.6. Pharmacokinetics

9.6.1. Pharmacokinetic Endpoints

- The C_{max}, T_{max}, AUC, $t_{1/2}$ and other PK parameters of MLE4901 and its major metabolite (as appropriate and as the data allow)
- The relationship between C_{max} and AUC vs. the change in the duration of menstrual cycles from Baseline to EoT; other PK/PD relationships may be explored as appropriate and as data allow

9.6.2. Pharmacokinetic Analyses

Individual PK parameters will be derived using the WinNonlin software and table summaries will be provided using descriptive summary statistics.

9.7. Interim Analysis

No interim analysis is planned for this study.

10. ADMINISTRATIVE CONSIDERATIONS

10.1. Institutional Review Board (IRB)/Ethics Committee (EC)

Prior to initiation of the study at each investigational site, the protocol, the informed consent form(s), the subject information sheet(s), details of the subject recruitment procedures and any other relevant study documentation will be submitted to the responsible local and/or national IRB/EC. A letter from the IRB/EC indicating approval of the Investigator and study site must be submitted to the study Sponsor. All reviews and approval by the IRB/EC will be in accordance with Title 21 of the Code of Federal Regulations (CFR), Part 56. Initial IRB approval and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will promptly report any new information that may adversely affect the safety of subjects or the conduct of the study to the IRB/EC. Similarly, the Investigator will submit written summaries of the study status to the IRB/EC annually, or more frequently if requested. Upon completion of the study, the Investigator will provide the IRB/EC with a brief report of the outcome of the study, if required.

10.2. Ethical Conduct of the Study

The guidelines of the World Medical Association Declaration of Helsinki in its revised edition (48th General Assembly, Somerset West, Republic of South Africa, October 1996), the guidelines of ICH GCP (CPMP/ICH/135/95), as well as the demands of national drug and data protection laws and other applicable regulatory requirements, will be strictly followed.

10.3. Subject Information and Consent

The Investigator is responsible for ensuring that subjects do not undergo any study-related examination or activity before giving informed consent. The subject must give written consent after the receipt of detailed information regarding the study. The verbal explanation will cover all the elements specified in the written information provided to the subject. If the written informed consent is provided by the legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained.

The Investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and must be provided with more information if requested. At the end of the interview, the subject may be given time to reflect and can request more time if needed. The subject and/or legal guardian will be required to sign and date the informed consent form. After completion, informed consent forms will be kept and archived by the PI in the PI study file.

It should be emphasized to the subject that he or she is at liberty to either discontinue study drug and/or withdraw consent to participate at any time, without penalty or loss of benefits to which he or she is otherwise entitled. Subjects who refuse to give or withdraw written informed consent may not be included or continued in this study, but this will not affect their subsequent care.

Please refer to Title 21 of the CFR, Part 50 – Protection of Human Subjects for specific details on this regulation.

10.4. Subject Confidentiality

Personal and sensitive data will be treated as confidential. The results of the study will be made available for review by authorized representatives of the Sponsor and/or submitted to the IRB/EC and regulatory authorities.

Prior to any screening procedures being performed, the subject's consent is required for the data to be used for these purposes and to gain direct access to their medical records for data verification purposes. The subject must be assured that their identity will be protected. To facilitate this, a unique identification number will be assigned and it will be used when reporting study-related data.

Additionally, in the US, the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") requires that all subjects grant permission to use their personal health information. Therefore, in addition to the protocol-specific ICF, each subject located in the United States (US) will be asked to provide authorization to use his/her personal health information by signing a separate HIPAA Authorization Form.

10.5. Study Monitoring

It is understood that the Sponsor or its designee (e.g., the CRA) will contact and visit the Investigator regularly for monitoring purposes. The CRA will be allowed, on request, to inspect the various records of the study (i.e., eCRFs, source documents and any other pertinent data), provided that subject confidentiality is maintained in accordance with local requirements. It will be the CRA's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify adherence to the protocol and to ensure the completeness, consistency and accuracy of the data entered. The CRA must have access to all subject records needed to verify the entries on the eCRF. The Investigator agrees to cooperate with the CRA to ensure that problems detected during these monitoring visits are resolved.

Before an investigational site can consent a subject into the study, a representative of Millendo Therapeutics, Inc. will evaluate the investigational study site to assess the site including but not limited to:

- Determine the adequacy of the facilities including the site's ability to carry out the protocol
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence and the responsibilities of Millendo Therapeutics, Inc. or its representatives. This will also be documented in a Clinical Study Agreement between Millendo Therapeutics, Inc. and the Investigator.

During the study, a monitor from Millendo Therapeutics, Inc. or representative will have regular contacts with the investigational site, for the following but not limited to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice and other records relevant to the study. This will require direct access to all original records for each subject (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to Millendo Therapeutics, Inc.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Millendo Therapeutics, Inc. and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

10.6. Audits and Inspections

Authorized representatives of Millendo Therapeutics, Inc., a regulatory authority, an Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. Millendo Therapeutics, Inc. may perform Clinical Quality Assurance (CQA) audit randomly at a sample of clinical sites, or for cause as warranted. The purpose of a Millendo Therapeutics, Inc. CQA audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization and any applicable regulatory requirements. These audits will be independent of routine monitoring by the CRA and initiated with prior written notification provided to the site.

The Investigator should contact Millendo Therapeutics, Inc. immediately if contacted by a regulatory agency about an inspection.

10.7. Case Report Forms and Study Records

This study will utilize an electronic data capture system for the management of clinical data. The data will be collected in electronic form (i.e., via an eCRF) to allow for data entry at the site from source documentation directly into the electronic database. Access to the electronic system will be restricted and users will only be able to access the system via authorized individual accounts. All changes to data in the database will be tracked and time stamped automatically, including updates to data entries and resolution of data queries generated by the CRA or data reviewer.

Training will be provided to all system users based on their individual access and use requirements initially and ongoing throughout the course of the study as needed. Documentation of training will be kept in the site regulatory file and in Sponsor's TMF.

A comprehensive Data Management Plan will be written outlining the standard operating procedures, internal/external security safeguards, system and change controls and training

procedures and will be filed in the Sponsor's TMF. A cumulative record will also be kept of the user and access privileges for all authorized users across the study.

The system and procedures for electronic database set-up, entry, review, access, security and auditing are designed in specific compliance with 21 CFR 11 and the Food and Drug Administration's (FDA's) Part 11 Guidance for Industry supplement "Computerized Systems Used in Clinical Investigations" dated May 2007. Any additional electronic systems that may be used by vendors (e.g., PK) or clinical sites (e.g., electronic medical records used as source documents) should comply with these same regulatory standards.

As a final step in the data management process, a 100% quality control review will be performed on the key efficacy and safety parameters. In addition, a random subject sample (approximately 10%) will be selected to perform a database audit. The purpose of this audit is to detect systematic and random errors.

All unused study materials are to be returned or destroyed as instructed by Millendo Therapeutics, Inc. after the study has been completed.

10.8. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) is planned for this study. The DSMB will be provided with a comprehensive safety package that includes AEs, SAEs and laboratory tests. Section 6.23 specifies the procedures for reporting AEs and SAEs. SAEs will be reviewed individually, cumulatively and in the context of what is already known about the safety profile of MLE4901 to assess whether the reported SAEs are a signal of a change in the benefit/risk profile. All SAEs are to be reported by the Investigator to the IRB in a timely manner. Further details regarding the responsibilities of the DSMB can be found in the DSMB Charter.

10.9. Protocol Deviations

Protocol deviations from inclusion/exclusion criteria, concomitant medication restrictions and from any other protocol requirements that could, at least hypothetically, result in significant risk to the subject and/or affect the outcome of the study will be collected. Additionally, nonadherence to the study procedures or schedule as defined by the protocol such as a missed procedure or an out-of-window study visit will be documented as protocol deviations.

10.10. Access to Source Documentation

The Investigator must permit the authorized Sponsor, agents of the Sponsor and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held and to inspect and copy all records relating to an investigation including subject records. To ensure the accuracy of data submitted, it is mandatory that representatives of Millendo Therapeutics, Inc. and of the regulatory agencies have direct access to source documents (e.g., subject medical records, charts, laboratory reports) for the purpose of quality assurance audits either by Millendo Therapeutics, Inc. or their appointed representatives. Subject confidentiality will be protected at all times.

10.11. Data Generation and Analysis

Data processing and management will be performed by Millendo Therapeutics, Inc. or its designee. Data will be promptly entered into the study database by the site and reviewed and issues resolved prior to database closure.

Personal and sensitive personal data will be treated as confidential. The results of the study will be made available for review by authorized representatives of the Millendo Therapeutics, Inc. and/or submitted to the IRB/EC and regulatory authorities.

10.12. Retention of Records

Copies of all study documents should be retained by the PI for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product, in accordance with 21 CFR 312.62. These documents should be retained for a longer period, however, if required by regulatory requirements or by agreement with the Sponsor. The Investigator must inform the Sponsor and obtain agreement prior to study documents being moved or destroyed. It is the responsibility of Millendo Therapeutics, Inc. to inform the Investigator/institution as to when these documents no longer need to be retained. The final database will be archived by the Millendo Therapeutics, Inc. according to regulatory requirements.

10.13. Financial Disclosure

Investigators and Subinvestigators are required to provide full disclosure of any financial relationship to the Sponsor or its designee(s) prior to participation in any study-related activities. Additionally, Investigators and Subinvestigators are required to promptly provide updated information to the Sponsor or its designee(s) regarding any relevant changes in financial interests that occur during the course of the study and for 1 year after completion of the study. For additional guidance, refer to 21 CFR 312.53(c) (4), 312.64(d), 812.43(c) (5), 812.110(d).

10.14. Premature Termination of the Study

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and the regulatory authority(s) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/EC will also be promptly informed and provided with the reason(s) for the termination or suspension by Millendo Therapeutics, Inc. or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

10.15. Clinical Study Report

A CSR will be written for this study with a structure and content that will conform to the ICH guidance, “Structure and Content of Clinical Study Reports, ICH Topic E3, July 1996.”

10.16. Subject Insurance and Indemnity

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects’ participating in this study. The terms of insurance will be kept in the Sponsor’s regulatory files.

10.17. Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The IRB/EC must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The Investigator must not implement any deviation from or change to the protocol without discussion and agreement by the Sponsor in writing and prior review and documented approval/favorable opinion of the amendment from the relevant IRB or EC, except where it is necessary to eliminate an immediate hazard to study subjects or where the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor or change of telephone number).

Protocol amendments will be submitted to the appropriate authority(s) as required by the applicable regulatory requirement(s).

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12. APPENDICES

Appendix 1. STUDY SCHEDULE

Table 7: Study Schedule

	Screening/ Wash-out		Lead-in		Treatment										Follow-up	
Week:†	**-20 to -8**		**-8**	**-4**	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**
Visit:†	**S1**	**(W1[c])**	**L1**	**L2**	**T 1**	**T 2**	**T3**	**T3.5**	**T4**	**T5**	**T5.5**	**T6**	**T6.5**	**T7/ EoT**	**F1**	**F2/ EoS**
Informed Consent	X															
Inclusion/ Exclusion Criteria	X		X		X											
Medical History & Demographics	X															
Number of Menstrual Periods/12 Months	X															
MBSQ	X		X	X	X	X	X		X	X		X		X	X	X
HRQ	X		X		X					X		X		X		X
PCOSQ and PCOS Acne Questionnaire					X					X				X		X
EQ-5D-5L					X					X				X		X
PHQ-4					X					X				X		X
WPAI:GH					X					X				X		X
PGIC														X		
Vital Signs, Height and Weight[a]	X		X	X	X	X	X		X	X		X		X	X	X
Physical Examination[b]	X				X					X				X		X
Pap Test[b]	X															

	Screening/ Wash-out		Lead-in		Treatment										Follow-up	
Week:†	**-20 to -8**		**-8**	**-4**	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**
Visit:†	**S1**	**(W1[c])**	**L1**	**L2**	**T 1**	**T 2**	**T3**	**T3.5**	**T4**	**T5**	**T5.5**	**T6**	**T6.5**	**T7/ EoT**	**F1**	**F2/ EoS**
Modified Ferriman-Gallwey Score	X				X									X		
ISGA Score	X				X	X	X		X	X		X		X	X	X
Savin Score	X				X									X		
12-lead ECG	X				X					X				X		
Hematology & Chemistry	X			X	X	X	X	AST, ALT, ALK-P, T. Bili	X	X	AST, ALT, ALK-P, T. Bili	X	AST, ALT, ALK-P, T. Bili	X	X	
Insulin, HbA1c, Lipid Panel	X[c]				X									X		
PT, aPTT, TSH	X	(TSH[c])		X										X		
Viral Screen (HBsAg, HCV, HIV)	X															
Serum Hormone Levels (SHBG, Total T, Free T, Bioavailable T, LH, FSH, E2, P, AMH, 17-OHP, Prolactin, DHEA-S)[c]	X[c]	X[c]		X	X		X		X	X		X		X	X	X
Serum Pregnancy Test	X															
Urine Pregnancy Test		X	X	X	X	X	X		X	X		X		X	X	X
Urinalysis	X				X									X		

	Screening/ Wash-out		Lead-in		Treatment										Follow-up	
Week:[†]	**-20 to -8**		**-8**	**-4**	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**
Visit:[†]	**S1**	**(W1[c])**	**L1**	**L2**	**T 1**	**T 2**	**T3**	**T3.5**	**T4**	**T5**	**T5.5**	**T6**	**T6.5**	**T7/ EoT**	**F1**	**F2/ EoS**
Urine Drug Screen[d]	X															
TVU[e]	X													X		
Menstrual Bleeding Electronic Diary Instruction/ Review			X	X	X	X	X		X	X		X		X	X	X
Thrice-Weekly Urine Sample Collection			Subjects to self-collect first void urine samples three times per week on non-consecutive days when possible at home and store samples as directed for assessment of pregnanediol-3-glucuronide for ovulation determination.													
Begin MPA x 5 Days			X													
Randomization					X											
Dispense Study Drug					X		X		X	X		X				
Collect Study Drug/Assess Compliance						X	X		X	X		X		X		
Time of Last Study Drug Dose							X			X				X		
Plasma PK[f]					X		X			X				X		
Medications	X	X	X	X	X	X	X		X	X		X		X	X	X
Adverse Events		X	X	X	X	X	X		X	X		X		X	X	X

17-OHP: 17-hydroxyprogesterone; ALK-P: alkaline phosphatase; AMH: anti-Müllerian hormone; aPTT: activated partial thromboplastin time; DHEA-S: dehydroepiandrosterone sulfate; E2: estradiol; ECG: electrocardiogram; EoS: End-of-Study; EoT: End-of-Treatment; EQ-5D-5L: EuroQoL-5 Dimensions-5 Levels Survey; FSH: follicle-stimulating hormone; HbA1c: hemoglobin A1c; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HRQ: Hair Removal Questionnaire; ISGA: Investigator's Static Global Assessment (of acne); LH: luteinizing hormone; MBSQ: PCOS Most Bothersome Symptom Questionnaire; MPA: medroxyprogesterone acetate; PCOSQ: PCOS Questionnaire; P: progesterone; Pap: Papanicolaou; PCOS: polycystic ovary syndrome; PE: physical examination; PGIC: Patient's Global Impression of Change; PHQ-4: Patient's Health Questionnaire-4; PK: pharmacokinetic(s) (samples); PT: prothrombin time; SHBG: sex hormone-binding globulin; T: testosterone; TBili: total bilirubin; TSH: thyroid-stimulating hormone; TVU: transvaginal ultrasound; WPAI:GH: Work Productivity and Activity Impairment Questionnaire: General Health

† Day 1 of the study is defined as the day the subject first receives study drug in the clinic. Study visits have a window of ± 3 days. Subjects should be fasting prior to Visits S1, T1, and T7. The subject should take her evening dose of study drug the evening prior to study visits during the Treatment Period (and also note the date and exact time of the last dose prior to Visits T3, T5 and T7). On the morning of Visits T1, T2, T3, T4, T5, and T6, subjects should wait to take their morning dose of study drug until directed by site personnel at the study site. On the morning of Visit T7, subjects should not take their morning dose of study drug. On the morning of Visits T3.5, 5.5, and 6.5, subjects should go ahead and take the study drug at home prior to the study visit.

[a] Height at Screening only.

[b] A complete physical examination (PE) will be performed at Visits S1, T1 and T7. A brief PE will be performed at Visits T5 and F2. At all other visits, targeted PEs may be performed if needed based on adverse events and positives from review of systems. A Papanicolaou (Pap) test is done as part of the physical examination during Screening only; documented results from a Pap test from within the year prior to Screening may be used instead. Women under 21 years of age at Screening do not require a Pap.

[c] Insulin, LH, E2, P, and AMH levels will not be done at Screening or Wash-out. Hormone levels should be drawn in the morning, as close to 8 AM as practicable and between 6-10 AM. 17-OHP, prolactin and DHEA-S will be done at Screening (or Wash-out, if wash-out is required) only. Subjects who require a wash-out of medications that affect hormone levels should NOT have their hormone levels (SHBG, total testosterone, free testosterone, bioavailable testosterone, FSH, 17-hydroxyprogesterone, prolactin, and DHEA-S) drawn at S1. Instead, they should complete the required wash-out and return to the site for hormone levels at the wash-out visit (Visit W1). Subjects on thyroid hormone replacement who require wash-out should also have an additional TSH level done at Visit W1. Subjects who do not require wash-out should not undergo a wash-out visit.

[d] Urine drug screen for cocaine, amphetamines and opioids.

[e] A TVU should be performed and results reviewed prior to randomization in subjects who meet all other inclusion and exclusion criteria. Subject who require wash-out of medications should have hormone levels drawn after wash-out. Subjects do not need to wait for Screening/Wash-out hormone results prior to proceeding with the TVU and the Lead-in Period. All Screening/Wash-out hormone results should be reviewed and confirmed to be inclusionary prior to Randomization.

[f] At Visit T1, plasma for PK assessments will be collected within 30 minutes before the first dose and at 1, 2, 2.5, 3 and 4 hours postdose. At Visits T3 and T5, a trough level will be collected within 30 minutes predose. At Visit T7/EoT, a trough level will be collected.

APPENDIX 2. PCOS MOST BOTHERSOME SYMPTOM QUESTIONNAIRE

The following are examples of the questions that would be asked if the questionnaire were in paper format. The questions may be modified slightly for other formats (e.g., tablet).

Visits: Screening, Lead-in and Randomization

A. Most Bothersome Symptom

Please select the symptom of PCOS that is **most bothersome** to you. If your most bothersome symptom is not listed, please select "Other" and write your most bothersome symptom in the space provided.

1 – Infrequent or absent menstrual periods

2 – Unwanted facial and/or body hair

3 - Acne

4 – Hair thinning or hair loss (on your head)

5 - Other:_____

B. Bothersomeness of PCOS symptoms

During the past two weeks, how much did each of the following symptoms bother you?

	Not at all	Slightly	Moderately	Quite a bit	Extremely
1. Infrequent or absent menstrual periods	☐	☐	☐	☐	☐
2. Unwanted facial and/or body hair	☐	☐	☐	☐	☐
3. Acne	☐	☐	☐	☐	☐
4. Hair thinning or hair loss (on your head)	☐	☐	☐	☐	☐

If your most bothersome PCOS symptom from Question A is not listed above, please write it in the space provided.

During the past two weeks, how much did this symptom bother you?

	Not at all	Slightly	Moderately	Quite a bit	Extremely
5. *<fill in>*	☐	☐	☐	☐	☐

Visits: Screening, Lead-in and Randomization, continued

C. Severity of PCOS symptoms

During the past two weeks, how would you rate your:

	None	Mild	Moderate	Severe	Very severe
1. Unwanted facial and/or body hair	☐	☐	☐	☐	☐
2. Acne	☐	☐	☐	☐	☐
3. Hair thinning or hair loss (on your head)	☐	☐	☐	☐	☐

If your most bothersome PCOS symptom from Question A is not listed above, please write it in the space provided.

During the past two weeks, how would you rate your:

	None	Mild	Moderate	Severe	Very severe
4. *<fill in>*	☐	☐	☐	☐	☐

Visits: All Post-Randomization Visits

A. Severity of PCOS symptoms

During the <u>past two weeks</u>, how would you rate your:

	None	Mild	Moderate	Severe	Very severe
1. Unwanted facial and/or body hair	☐	☐	☐	☐	☐
2. Acne	☐	☐	☐	☐	☐
3. Hair thinning or hair loss (on your head)	☐	☐	☐	☐	☐

If your most bothersome PCOS symptom from the <u>randomization visit</u> is not listed above, please write it in the space provided.

During the <u>past two weeks</u>, how would you rate your:

	None	Mild	Moderate	Severe	Very severe
4. *<fill in>*	☐	☐	☐	☐	☐

APPENDIX 3. HAIR REMOVAL QUESTIONNAIRE

Over the <u>past two months</u>, approximately how often did you remove unwanted hair from your:	Every day	2-3x/ week	Once per week	2-3x/ month	Once per month	Less often than once per month	Never
1. Upper lip:	☐	☐	☐	☐	☐	☐	☐
2. Chin:	☐	☐	☐	☐	☐	☐	☐

APPENDIX 4. POLYCYSTIC OVARY SYNDROME QUESTIONNAIRE AND PCOS ACNE QUESTIONNAIRE

POLYCYSTIC OVARY SYNDROME QUESTIONNAIRE (PCOSQ)

To what extent have you felt that growth of visible hair on your chin has been a problem for you during the last two weeks:

	A Severe Problem	A Major Problem	A Moderate Problem	Some Problem	A Little Problem	Hardly any Problem	No Problem
1. Growth of visible hair on chin?	☐	☐	☐	☐	☐	☐	☐

During the past two weeks, how much of the time have you felt:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the time	A Little of the Time	Hardly any of the Time	None of the Time
2. Depressed as a result of having PCOS?	☐	☐	☐	☐	☐	☐	☐
3. Concerned about being overweight?	☐	☐	☐	☐	☐	☐	☐
4. Easily tired?	☐	☐	☐	☐	☐	☐	☐
5. Concerned with infertility problems?	☐	☐	☐	☐	☐	☐	☐
6. Moody as a result of having PCOS	☐	☐	☐	☐	☐	☐	☐

In relation to your last menstruation, how much were the following issues a problem for you:

	A Severe Problem	A Major Problem	A Moderate Problem	Some Problem	A Little Problem	Hardly any Problem	No Problem
7. Headaches?	☐	☐	☐	☐	☐	☐	☐
8. Irregular menstrual periods?	☐	☐	☐	☐	☐	☐	☐

To what extent has growth of visible hair on your upper lip been a problem for you during the last two weeks:

	A Severe Problem	A Major Problem	A Moderate Problem	Some Problem	A Little Problem	Hardly any Problem	No Problem
9. Growth of visible hair on upper lip?	☐	☐	☐	☐	☐	☐	☐

During the past two weeks, how much of the time have you:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the time	A Little of the Time	Hardly any of the Time	None of the Time
10. Had trouble dealing with your weight?	☐	☐	☐	☐	☐	☐	☐
11. Had low self-esteem as a result of your having PCOS?	☐	☐	☐	☐	☐	☐	☐
12. Felt frustration in trying to lose weight?	☐	☐	☐	☐	☐	☐	☐
13. Felt afraid of not being able to have children?	☐	☐	☐	☐	☐	☐	☐
14. Felt frightened of getting cancer?	☐	☐	☐	☐	☐	☐	☐

Over the last two weeks, to what extent have the following issues been a problem for you:

	A Severe Problem	A Major Problem	A Moderate Problem	Some Problem	A Little Problem	Hardly any Problem	No Problem
15. Growth of visible hair on your face?	☐	☐	☐	☐	☐	☐	☐
16. Embarrassment about excessive body hair?	☐	☐	☐	☐	☐	☐	☐

During the past two weeks how much of the time have you been:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the time	A Little of the Time	Hardly any of the Time	None of the Time
17. Worried about having PCOS?	☐	☐	☐	☐	☐	☐	☐
18. Self-conscious as a result of having PCOS?	☐	☐	☐	☐	☐	☐	☐

In relation to your last menstruation, how much were the following issues a problem for you:	A Severe Problem	A Major Problem	A Moderate Problem	Some Problem	A Little Problem	Hardly any Problem	No Problem
19. Abdominal bloating?	☐	☐	☐	☐	☐	☐	☐
20. Late menstrual period?	☐	☐	☐	☐	☐	☐	☐
21. Menstrual cramps?	☐	☐	☐	☐	☐	☐	☐
How much of the time during the last two weeks did you:	All of the Time	Most of the Time	A Good Bit of the Time	Some of the time	A Little of the Time	Hardly any of the Time	None of the Time
22. Feel like you are not sexy because of being overweight?	☐	☐	☐	☐	☐	☐	☐
23. Feel a lack of control over the situation with PCOS?	☐	☐	☐	☐	☐	☐	☐
24. Have difficulties staying at your ideal weight?	☐	☐	☐	☐	☐	☐	☐
25. Feel sad because of infertility problems?	☐	☐	☐	☐	☐	☐	☐
To what extent has growth of visible body hair been a problem for you during the last two weeks:	A Severe Problem	A Major Problem	A Moderate Problem	Some Problem	A Little Problem	Hardly any Problem	No Problem
26. Growth of visible body hair?	☐	☐	☐	☐	☐	☐	☐

(Cronin 1998, Jones 2004, Guyatt 2004)

PCOS ACNE QUESTIONNAIRE

To what extent was acne a problem for you during the last two weeks:	A Severe Problem	A Major Problem	A Moderate Problem	Some Problem	A Little Problem	Hardly any Problem	No Problem
1. Acne during the last two weeks?	☐	☐	☐	☐	☐	☐	☐
How much of the time during the last two weeks did you:	All of the Time	Most of the Time	A Good Bit of the Time	Some of the time	A Little of the Time	Hardly any of the Time	None of the Time
2. Feel unattractive because of acne?	☐	☐	☐	☐	☐	☐	☐
3. Feel depressed as a result of acne?	☐	☐	☐	☐	☐	☐	☐
In relation to your last menstruation, how much was acne a problem for you:	A Severe Problem	A Major Problem	A Moderate Problem	Some Problem	A Little Problem	Hardly any Problem	No Problem
4. Acne in relation to your last menstruation?	☐	☐	☐	☐	☐	☐	☐

(Barnard 2007)

APPENDIX 5. EQ-5D-5L, TABLET VERSION

English version for the USA

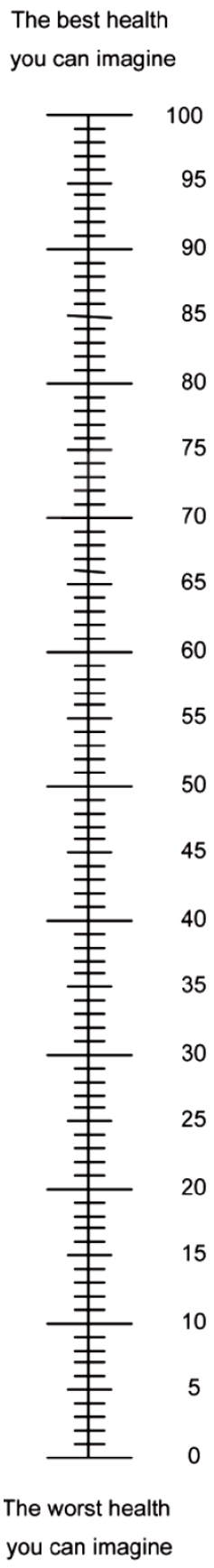
Please tap the ONE box that best describes your health TODAY.

MOBILITY	
I have no problems walking	☐
I have slight problems walking	☐
I have moderate problems walking	☐
I have severe problems walking	☐
I am unable to walk	☐
SELF-CARE	
I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐
PAIN/DISCOMFORT	
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐
ANXIETY/DEPRESSION	
I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

EQ-5D-5L Visual Analog Scale for the US

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
  100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please tap on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY ☐



http://www.euroqol.org/eq-5d-products/eq-5d-5l.html

APPENDIX 6. PATIENT'S HEALTH QUESTIONNAIRE-4

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Little interest or pleasure in doing things	0	1	2	3
4. Feeling down, depressed, or hopeless	0	1	2	3

(*For office coding: Total Score T*_____ = _____ + _____ + _____)

Scoring

PHQ-4 total score ranges from 0 to 12, with categories of psychological distress being:

- None 0-2
- Mild 3-5
- Moderate 6-8
- Severe 9-12

Anxiety subscale = sum of items 1 and 2 (score range, 0 to 6)

Depression subscale = sum of items 3 and 4 (score range, 0 to 6)

On each subscale, a score of 3 or greater is considered positive for screening purposes.

(Kroenke 2009)

APPENDIX 7. WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: GENERAL HEALTH V2.0

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

http://www.reillyassociates.net/WPAI_GH.html

APPENDIX 8. PATIENT'S GLOBAL IMPRESSION OF CHANGE

Compared to when I first started study drug:	Much better	Moderately better	A little better	No different	A little worse	Moderately worse	Much worse
1. My acne is now:	☐	☐	☐	☐	☐	☐	☐
2. The unwanted hair on my face and body is now:	☐	☐	☐	☐	☐	☐	☐
3. My PCOS is now:	☐	☐	☐	☐	☐	☐	☐
4. The regularity of my periods is now:	☐	☐	☐	☐	☐	☐	☐

APPENDIX 9. DAILY MENSTRUAL DIARY

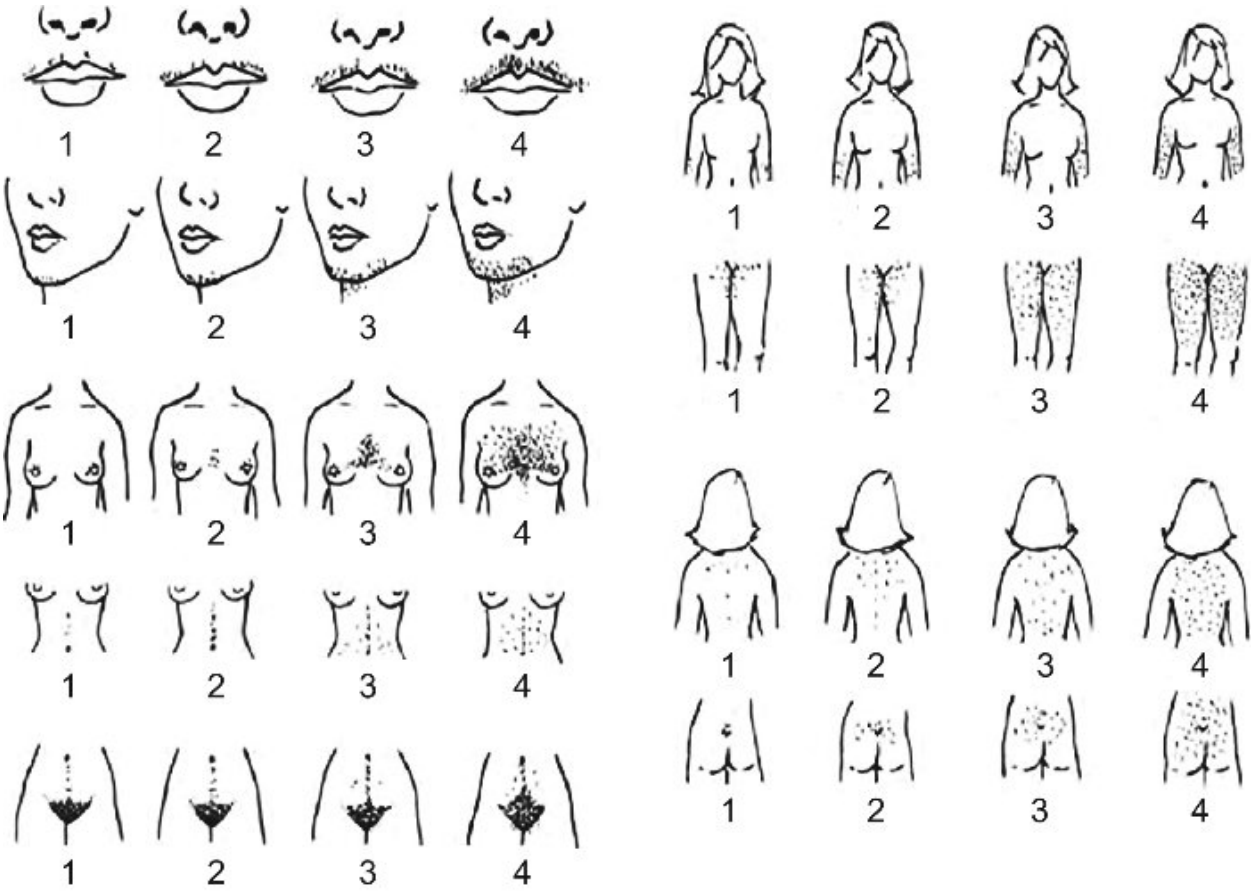
1. What type of vaginal bleeding did you have during the past 24 hours? If you experienced both spotting and bleeding, please select 'bleeding.'

- ☐ None
- ☐ Spotting
- ☐ Bleeding

2. During the past 24 hours, how heavy was your vaginal bleeding? *(Only ask if Q1 is answered with 'bleeding.')*

- ☐ Light
- ☐ Moderate
- ☐ Heavy

APPENDIX 10. MODIFIED FERRIMAN-GALLWEY HIRSUTISM SCALE



Each of the nine androgen-sensitive body areas in the diagram above is assigned a score from 0 (no excess hair) to 4 and these are summed to provide a hirsutism score (Ferriman 1961; Hatch 1981).

APPENDIX 11. INVESTIGATOR'S STATIC GLOBAL ASSESSMENT OF ACNE

0	=	Clear skin with no inflammatory or noninflammatory lesions
1	=	Almost clear: rare non-inflammatory lesions with no more than rare papules
2	=	Mild severity: greater than Grade 1, some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only; no nodular lesions)
3	=	Moderate severity: greater than Grade 2, up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4	=	Severe: greater than Grade 3, up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions
5	=	Very severe: many noninflammatory and inflammatory lesions and more than a few nodular lesions. May have cystic lesions

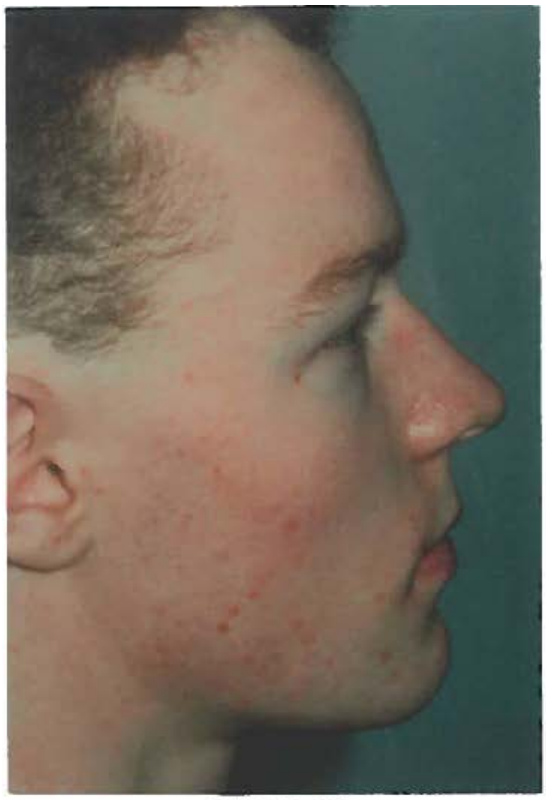
Adapted from US Food and Drug Administration Guidance for Industry: Acne Vulgaris: Developing Drugs for Treatment. September 2005, Table 1, page 9. Tazorac® Medical Review 2012, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202428Orig1s000MedR.pdf. Table 8, p 20.

For photographic equivalents for the above ISGA scores, see the Leeds Revised Acne Grading System in Appendix 12 .

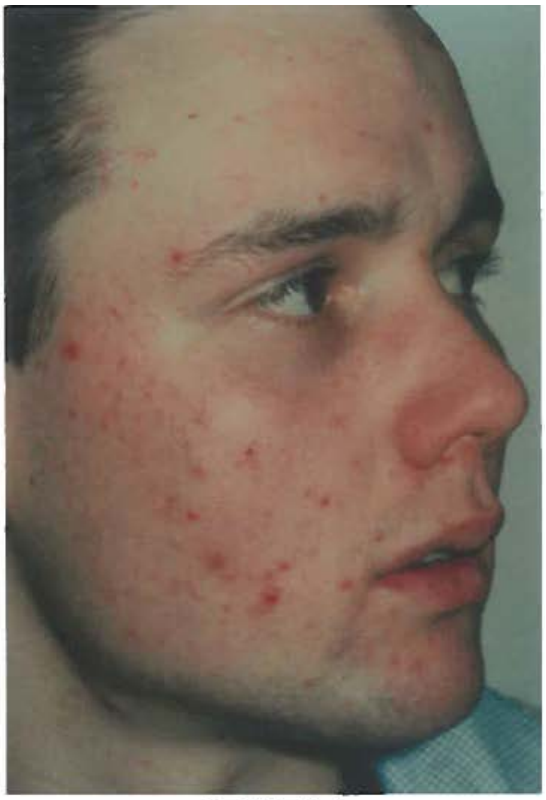
ISGA Score	Leeds Photographic Equivalents (Appendix 12)
1	Grade 1.0
2	Grade 2.0-3.0
3	Grades 4.0-6.0
4	Grade 7.0-9.0
5	Grades 10.0-12.0

APPENDIX 12. LEEDS REVISED ACNE GRADING SYSTEM

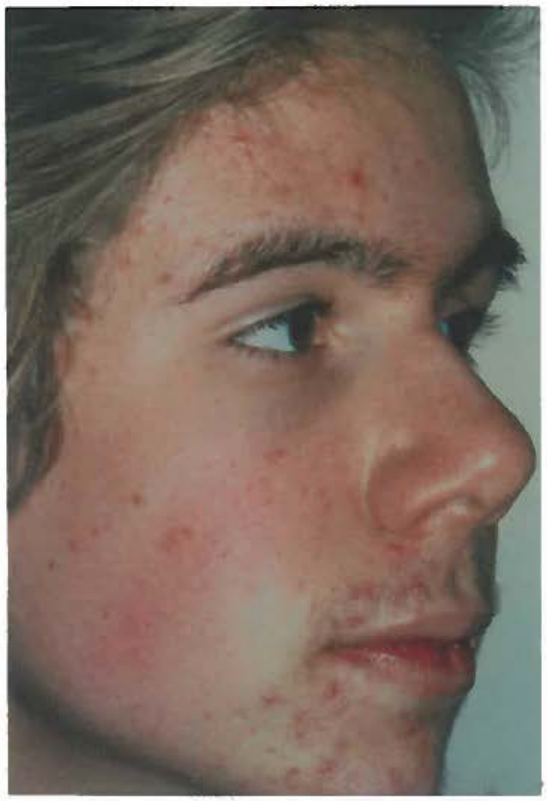
(O'Brien 1998)



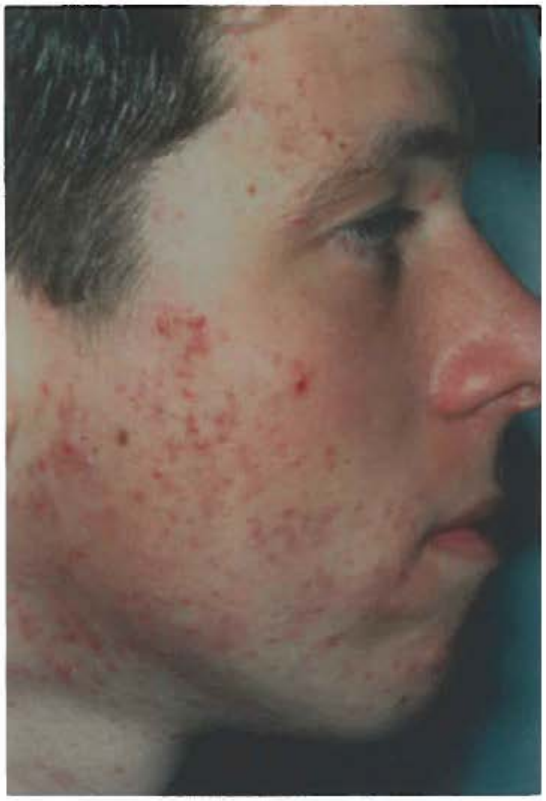
GRADE 1.0



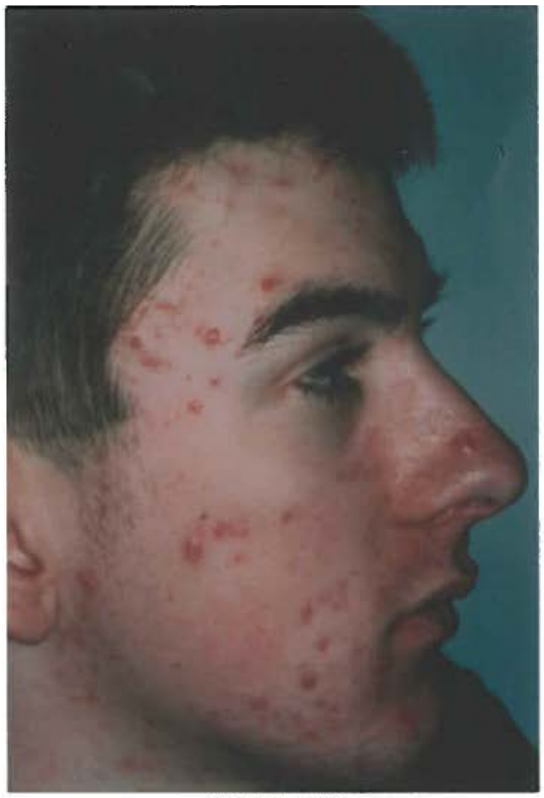
GRADE 2.0



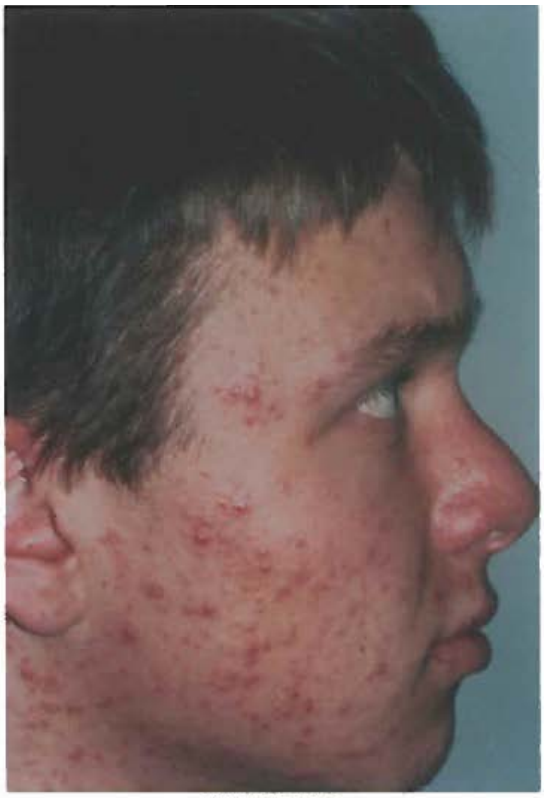
GRADE 3.0



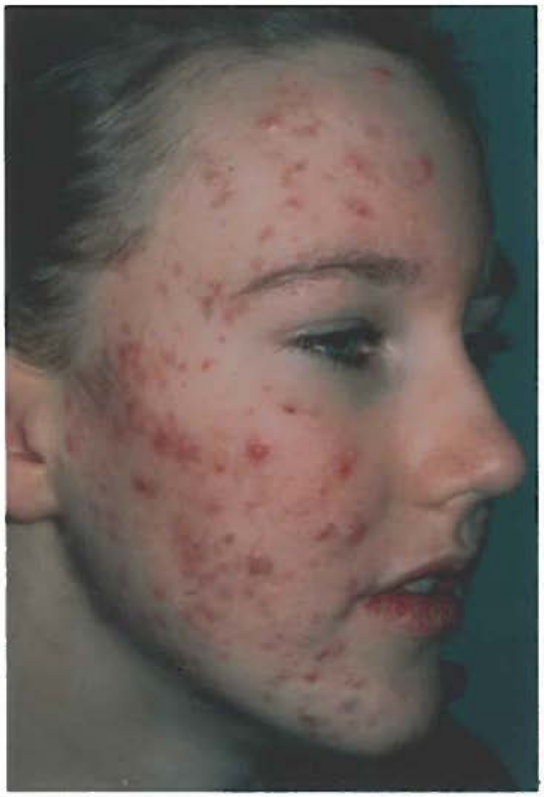
GRADE 4.0



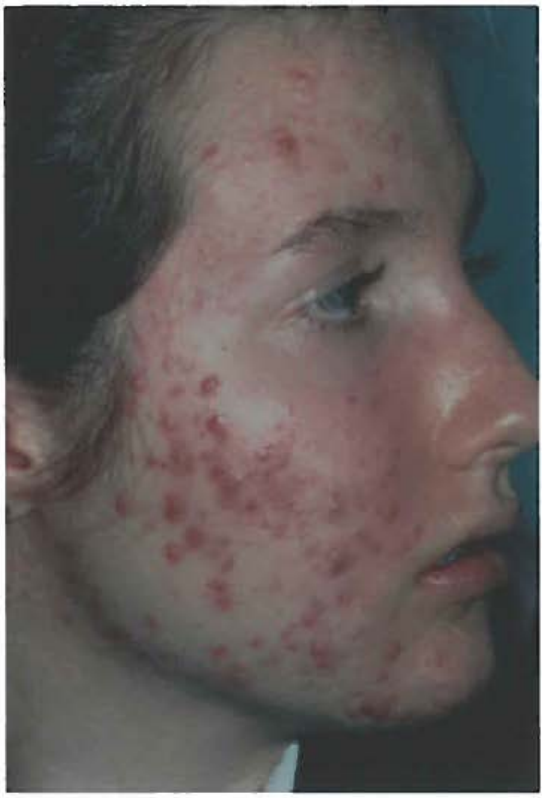
GRADE 5.0



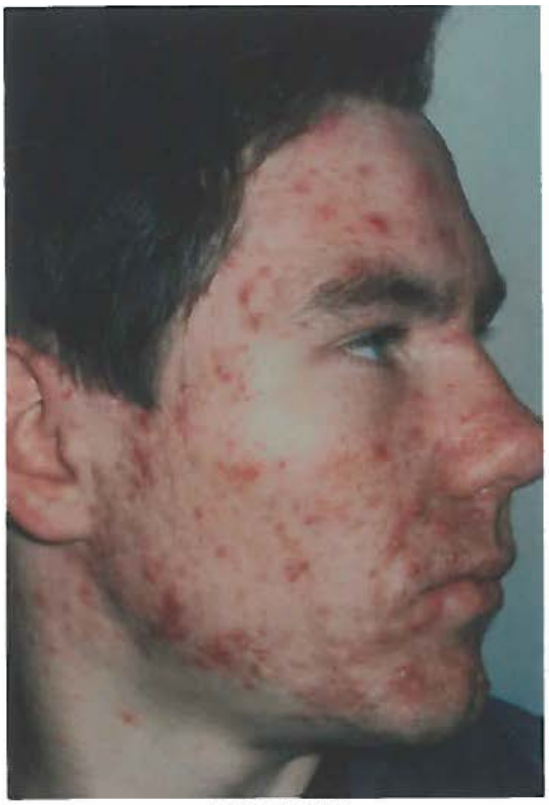
GRADE 6.0



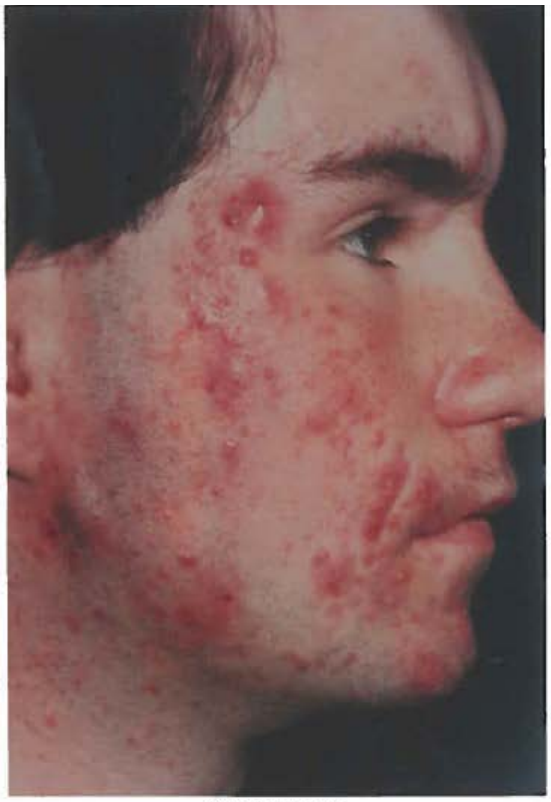
GRADE 7.0



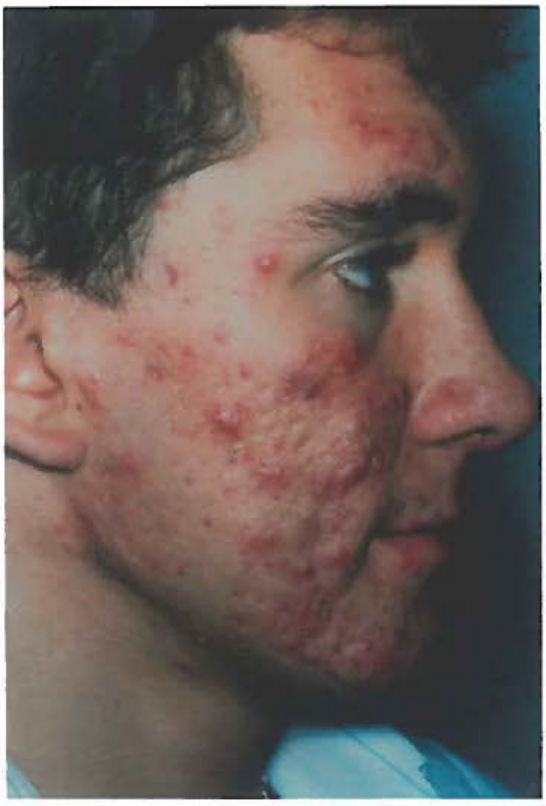
GRADE 8.0



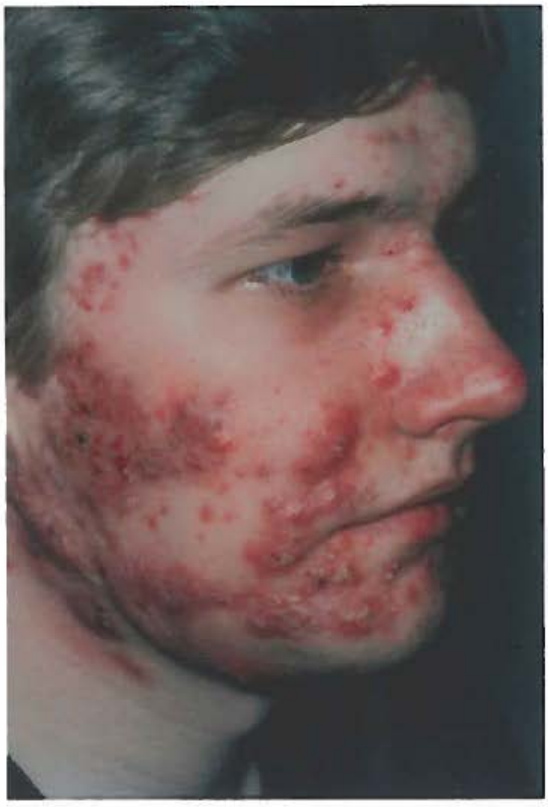
GRADE 9.0



GRADE 10

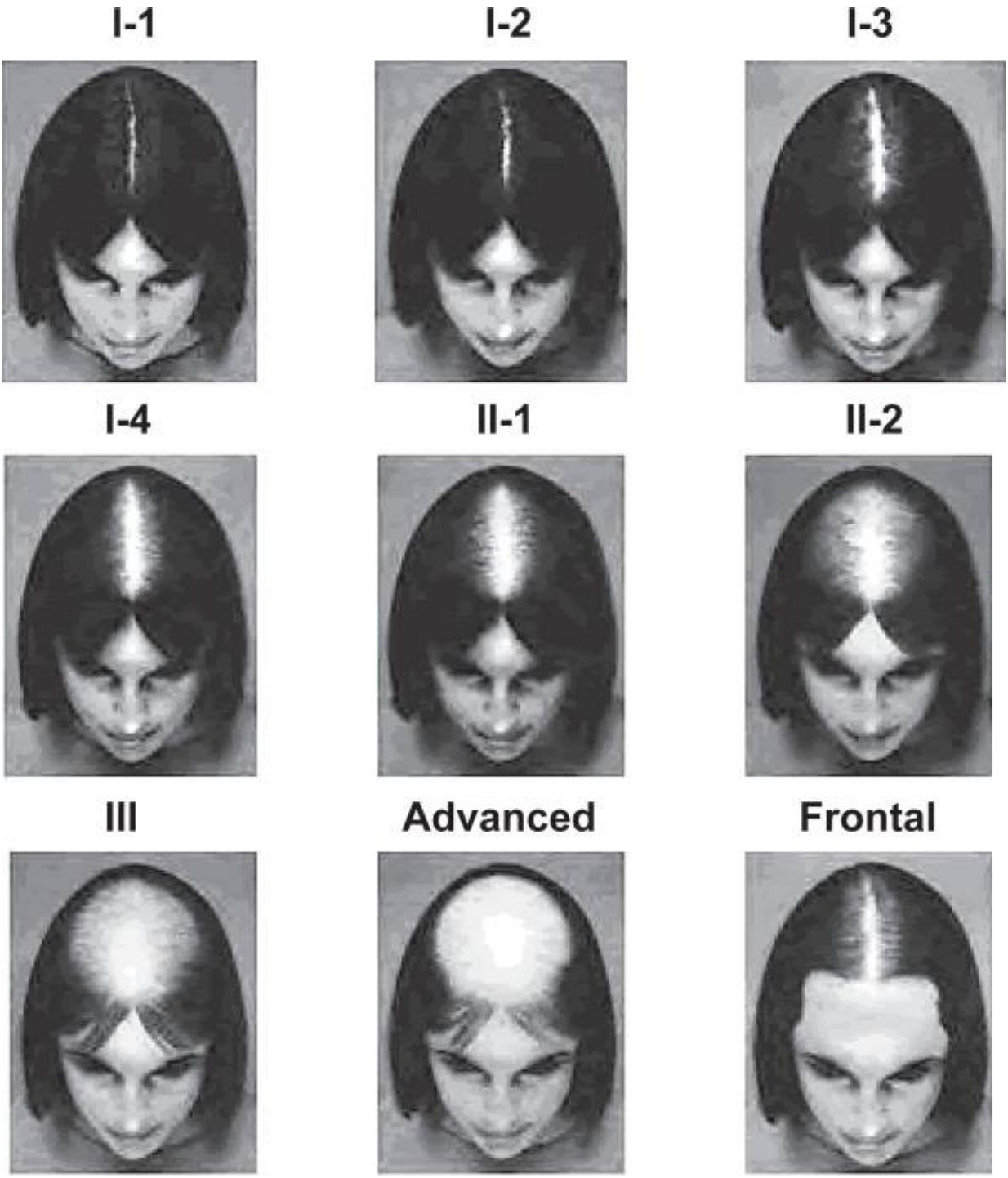


GRADE 11



GRADE 12

APPENDIX 13. SAVIN SCALE FOR ANDROGENIC ALOPECIA



The Savin scale measures overall thinning of the crown scalp and consists of 8 crown density images reflecting a range from no hair loss to severe hair loss (Stages I-1, I-2, I-3, I-4, II-1, II-2, III, advanced). The ninth image in the scale demonstrates frontal anterior recession. (Savin 1994)

APPENDIX 14. PROCEDURES FOR EMERGENCY UNBLINDING

Study drug for this study will be managed using an online interactive web response system (IWRS). Each user will have a unique username and passcode to access the IWRS.

Each site will additionally be provided with a 6-digit emergency unblinding code. Site users will be carefully trained to store the unblinding code in a secure but accessible location. Each code will be valid for one emergency unblinding action. A new code will be generated and sent to the site once an unblinding action has been carried out, or if the original code is lost. If a site performs an unblinding, all applicable audit-trail data is captured (username, participant number, unblinding date, etc.).

In order to unblind the treatment assignment for a subject, a site user would:

- Log in to the IWRS
- Provide the subject ID and birth date of the subject for whom unblinding is requested
- Provide the 6-digit emergency unblinding code

The IWRS would then provide the treatment group to which the subject was assigned.

APPENDIX 15. ALGORITHM FOR THE MANAGEMENT OF SUBJECTS WITH TRANSAMINASE (AST OR ALT) ELEVATIONS >3X ULN

- This appendix provides an algorithm for the management of subjects with transaminase (AST or ALT) elevations >3x ULN with or without bilirubin elevations in the MLE4901-101 study.

- Please discuss management of all cases of transaminase elevations >3x ULN with the Medical Monitor. Changes to this algorithm are permitted with agreement of the Medical Monitor.

- Other patterns of liver chemistry abnormalities (e.g., bilirubin elevations or alkaline phosphatase increased out of proportion to transaminases) may require evaluation and management specific to those patterns, please discuss with the Medical Monitor.

Transaminase (AST or ALT) elevation >3x to ≤8x ULN, total bilirubin <2x ULN

- **Within 24 hours of awareness of initial transaminase elevation, call the subject and:**
  - Continue study drug
  - Stop acetaminophen (Tylenol®)/any products containing acetaminophen (pain medications, over-the-counter cold medications, etc.), alcohol, herbal and dietary supplements, and any other potentially hepatotoxic agents
  - Review current health status for clinical symptoms potentially related to hepatotoxicity (e.g., flu-like symptoms, jaundice, fatigue, nausea or vomiting, etc.)
    - If clinical symptoms are reported such as jaundice, flu-like symptoms, general fatigue, nausea or vomiting, etc., or if in the investigator's judgment the subject requires emergent evaluation, immediately refer the subject to her local emergency department (ED).
  - Review risk factors for hepatitis and exposure to hepatotoxins
    - Obtain a liver-directed medical history (travel, occupational exposures, intercurrent illness, risk factors for intentional drug overdose, risk factors for acute viral hepatitis, risk factors for hepatic ischemia, family history of liver disease, etc.)
    - Review prescription medications, over the counter medications, herbal and dietary supplements, recreational drugs, and foods (e.g., inadvertent ingestion of amanita mushrooms)
    - Assess alcohol intake
  - If the subject is completely asymptomatic, and her history does not suggest that emergent evaluation is required, schedule a safety visit to occur within 3-4 days.

- **Within 3-4 days of awareness of the initial transaminase elevation, have the subject return to the site for further assessment and:**
  - Conduct a hepatic-focused safety visit
  - Confirm initial assessment of risk factors especially acetaminophen, alcohol, herbal and dietary supplements, and concomitant medications

- Perform a liver-directed physical examination (e.g., right-sided heart failure, hepatomegaly, splenomegaly, vesicular skin lesions (HSV), Kayser-Fleisher rings, hypertension, mental status, jaundice, ascites)
- Laboratory assessments:
  - Obtain AST, ALT, alkaline phosphatase, total bilirubin, LDH, GGT, CBC, PT, INR, serum chemistries, phosphate, serum iron, TIBC, anti-HAV IgM, HBsAg, anti-HBc IgM, and anti-HCV antibodies
  - Obtain an MLE4901 PK sample
  - If the subject has traveled to Russia, Pakistan, Mexico, or India, also obtain anti-HEV antibodies
  - Perform a urine pregnancy test
  - Obtain a urine toxicology screen
  - Obtain an acetaminophen level locally if there is suspicion for acetaminophen toxicity
- Consider obtaining a RUQ ultrasound, if clinically indicated
- A study visit that is already scheduled to occur and falls within the 3-4 day period following awareness of the initial transaminase elevation may be used to complete unscheduled safety visit requirements

- **Follow-up evaluation:**
  - Continue to monitor the subject and evaluate liver function tests until elevated values normalize or return to baseline status. Table 8 provides follow-up monitoring details.
  - Further unscheduled safety visits may be required depending upon the individual subject's clinical course. Please discuss monitoring plans with the Medical Monitor.

Transaminase (AST or ALT) elevation >8x to ≤20x ULN, total bilirubin <2x ULN

- **Within 24 hours of awareness of initial transaminase elevation, call the subject and:**
  - Immediately discontinue study drug (permanently)
  - Stop acetaminophen (Tylenol®)/any products containing acetaminophen (pain medications, over-the-counter cold medications, etc.), alcohol, herbal and dietary supplements, and any other potentially hepatotoxic agents
  - Review current health status for clinical symptoms potentially related to hepatotoxicity (e.g., flu-like symptoms, jaundice, fatigue, nausea or vomiting, etc.)
    - If clinical symptoms are reported such as jaundice, flu-like symptoms, general fatigue, nausea or vomiting, etc., or if in the investigator's judgment the subject requires emergent evaluation, immediately refer the subject to her local emergency department (ED).
  - Review risk factors for hepatitis and exposure to hepatotoxins
    - Obtain a liver-directed medical history (travel, occupational exposures, intercurrent illness, risk factors for intentional drug overdose, risk factors for acute viral hepatitis, risk factors for hepatic ischemia, family history of liver disease, etc.)

  - Review prescription medications, over the counter medications, herbal and dietary supplements, recreational drugs, and foods (e.g., inadvertent ingestion of amanita mushrooms)
  - Assess alcohol intake
- If the subject is completely asymptomatic, and her history does not suggest that emergent evaluation is required, schedule a safety visit as soon as possible (must occur within 24-48 hours)

- **As soon as possible within 48 hours after awareness of the initial transaminase elevation, have the subject return to the site for further assessment and:**
  - Conduct an unscheduled safety visit/Early Termination visit. The subject does not have to be fasting.
  - Confirm that study drug has been stopped
  - Confirm initial assessment of risk factors especially acetaminophen, alcohol, herbal and dietary supplements, and concomitant medications
  - Perform a liver-directed physical examination (e.g., right-sided heart failure, hepatomegaly, splenomegaly, vesicular skin lesions (HSV), Kayser-Fleisher rings, hypertension, mental status, jaundice, ascites), as part of the Early Termination procedures
  - Laboratory assessments:
    - Obtain Early Termination visit labs including AST, ALT, alkaline phosphatase, total bilirubin, CBC, PT, INR, serum chemistries, and an MLE4901 PK sample; and perform a urine pregnancy test (these are already included in the Visit T7 labs)
    - Obtain LDH, GGT, phosphate, serum iron, TIBC, anti-HAV IgM, HBsAg, anti-HBc IgM, and anti-HCV antibodies
    - If the subject has traveled to Russia, Pakistan, Mexico, or India, also obtain anti-HEV antibodies
    - Obtain a urine toxicology screen
    - Obtain an acetaminophen level locally if there is suspicion for acetaminophen toxicity
    - Consider obtaining a RUQ ultrasound, if clinically indicated
  - Consider referral to appropriate medical specialist (e.g., hepatologist) if deemed necessary
- **Follow-up evaluation:**
  - Continue to monitor the subject and evaluate liver function tests until elevated values normalize or return to baseline status. Table 8 provides follow-up monitoring details.

- Further unscheduled safety visits may be required depending upon the individual subject's clinical course. Please discuss monitoring plans with the Medical Monitor.

Transaminase (AST or ALT) elevation >20x ULN or meets Hy's Law criteria: AST or ALT >3x ULN AND total bilirubin ≥2x ULN:

- **As soon as possible after awareness of the initial transaminase elevation, call the subject and:**
  - Immediately discontinue study drug (permanently)
  - Stop acetaminophen (Tylenol®)/any products containing acetaminophen (pain medications, over-the-counter cold medications, etc.), alcohol, herbal and dietary supplements, and any other potentially hepatotoxic agents
  - Review current health status for clinical symptoms potentially related to hepatotoxicity (e.g., flu-like symptoms, jaundice, fatigue, nausea or vomiting, etc.)
    - If clinical symptoms are reported such as jaundice, flu-like symptoms, general fatigue, nausea or vomiting, etc., or if in the investigator's judgment the subject requires emergent evaluation, immediately refer the subject to her local emergency department (ED).
    - If the subject is completely asymptomatic, and her history does not suggest that emergent evaluation is required, schedule a safety visit as soon as possible. This unscheduled safety visit should take place within 24 hours. If a visit cannot be scheduled within 24 hours, then the subject should be referred to her local emergency department for evaluation and management.
  - Review risk factors for hepatitis and exposure to hepatotoxins:
    - Obtain a liver-directed medical history (travel, occupational hazards, intercurrent illness, risk factors for intentional drug overdose, risk factors for acute viral hepatitis, risk factors for hepatic ischemia, family history of liver disease, etc.)
    - Review prescription medications, over the counter medications, herbal and dietary supplements, recreational drugs, and foods (e.g., inadvertent ingestion of amanita mushrooms)
    - Assess alcohol intake
- **As soon as possible within 24 hours after awareness of the initial transaminase elevation, have the subject undergo further assessment (at the study site, by a hepatology consultant or in the emergency department)**:

  In the interests of time, the below suggested evaluations, along with any other evaluation that the treating physician (ED physician, specialty medical consultant, or PI) considers to be necessary, should be performed STAT locally; also send duplicate chemistry (including LFT) samples and a PK sample to Covance if possible.

- Have the subject return to the site for an unscheduled safety visit/Early Termination visit. The subject does not have to be fasting. Alternatively, the subject may be referred for immediate evaluation and management by a hepatology expert or in the local emergency department.
- Confirm that study drug has been stopped
- Consider a hepatology consultation (if not previously obtained)
- Confirm initial assessment of risk factors especially acetaminophen, alcohol, herbal and dietary supplements and concomitant medications
- Perform a liver-directed physical examination (e.g., right-sided heart failure, hepatomegaly, splenomegaly, vesicular skin lesions (HSV), Kayser-Fleisher rings, hypertension, mental status, jaundice, ascites)
- Obtain AST, ALT, alkaline phophatase, total bilirubin, direct bilirubin, LDH, GGT, CBC, PT, INR, serum chemistries, magnesium, phosphate, serum iron, TIBC, anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV antibodies, hepatitis C RNA, anti-HDV antibodies, TSH, acetaminophen level, toxicology screen, and a pregnancy test
- If subject has traveled to Russia, Pakistan, Mexico, or India, also test for anti-HEV antibodies
- Obtain a plasma sample for PK if possible (this should be stored frozen)
- Consider obtaining a RUQ ultrasound with Doppler if clinically indicated

- **Follow-up evaluation**
  - Continue to monitor the subject and evaluate liver function tests until elevated values normalize or return to baseline status. Table 8 provides follow-up monitoring details.
  - Further unscheduled safety visits may be required depending upon the individual subject's clinical course. Please discuss monitoring plans with the Medical Monitor.

Table 8: Evaluation of Follow-up AST and ALT Values

If follow-up AST and/or ALT is:	Action
>20x ULN or Hy's Law (AST or ALT >3x ULN AND total bilirubin ≥2x ULN)	• Stop study drug immediately, if not previously done • Refer the subject for appropriate medical specialty consultation, if not previously done • Obtain AST, ALT, alkaline phosphatase, and total bilirubin at least **every 3 days** until AST and ALT are ≤8x ULN
>8x ULN to ≤20x ULN	• Stop study drug immediately, if not previously done • Consider referral to appropriate medical specialist (e.g., hepatologist), if not previously done • Have the subject return to the site for an Early Termination visit, if not previously done • Obtain AST, ALT, alkaline phosphatase, and total bilirubin approximately **every 3 days** until AST and ALT are ≤8x ULN
Increasing and >3x to ≤8x ULN	• Obtain AST, ALT, alkaline phosphatase, and total bilirubin approximately **every 3 days** until AST and ALT are ≤3x ULN
Decreasing and >3x to ≤8x ULN	• Obtain AST, ALT, alkaline phosphatase, and total bilirubin approximately **every 7 days** until AST and ALT are ≤3x ULN
≤3x ULN	• Obtain AST, ALT, alkaline phosphatase, and total bilirubin approximately **every 14 days** until AST and ALT are ≤ baseline or stable
Persistent elevation >5x ULN for 14 or more days	• Stop study drug, if not previously done

Summary Flowchart for the Management of Subjects with Transaminase (AST or ALT) Elevations