Statistical Analysis Plan

A Two-part, Phase 1, Exploratory and Dose-range Finding Study to Evaluate Suppression of Ovulation and Pharmacokinetics of Medroxyprogesterone Acetate Following a Single Subcutaneous Administration of TV-46046 in Women with Ovulatory Cycle

Study Number TV46046-WH-10075

NCT02817464

SAP Approval Date: 26 September 2018

Statistical Analysis Plan

Teva Study Number: TV46046-WH-10075
FHI 360 Study Number: 780861-1

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Phase: 1

IND Number: 126249

Initial Approval Date: 14 October 2016

Revised: 26 September 2018

Study Sponsor

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: TV46046-WH-10075 (Teva), 780861-1 (FHI 360)

Study Title: A Two-part, Phase 1, Exploratory and Dose-range Finding Study to Evaluate Suppression of Ovulation and Pharmacokinetics of Medroxyprogesterone Acetate Following a Single Subcutaneous Administration of TV-46046 in Women with Ovulatory Cycle

Statistical Analysis Plan for:

- ☐ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

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[redacted] 11/26/2018
Approver: [redacted], Contraceptive Technology Innovation Department
FHI 360 **Date**

[redacted] 11/27/18
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[redacted] 11/25/2018
Approver: [redacted], Biostatistics Division
FHI 360 **Date**

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
λ	Terminal phase rate constant
AE	adverse event
AUC	area under the serum drug concentration by time curve
$AUC_{0-\infty}$	area under the serum drug concentration by time curve from time 0 to infinity
AUC_{0-x}	area under the serum drug concentration by time curve from time 0 to day x
BMI	body mass index
C_x	serum drug concentration at day x post-treatment initiation
CI	confidence interval
CM	concomitant medication
C_{max}	maximum serum drug concentration
CRF	case report form
CSR	clinical study report
%CV	percent coefficient of variation
DMPA	depot medroxyprogesterone acetate
DSMB	Data and Safety Monitoring Board
E2	Estradiol
FDA	Food and Drug Administration (US)
GM	geometric mean
ISR	injection site reaction
LOQ	limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MOP	manual of procedures
MPA	medroxyprogesterone acetate
P	Progesterone
SD	standard deviation
SOC	system organ class
$t_{1/2}$	Apparent terminal half-life
t_{max}	time to maximum serum drug concentration
WY	Women-years

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for *A Two-part, Phase 1, Exploratory and Dose-range Finding Study to Evaluate Suppression of Ovulation and Pharmacokinetics of Medroxyprogesterone Acetate Following a Single Subcutaneous Administration of TV-46046 in Women with Ovulatory Cycle*. The study is sponsored by Teva Branded Pharmaceutical Products R&D, Inc. and implemented by FHI 360. Version 1.0 of the SAP was written and approved prior to first subject enrolled.

The reader of this SAP is encouraged to review the study protocol for details on the conduct of the study, the operational aspects of clinical assessments, and the timing for completing the participation of a subject in this study. The SAP is intended to be in agreement with the protocol, especially with regards to the primary and secondary endpoints and their respective analyses. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (eg, other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this Statistical Analysis Plan, the SAP prevails; any differences between the two will be explained in the Clinical Study Report (CSR).

Changes made to the SAP after study initiation (other than formatting for regulatory submissions), including changes made to address revisions to the protocol, will be documented in Section 13. Mock tables, figures and listings designed to capture the results of analyses specified here will be approved by the Coordinating Investigator prior to un-blinding of statisticians, and included in an appendix to future versions of the SAP.

1. STUDY OBJECTIVES AND ENDPOINTS

The purpose of this pharmacodynamic and pharmacokinetic study is to identify a dose of TV-46046 (within the range 80 to 300 mg) that is both safe and consistent with a high degree of contraceptive efficacy when injected every 6 months.

1.1. Primary Study Objectives and Endpoints

1.1.1. Primary Objectives

This Phase 1 study has a data-driven, 2-part design: an exploratory pharmacokinetics component (Part 1) and a dose-range finding component (Part 2).

Part 1: To assess the pharmacokinetics of 120 mg medroxyprogesterone acetate (MPA) following a single subcutaneous injection of undiluted and saline-diluted TV-46046. This information will be used to inform up to 3 dose levels of undiluted TV-46046 and the study size for the dose-range finding component (Part 2) of the study, or to select a drug concentration for further investigation if undiluted TV-46046 does not exhibit an appropriate pharmacokinetic profile.

Part 2: If undiluted TV-46046 exhibits an appropriate pharmacokinetic profile in Part 1, then Part 2 will evaluate the pharmacodynamics of MPA after a single subcutaneous injection of undiluted TV-46046 at 3 dose levels (where pharmacodynamic response is defined as suppression of ovulation determined through serum progesterone [P] concentrations).[1]

1.1.2. Primary Endpoints

Part 1: Individual and mean serum MPA concentration-time profiles, and estimated non-compartmental pharmacokinetics parameters, including but not limited to: maximum serum drug concentration (C_{max}), time to maximum serum concentration (t_{max}), serum drug concentration at day 182 (C_{182}), area under the serum drug concentration by time curve from time 0 to day 182 ($AUC_{0\text{-}182}$), area under the serum drug concentration by time curve from time 0 to infinity ($AUC_{0\text{-}\infty}$), and apparent terminal half-life ($t_{1/2}$).

Part 2: Time to ovulation, where ovulation is defined as a single-elevated serum P ($\geq$4.7 ng/mL).

1.2. Secondary Study Objectives and Endpoints

1.2.1. Secondary Objectives

The secondary objectives of the study are the following:

- To characterize the pharmacokinetics of 3 dose levels of undiluted TV-46046
- To evaluate the relationship between serum MPA concentration and return to ovulation
- To evaluate the safety of a subcutaneous injection of TV-46046 over the range of different doses and concentrations

[1] Part 2 of the study was never implemented. As a consequence, no analyses related to Part 2 data described in this SAP will be implemented.

- To evaluate the acceptability of a subcutaneous injection of TV-46046 over the range of different doses and concentrations

1.2.2. Secondary Endpoints

- Pharmacokinetics of MPA based on individual and mean serum concentration-time profiles over the range of Part 2 doses, as well as estimated non-compartmental pharmacokinetics parameters, including but not limited to: C_{max}, t_{max}, C_{182}, C_{210}, AUC_{0-182}, AUC_{0-210}, $AUC_{0-\infty}$, and $t_{1/2}$. In addition, release rates, relative bioavailability, and other pharmacokinetic parameters derived from non-linear mixed effects model compartmental analysis of MPA concentrations over time.
- Safety endpoints include but are not limited to the occurrence of changes in vital signs and body weight; delayed return to ovulation (>12 months after study drug injection), adverse events (AEs), injection site reactions (ISRs), change in mood (Part 2, only), change in liver function tests (Part 2, only), use of concomitant medications (CMs), and change in menstrual bleeding patterns.
- Acceptability endpoints include subjects' responses to questions about injection pain, ISRs, and menstrual bleeding patterns; and the study staff's assessment of the ease of the injection.

2. STUDY DESIGN

This is a 2-part study designed to evaluate the pharmacokinetics and pharmacodynamics of MPA in healthy female subjects after a single subcutaneous injection of TV-46046. Part 1 is a non-randomized component which will explore the pharmacokinetics of a 120 mg dose of MPA when TV-46046 is administered at an undiluted concentration of 400 mg/mL (0.3 mL injection volume) or a 1:1 saline-diluted concentration of 200 mg/mL (0.6 mL injection volume). Cohorts of n=6 participants will be enrolled in sequential order: undiluted drug followed by 1:1 saline diluted drug. If results indicate that information on an intermediate concentration is required to characterize pharmacokinetics, then a 3rd cohort of 6 participants may be administered TV-46046 at a concentration of 300 mg/mL (0.4 mL injection volume).

Part 2 is a randomized, multi-center, dose-range finding component which will only be implemented if undiluted TV-46046 is selected for further testing based on Part 1 data. Criteria used to select each of up to 3 doses of undiluted TV-46046 in the range of 80 to 300 mg for Part 2 include: mean C_{max} predicted to be less than 3 ng/mL, time to achieve 0.2 ng/mL predicted to be no more than 24 hours after study drug administration, 6-month serum MPA concentration predicted to be greater than 0.1 ng/mL for 95% of women, and serum MPA concentration 24 months after last injection predicted to be below 0.1 ng/mL in 90% of women. As only a 120 mg dose of TV-46046 will be tested in Part 1, predictions about the pharmacokinetics of Part 2 doses will be partly informed by dose relationships observed in previous studies of depot medroxyprogesterone acetate (DMPA) delivered subcutaneously. The final study size for Part 2 will be informed by Part 1, but will not exceed 20 women per dose group (including 2 obese women per group).

Each subject enrolled in either Part 1 or Part 2 will contribute up to 19 months in the study, including up to 1-month pre-treatment, 6-months treatment, and 6-12 months of post-treatment follow-up. Study procedures and assessments with their timing are summarized in Table 1 of the study protocol.

2.1. Randomization and Blinding

Subjects in Part 1 will not be randomized. Rather, they will be enrolled in consecutive cohorts of n=6 women, as follows:

- Cohort 1A: a single 0.3mL injection of undiluted TV-46046 (120 mg MPA)
- Cohort 1B: a single 0.6mL injection of 1:1 saline diluted TV-46046 (120 mg MPA)
- Cohort 1C: a single 0.4mL injection of 3:1 saline diluted TV-46046 (120 mg MPA)

  (Depending on the results of Cohorts 1A and 1B, Cohort 1C may not be enrolled).

The random allocation ratio for the dose-range finding component of the study will depend on whether or not the 120 mg dose of undiluted TV-46046 used in Part 1 is selected for Part 2. If it is, then up to 12 subjects will be randomized to the 120 mg dose, and up to 18 subjects will be randomized to each of the other 2 selected dose groups, in a 2:3:3 allocation ratio. If the 120 mg dose is not selected for inclusion in Part 2 then the allocation ratio will be 1:1:1. In addition, 2 subjects with a body mass index (BMI) $\geq$ 40 will be separately randomized into each of the 3

treatment dose groups for exploratory analyses of the effect of extreme obesity on pharmacokinetics of MPA, resulting in a maximum of 20 participants in each Part 2 dose group.

The randomization sequence will be developed by an FHI 360 Randomization Statistician not otherwise involved in the study using a validated SAS® program. The randomization will be stratified on investigational center using appropriate block sizes to minimize imbalance with respect to the target allocation ratio at each planned interim and final analysis. Details will be documented in a separate Randomization Plan prior to initiating Part 2.

Treatment assignments for Part 2 will be concealed within sealed, opaque, sequentially numbered randomization envelopes provided to each investigational center. Trained staff will open the next available envelope, and allocate the next treatment assignment, only after a participant has completed all other baseline procedures and is determined to be eligible for the study. The randomization envelopes will be maintained in a secure location at each center, with access limited to authorized personnel per center-specific study procedures.

No enrolled subjects who have received a study drug injection will be replaced in either part of the study. However, enrollment in Part 2 may be expanded if more than 10% of subjects discontinue (or are predicted to discontinue) before week 52 from start of study drug treatment, have detectable levels of MPA at enrollment, or have protocol violations identified that may adversely affect assessment of pharmacokinetics or pharmacodynamics. Any decision to expand enrollment will be informed by recommendations from the DSMB, and will be implemented so as to preserve the validity of randomization-based inferences using the same allocation ratio.

No blinding will occur in Part 1, and Part 2 will not be fully blinded due to differences in volume of study drug. However, clinical staff providing the injections in Part 2 will be trained to shield the syringe from view of the subject or any other study staff prior to and at the time of injection. In addition, FHI 360 staff responsible for coding AEs, and laboratory staff analyzing MPA specimens, will remain blinded for the length of the study. The Coordinating Investigator, pharmacologists, study clinician, statisticians, and other essential study staff will be un-blinded at the group level following formal interim analyses of Part 2 data to inform project development. These reviews of unblinded data will take place independently of the DSMB reviews described below. Individual treatment assignments will also be made available to study medical monitor should it be necessary to inform medical treatment of the subjects. The number of personnel who are un-blinded while the study is ongoing will be kept as small as feasible, and the potential implications of un-blinding on study conduct and interpretation of study data will be described in the clinical report. Further details of blinding and un-blinding procedures are provided in the separate DSMB operational plan.

2.2. Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review accumulating pharmacodynamics, pharmacokinetic, and safety data to ensure the continuing safety of the study subjects and the integrity of the study. The DSMB will meet once before the study begins and at 2 scheduled points during the study. There will be both an open and closed session at each DSMB meeting where study data are reviewed. During open sessions, representatives of the study sponsor and study implementor may be present, and information will be provided and discussed in a blinded fashion. During closed sessions only the DSMB members, the DSMB Executive Secretary (to take notes only), and an FHI 360 statistician (to answer questions about

the analysis) will be present to discuss results by treatment group. Details of the DSMB procedures and responsibilities are documented in a separate DSMB Operational Plan.

2.3. Sample Size and Power Considerations

Part 1 is not powered to definitively assess pharmacokinetics. Rather, if the pharmacokinetics profile of undiluted TV-46046 appears consistent with a safe and efficacious 6-month injectable contraceptive method, then 3 dose levels within the dose range of 80 to 300 mg will be recommended for Part 2. Likewise, the study size for Part 2 was not chosen to make definitive conclusions regarding the effectiveness of TV-46046 in the range of doses selected. However, up to 20 subjects per group should be sufficient to provide meaningful insights into the distributions of pharmacokinetics and pharmacodynamics outcomes, and to inform selection of a dose for further study. Scientific judgment will be used to determine if the sample size in Part 2 can be reduced from 20 subjects per group, depending on the variability of parameter estimates observed in Part 1. Participants who are withdrawn from the study will not be replaced.

2.4. Sequence of Planned Analyses

2.4.1. Planned Interim Analyses

There are five planned reviews of the interim Part 1 and Part 2 data as outlined below, but the number and timing of reviews may change based on interim findings.

- The 1st planned interim analysis will be performed after the 6 subjects in Cohort 1A of Part 1 (receiving undiluted TV-46046) have completed 1 month of post-injection follow-up, and is intended to inform the early part of the pharmacokinetic profile.
- The 2nd interim analysis will be performed after the same 6 subjects in Cohort 1A of Part 1 have completed 4 months of post-injection follow-up, and is intended to inform the decision to move into, and the selection of doses for Part 2.
- The 3rd and 4th interim analyses are planned to occur after 50% of subjects in Part 2 have completed 4 and 7.5 months of post-injection follow-up, respectively, and are intended to help inform the decision to move to, and the dose selection for further clinical study.
- The 5th and final planned interim analysis is planned to occur when 100% of subjects in Part 2 have completed 7.5 months of post-injection follow-up (the entire intended dosing interval, plus 1.5 months). A preliminary report of study findings based on this analysis may be submitted to the U.S. Food and Drug Administration (FDA) as part of the planning phase for future studies.

Among these 5 planned interim analyses, the DSMB may only convene to review data prior to initiation of Part 2 (2nd planned interim analysis) and at the first interim analysis of Part 2 data (3rd planned interim analysis), with the other analyses used by the clinical team to inform the design of Part 2 and/or the product development program. However, the DSMB may request review of other planned or unplanned interim analyses for purposes of monitoring participant safety or to make recommendations regarding modifications to the study.

2.4.2. Final Analyses and Reporting

All final analyses identified in this SAP will be performed after the last participant has completed the study, although an earlier report of data collected through month 7.5 of follow-up

in Part 2 may be submitted to the FDA in advance of any planning meetings for future studies. Any supportive analyses which were not identified in the SAP prior to unblinding of statisticians will be documented as exploratory in the CSR.

3. ANALYSIS SETS

In the definitions that follow, an Analysis Population refers to a particular set of study subjects and an Analysis Set refers to the time contributed to analyses by subjects in a given population. Unless otherwise noted, the definitions for inclusion in these analysis populations and sets are assumed to be the same for Part 1 and Part 2.

3.1. Screened Population

The Screened Population consists of all screened participants who are consented to participate in the study, regardless of their enrollment status.

3.2. Treated Population

The Treated Population consists of all screened participants who are enrolled and receive a dose of study drug, and is the primary population for safety and acceptability analyses. The corresponding ***Treated Analysis Set*** includes all baseline and follow-up data contributed by participants in the Treated Population. Analyses will be performed based on treatment received. In the event of randomization errors, failure to follow the intention-to-treat principle will be justified on the grounds that the study will not be used to make definitive conclusions regarding the efficacy of TV-46046.

3.3. Primary Evaluable Population

The Primary Evaluable Population is a subset of the Treated Population, excluding subjects who have detectable MPA in their baseline specimen (more than 5% of their individual C_{max}) or for whom a major protocol violation occurred at enrollment, including: the absence of a confirmed ovulation in the pre-treatment period; BMI outside the eligible range (with the exception of the 6 subjects purposefully enrolled with BMI ≥40 in Part 2); or use of drugs known to impact ovulation or the pharmacokinetics of MPA (with the exception of selective COX-2 inhibitors that are taken for fewer than 5 consecutive days). The ***Primary Evaluable Analysis Set*** includes all time contributed by participants in the Primary Evaluable Population during which a pharmacokinetic or pharmacodynamics outcome is assessed, up to the initiation of any medication known to impact ovulatory function or the pharmacokinetics of MPA.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables will include the number of observed values, the mean, standard deviation (SD), median, minimum, and maximum values. Geometric mean (GM) and percent coefficient of variation (%CV) will also be used to describe continuous pharmacokinetic variables. For categorical variables, the number and percentage of subjects with a specific level of the variable will be presented.

Unless otherwise specified, all reported p-values will be assessed for statistical significance at the two-sided 0.05 level, and all confidence intervals (CIs) for individual group parameters will be computed at the 95% coverage level. Dilution (Part 1) and dose (Part 2) group comparisons will be made using 90% CIs for GM ratios, with no adjustment for multiple testing.

4.2. Specification of Baseline Values

The baseline values for any measurement is the last value obtained prior to injection of study drug, unless otherwise noted.

4.3. Handling Withdrawals and Missing Data

The primary pharmacodynamics outcome of time to ovulation, defined as a single elevated serum $P \geq 4.7$ ng/mL, will be censored at month 12 following treatment initiation. No imputation of event times prior to month 12 will take place for the primary analysis, although sensitivity analyses may consider outcomes as interval-censored between the dates of last $P < 4.7$ ng/mL and first $P \geq 4.7$ ng/mL. Missing MPA concentrations at key time points (eg, end-times of partial AUCs) will be imputed using methods specified in Section 14 of the SAP. Incomplete AE onset or CM initiation dates may be imputed to assess safety or when censoring participants from analyses due to excluded medication use, as follows:

- If a participant cannot recall the day or month of onset/initiation, then the date will be imputed as the last clinic visit without evidence of the AE or CM use, or other adjudicated date based on best clinical judgment.
- If a participant can only recall the month of onset/initiation, then the date will be imputed as the first day of the month or the last clinic visit prior to the AE/CM, whichever is later.

4.4. Study Days and Visits

The start of treatment (day 0) is defined as the date on which a subject receives a dose of study drug. The study day on which an event occurs or an outcome is assessed will be calculated as the date of the event or outcome, minus the date of treatment initiation; a negative study day indicates an event prior to study drug administration. When necessary and appropriate, fractions of study days will be computed based on the time (in hours and minutes) of a subject's injection and the time of her event or outcome assessment.

Some pharmacokinetic and pharmacodynamics data will be assigned to visit windows when reporting by-visit summaries (eg, serum concertation on day 182). In order to maximize the use of available data, the window periods used in these summary analyses may be wider than

specified in the study Manual of Procedures (MOP) (see Table 1, below). If multiple data fall in the same visit window, then the value closest to the nominal time will be used. If multiple data in the same visit window are equally distant to the nominal time, then the last value in the visit window will be used for the analysis.

Table 1: Windows used when summarizing Pharmacokinetic and Pharmacodynamics data by study visit

Target Visit	Window Period (MOP)	Window Period (Analysis)
Days 1, 2	± 1 hour	+/- 3 hours
Days 3, 5, 7	± 3 hours	+/- 6 hours
Days 10, 12, 14, 18	± 24 hours	+/- 24 hours
Days 21 and after	± 48 hours	+/- 84 hours

5. STUDY POPULATION

5.1. General

The study will enroll healthy women 18 to 40 years of age, inclusive, who are at low risk of pregnancy (eg, sterilized, in exclusively same-sex partnership, in monogamous relationship with vasectomized partner, or using a non-hormonal itrauterine device), and who are confirmed to have ovulated during the pre-treatment phase of the study.

5.2. Subject Disposition

The numbers of participants screened and enrolled in Part 1 and Part 2 of the study will be tabulated by investigational center and treatment group, and pooled across centers and groups. A flow diagram will be provided which presents the numbers and percentages of participants contributing to the Treated and Primary Evaluable Populations; reasons for exclusion from analysis populations; total women-years (WY) of follow-up contributed to each analysis set (by treatment group); and the numbers and percentages of participants who complete the study, discontinue early (overall and by reason), or who are lost to follow-up. Subjects that were excluded from the various analysis populations and reason for exclusions will be listed.

5.3. Demographics and Baseline Characteristics

Summary statistics appropriate to the measurement scale will be used to describe baseline demographic, behavioral, and contraceptive use history data. Continuous variables may also be described using categorical levels chosen based on previous experience with similar studies, and prior to un-blinding of statisticians. Baseline data will be presented for the Screened Population, the Treated Population, and the Primary Evaluable Population. Summaries will be provided by study Part (1 or 2), treatment group, investigational center, and pooled across centers and groups. No statistical testing will be performed to compare distributions of baseline characteristics between dilution or dose groups. However, baseline characteristics may be compared between investigational centers using exploratory analysis of variance for continuous variables or Chi-Squared tests for categorical variables in order to help interpret any apparent differences (or lack of differences) in pharmacodynamics and pharmacokinetic responses between centers.

5.4. Prior Therapy and Medication use

Start and stop dates of medication or non-drug therapy will be compared to the start date of study drug dosing to allow medications/treatments to be classified as either *prior* or *concomitant*. Prior medications include any previous therapy, medication, or procedure a subject has had within 30 days before study drug administration. Prior medication use will be documented, and the prevalence of use will be summarized by therapeutic class of medication and category (coded using Lexicomp and PDR Online).

5.5. Medical History

Pre-existing medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized in tables and listings by system organ class (SOC), preferred term, and highest severity, both within treatment group and overall.

5.6. Physical Examinations

See Section 8.58 for description of vital signs, body weight, and other physical exams results to be presented in the CSR.

5.7. Childbearing Potential and Methods of Contraception

Information related to childbearing potential (including average menstrual cycle length, duration of menstrual bleeding, etc.) and contraceptive method use during the study will be collected at baseline and summarized using descriptive statistics.

5.8. Study Protocol Violations

Data from subjects with any protocol violations (as recorded on protocol violation case report forms [CRFs]) during the study will be summarized in frequency tables. Categories of deviations will include violations of study entry criteria (eg, use of excluded medications), randomization errors, violation of study withdraw criteria and other violations captured on CRFs. All protocol violations will be further summarized in data listings.

6. EFFICACY ANALYSIS

Efficacy will not be evaluated in this study.

7. MULTIPLE COMPARISONS AND MULTIPLICITY

No adjustments will be made for the planned or unplanned multiple comparisons of primary or secondary pharmacokinetic or pharmacodynamic endpoints.

8. SAFETY ANALYSIS

8.1. General

Safety analyses will be performed on the Treated Population. Results of all safety assessments, including AEs, ISRs, delayed return to ovulation, menstrual bleeding pattern change, vital sign and body weight, and use of CMs will be summarized with descriptive statistics by treatment group and overall, and/or presented in data listings.

8.2. Adverse Events

All AEs will be coded using MedDRA by preferred term and SOC. The number and percentage of participants experiencing AEs will be presented by treatment group: overall, by severity, relatedness to treatment, and according to whether or not the event had an onset date within 7.5 months of initiation of treatment. Serious adverse events and adverse events leading to withdrawal from the study will be summarized separately.

A listing of all AEs will include treatment group, verbatim AE description, preferred term and SOC, duration, relatedness to product, seriousness, severity, outcome, and whether withdrawal from the study occurred as a result of the AE. All relevant information on any deaths will be discussed in the subject narrative included in the clinical study report.

8.3. Injection Site Reactions

Summaries of ISR data (including nature, timing and whether or not the ISR was Grade 1 or higher) will be provided by treatment group and overall, and the differences in proportions of subjects experiencing ISRs between groups will be compared in Part 2 using Fisher's exact tests.

8.4. Delayed Return to Ovulation

The probability of return to ovulation more than 12 months after treatment initiation will be estimated using Kaplan-Meier methods and presented with 95% CIs, by treatment group.

8.5. Menstrual Bleeding Disturbances

The percentage of women experiencing amenorrhea or other menstrual bleeding disturbances (irregular bleeding or spotting) assessed monthly and at day 7, week 13, week 32, and the final study visit will be compared between treatment groups using frequency tables (for monthly data, the bleeding history report obtained closest in time to the target monthly visit - among visits within 14 days of the target - will be used). The number and percentage of subjects ever reporting spotting, irregular bleeding, or unacceptable bleeding pattern will also be tabulated.

For Part 2 only, weekly diary data were divided into 30-day segments starting from the date of the injection. For each 30-day period, subjects were categorized into one of the following four types:

1. No bleeding or spotting: no bleeding or spotting days recorded during the entire 30-day period.
2. Spotting only: only days with spotting recorded during the 30-day period
3. Bleeding only: only days with bleeding recorded during the 30-day period

4. Bleeding and spotting: a mixture of bleeding and spotting days recorded during the 30-day period.

The percentage of subjects experiencing each of the four bleeding patterns during months 1, 3, 6, 9, and 12 will be compared between treatment groups using frequency tables.

8.6. Liver Function Tests

For Part 2 only, liver function tests, including but not limited to ALT and AST, will be assessed by tabulating and graphing change from baseline to week 13 (month 3), week 32 (month 7.5), and final study visit data.

8.7. Mood

For Part 2 only, mood will be assessed in frequency tables at baseline and at week 13 (month 3), week 32 (month 7.5), and final study visits.

8.8. Vital Signs and Body Weight

Pulse rate, systolic/diastolic blood pressure, body weight and BMI will be summarized in listings and tabulated descriptive statistics by center, treatment group and study visit. Vital signs will also be summarized graphically and using shift-tables (mean and median change from baseline to day 7, month 3, and month 7.5), by center and treatment group.

8.9. Concomitant Medications or Therapies

Concomitant medications include medications that started at any time and were taken at any time during the study, up to the end of study as defined in the study protocol. The use of concomitant medications will be summarized by therapeutic class and category (coded using Lexicomp and PDR Online) with descriptive statistics. Subjects are counted only once in each therapeutic class, and only once in each preferred term category.

9. ACCEPTABILITY DATA ANALYSIS

Acceptability analyses will be performed on the Treated Population and summarized using descriptive statistics and data listings. Responses to acceptability questions regarding menstrual patterns will be assessed at monthly and final study visits, and compared between treatment groups at month 7.5 using Fisher's exact tests. Perceptions of pain at time of injection and responses on other acceptability questionnaire items, as well as assessment of ease of injection by the study staff, will likewise be summarized.

10. PHARMACOKINETICS ANALYSIS

For both Part 1 and Part 2, individual MPA profiles will be displayed (both in the original scale and using semi-log plots) through month 12 following treatment initiation or earlier date of withdrawal from the study using the Primary Evaluable Analysis Set, with post-baseline MPA concentrations that fall below the limit of quantification (LOQ) replaced by half the applicable LOQ. If 120 mg/mL is selected as one of the Part 2 dose groups, then subjects in that Part 1 group will be incorporated in the primary Part 2 pharmacokinetics analysis. Data from the subset of 6 subjects (2 per dose group) with extreme obesity (BMI ≥40) in Part 2, and subjects with detectable MPA at baseline or who used drugs known to interfere with pharmacokinetics or pharmacodynamics of MPA prior to return to ovulation, will be excluded from the primary analysis but will be described separately. Sparse data collected after month 12 will likewise be described separately for the subset of subjects who have not ovulated by month 12.

The following non-exhaustive list of pharmacokinetic parameters and metrics will be estimated based on non-compartmental analysis implemented using Phoenix WinNonlin® or a validated SAS® macro (Matos-Pita 2005): C_{max}, t_{max}, C_{91}, C_{182}, C_{210}, $AUC_{0\text{-}91}$, $AUC_{91\text{-}182}$, $AUC_{0\text{-}182}$, $AUC_{0\text{-}210}$, $AUC_{0\text{-}\infty}$, the terminal phase rate constant (λ) and the apparent terminal half-life. Conventions and rules used to estimate these parameters are detailed in Section 14 of this SAP.

Summaries of pharmacokinetic parameter estimates in each treatment group will include means, medians, GMs, minima, maxima, SD, %CV, and 95% CIs for GMs. The number and percentage of participants with C_1, C_{91}, C_{182} and C_{210} below 0.1 ng/mL and 0.2 ng/mL, and the time above 0.1 ng/mL, will be summarized by group. The predicted drug accumulation after repeat dosing will be based on observed mean drug concentrations at months 6 and 12 (when routine PK testing ends). Steady state concontrations will be predicted using an appropriate PK model for drug concentrations at months 18, 24, etc., following each successive hypothetical dose given at 6-month intervals.

The pharmacokinetics of MPA will be compared between groups based on 90% CIs for GM ratios of C_{max}, C_{182}, C_{210}, $AUC_{0\text{-}182}$, $AUC_{0\text{-}210}$, $AUC_{0\text{-}\infty}$, and apparent half-life. The effects of dose group, investigational center, BMI, and age on C_{max}, C_{182}, $AUC_{0\text{-}182}$, and half-life in Part 2 will be explored graphically and using analysis of covariance on log-transformed outcomes. Dose proportionality of C_{max}, C_{182}, $AUC_{0\text{-}182}$, and half-life will be explored based on dose-normalized pharmacokinetic estimates. Sensitivity analyses will be performed after excluding participants determined to be outliers (eg, due to strong suspicion of injection on or near a blood vessel) or who fail to complete 7.5 months of follow-up.

In addition to non-compartmental analyses, nonlinear mixed effect pharmacokinetics modeling will be performed to estimate rates of absorption, relative bioavailability and other relevant pharmacokinetic parameters. Modeling and simulation will also be performed to assess the contraceptive potential of a dose other than that tested in Part 1 or Part 2, incorporating historical data as available and appropriate. Details of the methods used for modeling and simulation exercises will be described in a separate Modeling and Simulation Plan.

11. PHARMACODYNAMICS ANALYSIS

11.1. General

The Primary Evaluable Set will be used for the assessment of pharmacodynamics endpoints for both Part 1 and Part 2 data.

11.2. Primary Pharmacodynamics Endpoints and Analysis

The primary pharmacodynamics endpoint is time to ovulation, defined as a single elevated serum P $\geq$ 4.7 ng/mL. Time to ovulation will be computed as the difference in days between detection of the first post-randomization elevated P and the date of treatment initiation. Because measurement of P will only occur at weeks 61-65 and 75-78 for women who have not ovulated by month 12,participants who do not experience the endpoint on or before their month 12 visits will have their event times censored at month 12 for purposes of the primary analysis. However, these data may be included in secondary analyses that account for the interval-censored nature of endpoints observed after month 12. Although women with P $\geq$ 4.7 ng/mL are asked to return within 5 days, confirmation of an elevated P is not a component of the primary endpoint definition. The potential for incorrect timing of endpoints (eg, if a participant missed one or more visits prior to first elevated P) will be described on a case-by-case basis when interpreting the study findings or through sensitivity analyses.

If 120 mg is selected as one of the doses in Part 2, then subjects assigned to that group in Part 1 will be incorporated in the analysis of Part 2 data. Cumulative probabilities of return to ovulation will be estimated for each treatment group based on the Kaplan Meier method, with 95% CIs derived using the complementary log-log transformation.

Differences in the distribution of return to ovulation between groups will be explored based on two-sided log-rank tests conducted at the 0.05 significance level, stratified on investigational center. For descriptive purposes the median, inter-quartile range, minimum, and maximum time to ovulation will be reported by treatment group.

Any outcomes excluded from the Primary Evaluable Analysis Set, and the reason(s) for exclusion (eg, use of excluded medications), will be described separately. Data from the subset of 6 subjects (2 per treatment group) with extreme obesity (BMI$\geq$40) will likewise be described separately. If more than 10% of women go more than two weeks (14 days) between their last P < 4.7 ng/mL visit and their first P $\geq$ 4.7 ng/mL visit, then sensitivity analyses will be performed to estimate and compare cumulative probabilities of return to ovulation using Turnbull's extension of the Kaplan-Meier estimator for interval censored data (Turnbull 1976).

Individual P and estradiol (E2) concentration data will be displayed graphically from the pre-treatment period through time of ovulation. Mean and maximum E2 concentrations in each 30-day follow-up period will be summarized across subjects using means, medians, and SD.

11.3. Secondary and Exploratory Pharmacodynamics Analyses

Nonlinear mixed effects pharmacokinetic and pharmacodynamics modeling and simulation may be used to assess the relationship between individual serum MPA concentrations and duration of ovulation suppression, with emphasis on characterizing the distribution of any apparent

ovulatory suppression threshold and the lowest dose which may reliably inhibit ovulation for 6 months. [redacted]

12. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using Phoenix WinNonlin® and/or SAS® version 9.4 or later.

13. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL V1.0

13.1. Changes from V1.0 of protocol, Prior to Study Initiation

The protocol was amended twice prior to study initiation (original protocol: 01 May 2016; amendment 1: 29 May 2016; amendment 2: 04 November 2016). This section described changes to planned statistical analyses based on amendments 1 and 2, which were incorporated in V1.0 of the SAP.

- Addressed amendment 01 of protocol regarding timing of menstrual bleeding and related acceptability data.
- Specified that only participants with baseline MPA exceeding 5% of their individual C_{max} will be excluded from the Primary Evaluble Population. This change was made corresponding to the change in Protocol Amendment 2, Section 8.2.3 (Primary Evaluable Population).
- Specified selective Cox-2 inhibitors (eg, Meloxicam or Celecoxib) that are taken for fewer than 5 consecutive days will not lead to exclusion from the Primary Evalauble Population or Analysis Set. This change was made in responding to the change in Protocol Amendment 2, Section 5.3 (Prior and Concomitant Medication or Treatment)

13.2. Changes from V1.0 of SAP, After Initiation of Part 1 (26 October 2016) but Prior to Availability of any PK/PD data, including changes made in anticipation of Protocol Amendment 3 (27 March 2017)

- Changed method for estimating MPA accumulation following 2 or more hypothetical doses delivered at 6-month intervals. The method specified in V1.0 of SAP assumed a one-compartmental EV-model obeying monophasic decay which may or may not apply for TV-46046. Revised method is based on observed mean drug concentrations at month 6 and month 12 (when regular PK sampling ends), and an appropriate model for predicting drug concentrations at subsequent 6-month intervals.
- Changed plans for descriptive analyses of E2 data. This change was made to clarify the analyses of E2 described in SAP V1.0.
- Protocol Amendement 3 included language to the effect that fewer than 3 doses could be selected for Part 2, as well as new safety measures for Part 2, including: mood and liver function testing at the week 13, week 32, and finals study visit; weekly electronic diary data; menstrual bleeding pattern.

13.3. Changes from V1.0 of SAP, After initial Interim Review of PK/PD data (27 March 2017)

- Clarified visit window for monthly mensutrual bleeding data
- Added an exploratory assessment of the number and percentage of women ever reporting irregular bleeding, spotting, or unacceptable bleeding patterns.

- Although the pharmacokinetic profile of the current TV-46046 investigational product was found to be favorable in Part 1 of the study, a decision was made not to continue to Part 2 of the study due to challenges with the stability, syringeability, and manufacturing of the current formulation. As such, analyses planned for Part 2 of study are not relevant, since Part 2 was never implemented.

14. CONVENTION USED WHEN ESTIMATING INDIVIDUAL PHARMACOKINETIC PARAMETERS

- C_{max} and t_{max} will not be reported for participants who discontinue the study without providing at least one MPA specimen after the time of their maximum observed MPA concentration.
- The terminal phase rate constant (λ) will be estimated as minus the slope of the terminal phase, based on the last three or more log-transformed MPA concentrations regressed on time.[2] This regression will exclude specimens obtained on or after the first occurrence of a below LOQ value or month 12, whichever is earlier, as well as specimens collected before t_{max}. If the estimated slope is not negative, or if there are fewer than three time points available for estimating λ, then no value will be reported for that participant.
- Partial AUCs will be computed using a linear/log-trapezoidal rule, with concentrations at end-times imputed if no specimen was collected on the applicable day(s), as follows: if a participant discontinued or had her first LOQ measurement prior to reaching a partial AUC end time, then the missing concentration will be imputed using λ. If the end-time occurs within the range of the participants' evaluable data, then the concentration will be estimated using linear (up to C_{max}) or logarithmic regression (on or after C_{max}), based on the two specimens collected closest in time to the target date.
- $AUC_{0-\infty}$ will be computed as $AUC_{0-last} + C_{last}/\lambda$, where 'last' is the last day used to compute λ as previously defined.

[2] The actual number of time points used to compute λ will be chosen based on the regression with largest adjusted R^2 (see Matos-Pita and Miguel Lillo, 2005).

15. REFERENCES

Matos-Pita, AS and Miguel Lillo, B. Noncompartmental Pharmacokinetics and Bioequivalence Analysis. Proceeding of PharmaSUG 2005, Phoenix, AZ. SP07.

Turnbull, BW. The empirical distribution function with arbitrarily grouped, censored, and truncated data. Journal of the Royal Statistical Society, Series B 1976; 38:290-295.