Statistical Analysis Plan

A Randomized, Dose-range Finding Study to Evaluate Pharmacokinetics of Medroxyprogesterone Acetate Following a Single Subcutaneous Administration of TV-46046 in Healthy Women of Reproductive Age

Study Number TV46046-WH-10159

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Statistical Analysis Plan

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Teva Branded Pharmaceutical Products R&D, Inc
145 Brandywine Pkwy,
West Chester, PA 19380
United States of America

Study Implementation

FHI 360

Prepared by:
FHI 360

STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: TV46046-WH-10159

Study Title: A Randomized, Dose-range Finding Study to Evaluate Pharmacokinetics of Medroxyprogesterone Acetate Following a Single Subcutaneous Administration of TV-46046 in Healthy Women of Reproductive Age

Statistical Analysis Plan for:

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

Author: [redacted]

[redacted]

FHI 360

Approver signatures and dates:

[redacted]

[redacted]

[redacted], FHI 360

[redacted]

[redacted], FHI 360

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
λ	terminal phase rate constant
AUC_{0-x}	area under the serum drug concentration by time curve from time 0 to day x
$AUC_{0-\infty}$	area under the serum drug concentration by time curve from time 0 to infinity
BMI	body mass index
C_x	serum drug concentration at day x post-treatment initiation
C_{last}	last quantifiable serum drug concentration
C_{max}	maximum serum drug concentration
CI	confidence interval
CRF	case report form
CSR	clinical study report
%CV	percent coefficient of variation
E2	Estradiol
GM	geometric mean
IcE	intercurrent event
ISR	injection site reaction
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MPA	medroxyprogesterone acetate
NCA	non-compartmental analysis
NRS	numeric rating scale
P	progesterone
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SE	standard error
$t_{1/2}$	apparent terminal half-life
T_{last}	time (in days) to last quantifiable MPA measurement
T_{max}	time (in days) to maximum serum drug concentration
TEAE	treatment emergent adverse event
WY	women-years

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis for *A Randomized, Dose-range Finding Study to Evaluate Pharmacokinetics of Medroxyprogesterone Acetate Following a Single Subcutaneous Administration of TV-46046 in Healthy Women of Reproductive Age*. The study is sponsored by Teva Branded Pharmaceutical Products R&D, Inc. and is implemented by FHI 360.

The reader of this SAP is encouraged to read the protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a subject in this study. Version 1.0 of the SAP expands upon the analysis of primary and secondary endpoints outlined in Protocol Amendment 01 (the current version at the time of first subject enrolled), including definitions of estimands and methods for handling missing data and intercurrent events. When differences exist in descriptions or explanations provided in the study protocol and this Statistical Analysis Plan, the SAP prevails; any such differences will be explained in the Clinical Study Report (CSR).

Future changes to the SAP (e.g., to address amendments to the protocol) and their temporal relationship to unblinding will be documented in Section 12 and detailed in the CSR. Mock tables, figures and listings will be approved by the Coordinating Investigator prior to un-blinding of study statisticians and maintained in a separate document.

1. STUDY OBJECTIVES AND ENDPOINTS

The overall goal of this study is to select a dose of TV-46046 (medroxyprogesterone acetate [MPA] injectable suspension 300 mg/mL) that is safe, well tolerated, and has a pharmacokinetics profile consistent with contraceptive protection when injected every 6 months.

1.1. Primary Study Objective and Endpoints

1.1.1. Primary Objective

The primary objective of this study is to evaluate and compare the pharmacokinetics profile of MPA following subcutaneous administration of 3 doses of TV-46046 300 mg/mL (120 mg/0.4mL; 180 mg/0.6mL; 240 mg/0.8mL), and 104 mg/0.65 mL Depo-subQ Provera 104 in healthy female subjects.

1.1.2. Primary Endpoints

The following non-exhaustive list of pharmacokinetics parameters will be evaluated to support the primary objective of the study:

- C_{max} (maximum observed serum concentration)
- T_{max} (time to C_{max})
- Serum MPA concentrations at treatment days 91, 182, and 210 (C_{91}, C_{182}, C_{210})
- $AUC_{0\text{-}182}$ (area under the serum drug concentration-time curve from time 0 to day 182)
- $AUC_{0\text{-}210}$ (area under the serum drug concentration-time curve from time 0 to day 210)
- $AUC_{0\text{-}\infty}$ (area under the serum drug concentration-time curve extrapolated to infinity)
- Apparent terminal half-life ($t_{½}$)

1.2. Secondary Study Objectives and Endpoints

1.2.1. Secondary Objectives

The secondary objectives of the study are:

1) to evaluate and compare the safety and local tolerability of a subcutaneous injection of 3 doses of TV-46046 300 mg/mL (120 mg/0.4mL; 180 mg/0.6mL; 240 mg/0.8mL) and Depo-subQ Provera 104 in healthy female subjects
2) to evaluate the acceptability of a subcutaneous injection of TV-46046 over the range of different doses

1.2.2. Secondary Endpoints

The safety and local tolerability measures/parameters are:

- occurrence of adverse events
- use of concomitant medication
- vital signs
- body weight measurement
- vaginal bleeding pattern
- assessment of mood by Patient Health Questionnaire-9 (PHQ-9)
- liver function tests
- estradiol (E2) measurements throughout the study
- progesterone (P) measurements at Weeks 48, 49, 50, 51, and 52
- occurrence of injection site reactions (ISRs)
- subjects' responses to acceptability questions

2. STUDY DESIGN

2.1. General Design

This is a randomized, partially-blinded dose-range finding study to evaluate and compare the pharmacokinetics, safety, local tolerability, and acceptability of the subcutaneous administration of 3 different doses of TV-46046 300 mg/mL (120 mg/0.4 mL, 180 mg/0.6 mL, or 240 mg/0.8 mL) and the reference product Depo-subQ Provera 104 (104 mg/0.65mL) in healthy female subjects.

Study procedures and their timing in relation to treatment initiation are summarized in Table 1 of the protocol.[1] Briefly, study participation will consist of a screening period, treatment initiation and 52 weeks of primary follow-up. Enrolled subjects will provide blood samples for MPA testing at baseline (Day 0, prior to injection of study drug); Day 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, and 28 post-injection; and Week 6, 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, 32, 36, 40, 44, 48, and 52 post-injection. Specimens for P and E2 measurement will be collected at Day 0 and Weeks 48, 49, 50, 51 and 52, and specimens for E2 measurement will be collected at all visits where samples for MPA or P are taken starting on Day 28.

Subjects will be evaluated for vital signs, body weight, liver enzymes, and ISRs at Weeks 1, 13, 26, and 52 post-injection; vaginal bleeding patterns will be assessed at Weeks 13, 26, and 52; acceptability will be assessed at Weeks 26 and 52; and mood will be evaluated on Days 0 and 28 and Weeks 8, 13, 17, 21, 26, 32, 36, 40, 44, 48, and 52. Subjects with unresolved ISRs at Week 52 or who report a new ISR after Week 52 will be followed every 3 months through ISR resolution or Week 78, whichever comes first (adverse events and concomitant medication use will also be evaluated at post-week 52 visits, as relevant).

2.2. Randomization, Allocation Concealment, and Blinding

Subjects will be randomized in a 1:1:1:1 allocation ratio to one of the 3 TV-46046 test groups or the Depo-subQ 104 reference group, using a permuted block design stratified by investigational center. The randomization sequence will be developed by an FHI 360 programmer not otherwise involved in the study using a validated SAS/STAT® program (version 9.4). Randomized subjects who discontinue early will not be replaced. Additional details (including block sizes) are maintained in a separate document.

Allocation will be concealed using 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 subject has completed all other baseline procedures and is determined to be eligible for treatment. Randomization envelopes will be

[1] The study protocol defines day of treatment initiation as Day 0. Noting that the day of treatment initiation is defined as Day 1 in CDISC, protocol Day X will be mapped to treatment Day X+1 when creating ADaM data.

maintained in a secure location at each center, with access limited to authorized personnel per center-specific study procedures.

The study will only be partially blinded due to differences in appearance of the investigational products. Investigational center staff preparing and administering injections will not be blinded but will be trained to shield the syringe from view of the subject. FHI 360 and sponsor study team members involved in assessment of adverse events, data analysis, and results interpretation will be blinded to treatment assignment until the first interim analysis, after which time only investigational center staff assessing safety outcomes or performing subject interviews will remain blinded. Lab personnel performing MPA testing will remain blinded throughout the study. Emergency unblinding procedures for medical reasons are described in the study Pharmacy Manual and Safety Management Plan. Any instances of unscheduled unblinding will be described in the CSR.

2.3. Blinded Data Review

Prior to the first planned interim analysis, study data will be reviewed by the Coordinating Investigator and Lead Biostatistician or their designee(s) to inform analysis decisions. The Lead Biostatistician will be responsible for developing blinded listings for this review and will document the Coordinating Investigator's decisions prior to unblinding. These reviews will include (but not necessarily be limited to) important protocol deviations for inclusion/exclusion of subjects and/or data points from the primary analysis sets, assessment of potential outliers, and any necessary adjustments to imputation rules for missing MPA results due to out of window visits. Blinded data reviews may likewise occur to inform clinical queries to the site.

2.4. Interim Monitoring

A Study Review Committee (SRC) composed of FHI 360 and Sponsor staff will convene for one or more interim data reviews after at least 80% of treated subjects have had an opportunity to complete 7.5 months of follow-up. Unplanned reviews may be triggered by the occurrence of ISRs and/or serious and related adverse events as specified in the protocol and detailed in a separate SRC Operational Plan. The SRC may recommend that the trial be modified or halted to ensure the safety and well-being of study subjects at the time of any planned or unplanned interim analysis. There will be no adjustment to type I error or the coverage of confidence intervals (CIs) to account for interim reviews of data.

2.5. Sample Size and Power Considerations

There are no hypothesis tests in this phase 1 pharmacokinetics study, and the sample size was not based on formal power calculations. Rather, 60 treated subjects (15 per group) was determined to be sufficient to inform the selection of a dose of TV-46046 for future pivotal study based on the results of two recent trials of MPA products implemented under similar protocols. [redacted]

[redacted]

2.6. Sequence of Planned Analyses

2.6.1. Planned Interim Analysis

A planned review of interim data will occur when at least 80% of treated subjects have had an opportunity to complete 7.5 months of follow-up. This interim analysis is intended to inform the decision to move to - and the dose selection for - a future pivotal study. If recommended by the SRC, additional interim analyses of pharmacokinetic data may be performed in advance of an end of phase 2 meeting. Unplanned interim analyses for purposes of monitoring participant safety may be triggered by safety endpoints or otherwise made at the discretion of the SRC.

2.6.2. Final Analysis and Reporting

All final analyses will be performed after the last subject has completed the study. [redacted]

3. ANALYSIS SETS

3.1. Screened Analysis Set

The Screened Analysis Set will include all subjects who are screened for study participation, regardless of whether they are enrolled and randomized. In this analysis set, analyses will be performed according to enrollment status.

3.2. Randomized Analysis Set

The Randomized Analysis Set will include all randomized subjects, regardless of whether they received a dose of study drug. The Randomized Analysis Set will be used for assessment of subject disposition.

3.3. Safety Analysis Set

The Safety Analysis Set will be a subset of the Randomized Analysis Set, excluding any subject who failed to receive an injection of study drug. Subjects will be analyzed according to treatment received, regardless of any allocation errors. The Safety Analysis Set will be used for all assessments of baseline, safety, and acceptability data, as well as sensitivity analyses of pharmacokinetics data that include all treated subjects, regardless of any exclusions from the primary pharmacokinetics analyses.

3.4. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set will be a subset of the Safety Analysis Set, excluding any subjects who had a baseline MPA concentration that exceeded 5% of their individual Cmax, had an important protocol deviation that may affect interpretation of their MPA data, or failed to provide at least one evaluable post-treatment MPA specimen. The Pharmacokinetic Set will be analyzed according to treatment received. Failure to follow the intention-to-treat principle will be justified on the grounds that the study is not intended to make definitive conclusions regarding the efficacy of TV-46046.

A single intercurrent event (IcE) relevant to pharmacokinetic analyses is anticipated as possible for this study: the use of concomitant medications known to impact the pharmacokinetics of MPA (e.g. inducers or inhibitors of CYP3A4).[2] The strategy for handling this potential IcE is to exclude MPA results obtained during periods of relevant medication use (and assume that the excluded drug concentration data are missing completely at random) when defining estimands and constructing estimators based on non-compartmental analysis (NCA) methods. Additional details regarding the impact of IcEs on estimands and estimators are provided in Section 10.

[2] Intercurrent events typical to other studies, such as discontinuing treatment and treatment switching, are not relevant given that each subject is administered only a single dose of drug which can't be discontinued.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. Descriptive Statistics

Descriptive statistics pertinent to pharmacokinetic analyses are described in Section 10. For all other analyses, continuous variables will be summarized using the number [n] of non-missing values, the mean, standard deviation (SD), median, minimum, maximum and other descriptive statistics, as relevant. Categorical data will be summarized using the number and percentage of subjects with a specific level of the variable. Measures of central tendency and dispersion will be reported to one decimal place greater than the original data; the minimum, maximum, and percentiles other than the median will be reported to the same number of decimal places as the original data. Proportions will be presented to three decimal places and percentages to one decimal place.

4.2. Specification of Baseline Values

The baseline value for any measurement is the last value prior to injection of study drug.

4.3. Handling of Withdrawals and Missing Data

4.3.1. Discontinuation and Missing Data

Subjects who are discontinued from the study after being randomized will not be replaced. All available data up to the time of discontinuation will be included in relevant analyses. Except as noted in Section 4.3.2, missing data will not be estimated or imputed.

4.3.2. Imputed Data

Missing MPA concentrations at key time points (e.g., end-times of partial AUCs) and MPA concentrations that fall below the lower limit of quantification (LLOQ) will be imputed using methods specified in Section 10. Other laboratory measurements that fall below an applicable LLOQ will be imputed as half the LLOQ when summarizing continuous variables. If required to interpret safety, incomplete adverse event onset, resolution, or concomitant medication use dates may be imputed as follows:

- If the month of adverse event onset or initiation of medication use is known but the day is missing, then the onset/initiation date may be imputed as the first day of the month.
- If the month of adverse event resolution or medication use stop-date is known but the day is missing, then the resolution/stop data may be imputed as the last day of the month.

Other imputation rules may be required on a case-by-case basis, as determined by the Coordinating Investigator or delegated staff member. Imputation decisions will be documented in the CSR as occurring after unblinding, as applicable.

4.4. Study Days and Visits

For purposes of analysis, the number of days post-injection 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 day indicates an event prior to study drug administration. When 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.

Although actual MPA sampling times will be used in applicable pharmacokinetics analyses (e.g., when computing AUC values), sampling times will be assigned to visit windows when reporting by-visit summaries of MPA concentrations (e.g., C_{182}). In order to maximize available data, the window periods used in these by-visit summaries may be wider than the target visit windows specified in the protocol (see Table 2).

Table 2. Pharmacokinetic data visit windows

	Visit Window	
Days since Treatment Initiation	**Protocol Target**	**Visit-specific Analyses**
1, 2	± 1 hour	+/- 3 hours
3, 5, 7	± 3 hours	+/- 6 hours
10, 12, 14, 18	± 24 hours	+/- 24 hours
21 and after (except days 91 and 182)	± 48 hours	+/- 168 hours
91, 182	± 48 hours	-84 / +168 hours

5. STUDY POPULATION

5.1. General

This study will recruit healthy subjects to eliminate confounding factors (comorbidities, comedications) with potential impact on study outcome. Since TV-46046 is a hormonal contraceptive, only women will be enrolled in the study. Since the contraceptive dose and duration action of TV-46046 is unknown, we will enroll women who are not pregnant, not wanting to become pregnant in the next 24 months, and who are at low risk of pregnancy because they are sterilized, in exclusively same-sex partnership, abstinent, in monogamous relationship with vasectomized partner, using non-hormonal IUD, consistent use of condoms or other barrier methods of contraception. Enrolled women will be 18 to 45 years of age and with body mass index (BMI) 18 to 35 kg/m^2 (inclusive).

5.2. Subject Disposition

Summaries of subject disposition will include the numbers and percentages of screened subjects who are enrolled, randomized, and contribute to the Randomized, Safety and Pharmacokinetic Analysis Sets; reasons for exclusion from analysis sets; women-years (WY) of follow-up contributed (for Randomized and Safety analysis sets) and WY of MPA testing contributed (for Pharmacokinetic analysis set); and the numbers and percentages of subjects who complete the study, discontinue early (overall and by reason), or are lost to follow-up. Disposition will be summarized by treatment group, investigational site and overall.

5.3. Demographic and Baseline Characteristics

Summary statistics appropriate for the measurement scale will be used to describe baseline data. Continuous variables may also be described using categorical levels based on previous experience with similar studies. Baseline data will be presented for the Safety Analysis Set and the Pharmacokinetic Analysis Set (the later only if any subjects are excluded from the Safety Set). Summaries will be provided by treatment group within each investigational center and pooled across centers and treatment groups. No statistical tests will be performed to compare baseline characteristics between treatment groups. [redacted]

5.4. Protocol Deviations

Protocol deviations will be tabulated by treatment group (as relevant) according to categories of deviations and described in data listings, including any action taken in response to the deviation.

6. EFFICACY ANALYSIS

N/A. Efficacy will not be evaluated in this study.

7. MULTIPLE COMPARISONS AND MULTIPLICITY

No adjustments will be made for planned or unplanned multiple comparisons of study endpoints.

8. SAFETY ANALYSIS

8.1. General

An adverse event with onset during or after injection of study drug, or a worsening of an existing condition during or after injection, is considered a treatment emergent adverse event (TEAE); only TEAEs will be included in the safety analysis. All safety and local tolerability endpoints will be summarized for the Safety Analysis Set.

8.2. Compliance to Study Drug

All treated subjects will by definition be 100% compliant, as they are administered a single dose of drug which can't be discontinued.

8.3. Adverse Events

A summary table of TEAEs will include numbers of events, and numbers and percentages of subjects, experiencing: any TEAEs; serious TEAEs; related TEAEs; TEAEs by severity; TEAEs leading to study discontinuation; and TEAEs leading to death. Treatment-group differences in the percentages of subjects experiencing each TEAE category will be explored using descriptive Fisher's Exact tests. The summary table will be repeated when restricted to TEAEs with onset on or before week 52 (the end of routine follow-up).

TEAEs will be further grouped by System Organ Class (SOC) and preferred term using MedDRA™ (v23.0 or higher). Results will be displayed in order of decreasing frequency, both across SOCs and within each SOC term, by treatment group. TEAEs will also be tabulated by severity (mild, moderate, severe) and relationship to study drug, by SOC and preferred term. TEAEs (preferred term) which occur in at least 10% of subjects will be summarized separately.

Listings of TEAEs will include verbatim event description, SOC and preferred term, duration, relatedness, seriousness, severity, outcome, whether onset was during the first 52 weeks of follow-up, and whether the subject withdrew from the study as a result of the event. Information on any deaths will be described in subject narratives included in the CSR.

8.4. Injection Site Reactions

A summary table of ISRs will include numbers of events, and numbers and percentages of subjects, experiencing a) any ISR; b) ISRs documented as adverse events on CRF data (per protocol criteria); and c) hypopigmentation events. Exact Cochran-Armitage tests of trend will be used to explore relationships between MPA dose and the probability of experiencing ISRs.

ISRs will be further tabulated according to specific categories, including but not necessarily limited to erythema, swelling, pruritus, bleeding, bruising, hypopigmentation, atrophy, and injection site pain. The maximum recorded size of ISRs (if applicable) will be summarized using descriptive statistics for continuous variables. An 11-point numeric rating scale will be used to describe reports of injection site pain. Listings of ISRs will include time to onset, duration,

outcome, and whether the ISR was self-reported by the subject or noted by clinic staff when performing an assessment of the injection site.

8.5. Delayed Return to Ovulation

The number and percentage of subjects with no evidence of ovulation (i.e. no observed P ≥ 4.7 ng/mL) in the 12th month of follow-up, and an exact 95% CI for the probability of delayed return to ovulation based on a binomial distribution assumption, will be reported by treatment group. These calculations will exclude subjects with 1 or more missing progesterone measurements at weeks 48, 49, 50, 51 or 52 unless ovulation was detected at one of their non-missing visits.

8.6. Vaginal Bleeding

Subjects' responses to questions about their vaginal bleeding patterns since last visit will be summarized in frequency tables at Weeks 13, 26, and 52.

8.7. Liver Function Tests

Liver function (ALP, AST, ALT, total protein, albumin, and total and direct bilirubin) will be summarized by treatment group by tabulating mean, SD, median, minimum and maximum values at Day 7, Week 13, Week 26, and Week 52. Mean, standard error (SE), minimum and maximum change from baseline will be summarized using shift-tables, by treatment group.

8.8. Mood

A 10-item Patient Health Questionnaire will be used to produce an overall depression severity score. Depression scores will be summarized by treatment group in frequency tables (based on a 5-point Likert scale) at Day 0, Day 28, and Weeks 13, 26, and 52, and displayed graphically over time.

8.9. Vital Signs and Body Weight

Pulse, temperature, systolic and diastolic blood pressure, respiration rate, body weight, and BMI will be tabulated by treatment group using descriptive statistics at baseline and Day 7, Week 13, Week 26, and Week 52. Change from baseline in vital signs and body weight will be described in shift tables using mean, SE, minimum, and maximum values, by treatment group.

8.10. Estradiol

Individual E2 concentrations will be displayed graphically from pre-treatment through Week 52. E2 data will also be tabulated for each treatment group using mean, SD, median, minimum and maximum values at Day 28 and Weeks 13, 26, 30, and 52, by treatment group.

8.11. Concomitant Medications or Therapies

Concomitant medications used in 30 days prior to treatment and after treatment initiation will be summarized separately by treatment group in frequency tables, by therapeutic class and medicine category (per the WHO Drug Dictionary). Listings of medication use, including those initiated

after week 52 of follow-up (among the subset of subjects monitored for ISRs after week 52) will include indication and start and stop dates.

9. ACCEPTABILITY DATA ANALYSIS

Responses to acceptability questionnaire items at Week 26 and Week 52 will be summarized using frequency tables and compared between test and reference groups using descriptive Pearson's Chi-square tests.

10. PHARMACOKINETICS ANALYSIS

10.1. General

All pharmacokinetic analyses will be presented for the Pharmacokinetic Analysis Set unless otherwise specified.

10.2. MPA Concentrations below the LLOQ

The following rules will be applied to account for MPA concentrations below the LLOQ:

- Baseline values below the LLOQ will be imputed as 0 ng/mL
- Values that fall below the LLOQ after Day 0 will be imputed as ½ the LLOQ when summarizing visit-specific MPA concentration data. However, any below LLOQ value that occurs after the day of a woman's last quantifiable measure (T_{last}) will be imputed as zero when computing AUC values, and ignored when computing the terminal rate constant (λ).

10.3. Intercurrent Events

A single IcE is anticipated as possibly occurring in this study: the use of concomitant medications known to impact the pharmacokinetics of MPA. Any MPA results obtained from a subject between the initiation date of a relevant medication and the last date that the medication may have impacted the pharmacokinetics of MPA will be excluded from the Pharmacokinetics Analysis Set. This strategy corresponds to the hypothetical scenario in which the IcE did not occur when defining pharmacokinetic estimands, and the corresponding estimators will be (asymptotically) unbiased under the assumption that the excluded data are missing completely at random (i.e., the reason for use of the medication is independent of the pharmacokinetics of MPA). The precise dates of exclusion will be adjudicated by the Lead Biostatistician and Clinical Investigator in blind review whenever possible. The impact of exclusions on pharmacokinetic parameter estimators are described further in Section 10.4.

10.4. Descriptive Pharmacokinetic Summaries

Overlays of individual MPA profiles will be displayed by treatment group in the original scale and using semi-log[base 10] plots. Serum MPA concentrations will be summarized by treatment group using the mean (SD), median, minimum, maximum, percent below 0.2 ng/mL, and percent below the LLOQ at select sampling timepoints, including but not limited to: Baseline, Day 1, Day 91 (Month 3), Day 182 (Month 6), Day 210 (Month 7), and Day 364 (Month 12). Geometric Mean (GM) +/- geometric SD concentrations will be graphically displayed by treatment group at all sampling visits through Week 52 (Day 364). A graphical overlay of treatment-group GMs (with 95% CIs computed based on log-normality assumptions) will also be provided. If a subject has more than one MPA result in the same visit window (Table 2) then the value closest to the nominal time will be used when describing visit-level data. Summary measures of visit-specific

drug concentration data will be reported to the same number of decimal places as the original data.

10.5. Noncompartmental Analysis

The following protocol-specified pharmacokinetic parameters will be estimated based on NCA: C_{max}, T_{max}, C_{91}, C_{182}, C_{210}, $AUC_{0\text{-}182}$, $AUC_{0\text{-}210}$, $AUC_{0\text{-}\infty}$, and the apparent terminal half-life (computed as $\log_e[2]/\lambda$). Additional estimates will include AUC through day of last quantifiable sample ($AUC_{0\text{-}last}$), and time above 0.2 ng/mL (extrapolated to infinity). Detailed rules used to estimate these parameters, and conditions that must be met to report the estimate, are as follows:

- C_{max} will be based on the maximum observed MPA concentration for subjects who a) provide at least one MPA result after their highest observed concentration and b) do not use a concomitant medication known to impact the pharmacokinetics of MPA before the occurrence of C_{max}. Values of C_{max} for subjects who fail to meet these two criteria will be considered non-evaluable and excluded from the primary pharmacokinetic analysis.
- T_{max} will be based on the day (rounded to the first decimal place) when C_{max} was initially observed. Values of T_{max} for subjects who's C_{max} is non-evaluable (per above) will be excluded from primary analyses.
- C_{91}, C_{182}, and C_{210} will be based on evaluable results in the corresponding pre-defined visit windows (Table 2). If a subject has more than one MPA result in the same visit window, then the value closest to the nominal time will be used.
- λ will be estimated as minus the slope of the terminal phase, based on the last three or more log-transformed MPA concentrations after C_{max} but on or before T_{last}, regressed on time. The specific number of time points used to compute λ will be determined based on the unweighted regression with largest adjusted R^2. If the estimated slope is not negative, or if fewer than three time points are available for estimating λ, then no value will be reported.
- Partial AUC values will be computed using the 'linear up log down' rule as implemented in Phoenix WinNonLin (version 8.3 or higher). No AUC value will be reported if C_{max} was not estimable per above.
- $AUC_{0\text{-}\infty}$ will be computed as $AUC_{0\text{-}last} + C_{last}/\lambda$, where C_{last} is the last quantifiable drug concetration measurement
- Time at or above 0.2 ng/mL will be computed using linear up log down interpolation if the 0.2 ng/ml threshold is crossed between two sampling time points, and log down interpolation when extrapolating to infinity.

Except for $t_{1/2}$, the primary measure of central tendency and dispersion for each pharmacokinetic parameter estimate will be the GM and geometric %CV; for $t_{1/2}$, the harmonic mean and %CV based on a jackknife estimate of SD will be reported. Additional summaries will include mean, SD, SE, median, minimum, maximum, and 95% CIs for means. Measures of AUC, T_{max}, and $t_{1/2}$ will be reported to one decimal place. Drug concentration parameter estimates (e.g. C_{max} and

C_{182}) will be summarized using the same number of decimal places as the original data. Subject listings will include each of the above parameter estimates as well as the percent of AUC extrapolated to infinity.

10.6. Treatment Group Comparisons

Comparisons between each dose of TV-46046 and the Depo-subQ reference product will be made based on GM ratios (test/reference) and 90% CIs for GM ratios, for the following exposure parameters: C_{max}, C_{91}, C_{182}, C_{210}, $AUC_{0\text{-}182}$, $AUC_{0\text{-}210}$, $AUC_{0\text{-}\infty}$, and trough concentrations (C_{182} for each TV-46046 test group and C_{91} for the Depo-subQ provera 104 reference). Confidence intervals will be computed based on the antilog of corresponding limits for the difference in mean log concentrations (computed assuming a student-t distribution for log-transformed values). The assumptions of log-normality and homogeneity of variance will be assessed by inspection of quantile-to-quantile plots, residuals, and tests of departure from these assumptions. The lead biostatistician will use these results to determine whether either assumption is violated to a degree that alternative methods (e.g. boostrap resampling) should be employed when reporting CIs for GM ratios.

10.7. Planned Sensitivity Analyses

The NCA analysis will be repeated based on the Safety Set (not excluding any subjects or data points, regardless of IcEs or violations of entry criteria). In addition, if more than 10% of subjects have missing data on visit Day 91, 182, or 210 then the primary comparison of those outcomes between test and reference groups will be repeated based on imputed C_{91}, C_{182}, or C_{210} values, using the same imputation rules as for the end-times of partial AUCs.

10.8. [redacted]

[redacted]

11. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS/STAT® (version 9.4 or later) or Phoenix WinNonlin® (version 8.3 or later).

12. CHANGES TO PLANNED ANALYSES

12.1. Changed from V1.0 of the SAP

The following cumulative changes were made from Version 1.0 of the SAP, prior to unblinding:

Version 2.0 (May 18, 2021)

- Section 1.2.2: Safety and local tolerability measures/parameters updated to be consistent with changes made in Protocol Amendment 02.
- Section 2.1: revised to reflect updates to assessment timepoints in Table 1 of the protocol. Specifically, addition of collection of P specimens and mood evaluation on Day 0; specimens for E2 collected on Day 0 and weeks 48, 49, 50, 51 and 52; and clarifying which visits E2 specimens will be collected if MPA or P samples are taken (starting on Day 28).
- Section 10.7: [redacted].

Version 3.0 (April 12, 2022)

Version 3.0 of the SAP was created to document that the above changes took place.

Version 4.0 (June 29, 2022)

Version 4.0 of the SAP clarified computation methods for apparent half-life and time above 0.2 ng/mL. The imputation of partial AE and concomintant medication start and stop dates using previous visit dates was removed as reporting date for these events was not collected. Changes to planned analyses were documented and approved prior to unblinding.

Version 5.0 (February 15, 2023)

Version 5.0 of the SAP expanded the analysis visit windows in Table 2 after blinded review of samples excluded for being out of window. These changes were not implemented for the interim analysis but were documented and approved prior to unblinding. In section 8.5, the definition of ovulation in month 12 was added as well as a definition of which subjects would be included in the denominator for the percentage calculations.

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