Statistical Analysis Plan

A Randomized Crossover Study to Evaluate Local Tolerability Following Subcutaneous Administration of TV-46046

Study Number **TV46046-WH-10147**

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Statistical Analysis Plan

Version 2.0

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A Randomized Crossover Study to Evaluate Local Tolerability Following Subcutaneous Administration of TV-46046

Phase 1

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Sponsor

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STATISTICAL ANALYSIS PLAN V 2.0 APPROVAL

Study No.: TV46046-WH-10147 (Teva), 1191167 (FHI 360)

Study Title: A Randomized Crossover Study to Evaluate Local Tolerability Following Subcutaneous Administration of TV-46046

Statistical Analysis Plan for:

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
CI	confidence interval
CM	concomitant medications
CRF	case report form
CSR	clinical study report
FDA	Food and Drug Administration (US)
ISR	injection site reaction
LTS	Local Tolerability Study
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SRC	study review committee
TEAE	treatment-emergent adverse event
WHO	World Health Organization

REVISION HISTORY

Document Version	Changes Made	Document Date
Version 1.0	First approved version	23OCT2018
Version 2.0	Added analysis decision for partial injections (see Section 8.1)	3MAY2019

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for study (TV46046-WH-10147), *A Randomized Crossover Study to Evaluate Local Tolerability Following Subcutaneous Administration of TV-46046*. 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. 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 8. Mock tables, figures and listings designed to capture the results of analyses specified here will be approved by the coordinating investigator prior to database lock, and maintained as a separate document.

1. STUDY OBJECTIVES AND ENDPOINTS

The purpose of this study is to evaluate the local tolerability associated with the subcutaneous administration of TV-46046, and inform next steps of the TV-46046 development program.

1.1. Primary Study Objectives and Endpoints

1.1.1. Primary Objectives

The primary objective is to evaluate and compare local tolerability associated with subcutaneous administration of 120 mg/0.3 mL of TV-46046, 60 mg/0.3 mL of 1:1 saline-diluted TV-46046, 0.3 mL of TV-46046 Placebo, and 104 mg/0.65 mL of Depo-subQ Provera 104®

(medroxyprogesterone acetate injectable suspension, 104 mg/0.65 mL, hereafter referred to as Depo-subQ 104).

1.1.2. Primary Endpoints

The primary endpoint is injection site reaction (ISR), excluding injection site pain, as assessed by self-reports and direct observation for each injection at least twice on the day of injection (Day 0: immediately after [ie, as soon as possible but no later than 10 minutes upon removing the needle] and 1 hour [±5 minutes] after the injection), at Days 1, 3, 7 and 14, at Months 3 and 6, and at additional visits, if indicated.

1.2. Secondary Study Objectives and Endpoints

1.2.1. Secondary Objectives

The secondary objectives of the study are the following:

- To evaluate and compare injection site pain associated with subcutaneous administration of 120 mg/0.3 mL of TV-46046, 60 mg/0.3 mL of 1:1 saline-diluted TV-46046, 0.3 mL of TV-46046 Placebo, and 104 mg/0.65 mL of Depo-subQ 104
- To evaluate the overall safety of subcutaneous, same-day administration of 120 mg/0.3 mL of TV-46046, 60 mg/0.3 mL of 1:1 saline diluted TV-46046, 0.3 mL of TV-46046 Placebo, and 104 mg/0.65 mL of Depo-subQ 104

1.2.2. Secondary Endpoints

1.2.2.1. Injection Site Pain

- Injection site pain for each injection assessed by:
  - Numerical Rating Scale (NRS) score twice on the day of injection (Day 0: immediately [ie, as soon as possible but no later than 10 minutes upon removing the needle] after and 1 hour [±5 minutes] after the injection)
  - Self-reports using the NRS on Days 1, 3, 7 and 14, at Months 3 and 6, and at additional visits, if indicated
- Subjects' perception of injection site pain as assessed by an overall ranking of the 4 study injections from least [1] to most [4] painful on the day of injection (Day 0)

1.2.2.2. Overall Safety

- Occurrence of adverse events (AEs)
- Use of concomitant medications (CMs)

  Change in vital signs and weight

2. STUDY DESIGN

2.1. General Design

This is a randomized, crossover, single-center, Phase 1 study to evaluate and compare local tolerability following subcutaneous administration of TV-46046, diluted TV-46046, TV-46046 Placebo, and Depo-subQ 104, in 24 healthy female subjects 18 to 55 years of age. After signing the informed consent form, eligible subjects will be enrolled and receive one of each of the four subcutaneous study injections in each abdominal quadrant: 120 mg/0.3 mL of TV-46046, 60 mg/0.3 mL of 1:1 saline diluted TV-46046, 0.3 mL of TV-46046 Placebo and 104 mg/0.65 mL Depo-subQ 104 per the randomly assigned sequence. Injections will be administered in different quadrants of the abdomen, each separated by approximately 1 hour (sufficient time to eliminate carry-over effect of pain at previous injection). Subjects will be randomized to one of 24 different injection sequences (one subject per sequence) to counterbalance potential effects of injection order or abdominal quadrant on study outcomes.

All subjects will be followed for at least 6 months after receiving their injections. Local tolerability will be assessed by evaluating ISRs at least twice on the day of the study injections (Day 0: immediately after [ie, as soon as possible but no later than 10 minutes upon removing the needle] and 1 hour [±5 minutes] after the injection), at Days 1, 3, 7, and 14; at Months 3 and 6; and at other visits, if indicated. Subjects with unresolved ISR(s) at Month 6 will be followed monthly through the resolution of ISR(s) or Month 18, whichever comes first.

Subjects will assess their injection site pain using an 11-point NRS (0 = no pain at all; 10 = worst pain) twice on the day of injection (Day 0: immediately after [ie, as soon as possible but no later than 10 minutes upon removing the needle] and 1 hour [±5 minutes] after the injection). In addition, 1 hour after the fourth (final) injection subjects will provide an overall ranking of administrations from least [1] to most [4] painful. Thereafter, injection site pain will be assessed

by self-reports at all subsequent visits. Adverse events and concomitant medications will be recorded throughout the study. Vital signs and weight will be measured at baseline and study exit.

Study procedures and assessments with their timing are summarized in Table 1 of the study protocol, Section 3.4.

2.2. Randomization and Blinding

Each eligible subject will be randomized to one of the 24 possible treatment sequences (one subject per sequence). The randomization scheme will result in each drug being injected first, second, third, and fourth on 6 occasions; and each drug being injected in each quadrant of the abdomen on 6 occasions.

The randomization sequence will be developed by an FHI 360 Randomization Statistician not otherwise involved in the study using a validated SAS® program. Details will be documented in a separate Randomization Request Form prior to study initiation.

Allocation assignments will be concealed for the duration of the trial using a centralized randomization application implemented within the OpenClinica data management system, with sequentially-numbered concealed envelopes available at the investigational center as a back-up method of assignment. The next available randomization sequence will be assigned to each subject only after she has been enrolled into the study.

The study will only be partially blinded due to differences in appearance and volume of the treatments. Designated unblinded site study staff will conduct allocation procedures. Records of treatment sequence assignment will be maintained in a secure manner accessible only to authorized unblinded site study staff. All unblinded site staff involved in allocation procedures will conceal the study drug sequence assignment and all records containing allocation sequence from the subject and blinded site staff. All FHI 360 staff (aside from the unblinded clinical monitor) and sponsor staff will be blinded to treatment sequence until at least the first interim analysis, at which time results may be reviewed by treatment to inform decisions whether to stop enrollment or modify the study. Any cases of unscheduled unblinding, whether for safety reasons or inadvertently, will be described in the CSR.

2.3. Blinded Data Review

Prior to scheduled study unblinding, the data will be reviewed by the Coordinating Investigator or designee and lead biostatistician to inform analysis decisions. The lead statistician will be responsible for developing specific blinded listings for this review and will document the coordinating investigator's decisions prior to database lock and unblinding. These reviews will include (but not necessarily be restricted to) important protocol deviations for inclusion/exclusion of subjects and/or data points from the primary analysis set (i.e., the Treated Analysis Set, see Section 3), and determination of an appropriate assumption for the distribution of pain scores (e.g., negative binomial or Poisson) for use in analysis (see Section 6.2 & 6.3). Blinded data review may also include clinical evaluation of safety data or to issue clinical queries to the site if needed. Any decisions affecting analysis will be described in the clinical study report.

2.4. Data Monitoring Committee

The study will be overseen by an internal Study Review Committee (SRC), the composition and responsibilities of which will be detailed in a separate SRC Operational Plan. In addition to unplanned reviews that may be triggered by the occurrence of ISRs, serious and related adverse events, and/or injection site discoloration (hypopigmentation) events, at least one planned review (see Section 2.6.1) by the SRC will take place, at which time the SRC could advise that the study stop or be modified based on concerns for safety of subjects.

2.5. Sample Size and Power Considerations

The study size of 24 subjects (N=24) will provide at least 80% power to detect differences in ISR rates of the magnitude (>40%) observed in recent non-comparative studies of TV-46046 and Depo-subQ 104. Although not designed to obtain precise estimates of less frequent ISR rates (eg, injection site discoloration [hypopigmentation]), there is a high (>90%) probability of detecting one or more specific ISR types if the true rate of such events is at least 10%. No randomized subjects will be replaced. However, if more than two subjects fail to receive all four injections or discontinue before Month 6, then additional subjects may be enrolled to help ensure that there are at least 22 who complete the treatment sequence and are evaluable for at least 6 months. The

additional subjects will be assigned new randomization numbers, and will not re-use the randomization numbers from subjects who did not received all 4 injections.

2.6. Sequence of Planned Analyses

2.6.1. Planned Interim Analyses

The SRC will convene for a single planned review of interim data when approximately 50% of study subjects have been enrolled and treated. If, however, enrollment is predicted to take less than 2 months, then the interim review may instead be scheduled to occur after all subjects have been treated. In addition to this single planned review of interim data, the SRC will convene if at any time there have been two or more injection site reactions (ISRs) graded as severe AEs, two injection site discoloration (hypopigmentation) events ongoing for more than 7 days, or two serious and related AEs across all injection sites. If necessary to inform the program, interim data may be also reviewed at the time when all 24 enrolled women have completed 6 months of follow-up. Any such additional interim analysis will be documented in the final SAP and CSR. At the time of any planned or unplanned interim review of data, the SRC may recommend that the trial be modified or halted to ensure the safety and well-being of study subjects. There will be no adjustment to type I error to account for any interim reviews of study data.

Analyses planned for the interim review, including statistical methods, mock tables, listings, and graphs, will be described in detail in the SRC Operational Plan and approved prior to the first subject enrolled.

2.6.2. Final Analyses and Reporting

All final analyses identified in this SAP will be performed after the last subject has completed the study. This SAP and any corresponding amendments will be approved before database lock. Any supportive analyses which were not identified in the final approved version of this SAP (and prior to unblinding of statisticians) will be documented as exploratory in the CSR.

3. ANALYSIS SETS

There will be a single analysis set defined for this study: the Treated Analysis Set, which will include all subjects who receive at least 1 of the 4 study injections. All analyses will be performed according to treatment group received, even if the result of a randomization or

allocation error. During the study, several subjects reported receiving partial injections due to syringe blockage. In a blinded review of the data and in consultation with the SRC, it was decided that partial injections will be excluded from the primary safety analysis and subjects who experienced any partial injection will be excluded entirely from the secondary pain score analysis. Detailed information regarding the partial injections and the impact on study conduct as well as analyses are documented in Section 8.1.

Any other decision to exclude subjects or data points from this analysis set (e.g. due to important protocol deviations) will be made in blinded data review and documented in the CSR.

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. For categorical variables, the number and percentage of subjects with a specific level of the variable will be presented.

All reported p-values will be assessed for statistical significance at the two-sided 0.05 level, and all confidence intervals (CIs) will be computed at the two-sided 95% coverage level.

4.2. Specification of Baseline Values

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

4.3. Handling Withdrawals and Missing Data

4.3.1. Discontinuation and Missing Data

Per protocol, subjects who are discontinued from the study after being randomized (regardless of reason) will not be replaced. However, if more than two subjects fail to receive all four injections or discontinue before Month 6, then additional subjects may be enrolled to help ensure that there are at least 22 subjects who complete the treatment sequence and are evaluable for at least 6 months.

For any subject who withdraws prematurely from the study, 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 Date

If missing event dates are needed to compute durations of outcomes, the following rule will be applied:

- If the month and year are known, but the date is missing, the earlier of a) the 15th or b) the last day of the month the event could possibly have occurred will be used.

Other imputation rules may be required on a case-by-case basis, as determined in blind review of missing outcome data by the coordinating investigator or other delegated staff member. If these rules are defined after the approval of the SAP, they will be documented in the CSR.

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.

5. STUDY POPULATION

5.1. General

The study will enroll healthy women 18 to 50 years of age, inclusive, who are at low risk of pregnancy and have no skin disorders or skin allergies. The set of randomized subjects who receive at least one injection will be used for all study population summaries, unless otherwise noted.

5.2. Subject Disposition

The numbers of subjects screened and randomized, number of subjects who failed to receive all four injections, number of subjects who received partial injections, and scheduled study visits (days 0, 1, 3, 7, 14; months 3 and 6) completed will be tabulated in a frequency table. The

numbers and percentages of subjects who complete the study or discontinue early (overall and by reason) will be summarized as well. Reasons for early withdrawal will be listed.

5.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics (age, marital status, education, and race) will be summarized for the Treated Analysis Set and the subset of subjects who received no partial injections of any drug. All data reported by the subjects in the Treated Analysis Set will be listed.

For continuous variables, descriptive statistics will be provided. For categorical variables, subject counts and percentages will be provided. Categories of missing data will be presented if necessary.

5.4. Protocol Deviations

Protocol deviations will be reviewed during a blinded data review by the Coordinating Investigator or other designated staff, and any analysis decisions due to these deviations will be documented prior to database lock and unblinding. Important protocol deviations captured on CRFs will be listed.

5.5. Treatment Compliance

For purposes of the SAP, perfect treatment compliance is defined as having received all four injections. Subjects with less than full compliance will be listed with reasons.

5.6. Medical History

Pre-existing medical condition data will be summarized in tables or listings.

6. SAFETY ANALYSIS

6.1. General

Safety data will be summarized for all treated subjects. However, primary safety analyses of ISRs will exclude incomplete (partial) injections, and secondary analyses of pain scores will exclude subjects who experienced a partial injection, per Section 3. Results of all safety assessments, including local tolerability, AEs, injection site pain, change in vital sign and body weight, and use of CMs will be tabulated with descriptive statistics and/or presented in data

listings. Only outcome and event types that can be ascribed to a particular treatment (e.g., ISRs or injection site pain occurring in a particular quadrant of the abdomen) will be summarized by treatment group.

6.2. Local Tolerability

The primary ISR endpoint will be assessed at least twice on Day 0: immediately after [ie, as soon as possible but no later than 10 minutes upon removing the needle] and again 1 hour after each of the four injections; on Days 1, 3, 7 and 14; at Months 3 and 6, and at additional visits, if indicated. The frequency with which subjects experience any ISR as well as those experiencing each category of ISR documented on the case report form (i.e., redness, swelling, itching, bleeding, bruising, skin discoloration, atrophy/dimple) will be summarized by treatment group, as well as ISRs that meet the per-protocol definition of an AE. Data listings will include time to onset, duration, and resolution of the ISR.

For an ISR type, if there are sufficient numbers of ISRs to warrant the use of asymptotic methods, pair-wise treatment odds ratios (for all 6 possible comparisons among 4 treatment groups) will be assessed using logistic regression models with generalized estimating equations and robust variance estimation to account for the correlated nature of the data. The primary model will only include effects of treatment group. An exchangeable working correlation structure will be used to estimate covariance parameters. Parameter estimates, standard errors, 95% CIs, Z scores, and p-values for parameter group comparisons will also be produced. Exploratory analyses may be performed to assess effect of injection order, age and race if the population is deemed sufficiently heterogeneous with respect to these factors (based on opinion of lead statistician, in blind review of data). For less frequent ISR types (i.e., those determined not to be amenable to asymptotic method analysis), differences between groups will be assessed using exact McNemar's tests (separately for each of the 6 possible treatment comparisons). A final determination of whether the asymptotic method is appropriate will be made by the lead statistician based on observed correlation structures and event rates, blinded to treatment group prior to database lock and unblinding. In particular, if the expected coverage error of 95% confidence intervals is predicted to be below 90% (as determined in simulation studies), then the exact method will be used.

Although excluded from the primary analysis of ISRs, data from partial injections will be summarized in listings and described when summarizing the overall safety results.

6.3. Injection Site Pain

NRS pain scores for assessments on the day of injection (Day 0) will be summarized by treatment group in frequency tables, separately for pain measured immediately after injection and at 1 hour after injection. If an appropriate distribution of pain scores can be identified in blinded review (e.g., negative binomial or Poisson), then generalized linear models with exchangeable working correlation structure to account for correlated data will be used to compare treatment groups. The analysis model will only include effects of treatment, but exploratory analyses will be performed to assess effects of injection order, age, and race. If the dispersion of NRS scores is not amenable to parametric regression methods, then rank-order, permutation tests will be used to compare treatment groups (excluding any subjects who did not receive both injections being compared).

Approximately 1 hour after completing their sequence of the four treatments, each subject will also be asked to rank the injections according to overall pain from least [1] to most [4] painful. The ranking of treatment group pain will be summarized in bar charts and frequency tables, restricted to subjects who received all four injections. Differences in ranking of most painful injection will be assessed using an exact multinomial test for homogeneity across groups. If a subject cannot rank all of her injections from least to most painful, or cannot uniquely identify which injection was most painful, then her responses will be appropriately weighted across groups (e.g., if a subject ranks all 4 treatments as equally most painful, then that subject will contribute a score of 0.25 to each group when assessing distribution of most painful injection).

The proportion of subjects with unsolicited reports of injection site pain at one or more follow-up visits after Day 0 will be tabulated and compared between treatment groups using exact, pair-wise McNemar tests.

Listings of pain score data will include subjects who received partial injections.

6.4. Adverse Events

All AEs will be summarized for all treated subjects, regardless of the occurrence of a partial injection. The onset time of each AE will be compared to the time of 1st injection to determine if

the event is treatment emergent or not. Adverse events are considered treatment emergent (TEAEs) if (a) onset occurs on or after the time of first injection, or (b) an event with onset prior to the first injection but increases in severity after administration of the injection. Only treatment-emergent AEs (TEAEs) will be included in the analysis.

TEAE will be summarized in a table that presents the number and percent of subjects with any TEAE, with any serious TEAE, and with any TEAE leading to discontinuation from the study. All TEAEs will be summarized in frequency tables by MedDRA version 21.1 System Organ Class (SOC) and preferred term. Only adverse events which can be ascribed to a particular treatment group (e.g., ISRs that meet the definition of an AE) will be compared between groups using Fisher's Exact tests.

A listing of all AEs will include treatment group (where possible), verbatim AE description, preferred term and SOC, duration, relatedness to product (where relatedness is possible to ascribe), seriousness, severity, outcome, and whether the subject withdrew from the study as a result of the AE.

6.5. Vital Signs and Body Weight

Pulse rate, respiration rate, systolic/diastolic blood pressure, body weight and temperature will be summarized using descriptive statistics by study visit as well as listed by subject and visit when assessments take place. Change from baseline to Month 6 in vital signs and body weight will also be summarized descriptively. Data will be summarized for all treated subjects, regardless of the occurrence of a partial injection.

6.6. Concomitant Medications

Concomitant medications include medications that were taken at any time during the study, up to the end of study as defined in the study protocol. All concomitant medications will be coded according to the World Health Organization (WHO) drug dictionary (WHO Drug Global B3/C3). The use of concomitant medications will be summarized by therapeutic class and category with descriptive statistics. Subjects are counted only once in each therapeutic class, and only once in each CM category. Data will be summarized for all treated subjects, regardless of the occurrence of a partial injection

7. STATISTICAL SOFTWARE

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

8. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL V1.0

8.1. Changes from V1.0 of SAP, prior to interim analysis

In consultation with the SRC and in a completely blind data review, the decision was made on April 26th 2019 to enroll 3 additional subjects because 3 of the planned total of 24 received only partial injections of one of the drugs. Based on this consultation, the decision was made to exclude partial injections from the primary safety analysis and to entirely exclude subjects who experienced a partial injection from the secondary pain score analysis. All subjects, regardless of any partial injections, remain included in the assessment of overall safety per section 1.2.2.2. Demographic data will be summarized for both the Treated Analysis Set and the subset of subjects who received no partial injections of drug.

9. TABLES, FIGURES, AND LISTINGS

Table shells are maintained in a separate document.

10. REFERENCES