Clinical Study Protocol

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

Protocol with Amendment 04 Approval Date: 09 August 2017

Clinical Study Protocol with Amendment 04

Study Number TV46046-WH-10075

FHI 360 Study Number: 780861

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

Phase 1

IND number: 126249

Amendment 04 Approval Date: 09 August 2017

Amendment 03 Approval Date: 27 March 2017

Amendment 02 Approval Date: 04 November 2016

Amendment 01 Approval Date: 29 May 2016

Original Protocol Approval Date: 01 May 2016

Sponsor

Teva Branded Pharmaceutical Products R&D, Inc.

41 Moores Road

Frazer, Pennsylvania 19355

United States of America

Confidentiality Statement

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR) and European Union (EU) Directives (as applicable in the region of the study); local country regulations; and the sponsor's Standard Operating Procedures (SOPs).

AMENDMENT HISTORY

The protocol for Study TV46046-WH-10075 (original protocol dated 01 May 2016) has been amended and reissued as follows:

Amendment 01	29 May 2016 No subjects have been enrolled to date.
Amendment 02	04 November 2016 No subjects have been enrolled to date.
Amendment 03	27 March 2017 6 subjects have been enrolled to date
Amendment 04	09 August 2017 12 subjects have been enrolled to date

Details about the changes and reason/justification for each change are provided in Section 16.

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 04

Original Protocol Dated 01 May 2016

Study Number TV46046-WH-10075

FHI 360 Study Number: 780861

IND number: 126249

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

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the drug that were furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the drug and the conduct of the study. I agree to keep records on all subject information, study drug shipment and return forms, and all other information collected during the study, in accordance with local and national Good Clinical Practice (GCP) regulations.

Principal Investigator	Signature	Date

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Protocol Final Date
[redacted]	[redacted]	8.8.17

COORDINATING INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 04

Original Protocol Dated 01 May 2016

Study Number TV46046-WH-10075

FHI 360 Study Number: 780861

IND number: 126249

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

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Coordinating Investigator: [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

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CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the physician listed below:

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Medical Monitor
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Tel: [redacted]
Fax: [redacted]

For operational issues, contact the operational lead listed below:

[redacted], FHI 360
Tel: [redacted]
Email: [redacted]

For protocol issues, contact the study leader listed below:

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Tel: [redacted]
Tel: [redacted]
Fax: [redacted]

For serious adverse events:

Send by e-mail to the local safety officer (LSO) and to the FHI 360 medical monitor. The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.

CLINICAL STUDY PROTOCOL SYNOPSIS

Study Number: TV46046-WH-10075

Title of Study: 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

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

IND Number: 126249 **EudraCT number**: Not applicable

Name of Active Ingredient: Medroxyprogesterone acetate (MPA)

Name of Investigational Product or Device: Depot Medroxyprogesterone Acetate (DMPA [TV-46046])

Phase of the Study: 1

Number of Investigational Centers Planned: up to 5

Countries Planned: United States (US), Chile, and the Dominican Republic

Planned Study Period: November 2016 (first subject screened) to November 2019 (last subject last visit).

Number of Participants Planned: 12 to 78 healthy female participants. In an initial exploratory pharmacokinetics component (Part 1), 12 women (6 per group) will be assigned sequentially to a single subcutaneous injection in the abdomen of 120 mg TV-46046 at 1 of 2 concentrations: 0.3 mL of undiluted (400 mg/mL) product (initial 6 subjects) or 0.6 mL of 200 mg/mL saline-diluted product (next 6 subjects). If the undiluted formulation exhibits a promising pharmacokinetics profile, then up to 60 additional subjects (20 per treatment group) will be randomized to up to 3 additional recommended dose levels of undiluted TV-46046 within the range 80 to 300 mg (up to 20 subjects per treatment group) in a dose-range finding component of the study (Part 2). If undiluted TV-46046 does not exhibit an appropriate pharmacokinetic profile then Part 2 of the study will not be initiated.

If the results from Part 1 indicate that information on an intermediate concentration of TV-46046 is necessary to inform the TV-46046 development program, then 6 additional subjects will be enrolled in Part 1 as treatment group 3, to receive a subcutaneous injection of 120 mg TV-46046 at 0.4 mL of 300 mg/mL saline-diluted concentration.

Study Population: Healthy female subjects 18 to 40 years of age, inclusive, at low risk of pregnancy (ie, sterilized, in exclusively same-gender partnership, in monogamous relationship with vasectomized partner, or using non-hormonal intrauterine device [IUD]), and who are confirmed to have ovulated during the pretreatment phase of the study.

Primary Objectives

Part 1, Exploratory Pharmacokinetics: To assess the pharmacokinetics of medroxyprogesterone acetate (MPA) following a single subcutaneous injection of undiluted and saline-diluted 120 mg 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, Dose-range Finding: 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

up to 3 recommended dose levels (where pharmacodynamic response is defined as suppression of ovulation determined through serum progesterone concentrations).

Secondary Objectives

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

Study Endpoints:

Part 1, Exploratory Pharmacokinetics: Individual and mean serum MPA concentration-time profiles, and estimated noncompartmental pharmacokinetics parameters, including but not limited to maximum observed serum drug concentration (C_{max}), time to maximum observed serum drug concentration (t_{max}), observed serum drug concentration at day 182 ($C_{182,}$ week 26), area under the serum drug concentration by time curve from time 0 to day 182 (AUC_{0-182}), area under the serum drug concentration by time curve from time 0 to infinity ($AUC_{0-\infty}$), and apparent terminal half-life.

Part 2, Dose-range Finding: Time to ovulation, where ovulation is defined as a single-elevated serum progesterone (P ≥4.7 ng/mL). Secondary endpoints include pharmacokinetics of MPA based on individual serum MPA concentration-time profiles and estimated noncompartmental pharmacokinetics parameters, including but not limited to C_{max}, t_{max}, C_{182}, observed serum drug concentration at day 210 ($C_{210,}$ week 30), AUC_{0-182}, area under the serum drug concentration by time curve from time 0 to day 210 (AUC_{0-210}), $AUC_{0-\infty,}$ and apparent terminal half-life. In addition, release rates, relative bioavailability, and other pharmacokinetic parameters derived from non-linear mixed effects model compartmental analysis of MPA concentrations over time will be reported. Safety endpoints include but are not limited to the occurrence of changes in vital signs and body weight; delayed return to ovulation (>12 months [>52 weeks] post-study drug injection), adverse events, injection site reactions (ISRs), use of concomitant medications, and changes in mood, liver function tests, and menstrual bleeding patterns. Acceptability endpoints include subjects' responses to questions about injection pain, ISR complaints, and menstrual bleeding patterns; and the study staff's assessment of the ease of the injection.

General Design and Methodology: This is a 2-part study to evaluate the pharmacokinetics and pharmacodynamics of MPA in healthy female subjects after a single subcutaneous injection of TV-46046. Prior to injection, ovulation will be confirmed by measuring serum progesterone twice a week during the 2 to 3 weeks preceding expected menses. Twelve subjects (6 per treatment group) with confirmed ovulation and who meet all other eligibility criteria will be admitted to Part 1 and assigned sequentially to receive a single subcutaneous injection in the abdomen of 120 mg TV-46046 at 1 of 2 concentrations: 0.3 mL of undiluted 400 mg/mL (initial 6 subjects in treatment group 1) or 0.6 mL of saline-diluted 200 mg/mL (next 6 subjects forming treatment group 2). Depending on the results, a 3rd treatment group may subsequently be enrolled to receive a single subcutaneous injection of 120 mg TV-46046 at a concentration of 300 mg/mL (0.4 mL) (saline-diluted).

The decision to move into Part 2 will be based on predicted pharmacokinetic parameters for a range of potential Part 2 doses, as informed by observed Part 1 pharmacokinetic data. Features of the undiluted drug may also enter the decision-making, including stability, re-suspendability, syringeability and safety. Part 2 will only be implemented if the administration of undiluted TV-46046 (400 mg/mL) in Part 1 demonstrates an appropriate pharmacokinetic

profile. Pharmacokinetic criteria considered before moving into Part 2 include: predicted mean C_{max} less than 3 ng/mL, predicted time to achieve 0.2 ng/mL no more than 24 hours after study drug administration for all subjects, predicted 6-month concentration greater than 0.1 ng/mL in 95% of subjects, and predicted concentration 24 months after the last injection below 0.1 ng/mL in 90% of subjects, for all treatment groups selected for Part 2. The interim pharmacokinetic analysis to inform the decision to move into Part 2 will be performed after all 6 subjects in group 1 receiving undiluted TV-46046 in Part 1 have had a chance to complete at least 4 months (17 weeks) of treatment. At that time, available pharmacokinetic data from women in treatment group 2 (ie, the next 6 women receiving diluted TV-46046) will also be analyzed. Additional assessments will be made if warranted. If the undiluted formulation exhibits a promising pharmacokinetic profile per the criteria described above, then a dose-range finding component of the study (Part 2) will be initiated and up to 60 additional subjects (up to 20 subjects per treatment group) will be randomized to receive a single subcutaneous injection of up to 3 recommended dose levels of undiluted TV-46046 within the range of 80 to 300 mg. The selection of specific doses and number of subjects per TV-46046 dose in Part 2 will be informed by pharmacokinetics analysis and modeling of interim Part 1 data. If a diluted concentration of TV-46046 exhibits a more promising pharmacokinetic profile in Part 1, then Part 2 of the study will not be initiated. In that event, a clinical formulation of a diluted concentration may be developed and tested in a separate protocol under an amended Investigational New Drug (IND) application. If the results of Part 1 indicate that information on an intermediate concentration of TV-46046 is necessary to inform the TV-46046 development program, then 6 additional subjects will be enrolled in Part 1 as treatment group 3, to receive a subcutaneous injection of 120 mg TV-46046 at 0.4 mL of 300 mg/mL saline-diluted concentration. Study procedures for the 6 subjects in treatment group 3 of Part 1 would be the same as for the other treatment groups. The data-driven decision to add a treatment group to Part 1 minimizes subject numbers and balances the need for more information on pharmacokinetics with an alternative dilution. If interim analysis of Part 1 data indicates that neither undiluted nor diluted TV-46046 is appropriate for further testing, then all subjects enrolled in Part 1 may be discontinued early, with only post-discontinuation follow-up visits for safety purposes.

Study participation will consist of a screening and pre-treatment phase (approximately 1 month, or 4 weeks), a treatment phase (6 months, or 26 weeks), and post-treatment follow-up (an additional 6 to 12 months). During the pre-treatment phase, ovulation will be confirmed in all subjects who are otherwise eligible for the study by measuring serum progesterone twice a week (preferably 3 days apart) during the 2 to 3 weeks preceding expected menses. Enrolled subjects will receive an injection of the study drug and then be followed for at least 12 months (52 weeks) to characterize pharmacodynamics and pharmacokinetics of MPA (ie, 6 months of treatment plus 6 months of post-treatment follow-up), regardless of earlier return to ovulation. There will be three in-depth scheduled follow-up visits at day 7, week 13, and week 32 after injection, as well as frequent, brief laboratory visits that include collection of blood samples.

Subjects in both parts of the study will be routinely evaluated for vital signs, body weight, and acceptability (ie, responses to questions about injection pain, ISR complaints, and menstrual bleeding patterns), and will provide blood samples for serum progesterone, estradiol, and MPA at frequent predefined time points for 12 months (52 weeks) from start of study drug administration (regardless of earlier return to ovulation). Subjects who have not ovulated by month 12 (week 52) will be monitored by less frequent measurements of serum progesterone, estradiol, and MPA until ovulation returns for safety reasons for up to another 26 weeks (up to a total of 78 weeks from the injection of study drug). Injection sites will be observed for ISRs on the day of the study drug injection (day 0), post-injection at days 1, 2, 3, 5, and 7, week 13, week 32, at the final study visit, and other visits, if indicated. The subject's menstrual bleeding pattern will be ascertained by interviewer-administered questionnaire at monthly intervals during scheduled laboratory visits (in Part 1 only), at two scheduled follow-up visits (weeks 13 and 32 only), and at the final study visit. In addition, during Part 2 the subject's menstrual bleeding patterns will be ascertained weekly using an on-line diary; and liver function testing and mood assessment will be done at screening,

the scheduled follow-up visits at week 13 and week 32, and the final study visit. Information on adverse events and concomitant medications will be collected throughout the study. The study staff will provide assessment on the ease of the injection.

Method of Blinding and Randomization: Part 1 is open-label and without random assignment: the 1st 6 enrolled subjects will be assigned 0.3 mL of 400 mg/mL TV-46046 (undiluted) and the next group of 6 subjects will be assigned 0.6 mL of 200 mg/mL TV-46046 (saline-diluted). If warranted to inform the TV-46046 development program, a 3rd group of 6 subjects will be assigned 0.4 mL of 300 mg/mL TV-46046 (saline-diluted). If 120 mg TV-46046 is selected as 1 of the treatment groups for Part 2, then up to 48 subjects will be randomized either to the 120 mg treatment group or to 1 of 2 other selected treatment groups in a 2:3:3 ratio. If the 120 mg dose of TV-46046 is not selected as a dose for Part 2, then up to 54 subjects will be randomized in a 1:1:1 ratio to 1 of up to 3 selected treatment groups. In addition, 2 subjects with a body mass index (BMI) ≥ 40 will be randomized to each treatment group, for a maximum total of 60 subjects (up to 20 per treatment group) enrolled in Part 2.

Part 2 will be a subject-blinded study. Study staff will shield the syringe from view of the subject and any other study staff prior to and at the time of injection to ensure they remain blinded. The center investigator(s) staff responsible for reviewing and grading adverse events and laboratory staff analyzing specimens will be fully blinded.

Study Drug Dose, Mode of Administration, and Administration Rate:

Investigational Product: Part 1 of the study will evaluate a 120 mg dose of TV-46046 administered in up to 3 different concentrations: 0.3 mL of 400 mg/mL undiluted TV-46046, 0.4 mL of 300 mg/mL saline-diluted TV-46046 (if warranted), and 0.6 mL of 200 mg/mL saline-diluted TV-46046. Saline-dilution of TV-46046 will be performed at the investigational centers by a pharmacist or other trained personnel before administering the study drug.

If undiluted TV-46046 is selected for further investigation, Part 2 of the study will evaluate undiluted TV-46046 at up to 3 additional dose levels within the range of 80 to 300 mg, which will be selected on the basis of the results in Part 1.

In both the exploratory pharmacokinetics and dose-range finding parts of the study, a single subcutaneous injection of TV-46046 will be administered in the abdomen during the first 5 days of the menstrual cycle using a 23-gauge 3/8 inch needle.

Reference Treatment: Not applicable

Duration of Study Participation: The total duration of participation is up to approximately 78 weeks after the start of study drug administration.

Inclusion Criteria: Subjects may be included in the study if they meet all of the following criteria:

a. has regular menstrual cycle (24 to 35 days)

b. has confirmed ovulatory cycle during the pretreatment phase (serum progesterone ≥ 4.7 ng/mL in 2 consecutive samples)

c. is at low risk of pregnancy (ie, sterilized, in exclusively same-sex partnership, in monogamous relationship with vasectomized partner, or using non-hormonal IUD)

d. is in good general health as determined by a medical history

e. 18 to 40 years of age, inclusive

f. willing to provide informed consent and follow all study requirements

g. is not pregnant and does not have desire to become pregnant in the subsequent 36 months

h. has a BMI of 18 to 35, inclusive (unless included in the subset of subjects with extreme obesity (BMI ≥40), 2 in each dose-range finding group from a single investigational center, in Part 2)

i. has hemoglobin ≥10.5 g/L

j. has had a normal mammogram within the last year (for Part 1 only).

Exclusion Criteria: Subjects will be excluded from participating in this study if they meet any of the following criteria:

a. has hypertension:
   - systolic blood pressure (BP) ≥160 mm Hg or diastolic BP ≥100 mm Hg
   - vascular disease

b. has current or history of ischemic heart disease

c. has history of stroke

d. has history of thromboembolic event

e. has systemic lupus erythematosus
   - positive (or unknown) antiphospholipid antibodies
   - severe thrombocytopenia

f. has rheumatoid arthritis on immunosuppressive therapy

g. has migraine with aura

h. has unexplained vaginal bleeding

i. has diabetes

j. has strong family history of breast cancer (defined as one or more first degree relatives, breast cancer occurring before menopause in three or more family members, regardless of degree of relationship, or any male family member with breast cancer), or current or history of breast cancer, or undiagnosed mass detected by breast exam

k. has current or history of cervical cancer

l. has severe cirrhosis (decompensated) or liver tumors

m. has one or more baseline liver function test(s) outside the local laboratory's normal range (Part 2 only)

n. has known significant renal disease

o. history of diagnosed clinical depression or bipolar disorder, with or without suicidal ideation, and/or history of suicide attempt

p. in last two years, history of either hospitalization or medication management for psychiatric disorder that in the opinion of the investigator would make study participation unsafe, would interfere with adherence to study requirements or complicate data interpretation

q. used DMPA products (Depo-Provera CI or Depo-subQ Provera 104) in the past 12 months

r. used any of the following medications within 1 month prior to enrollment:
   - any investigational drug

- prohibited drugs per protocol
- oral contraceptives, contraceptive ring or patch
- levonorgestrel intrauterine system (LNG IUS) or contraceptive implant

s. used a combined injectable contraceptive in the past 6 months

t. less than 3 months since the end of last pregnancy

u. currently lactating

v. is using or plans to use prohibited drugs per protocol in the next 18 months

w. has known sensitivity to MPA or inactive ingredients

x. has a plan to move to another location in the next 24 months

y. in the opinion of the investigator, potentially at elevated risk of HIV infection (eg, HIV-positive partner, IV drug use by self or by partner)

z. has any condition (social or medical), which in the opinion of the investigator would make study participation unsafe, would interfere with adherence to the clinical study requirements or complicate data interpretation.

Measures and Time Points:

Pharmacodynamic Measure and Time Points: The primary pharmacodynamics measure is serum progesterone concentration, evaluated as follows: on day 0 (baseline); then at day 7, and then weekly through week 32, regardless of ovulation status. If ovulation does not return by week 32, then weekly blood samples for serum progesterone will continue to be collected until ovulation or through week 52, whichever is earlier. If there is no ovulation by week 52, then blood samples for serum progesterone will be collected weekly between weeks 61 through 65 and between weeks 74 through 78, until ovulation is detected.

Pharmacokinetic Measures and Time Points: The primary pharmacokinetics measure is serum MPA concentration. Medroxyprogesterone acetate serum concentrations will be evaluated on days 0 (baseline), 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, 28, 35, and 42; then at weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52, regardless of ovulation status. In addition, subjects for whom ovulation does not return by month 12 (week 52), blood samples for MPA will be collected and tested up to 2 more times (at weeks 61 and 74), but not past return to ovulation. Blood samples will also be collected and stored for possible future MPA testing (if necessary) any time samples are collected for serum progesterone and estradiol, with the exception of pre-treatment visits and visits for confirmation of ovulation. The sampling schedule and duration of testing may be modified based on the interim results of Part 1 to ensure that primary and secondary outcomes are precisely measured in both parts of the study.

Efficacy: Efficacy will not be evaluated in this study.

Safety Measures and Time Points: Safety will be assessed throughout the study by monitoring adverse events, ISRs, concomitant medications, delayed return to ovulation (>12 months [>52 weeks] post-study drug injection), menstrual bleeding patterns, body weight, and vital signs (blood pressure [BP; systolic/diastolic], pulse, and respiration). Injection site reactions will be evaluated on the day of study drug injection (day 0) immediately after the injection (within 10 minutes) and within the 1st hour after injection; at days 1, 2, 3, 5, and 7, week 13 and week 32 visits, at the final visit; and at other visits, if indicated. Vital signs and body weight will be assessed at scheduled follow-up visits at day 7, week 13, and week 32, and at the final study visit. Adverse events and use of concomitant medications will be measured throughout the study. If there is no ovulation by week 52, then blood samples for serum progesterone and estradiol will be collected weekly between weeks 61 through 65 and between weeks 74 through 78, but not past return to ovulation. Acceptability of subcutaneous administration of TV-46046 will be evaluated on the day of study drug injection, at the three scheduled follow-

up visits (day 7, week 13, and week 32), and at the final study visit. Menstrual bleeding patterns will be recorded during interviews at monthly intervals during scheduled laboratory visits (in Part 1 only), at 2 scheduled follow-up visits (weeks 13 and 32 only), and at the final study visit. In addition, in Part 2, menstrual bleeding data will be collected weekly using an on-line diary completed by the subjects; and change in liver function and mood will be assessed at screening, scheduled follow-up visits at week 13 and week 32, and at the final study visit.

Prohibited Medications Before and During the Study: Any drug(s) that may interfere with metabolism of MPA or affect ovarian function will be prohibited during the study.

Statistical Considerations:

Sample Size Rationale: 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 up to 3 additional 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 treatment 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.

Analysis of Primary Endpoints: The decision to move into Part 2 will be based on predicted pharmacokinetic parameters for a range of potential Part 2 doses, as informed by observed Part 1 pharmacokinetic data. Part 2 will only be implemented if the administration of undiluted TV-46046 (400 mg/mL) in Part 1 demonstrates an appropriate pharmacokinetic profile (eg, predicted mean C_{max} less than 3 ng/mL, predicted time to achieve 0.2 ng/mL no more than 24 hours after study drug administration for all subjects, predicted 6-month concentration greater than 0.1 ng/mL in 95% of subjects, and predicted concentration 24 months after the last injection below 0.1 ng/mL in 90% of subjects for all treatment groups selected for Part 2).

The primary objective of Part 2 will be assessed by estimating the cumulative probability of return to ovulation through 52 weeks from start of study drug treatment using Kaplan-Meier methods. Time to ovulation will be estimated as the difference (in days) between enrollment and the date of first elevated serum progesterone concentration (≥4.7 ng/mL). Data from a subset of 6 subjects (2 per treatment group) with extreme obesity (BMI ≥40), and subjects with detectable MPA at baseline (more than 5% of their C_{max}) or who used drugs known to interfere with pharmacokinetics or pharmacodynamics of MPA, will be excluded from the primary analysis but will be described separately.

Also in Part 2, individual and mean serum MPA concentration-time profiles, and estimated non-compartmental pharmacokinetics parameters including but not limited to C_{max}, t_{max}, C_{182}, C_{210}, $AUC_{0\text{-}182}$, $AUC_{0\text{-}210}$, $AUC_{0\text{-}\infty}$, and apparent terminal half-life will be summarized for each treatment group.

Nonlinear mixed effects pharmacokinetics/pharmacodynamics modeling and simulation will be used to explore the relationship between individual serum MPA concentrations and duration of ovulation suppression, with particular emphasis on characterizing the distribution of any apparent ovulatory suppression threshold, and the lowest dose, which may reliably inhibit ovulation for 6 months.

Multiple Comparisons and Multiplicity: No adjustments will be made for the planned or unplanned multiple comparisons of primary or secondary endpoints.

Acceptability Analysis: The responses to acceptability questions regarding menstrual patterns will be descriptively compared between treatment groups. Perceptions of pain at time of injection and responses on other acceptability questionnaire items will likewise be summarized and compared between treatment groups.

Safety Analyses: Vital signs (BP [systolic/diastolic], pulse, and respiration) and body weight will be summarized graphically and using shift-tables. The number and percentage of subjects experiencing adverse events will be presented by treatment group: overall, by severity grade, and relatedness to treatment. Serious adverse events and adverse events leading to withdrawal from the study will be summarized separately. Summaries of ISR data will be provided by group in frequency tables and using subject-data listings. The percentage of women experiencing amenorrhea or other menstrual bleeding disturbances (irregular menstrual bleeding or spotting) will likewise be summarized descriptively and compared between treatment groups in Part 1 and Part 2 of the study. In Part 2 only: liver function will be assessed by tabulating and graphing change in liver function tests including but not limited to ALT and AST, from screening to week 13 (month 3), week 32 (month 7.5), and final study visit. In Part 2 only: mood will be assessed in frequency tables at screening and at week 13 (month 3), week 32 (month 7.5), and final study visits. The probability of return to ovulation more than 12 months after treatment initiation with TV-46046 will be estimated using Kaplan-Meier methods.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
%CV	percent coefficient of variation
ALT	Alanine aminotransferase
API	active product ingredient
ARV	antiretroviral drug
AST	Aspartate aminotransferase
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_{0-6}	area under the serum drug concentration by time curve from time 0 to day 6
AUC_{0-89}	area under the serum drug concentration by time curve from time 0 to day 89
AUC_{0-182}	area under the serum drug concentration by time curve from time 0 to day 182
AUC_{0-210}	area under the serum drug concentration by time curve from time 0 to day 210
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
C_{182}	observed serum drug concentration at day 182
CDC	Centers for Disease Control and Prevention
CDMS	clinical data management system
CFR	Code of Federal Regulations (US)
CIOMS	Council for International Organizations of Medical Sciences
COX-2	cyclooxygenase-2
C_{max}	maximum observed serum drug concentration
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
DAIDS	Division of Acquired Immune Deficiency Syndrome (AIDS)
Depo-Provera CI	Depo-Provera Contraceptive Injection
Depo-subQ 104	Depo subQ provera 104
DMPA	depot medroxyprogesterone acetate
DSMB	Data and Safety Monitoring Board

Abbreviation	Term
DSS	docusate sodium sulfosuccinate
ePRO	electronic patient-reported outcome
EU	European Union
FDA	Food and Drug Administration (US)
FIH	first in human
FP	family planning
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
HSV-2	herpes simplex virus type 2
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMER	Instituto Chileno de Medicina Reproductiva
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
ISR	injection site reaction
IUD	intrauterine device
LNG IUS	levonorgestrel intrauterine system
LOQ	limit of quantification
LSO	local safety officer
MEC	Medical Eligibility Criteria
MedDRA	Medical Dictionary for Regulatory Activities
MPA	medroxyprogesterone acetate
NDA	New Drug Application
OTC	over the counter
PHSC	Protection of Human Subjects Committee
PPD	Pharmaceutical Product Development, LLC
rpm	revolutions per minute
SD	standard deviation

Abbreviation	Term
SOC	system organ class
SOP	standard operating procedure
SSA	sodium sulfate anhydrous
STI	sexually transmitted infection
SUSAR	suspected unexpected serious adverse reaction
t_{max}	time to maximum observed serum drug concentration
US(A)	United States (of America)
USP	United States Pharmacopeia
WHO	World Health Organization
WY	women-years
XML	Extensible Markup Language

1. BACKGROUND INFORMATION

Teva and FHI 360 are in collaboration to develop a new formulation of depot medroxyprogesterone acetate (DMPA), TV-46046, for the prevention of pregnancy when injected every 6 months.

1.1. Introduction

Injectable contraception has been a cornerstone of international family planning (FP) programs for decades. Currently, over 40 million women worldwide use injectable contraceptives (injectables) to prevent pregnancy (United Nations Department of Economic and Social Affairs 2011). In sub-Saharan Africa, more than one-third of modern method contraceptive users rely on injectable contraceptives (Stanback et al 2010). Despite the broad and increasing use of injectables, discontinuation and late return rates for reinjection are high, frequently due to users' difficulty complying with re-injection schedules (Baumgartner et al 2007). Depending on the formulation, currently available injectables are effective for 1 to 3 months, requiring women to return to their provider monthly, every other month or quarterly; this is recognized as a significant disadvantage of these methods compared to longer-acting reversible contraceptives (eg, intrauterine devices or implants) (Lakha et al 2005).

Depo-Provera®[1] Contraceptive Injection (Depo-Provera CI) and its subcutaneous formulation depo-subQ provera 104®[1] (hereafter referred to as Depo-subQ 104), both also known as DMPA, provide contraceptive protection for 3 months and are the most popular injectable contraceptives worldwide. A longer-acting injectable contraceptive that lasts for 6 months would be a valuable addition to the method mix and ideal for women who are interested in spacing births, and/or are uncertain about their future reproductive plans. In addition to advantages for users, these methods would reduce the burden of participant load on clinical facilities and community-based programs. While efforts are under way to invest in novel sustained drug delivery technologies that hold promise for the development of a new longer-acting injectable contraceptive product (Halpern et al 2015), the adaptation of existing methods carries a distinct comparative advantage by shortening the time to market and reducing development costs.

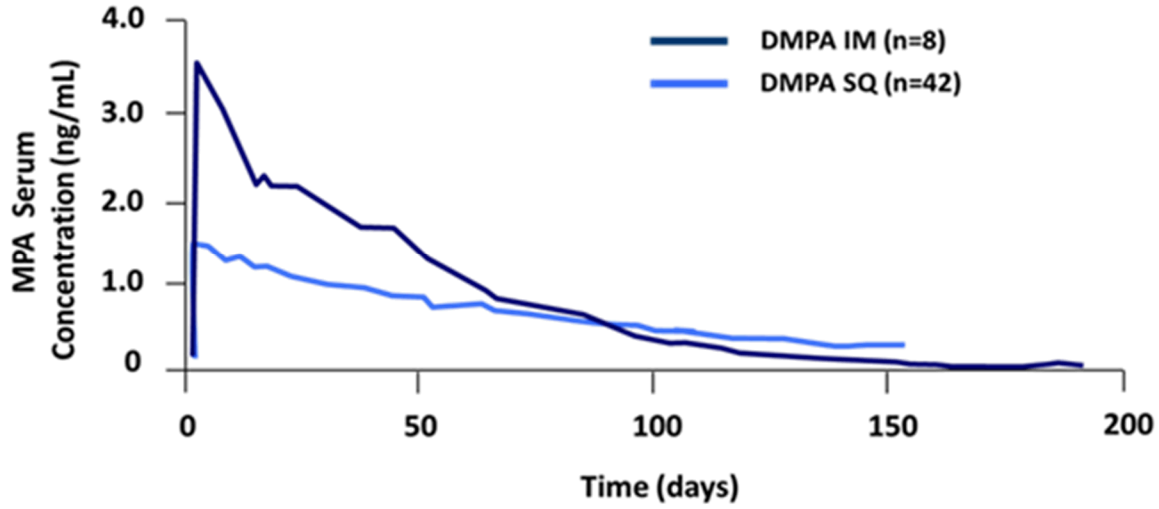
Depo-Provera CI for intramuscular use provides contraceptive protection for 3 months and is the most popular injectable contraceptive worldwide. The subcutaneous route of administration is characterized by slower absorption and a more sustained release when compared to intramuscular injection. By changing the route of administration from intramuscular to subcutaneous and volume of injection, Pfizer developed a modified formulation for subcutaneous injection (ie, Depo-subQ 104) that is also effective for at least 3 months but uses approximately 31% less of the active ingredient MPA (Figure 1). When compared to Depo-Provera CI, Depo-subQ 104 exhibited a lower average maximum observed serum drug concentration (C_{max})

[1] Depo-Provera® CI and depo-subQ provera 104® are registered trademarks of Pfizer Inc.

(1.56 ng/mL compared to 3.73 ng/mL), a longer mean half-life (43 days compared to 13 days), and lower overall drug exposure (area under the serum drug concentration by-time curve from time 0 to infinity [$AUC_{0-\infty}$] of 92.84 ng•day/mL compared to 134 ng•day/mL) (Jain et al 2004).

Teva and FHI 360 propose to evaluate the potential of TV-46046 to provide contraceptive protection when injected subcutaneously at a dose no higher than 300 mg every 6 months.

Figure 1: Pharmacokinetic Profiles of Depo-Provera CI and Depo-subQ 104



Source: Adapted from Pfizer, Spieler, JM. New Contraceptive Technology and Unfinished Agenda. Presentation at the Johns Hopkins Bloomberg School of Public Health, 2012.
Depo-Provera CI=Depo-Provera Contraceptive Injection; Depo-subQ 104 Depo subQ provera 104; IM=intramuscular; SQ=subcutaneous; MPA= medroxyprogesterone acetate; DMPA= depot-medroxyprogesterone acetate.

1.2. Name and Description of Investigational Product

TV-46046 (MPA injectable suspension, 400 mg/mL) for subcutaneous injection (TV-46046), the investigational product, is a sterile aqueous suspension of MPA, with the chemical name 6α-methyl-3,20-dioxopregna-4-en-17-yl acetate.

TV-46046 is supplied in pre-filled vials each containing 400 mg of MPA per 1 mL. In Part 1, TV-46046 will be administered as a 120 mg fixed dose at up to 3 different concentrations (0.3 mL of 400 mg/mL, 0.4 mL of 300 mg/mL [if warranted], and 0.6 mL of 200 mg/mL) by the subcutaneous route. The 300 and 200 mg/mL concentrations will be achieved by diluting the original 400 mg/mL formulation with sterile saline by a pharmacist or other trained personnel prior to injection.

If undiluted TV-46046 is selected for further testing, then the study will proceed to Part 2, wherein up to 3 additional doses of undiluted TV-46046 within the range of 80 to 300 mg will be administered as a single subcutaneous injection.

TV-46046 is manufactured by Teva. A more detailed description of the product is given in Section 3.9 .

1.3. Findings from Nonclinical and Clinical Studies

The active ingredient, MPA is a synthetic analog of 17α-hydroxyprogesterone and it has been marketed globally for many years as oral (Provera® tablets), intramuscular injection formulations (Depo-Provera CI [150 mg/mL] and Depo-Provera® [400 mg/mL]) and, more recently, as a subcutaneous injection formulation (Depo-subQ 104 [104 mg/0.65 mL]). Depo-Provera CI is approved for use as an intramuscular contraceptive in the United States (US) (New Drug Application [NDA] 20-246). The first injectable formulation was approved in 1992 and is administered at a single dose of 150 mg every 3 months. Depo-subQ 104 was approved by the US Food and Drug Administration (FDA) in 2004 (NDA 21-583) to be administered subcutaneously in doses of 104 mg/0.65 mL every 3 months. Depo-subQ 104 was also approved for management of endometriosis-associated pain (NDA 21-584). Depo-Provera 400 mg/mL, administered intramuscularly, is indicated for the adjunctive and palliative treatment of advanced endometrial or renal carcinoma.

Although TV-46046 has not been tested clinically, both Depo-Provera CI and Depo-subQ 104 have well-characterized safety profiles. They have been marketed in more than 80 countries worldwide, including the US. In addition to the successfully completed Investigational New Drug (IND) and NDA applications, a significant nonclinical and clinical safety database has been established with more than 800 published citations.

1.3.1. Nonclinical Studies

Depot medroxyprogesterone acetate/medroxyprogesterone acetate (DMPA/MPA) has been extensively investigated in a number of animal species. Consequently, the nonclinical pharmacology and toxicology profiles of DMPA/MPA have been well established. Published nonclinical pharmacological and toxicological studies from literature, including nonclinical pharmacology and toxicology/toxicokinetic activities of DMPA/MPA support the contraception indication, nonclinical pharmacokinetics, and expected safety profile of TV-46046.

The nonclinical drug metabolism, pharmacokinetics, and toxicology profiles have been described within published literature using both in vitro and in vivo models. These data are briefly summarized below, along with the studies conducted by Teva.

Details may be found in the current Investigator's Brochure (IB).

1.3.1.1. Nonclinical Studies Conducted by Teva

Teva's current nonclinical safety program consists of 4 in vivo nonclinical studies: a Good Laboratory Practice (GLP) female rabbit subcutaneous local tolerance/distant target organ tissue evaluation with long term toxicokinetic study (Study DS-2015-009); a GLP murine local lymph node assay study (Study DS-2015-017); a non-GLP murine local lymph node assay study (Study DS-2014-064); and a non-GLP female rabbit subcutaneous pharmacokinetic and gross tolerability study (Study DP-2014-135).

Subcutaneous administration of TV-46046 at a 2- or 3-fold higher dose compared to Depo-subQ 104 resulted in similar or slightly higher plasma concentrations in female rabbits (Study DP-2014-135 and Study DS-2015-009). A significant burst was not observed. The duration of exposure after a single dose of 208 mg of TV-46046 appears to be at least similar to 2 injections of Depo-subQ 104 given 3 months apart.

No significant injection site reactions (ISRs) occurred following treatment with TV-46046 containing 0.15% docusate sodium sulfosuccinate (DSS) and 1.1% sodium sulfate anhydrous (SSA) (Study DS-2015-009). Furthermore, there were no significant injection site differences in microscopic findings between TV-46046 and Depo-subQ 104 (a comparator) at day 7 and day 90. The expected pharmacologic effects of MPA were observed for TV-46046 and Depo-subQ 104, through day 90 of a single-dose subcutaneous injection study in rabbits. The magnitude of some effects (eg, higher triglycerides, liver and adrenal findings) observed in the TV-46046 group was slightly greater compared to the group given Depo-subQ 104. Subcutaneous injection of TV-46046 in rabbits results in no new toxicities, when compared to the group given Depo-subQ 104. However, the slight increase in the magnitude of effects in the TV-46046 group correlates with the higher MPA exposure levels observed on study, as measured by C_{max} (8.6 ng/mL), area under the plasma drug concentration by time curve from time 0 to day 6 (AUC_{0-6}) (42.6 ng•day/mL), and area under the plasma drug concentration by time curve from time 0 to day 89 (AUC_{0-89}) (504.3 ng•day/mL). No toxic effects were associated with TV-46046 excipients.

Results of GLP and non-GLP murine local lymph node assays indicated that the TV-46046 formulation was not a contact sensitizer (Studies DS-2015-017 and DS-2014-064, respectively). In the GLP mouse lymph node assay, DSS in vehicle did not elicit a contact sensitizing reaction at up to an 8-fold higher concentration than the concentration of DSS used to formulate TV-46046 (which contains 0.15% DSS).

1.3.1.2. Nonclinical Literature

In in vitro genotoxicity studies, DMPA/MPA was negative in bacterial and mammalian somatic cell lines. Chromosomal aberrations were noted in germ cells of dogs and hamsters given single doses of DMPA (Williams et al 1971, 1972).

In earlier rabbit and monkey repeat-dose studies, the toxicology of DMPA/MPA was fairly unremarkable (Jordan 1994). At high doses, DMPA had an apparent glucocorticoid effect causing reduced adrenal weights. Another consistent finding was the expected uterine atrophy. Effects unique to dogs included drug-induced mortality at relatively low multiples of the human dose, due primarily to pyometra/metritis, malignant mammary tumors, thrombosis, and infarction. Additionally, DMPA decreased erythrocyte, hemoglobin, and hematocrit levels, produced acromegaly with increased plasma growth hormone levels, and impaired glucose metabolism.

In long-term studies, female beagle dogs developed mammary gland tumors when treated with DMPA, and 2 of 16 rhesus monkeys developed endometrial cancer with doses 50 times higher than the dose required for contraception. Subsequent studies found that the initial carcinogenicity findings in dogs could be explained by differences between dog and human pituitary responses to MPA (Jordan 1994). In dogs but not humans, MPA causes increased pituitary growth hormone secretion, with the increases in growth hormone causing hypertrophic mammary glands and development of acromegaly. Because of these differences, it was determined that the beagle dog is an unsuitable model for assessing the long-term effects of progestogens in women (World Health Organization [WHO] 1993). Also, differences in dose and bioavailability may explain differences in carcinogenicity between animals and women.

When administered during pregnancy, DMPA/MPA masculinized female fetuses and feminized male fetuses of rats, monkeys, and baboons and caused cleft palate in rabbits and possibly mice, probably due to its glucocorticoid-like effects.

More recent publications pertaining to the safety of MPA have focused on the new concerns raised about the possibility that the users of DMPA might be more susceptible to sexually transmitted diseases than non-DMPA-treated individuals. A number of studies in mice have shown that DMPA treatment changes susceptibility and local immune responses to genital herpes simplex virus type 2 (HSV-2) infection. Pretreatment with DMPA has been shown to induce a prolonged diestrus state in mice with significant increases in susceptibility to genital HSV-2 infection as well as suppression of immune responses following immunization (Kaushic et al 2003). Those immunized mice subsequently treated with DMPA have shown decreases in local HSV-2-specific immunoglobulin (Ig) G and IgA in vaginal washes. Both male and female rhesus monkeys treated with DMPA had decreased protective efficacy following immunization (Abel et al 2004, Genesca et al 2007), indicating that MPA may affect both local and systemic immune responses. Some investigators have attributed increased viral transmission in DMPA-treated female animals to atrophied vaginal epithelium, as the thin epithelium might allow the virus to more easily penetrate the epithelial layer and/or establish infection in susceptible target cells under the epithelium (Hild-Petito et al 1998).

Based on the published literature and results of Teva's GLP-compliant nonclinical studies, subcutaneous administration of TV-46046 in humans should have a safety profile similar to that of the FDA-approved Depo-subQ 104.

1.3.2. Clinical Studies

This is the first in human (FIH) clinical study for TV-46046. However, an extensive body of pharmacokinetic and safety data is available through peer-reviewed literature and product labeling for Depo-subQ 104 and for Depo-Provera CI.

1.3.2.1. Clinical Pharmacology Studies

Information pertaining to the absorption, distribution, metabolism and excretion of MPA following intramuscular and subcutaneous administration is summarized in their respective prescribing information (Depo-Provera CI US Prescribing Information and Depo-subQ 104 US Prescribing Information).

Due to physical characteristics, MPA is slowly absorbed following either route of administration. Depo-Provera CI, when administered intramuscularly at the recommended dose to women every 3 months, inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and results in endometrial thinning. These actions are primarily responsible for its contraceptive effect. Following a single 150 mg intramuscular injection of Depo-Provera CI to women between 19 to 33 years of age, MPA concentrations increased for approximately 3 weeks to reach peak concentrations of 1 to 7 ng/mL and then decreased exponentially until they became undetectable (<100 pg/mL) between days 120 to 200 post-injection (Depo-Provera CI US Prescribing Information 2016).

Serum MPA concentrations following a single subcutaneous injection of Depo-subQ 104 reached greater than or equal to 0.2 ng/mL (the threshold considered sufficient to exert a consistent contraceptive effect) within 24 hours and the mean time to maximum observed

plasma/serum drug concentration (t_{max}) was attained approximately 1 week after injection (Depo-subQ 104 US Prescribing Information). Jain et al. (2004) compared the pharmacokinetic profile of Depo-subQ 104 and Depo-Provera CI and reported average C_{max} of 1.56 ng/mL and 3.73 ng/mL, mean half-life of 43 and 13 days, and $AUC_{0-\infty}$ of 92.84 and 134 ng•day/mL, respectively. These data provide additional evidence that the subcutaneous route of administration provides lower peak levels and more sustained blood levels than the intramuscular route. This pharmacokinetic/pharmacodynamics study will evaluate the potential of TV-46046 to provide contraceptive protection when injected subcutaneously every 6 months.

1.3.2.2. Clinical Safety Studies

Depot medroxyprogesterone acetate has a well-characterized safety profile on the basis of numerous clinical trials, post-marketing research and real life use by millions of women globally, although its use is associated with a number of side effects that include but are not limited to: disruption of menstrual bleeding patterns; decrease in bone mineral density (BMD); weight gain; and delayed return to ovulation and fertility. The use of Depo-subQ 104 is associated slightly higher rate of ISRs compared to the intramuscular formulation.

Several worldwide clinical studies have indicated that higher doses of Depo-Provera, when administered by intramuscular injection, are also safe and well-tolerated. A clinical study in 61 women was conducted in Australia to determine the safety and efficacy of DMPA administered as 6-monthly intramuscular injections of 300 mg. Side effects were varied but mild and generally related to changes in menstrual bleeding pattern (Mackay et al 1971). In the 4- and 5 ½-year-long clinical studies conducted in Thailand, 991 and 1132 women received Depo-Provera by intramuscular injection in doses of 300 and 400 mg every 6 months, respectively. In both studies, mild side effects included spotting, amenorrhea, and irregular menses (Schwallie and Assenzo 1972; McDaniel and Pardthaisong 1974). In a comparative clinical study in 1000 South African women, doses of 150 and 450 mg intramuscular injections of DMPA administered every 3 or 6 months, respectively, to 500 women were well-tolerated with fewer women discontinuing the treatment in the 6-month group (Castle et al 1978). Depo-Provera is also currently approved in Canada as an intramuscular injectable formulation at a dose of 50 mg weekly or 100 mg every 2 weeks intramuscularly for at least 6 months for the treatment of endometriosis ([PR]Depo-Provera and [PR]Depo-Provera-SC Product Monograph Canada 2013).

1.4. Known and Potential Benefits and Risks to Human Subjects

Additional information regarding benefits and risks to subjects may be found in the current IB.

1.4.1. Benefits of TV-46046

All potential subjects will be tested for anemia to meet inclusion criterion “i” before being enrolled in the study. There will be no other direct benefit to the subjects. The results of this study may facilitate the development of a new longer-acting injectable contraceptive.

1.4.2. Risks of TV-46046

Pregnancy

The contraceptive dose, as well as the duration of contraceptive effects, of TV-46046 are unknown. Therefore, all necessary precautions will be taken to minimize the risk of pregnancy

among study participants. Only women who are not pregnant, not wanting to become pregnant in the next 36 months, and who are at low risk of pregnancy because they are sterilized, in a same-sex relationship, have vasectomized partner, or use non-hormonal intrauterine device (IUD) (see Section 4 for Inclusion Criteria) will be enrolled in this FIH study. During the study, pregnancy testing will be performed if the woman is experiencing any symptoms or signs of pregnancy, or if she thinks she may be pregnant.

Although no contraceptive injectables should be used during pregnancy, there appears to be little or no increased risk of birth defects in women who have inadvertently been exposed to MPA injections in early pregnancy. Neonates exposed to MPA in-utero and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual, or social development (Depo-Provera CI US Prescribing Information 2016). According to the prescribing information, women who are breast-feeding should not have their first injection until the sixth postpartum week (Depo-Provera CI US Prescribing Information 2016). However, neonates and infants exposed to MPA from breast milk have been studied for developmental and behavioral effects through puberty, and no adverse effects have been noted. According to the Centers for Disease Control and Prevention (CDC) US Medical Eligibility Criteria (MEC) for Contraceptive Use, all progestin-only hormonal methods, including progestin-only pills, DMPA, and implants, are safe for postpartum women, including women who are breastfeeding, and can be initiated immediately postpartum (CDC 2011).

Injection Site Reactions

In 5 clinical studies involving 2325 women using Depo-subQ 104 (282 treated for up to 6 months, 1780 treated for up to 1 year and 263 women treated for up to 2 years, ie, 8 injections), 5% reported ISRs, and 1% had persistent skin changes, typically described as small areas of induration or atrophy (Depo-subQ 104 US Prescribing Information 2016). One of these studies found more injection site reactions (which were all mild to moderate in severity) in the Depo-subQ 104 group (8%) than in the Depo-Provera CI group (0.4%), an expected finding with a subcutaneous route of administration (Kaunitz et al 2009).

The potential for local irritation of TV-46046 has not yet been clinically tested. In order to assess the potential of TV-46046 for local irritation, a GLP-compliant 9-month local tolerance study in rabbits (Study DS-2015-009) has been carried out by Teva. Based on the nonclinical data obtained to date, Teva does not anticipate the rate of ISRs associated with the subcutaneous administration of TV-46046 in humans to be higher than that of Depo-subQ 104. The risk of ISRs will be carefully evaluated in this FIH study. For details, see the Study Procedures and Assessments table (Table 1).

Menstrual Changes

Most women using Depo-Provera CI or Depo-subQ 104 experience disruption of menstrual bleeding patterns. Altered menstrual bleeding patterns include amenorrhea, irregular or unpredictable bleeding or spotting, prolonged spotting or bleeding, and heavy bleeding. As women continue using Depo-Provera CI or Depo-subQ 104, fewer experience irregular menstrual bleeding and more experience amenorrhea. In 3 contraception trials, 39.0% of women experienced amenorrhea during month 6, and 56.5% experienced amenorrhea during month 12 (Depo-subQ 104 US Prescribing Information 2016). The effect on bleeding pattern of a single subcutaneous administration of TV-46046 has not been clinically tested. Women with

unexplained vaginal bleeding or anemia (hemoglobin <10.5 g/dL) will not be eligible for the study. Changes in menstrual bleeding patterns and its acceptability will be evaluated at specified study visits. For details, see the Study Procedures and Assessments table (Table 1).

Weight Gain

Women tend to gain weight while using both Depo-Provera CI and Depo-subQ 104. From an initial average body weight of 136 pounds, women who completed 1 year of treatment with Depo-Provera CI (ie, 4 intramuscular injections resulting in a cumulative dose of 600 mg) gained an average of 5.4 pounds (Depo-Provera CI US Prescribing Information 2016). In 3 large clinical trials using Depo-subQ 104, the mean weight gain was 3.5 pounds in the first year of use (Depo-subQ 104 US Prescribing Information 2016). While the effect on weight of a single subcutaneous administration of TV-46046 has not been tested clinically, it is anticipated that it will be less than the weight gain associated with the chronic use of the approved 3-month contraceptives. Body weight will be assessed periodically throughout the study.

Risk of Human Immunodeficiency Virus

Depo-Provera CI and Depo-subQ 104 provide no protection against sexually transmitted infections, including human immunodeficiency virus (HIV). While some observational data have suggested an association between the use of Depo-Provera CI and increased risk of HIV acquisition (Morrison et al 2015; Ralph et al 2015; Polis 2016) the data are inconsistent and causality has not been established. In light of the inconclusive evidence, the WHO recently revised their MEC for contraceptive use (WHO 2017); per the revised criteria, women at low risk of HIV can continue using all hormonal methods of contraception including DMPA without restriction. Women who are at high risk of HIV, however, can use DMPA if they are informed of the possible increased risk of HIV acquisition among DMPA users, the uncertainty over a causal relationship, and how to minimize their risk of acquiring HIV. This FIH study will not recruit women at high risk for HIV, but the information on how to minimize risk of acquiring HIV as well as the recommendation to use condoms for protection against HIV and STIs will be provided to all subjects in this study.

Return to fertility

Return to ovulation is delayed after stopping DMPA. Among 15 women who received multiple doses of Depo-subQ 104, the median time to ovulation was 10 months after the last injection; earliest return to ovulation was 6 months after the last injection; and 12 women (80%) ovulated within 1 year of the last injection. Subcutaneous administration of DMPA is associated with a delayed return to ovulation compared to the intramuscular route. Median time to return of ovulation after a single intramuscular injection of Depo-Provera CI (150 mg) and a single injection of Depo-subQ (104 mg) were 183 and 212 days, respectively (although the difference was not statistically significant) (Jain et al 2004).

Return to fertility is also delayed. On the basis of the prescribing information, 68% of women who stop use may conceive within 12 months, 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection of Depo-Provera CI (Depo-Provera CI US Prescribing Information 2016). Among 28 women using Depo-subQ 104 for contraception who stopped treatment to become pregnant, only 1 became pregnant within a year of last injection and a second became pregnant 443 days after the last injection (7 women were lost to follow-up) (Depo-subQ 104 US Prescribing Information 2016).

Return to ovulation and fertility after a single subcutaneous injection of TV-46046 has not been tested but is also likely to be delayed. Therefore, only women who are at low risk of pregnancy and who do not desire pregnancy for a minimum of 36 months will be enrolled in the study. All women will be followed to assess return of ovulation. For details, see the Study Procedures and Assessments table (Table 1).

Bone Mineral Density

In 2004, a boxed warning regarding skeletal health was added to the label of Depo-subQ 104 indicating that women who use these methods may lose significant BMD (Depo-subQ 104 US Prescribing Information 2016). Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of depo-subQ provera 104 during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. The label also states that Depo-subQ 104 should not be used as a long term birth control method (ie, longer than 2 years) unless other birth control methods are considered inadequate. Similar boxed warning was added to the Depo-Provera CI prescribing information.

Existing evidence indicate that the changes in BMD are largely reversible and comparable to the changes associated with the hypoestrogenism that occurs with pregnancy and lactation. Also, there is no evidence that long term use is actually associated with increased risk of fracture, the clinically relevant outcome (Kaunitz and Grimes 2011).

In this FIH study, any permanent adverse impact on BMD of a single administration of TV-46046, even at a higher dose of 300 mg, is unlikely. The loss of BMD associated with the chronic use of Depo Provera CI and Depo-subQ 104 is of particular concern during adolescence and early adulthood, a critical period of bone accretion. Women younger than 18 years of age will not be eligible for this FIH study.

Other

The clinical performance of TV-46046 has not been tested but it is likely to cause similar side effects as Depo-Provera CI or Depo-subQ 104.

According to the US Depo-subQ 104 and Depo-Provera CI labels, women with a strong family history of breast cancer should be monitored with particular care when receiving DMPA. Five large case-control studies assessed the association between DMPA use and the risk of breast cancer: three studies suggested a slightly increased risk of breast cancer in the overall population of users (Lee et al 1987, WHO 1991, Shapiro et al 2000); 2 studies demonstrated the statistically significant increased risk of breast cancer among recent DMPA users (Li et al 2012, Paul et al 1989).

Infrequent reports of anaphylaxis and anaphylactoid reaction have been received associated with the use of Depo-Provera CI. Subjects in this FIH study will remain at the investigational center for observation for at least 15 minutes after the injection and receive counseling of possible signs

of anaphylactic reaction prior to leaving the investigational center. The investigational centers will have EpiPen®[2] (epinephrine injection) on hand and easy access to emergency care of necessary in the unlikely event of an anaphylactic reaction with TV-46046.

Additional information regarding risks and benefits to human subjects may be found in the current IB.

1.5. Selection of Drugs and Doses

The proposed 2-part dose-range finding study will evaluate the potential of TV-46046 to provide contraceptive protection when injected subcutaneously every 6 months. The study will consist of 2 parts. In Part 1, exploratory pharmacokinetics, the pharmacokinetics of MPA following a single subcutaneous injection of 120 mg TV-46046 at up to 3 different concentrations (0.3 mL of 400 mg/mL, 0.4 mL of 300 mg/mL, and 0.6 mL of 200 mg/mL) will be evaluated. In Part 2, dose-range finding, the pharmacodynamics and pharmacokinetics of MPA after a single subcutaneous injection in the abdomen of undiluted TV-46046 at up to 3 additional dose levels within the range of 80 to 300 mg, which will be selected on the basis of the results in Part 1.

A detailed description of study drug administration is presented in Section 5.1.

Justification for Dose of Active Drug

The decision to move into Part 2 will be based on predicted pharmacokinetic parameters for a range of potential Part 2 doses, as informed by observed Part 1 pharmacokinetic data. Part 2 will only be implemented if the administration of undiluted TV-46046 (400 mg/mL) in Part 1 demonstrates an appropriate pharmacokinetics profile (eg, predicted mean C_{max} less than 3 ng/mL, predicted time to achieve 0.2 ng/mL no more than 24 hours after study drug administration for all subjects, predicted 6-month concentration greater than 0.1 ng/mL in 95% of subjects, and predicted concentration 24 months after the last injection below 0.1 ng/mL in 90% of subjects, for all treatment groups selected for Part 2). The 3 dose levels selected for Part 2 will depend on results of Part 1, and will be within the dose range of 80 to 300 mg.

A dose range of 80 to 300 mg is believed to be sufficiently broad to identify a safe dose of TV-46046 that will provide sustained blood levels of MPA sufficient for a contraceptive effect (ie, suppression of ovulation) when administered subcutaneously every 6 months. The maximum dose of 300 mg is defined by the goal of this project to develop a highly effective 6-month MPA contraceptive product administered subcutaneously at a dose not exceeding the highest total dose of 300 mg of an FDA-approved injectable DMPA product for intramuscular use when used for 6 months (ie, two 3-month injection cycles of Depo-Provera CI, 150 mg/mL each).

The minimum dose of 80 mg is partially informed by the pharmacokinetic and pharmacodynamics data for MPA generated in the dose-range finding study for Depo-subQ 104 (NDA 21-583; Study No. 265) that suggest the potential for contraceptive effectiveness of MPA for longer than 3 months at doses as low as 100 mg when given subcutaneously. In addition, the

[2] EpiPen is a registered trademark of Mylan Inc.

use of Depo-subQ 104 was associated with complete suppression of ovulation between days 93 and 150 following a single injection in 60 women (93%) in 1 study (see in MHRA Public Assessment Report 2015) and 90% suppression for 150 days among 39 women in another study (Jain et al 2004). On the basis of limited clinical data demonstrating a slower rate of intramuscular absorption with a higher concentration of MPA (Wright III et al 1983), MPA from the undiluted TV-46046 (400 mg/mL) may be absorbed more slowly than from Depo-subQ 104 (160 mg/mL). This also has been suggested by animal data in rabbits showing that a 3-fold higher dose administered subcutaneously as TV-46046 resulted only in 50% higher MPA plasma exposure compared to Depo-subQ 104 through study day 90 (Study DS-2015-009). Hence, if the release pattern of MPA following the subcutaneous administration of TV-46046 in humans is similar to that observed in rabbits, it is possible that TV-46046 at a dose even lower than 100 mg will provide efficacious levels of MPA, and, therefore suppress ovulation for 6 months.

1.6. Compliance Statement

This study will be conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, European Union [EU] Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor and other forms as required by national authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the subjects during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the applicable study staff must be familiar with the background to, and requirements of, the study and with the properties of the study drug(s) as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the study at that center and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with local authorities.

1.7. Study Population and Justification

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

1.8. Location and Duration of Study

This 2-part study is planned to be conducted in up to 5 investigational centers. For Part 1, the study is planned to be conducted at 1 to 2 investigational centers in the US. An additional US-based investigational center will only be considered if necessary to accomplish enrollment in a timely fashion. For Part 2, up to 3 more investigational centers will be added (at least two in Latin America). The expected duration of the 2-part study is from November 2016 (first subject screened) to November 2019 (last subject last visit). The number of investigational centers and expected duration of the study may be modified dependent on enrollment speed and other factors.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

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.

2.2. Study Objectives

2.2.1. 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). The primary objective of Part 1 is to assess the pharmacokinetics of MPA following a single subcutaneous injection of undiluted and saline-diluted 120 mg 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.

The primary objective of Part 2 is to evaluate the pharmacodynamics of MPA after a single subcutaneous injection in the abdomen of undiluted TV-46046 at up to 3 additional dose levels (where pharmacodynamics response is defined as suppression of ovulation determined through serum progesterone concentrations).

2.2.2. Secondary Objectives

The secondary objectives of the study (relevant to both Part 1 and Part 2) are the following:

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

2.3. Study Endpoints

2.3.1. Primary Endpoints

In Part 1 (exploratory pharmacokinetics), the primary endpoints are individual and mean serum MPA concentration-time profiles measured during follow-up visits, and estimated noncompartmental pharmacokinetics parameters, including but not limited to C_{max}, t_{max}, observed serum drug concentration at day 182 (C_{182}), area under the serum drug concentration by time curve from time 0 to day 182 (AUC_{0-182}), $AUC_{0-\infty}$, and apparent terminal half-life.

In Part 2 (dose-range finding), the primary endpoint is time to ovulation, where ovulation is defined as a single elevated serum progesterone (P ≥4.7 ng/mL) measured during follow-up visits.

2.3.2. Secondary Endpoints

In Part 2, secondary endpoints include pharmacokinetics of MPA based on individual and mean serum MPA concentration-time profiles and estimated noncompartmental pharmacokinetics parameters, including but not limited to C_{max}, t_{max}, C_{182}, observed serum drug concentration at day 210 (C_{210}), $AUC_{0\text{-}182}$, area under the serum drug concentration by time curve from time 0 to day 210 ($AUC_{0\text{-}210}$), $AUC_{0\text{-}\infty}$, and apparent terminal half-life. In addition, release rates, relative bioavailability, and other pharmacokinetic parameters derived from non-linear mixed model compartmental analysis of MPA concentrations over time will be reported.

2.3.3. Safety Endpoints

The safety endpoints for this study are as follows:

- change in vital signs
- change in body weight
- delayed return to ovulation (ie, >52 weeks after start of study drug treatment)
- occurrence of adverse events
- change in menstrual bleeding patterns
- change in mood (Part 2 only)
- change in liver function tests (Part 2 only)
- use of concomitant medications
- occurrence of ISRs

2.3.4. Acceptability Endpoints

Acceptability will be evaluated based on subject's responses to acceptability questions including but not limited to, questions about injection pain, ISRs, and menstrual bleeding patterns; and on the study staff's assessment of the ease of the injection.

3. STUDY DESIGN

3.1. General Design and Study Schematic Diagram

This is a 2-part study to evaluate the pharmacokinetics and pharmacodynamics of MPA in healthy female subjects after a single subcutaneous injection of TV-46046. Prior to injection, ovulation will be confirmed in all subjects by measuring serum progesterone approximately twice a week during the approximately 2 to 3 weeks preceding expected menses. Twelve subjects (6 per treatment group) with confirmed ovulation and who meet all other eligibility criteria will be admitted to Part 1 and will be assigned sequentially to receive a single subcutaneous injection in the abdomen of 120 mg TV-46046 at 1 of the 2 concentrations: 0.3 mL of undiluted 400 mg/mL (initial 6 women forming treatment group 1) or 0.6 mL of saline-diluted 200 mg/mL (next 6 women forming treatment group 2). Depending on the results, a 3rd treatment group may subsequently be enrolled to receive a single subcutaneous injection of 120 mg TV-46046 at a concentration of 300 mg/mL (0.4 mL) (saline-diluted).

An interim pharmacokinetic analysis is planned to inform the decision to move into Part 2 and will be performed after all subjects in treatment group 1 (ie, the first 6 women receiving undiluted TV-46046) in Part 1 have had a chance to complete at least 4 months (17 weeks) of treatment. At that time, available pharmacokinetic data from women in treatment group 2 (ie, the next 6 women receiving diluted TV-46046) will also be analyzed. Additional assessments will be made if warranted (eg, when 12 women [in both the undiluted and diluted groups] complete 4 months [17 weeks]). The decision to move into Part 2 will be based on predicted pharmacokinetic parameters for a range of potential Part 2 doses, as informed by observed Part 1 pharmacokinetic data. Part 2 will only be implemented if the administration of undiluted TV-46046 (400 mg/mL) in Part 1 demonstrates an appropriate pharmacokinetic profile. Other features of the undiluted drug may also enter the decision-making, including stability, re-suspendability, syringeability and safety.

Pharmacokinetic criteria considered before moving into Part 2 include: predicted mean C_{max} less than 3 ng/mL, predicted time to achieve 0.2 ng/mL no more than 24 hours after study drug administration for all subjects, predicted 6-month concentration greater than 0.1 ng/mL in 95% of subjects, and predicted concentration 24 months after the last injection below 0.1 ng/mL in 90% of subjects, for all treatment groups selected for Part 2.

If the undiluted formulation exhibits a promising pharmacokinetic profile per the criteria described above, then a dose-range finding component of the study (Part 2) will be initiated and up to 60 additional subjects (up to 20 subjects per treatment group) will be randomized to receive a single subcutaneous injection of up to 3 recommended doses of undiluted TV-46046 within the range of 80 to 300 mg. The selection of specific doses and number of subjects per TV-46046 dose in Part 2 will be informed by pharmacokinetic analysis and modeling of interim Part 1 data. If a diluted concentration of 200 mg/mL of TV-46046 exhibits a more promising pharmacokinetics profile, then Part 2 of the study will not be initiated. In that event, a clinical formulation of a diluted concentration may be developed and tested in a separate protocol under an amended IND.

If the results of Part 1 indicate that information on an intermediate concentration of TV-46046 is necessary to inform the TV-46046 development program, then 6 additional subjects will be enrolled in Part 1 as treatment group 3, to receive a subcutaneous injection of 120 mg TV-46046 at 0.4 mL of 300 mg/mL saline-diluted concentration. Study procedures for the 6 subjects in treatment group 3 of Part 1 would be the same as for the other treatment groups. The data-driven decision to add a treatment group to Part 1 minimizes subject numbers and balances the need for more information on pharmacokinetics with an alternative dilution.

If interim analysis of Part 1 data indicates that neither undiluted nor diluted TV-46046 is appropriate for further testing, then all subjects enrolled in Part 1 may be discontinued early, with only post-discontinuation follow-up visits for safety purposes.

Study participation will consist of a screening and pre-treatment phase (approximately 1 month, or 4 weeks), a treatment phase (6 months, or 26 weeks), and post-treatment follow-up (an additional 6 to 12 months). During the pre-treatment phase ovulation will be confirmed in all subjects who are otherwise eligible for the study by measuring serum progesterone approximately twice a week (preferably 3 days apart) during the approximately 2 to 3 weeks preceding expected menses. Enrolled subjects will receive an injection of the study drug and then be followed for at least 12 months (52 weeks) to characterize pharmacodynamics and pharmacokinetics of MPA (ie, 6 months of treatment plus 6 months of post-treatment follow-up), regardless of earlier return to ovulation.

During the study, subjects will provide blood samples for serum progesterone, estradiol, and MPA at frequent pre-defined time points (see Table 1 for the study procedures and assessments).

In addition to frequent laboratory visits to collect blood samples, there will be 3 scheduled follow-up visits: at day 7, month 3 (13 weeks), and month 7.5 (32 weeks) after start of study drug treatment, during which subjects will be weighed and evaluated for ISRs, vital signs, and acceptability. Injection sites will be observed for ISRs on days 0 (within 10 minutes and within the 1st hour after injection), 1, 2, 3, and 5; at 3 scheduled follow-up visits (at day 7, week 13, week 32); at the final study visit, and at other visits, if indicated. The subject's menstrual bleeding patterns will be obtained by an interview questionnaire at monthly intervals (in Part 1 only), by weekly diary completed by the subjects on-line (in Part 2 only), and at follow-up visits (month 3 and month 7.5 only), and the final study visit. In Part 2 only, liver function will be assessed by tabulating and graphing change in liver function tests including but not limited to ALT and AST, from screening to week 13 (month 3), week 32 (month 7.5), and final study visit. In Part 2 only, mood will be assessed in frequency tables at screening and at week 13 (month 3), week 32 (month 7.5), and final study visits. Information on adverse events and concomitant medicines will be collected throughout the study. The study staff will provide assessment on the ease of the injection.

Subjects in whom ovulation does not return by month 12 (week 52) after initiation of treatment will be monitored by less frequent measurements of serum progesterone, estradiol, and MPA until ovulation returns for safety reasons for up to another 26 weeks (up to a total of 78 weeks from the injection of study drug).

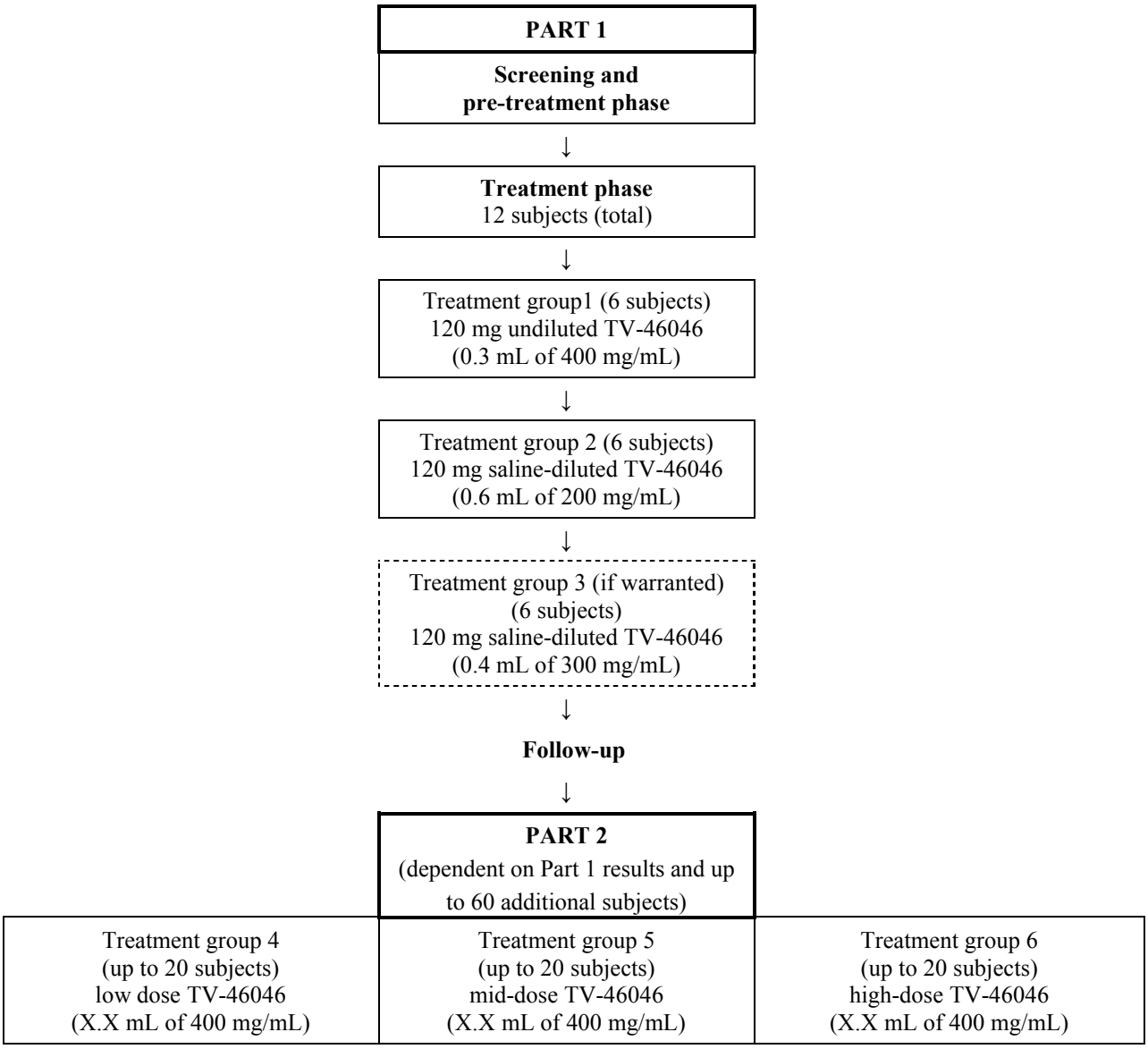
The assessments and procedures performed during each study visit are detailed in Table 1 and Section 3.14.

Part 1 is planned to be conducted at a single investigational center: Women's Health Clinical Research Center, University of Pennsylvania. An additional US-based center may be considered if necessary to accomplish enrollment in a timely manner. Up to 4 additional investigational centers will be added for Part 2 including Eastern Virginia Medical School in the US, Instituto Chileno de Medicina Reproductiva (ICMER) in Chile and the Biomedical Research Department with Profamilia in the Dominican Republic (Profamilia).

An independent Data and Safety Monitoring Board (DSMB) will oversee both parts of the study (see Section 3.8.3).

The study schematic diagram is presented in Figure 2.

Figure 2: Overall Study Schematic Diagram



X.X=will be determined on the basis of Part 1 results. Part 2 will include up to 3 additional groups, depending on Part 1 results.

3.2. Justification for Study Design

The pharmacokinetic profile of MPA following subcutaneous injection of TV-46046 in humans is not known. The exploratory pharmacokinetics component (Part 1) will allow assessment of the pharmacokinetics profile of TV-46046 at 2 different concentrations (400 mg/mL and 200 mg/mL) in humans because injection volume may be a covariate in the release rate as characterized by the pharmacokinetics profile. If undiluted TV-46046 has an acceptable pharmacokinetics profile (based on predicted mean C_{max} less than 3 ng/mL, predicted time to achieve 0.2 ng/mL no more than 24 hours after study drug administration for all subjects, predicted 6-month concentration greater than 0.1 ng/mL in 95% of subjects, and predicted concentration 24 months after the last injection below 0.1 ng/mL in 90% of subjects, for all

treatment groups selected for Part 2), then the data will be used to select up to 3 additional dose levels of TV-46046 for the dose-range finding component (Part 2) of the study. This conservative, staged approach provides an assessment of the formulation following a TV-46046 dose of 120 mg before exploring a full range of doses of TV-46046 of up to 300 mg.

If undiluted TV-46046 does not exhibit an appropriate pharmacokinetic profile for dose-range finding, then Part 2 of the study will not be initiated. In that case, treatment group 3 of Part 1 may be enrolled to inform the TV-46046 development program further. If saline-diluted TV-46046 is associated with a more promising pharmacokinetics profile, then a less concentrated product formulation may be developed and tested in a separate protocol under an amended IND.

3.3. Pharmacokinetic Measures and Time Points

The primary pharmacokinetics measure is serum MPA concentration. For Part 1, blood samples for measurement of serum concentrations will be obtained on days 0 (baseline), 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, 28, 35, and 42; weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52, regardless of ovulation status.

Among subjects in whom ovulation has not returned by month 12 (week 52), blood samples for MPA will be tested up to 2 more times (once at week 61 and once at week 74), but not past return to ovulation. The sampling schedule and duration of MPA testing may be modified based on accumulating data for a more accurate characterization of the pharmacokinetic profile of TV-46046. In addition, blood samples will also be collected and stored for possible future MPA testing (if necessary) at all weekly visits when samples are collected for serum progesterone and estradiol, except for pre-treatment visits and visits for confirmation of ovulation.

3.4. Pharmacodynamic Measures and Time Points

The primary pharmacodynamics measure is serum progesterone concentration. Blood samples for measurement of progesterone and estradiol will be obtained as follows: on day 0 (baseline); then at day 7 and then weekly through week 32, regardless of ovulation status. If ovulation does not return by week 32, then weekly blood samples for serum progesterone and estradiol will continue to be collected until ovulation or through week 52, whichever is earlier. If there is no ovulation by week 52, then blood samples for serum progesterone and estradiol will be collected weekly between weeks 61 through 65 and between weeks 74 through 78, but not past return to ovulation.

At any time point during follow-up, a subject with progesterone ≥3.0 ng/mL will be asked to return within 5 days for repeated progesterone measurement to ensure close monitoring of the potential post-ovulatory rise of progesterone. If the repeated measurement within 5 days is at or below 3.0 ng/mL, the subject will continue follow-up per her visit schedule. At any time point during follow-up, a subject with initial progesterone ≥4.7 ng/mL will be asked to return within 5 days for repeated progesterone measurement for more accurate ascertainment of ovarian function.

Estradiol will be measured at the same time points as progesterone as a supporting pharmacodynamics measure.

3.5. Safety Measures and Time Points

The following safety measures will be implemented throughout the study:

- vital signs (blood pressure [BP; systolic/diastolic], pulse, and respiration) on the day 7, and week 13 (month 3), and week 32 (month 7.5) visits, and at the final study visit
- data on menstrual bleeding pattern by interview monthly interval during scheduled laboratory visits (in Part 1 only), as well as at the week 13 (month 3), week 32 (month 7.5), and final visits
- in Part 2 only:
  - in addition to the scheduled and final visits, menstrual bleeding data weekly via an on-line diary
  - data on mood at the week 13 (month 3), week 32 (month 7.5), and final study visits
  - liver function testing at the week 13 (month 3), week 32 (month 7.5), and final study visits
- body weight on day 7, and the week 13 (month 3) and week 32 (month 7.5) visits; and at the final study visit
- delayed return to ovulation (ie, >12 months [>52 weeks] after start of study drug treatment)
- occurrence of adverse events throughout the study
- use of concomitant medications throughout the study
- ISRs immediately after the injection (within 10 minutes), within the 1st hour, at days 1, 2, 3, 5, and 7, at the week 13 (month 3) and week 32 (month 7.5) visits; and at the final study visit; and at other visits, if indicated.

3.6. Acceptability Measures and Time Points

Acceptability of subcutaneous administration of different dose/volumes of TV-46046 will be assessed through acceptability interview questionnaire on the day of injection during the enrollment/injection visit, at the scheduled follow-up visits (day 7, month 3, and month 7.5) and at the final study visit. In addition, the ease of performing the injection will be assessed through responses provided by the study staff performing the injection during the enrollment/injection visit. Acceptability of the menstrual bleeding patterns will be assessed through responses by subjects obtained by an interview questionnaire at monthly intervals during scheduled laboratory visits (in Part 1 only); at scheduled follow-up visits (except day 7); and at the final study visit.

3.7. Randomization

In Part 1 (exploratory pharmacokinetics), 12 subjects (6 subjects per concentration of TV-46046) will be sequentially enrolled. Random assignment will not be performed.

If the results from Part 1 indicate that information on an intermediate concentration of TV-46046 is necessary to inform the TV-46046 development program, then 6 additional subjects will be enrolled in Part 1 as treatment group 3, to receive a subcutaneous injection of 120 mg TV-46046 at 0.4 mL of 300 mg/mL saline-diluted concentration.

In Part 2 (dose-range finding), from up to 3 additional doses will be studied, depending on the interim results of Part 1. The treatment allocation ratio will depend on the number of doses selected for study, and whether or not the 120 mg dose of undiluted TV-46046 is selected for inclusion. If only 1 dose is selected for Part 2, no randomization will be done. If more than 1 dose is selected, including the 120 mg dose, then up to 12 subjects will be randomized to that group, and up to 18 subjects will be randomized to each of the other selected treatment groups (2:3:3 ratio). If the 120 mg dose is not selected for inclusion in Part 2 then the allocation ratio will be balanced (1:1 or 1:1:1) at each investigational center, with up to 18 subjects randomized to each treatment group. In addition, 2 subjects with a body mass index (BMI) ≥40 will be separately randomized into each treatment group (equaling a total of 20 subjects in each treatment group in Part 2) for exploratory analyses of the effect of extreme obesity on pharmacokinetics of MPA. Randomization will be stratified on investigational center, using appropriate random block sizes to minimize imbalance with respect to the overall target allocation ratio at each planned interim and final analysis. The randomization sequence will be developed by a qualified FHI 360 Randomization Statistician not otherwise involved in the study using a validated program written in SAS®.

No enrolled subjects who have received a study drug injection will be replaced in either part of the study. However, enrollment 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.

Part 1 is not blinded. Part 2 is subject-blinded, with some but not all study staff blinded to the study drug assignment.

3.8. Maintenance of Randomization and Blinding

3.8.1. Maintenance of Randomization

In Part 2 of the study, sequentially-numbered opaque randomization envelopes matching the randomization sequence will be provided to the investigational centers. Each envelope will have the randomization number printed on the outside, with the corresponding treatment group assignment concealed within the envelope. The randomization envelopes will be maintained in a secure office, with access limited to designated investigational center staff. The next available randomization number will be assigned to each subject only after she has been enrolled into the study. Randomization in Part 2 will be stratified on investigational center.

3.8.2. Blinding/Unblinding

Investigational center-specific details of how randomization and allocation concealment are maintained in Part 2 of the study will be documented in the Study Manual. Briefly, study staff

who retrieve and open randomization envelopes may also administer the study drug injection but will not have any additional role on the study. Study staff will document treatment assignments in a log, securely store the log and randomization envelopes, and restrict access to this information to necessary study staff and clinical monitors.

Part 2 will be a subject-blinded study. The clinical staff who administers injections will not be blinded due to differences in preparation of the dose and volume of the study drug. However, in order to minimize potential bias with regard to the assessment of subjective outcomes (eg, pain at injection, ISR) all efforts will be made to keep the subjects and study staff conducting follow-up interviews and completing case report forms (CRFs), unaware of treatment assignments. The clinical staff providing the injections 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. Ideally, clinical staff providing the injection should not be involved in any other study procedures.

The medical monitors responsible for reviewing and grading adverse events, and laboratory staff analyzing specimens will be fully blinded. 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 in the section 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 statistical analysis and DSMB operational plans.

3.8.3. Data and Safety Monitoring Board

During the conduct of this study, an independent 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 consist of 3 members, including at least 1 clinician with expertise in hormonal contraception. The DSMB will meet once before the study begins and at 2 or more scheduled points during the study (Section 8.10). There will be both an open and closed session at each DSMB meeting where study data are reviewed. During open sessions, representatives of the sponsor (Teva) and the Study Monitor (FHI 360) may be present and information is provided and discussed in a blinded fashion. During closed sessions, only the DSMB members, the DSMB Executive Secretary (to take notes only), and an independent analyst (possibly a clinical pharmacologist or statistician) will be present to discuss results by treatment group. Details of the DSMB procedure and responsibilities are documented in a separate DSMB Operational Plan.

If there is a request to unblind any treatment assignment, a written request from the DSMB (as a committee), signed by the DSMB chairperson, should be made to the unblinded statistician. The appropriate medical and operational personnel will be notified but will not receive the unblinded treatment information. Any use of unblinded treatment assignments should be clearly documented and reported to the sponsor at study termination.

The DSMB chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the study. The sponsor will work closely with the committee to provide the necessary data for review.

The conduct and specific details regarding the DSMB sessions and requests to unblind any treatment assignment are outlined in the DSMB charter.

3.9. Drugs Used in the Study

TV-46046 (MPA injectable suspension, 400 mg/mL) for subcutaneous injection (TV-46046) will be provided by the sponsor as a sterile suspension at concentration of 400 mg per 1 mL. In Part 1 of the study, TV-46046 will be used at up to 3 different concentrations: 0.3 mL of 400 mg/mL (undiluted), 0.4 mL of 300 mg/mL (saline-diluted) (if warranted), and 0.6 mL of 200 mg/mL (saline-diluted). To obtain lower concentrations the 400 mg/mL TV-46046 will be diluted with sterile saline by the investigational center pharmacist following the sponsor's recommendations. In Part 2 of the study, only undiluted TV-46046 will be administered at up to 3 additional doses between 80 to 300 mg.

Each TV-46046 dose will be presented in a 3 mL United States Pharmacopeia (USP) Type 1 clear glass vial, 13-mm rubber stopper, and 13-mm aluminum seal covered with a green cap (STERI-TAMP®[3] single-use tamper evident sticker). The study drug product is to be administered with a 23 gauge, 3/8 inch safety needle. Additional details may also be found in the current IB for TV-46046.

A brief description of dilution and administration procedures is provided in Section 5.1.

This is an uncontrolled study with no other study drug.

3.10. Drug Supply and Accountability

3.10.1. Drug Storage and Security

The study drug consists of TV-46046 vials, saline vials, and 23 gauge 3/8" syringes. TV-46046 should be stored at controlled room temperature 20 to 25°C (68 to 77°F). All components including the saline vials and syringes must be stored according to the manufacturer's drug product stipulation, in a dry place, and in a securely locked, substantially constructed cabinet or enclosure.

3.10.2. Drug Accountability

Each study drug shipment will include a packing slip listing the contents of the shipment, drug return instructions, and any applicable forms. The center investigator or designee will acknowledge receipt of clinical study products indicating shipment content and condition and follow drug accountability procedures throughout the study.

[3] STERI-TAMP is a registered trademark of STERI-TAMP, LLC.

Drug accountability includes maintaining accurate records, including quantity of products received, date of receipt, condition at receipt, temperature noted during transit, lot number of clinical study products received and dispensed, description of damaged units if any, dispensation, and product disposition or destruction. Storage temperature continuity tracking will occur for clinical study products during storage and transit time. Study personnel are also responsible for daily temperature monitoring and safe storage of the study products. Empty and partially used containers of study drug will be destroyed at the investigational center in accordance with investigational center SOPs, with sponsor approval. In the event the investigational center is unable to destroy the empty and/or unused units of study drug, the study drug will be disposed of, retained, or returned to the sponsor or designee per FHI 360 instructions.

Only authorized investigational center personnel will administer study product and only to participants enrolled into this study.

The center investigator is responsible for ensuring that deliveries of study drug and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the CFR or national and local regulations, and used in accordance with this protocol.

3.11. Duration of Subject Participation and Justification

This study will consist of a pre-treatment period of approximately 1 month, a treatment period of 6 months (26 weeks), and a post-treatment follow-up period of up to 12 months (up to 52 weeks). If subjects have not ovulated by 12 months (week 52) they may be followed-up until return to ovulation or week 78. If Part 2 of the study is not initiated, participation in Part 1 of the study may be as short as approximately 7 months, or 30 weeks (approximately 1 month of pretreatment and 6 months of treatment). If Part 2 is initiated, minimal participation in the study for each subject is approximately 13 months, or 56 weeks (1 month of pre-treatment, 6 months of treatment plus 6 months of post-treatment follow-up); maximum participation in the study should not exceed 19 months, or approximately 82 weeks (1 month of pre-treatment, 6 months of treatment plus a maximum of 12 months of post-treatment follow-up). See Section 11.4 for the end of study definition.

3.12. Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of the study due to apparent effectiveness or lack of effectiveness of TV-46046. However, Part 2 will not be initiated if undiluted TV-46046 does not exhibit an appropriate pharmacokinetic profile for moving into dose-range finding. This determination is intended to be made after all subjects enrolled in treatment group 1 of Part 1 (ie, 6 subjects receiving undiluted TV-46046) have had a chance to complete at least 4 months (17 weeks) of follow-up, but the timing may be modified based on accumulating data (eg, additional review of the data for all 12 women [in both undiluted and diluted groups] when they complete 4 months [17 weeks] may be needed). Criteria for initiating Part 2 include a predicted mean C_{max} less than 3 ng/mL, predicted time to achieve 0.2 ng/mL no more than 24 hours after study drug administration for all subjects, predicted 6-month concentration greater than 0.1 ng/mL in 95% of subjects, and predicted concentration 24 months after last injection below 0.1 ng/mL in 90% of subjects, for all treatment groups selected for Part 2.

The study may also pause enrollment or stop early due to concerns for safety of subjects. In particular, the investigational center will be advised to pause enrollment if at any time 2 or more subjects in Part 1 are diagnosed with severe ISR (ie, graded as Grade 3 or higher using the Division of Acquired Immune Deficiency Syndrome (Division of AIDS; DAIDS) Table for Grading Adult and Pediatric Adverse Events; see Appendix A), if severe ISRs are reported for 2 injections in a particular treatment group among all investigational centers in Part 2, or if 5 or more severe ISRs have occurred at any time across all treatment groups and investigational centers in Part 2. Such occurrences will trigger an unplanned review of interim data by the DSMB, at which time a recommendation to halt the study, to reinitiate enrollment with continued careful monitoring of ISRs, or to drop one or more groups for safety (including the occurrence of dose-limiting toxicities in Part 2) will be made. Other planned data reviews will likewise take place at regular intervals (see Section 8.10), at which time the DSMB could advise that the study stop or be modified based on concerns for safety of subjects.

Since TV-46046 is expected to remain in the body months after injection, study discontinuation will not be the same as treatment discontinuation. Study staff will explain to subjects who wish to discontinue the study early that it is important to stay in the study at least until safety assessments are completed (including delayed return to ovulation). However, a subject may discontinue participation in the study at any time for any reason (eg, withdrawal of consent or an adverse event) without loss of other benefits or services to which they may be entitled. The final follow-up visit procedures should be completed in all subjects who discontinue early, if possible. Reasons for discontinuation from the study will be recorded on the appropriate CRF.

Others reasons the study may be stopped include:

- The sponsor decides to reduce the scope (eg, reduce sample size, drop one or more study groups) or discontinue the study (eg, due to noncompliance with protocol or regulatory requirements, feasibility, etc.).
- FHI 360's Protection of Human Subjects Committee (PHSC) recommends to terminate the study
- Local IRB(s) recommend to terminate the study
- The FDA requests that the study be discontinued or placed on hold.

3.13. Source Data Recorded on the Case Report Form

Subject data should have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF; data will not be recorded directly on the case report form (CRF) and considered as source data unless FHI 360 provides written instructions specifying which data are permitted to be recorded directly to the CRF (eg, subject's responses to interview questions about menstrual bleeding patterns and acceptability).

If data are processed from other institutions or means (eg, clinical laboratory, central image center, or on-line diary data), the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to FHI 360 for direct entry into the clinical database (see Section 12.1). All data from other institutions will be available to the investigator.

The CRFs are filed in the clinical sites' files and CRFs will be shipped to the sponsor at the end of the trial.

Some CRFs data fields used in this study will have data directly recorded into them and will be considered source. Other source documents will include but will not be limited to, staff journals, medical notes, screening and enrollment logs, laboratory results, and implant dispensing records and consent forms. Source for all key study data will be defined and documented in site-specific source documentation guides.

The MPA testing will be conducted by Pharmaceutical Product Development, LLC (PPD) (Richmond, Virginia, United States of America) who will maintain source documentation for the MPA data; MPA results will not be entered into CRFs but transferred electronically to the FHI 360 data management group.

Hemoglobin, liver function testing, progesterone, and estradiol testing will be conducted at the local laboratories and made available to source verify.

3.14. Study Procedures

Before implementation, the protocol and all relevant study documents including recruiting materials will be approved by the local IRB selected by the clinical site(s) and by the PHSC of FHI 360.

Participants will come to the study clinic for 1 screening visit, up to 6 pre-treatment visits, 1 enrollment/injection visit, 3 scheduled follow-up visits, a final visit, and frequent laboratory visits to draw blood samples for progesterone, estradiol, and/or MPA. The number of laboratory visits will be in the range of 22 to 72 depending on whether Part 2 is initiated, and when ovulation returns in each individual subject. The sampling schedule and duration of testing may be modified based on the interim results of Part 1 to ensure that primary and secondary outcomes are precisely measured in both parts of the study.

Study procedures and assessments for Parts 1 and 2 with their timing are summarized in Table 1. Detailed visit-specific information is provided in this section. Detailed descriptions of each assessment are provided in Section 6 (pharmacokinetic and pharmacodynamic assessments) and Section 7 (safety assessments).

Table 1: Study Procedures and Assessments (Parts 1 and 2)

Procedures and assessments	Screening	Pretreatment	Enrollment	Follow-up		
			Day 0	Day 1 to week 78		
				Scheduled Follow-up (day 7, week 13, and week 32)	Lab visits	Final visit [a]
Informed consent	X					
Medical history	X		X			
Inclusion and exclusion criteria	X		X			
Demographics and baseline characteristics	X					
Height	X		X			
Vital signs measurement	X		X	X		X
Body weight	X		X	X		X
Breast exam	X					X
Urine pregnancy test [b]			X			
Randomization (Part 2)			X			
Study drug administration (injection) [c]			X			
Study staff assessment for ease of performing the injection			X			
Serum progesterone [e, f, g]		X [d]	X	X	X	X
Estradiol [e, f, g]		X [d]	X	X	X	X
Serum MPA [h]			X	X	X	X
Injection site reactions [i]			X	X		X
Adverse event inquiry			X	X	X [j]	X
Concomitant medication inquiry			X	X	X [j]	X
Hemoglobin	X					
Liver function testing (Part 2 only)	X			X [k]		X
Mood evaluation (Part 2 only)	X			X [k]		X
Acceptability			X	X		X
Menstrual bleeding pattern [l]				X	X	X
Mammogram [m]	X					

[a] For subjects in whom ovulation returns before month 12 post-injection, the final study visit will be scheduled at month 12. If ovulation occurs between months 12 and 18 (between weeks 52 and 78), at the time when the defining serum progesterone result becomes available, the study staff will inform the subject that she needs to return within 5 days to the investigational center for the final study visit. For subjects in whom ovulation does not return by month 18, the laboratory visit at week 78 will be considered the final study visit

[b] A urine pregnancy test will be performed at enrollment; and during the study, if indicated.

[c] Day 0; within the 1st 5 days of the start of subject's menstrual cycle.

[d] Blood samples for serum progesterone and estradiol will be collected approximately twice weekly during the approximately 2 to 3 weeks preceding the subject's expected menses for confirmation of ovulation (ideally at least 4 measurements).

[e] Blood samples for serum progesterone and estradiol will be collected on day 0 (baseline); then at day 7 and then weekly through week 32, regardless of ovulation status. If ovulation does not return by week 32, then weekly blood samples for serum progesterone and estradiol will continue to be collected until ovulation or through week 52, whichever is earlier. If there is no ovulation by week 52, then blood samples for progesterone and estradiol will be collected at weeks 61, 62, 63, 64, and 65; and at weeks 74, 75, 76, 77, and 78, if ovulation has not returned by week 65. During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol at all visits, but not past return to ovulation.

[f] At any time during follow-up, subjects with initial serum progesterone ≥3.0 ng/mL will be asked to return within 5 days for repeated progesterone and estradiol measurement. If repeated progesterone is at 3 ng/mL or below, the subject will continue follow-up per their visit schedule.

[g] At any time during follow-up, if the serum progesterone level is ≥4.7 ng/mL, subjects will be asked to return within 5 days for repeated progesterone and estradiol measurement.

[h] Blood samples for MPA will be collected on day 0; then on days 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, 28, 35, and 42; then at weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52, regardless of ovulation status. Among subjects in whom ovulation does not return by week 52, blood samples for MPA will be collected up to 2 more times (at weeks 61 and 74), but not past return to ovulation. Blood samples will also be collected and stored for possible future MPA testing (if necessary) any time samples are collected for serum progesterone and estradiol, except for pre-treatment visits and visits for confirmation of ovulation.

[i] Injection site reactions will be recorded on day 0 immediately after the injection (within 10 minutes) and within the 1st hour after injection; at days 1, 2, 3, 5, and 7; week 13 and week 32 visits; at the final visit; and at other visits, if indicated.

[j] During laboratory visits, information on adverse events and concomitant medications will not be solicited, but will be documented if reported by the subject.

[k] Liver function testing and mood evaluation will be evaluated at the week 13 and week 32 follow-up visits.

[l] Menstrual bleeding patterns will be obtained by an interview questionnaire approximately monthly; at scheduled follow up visits (weeks 13 and 32 only); and the final study visit. In addition, in Part 2 menstrual data will be collected weekly via an on-line diary.

[m] Part 1 only, prior to enrollment.

Lab=laboratory, MPA=medroxyprogesterone acetate.

3.14.1. Procedures Before Study Drug Treatment

Screening Visit

Women will be referred to the investigational center through various recruitment channels which may include, but not limited to internal participant databases, advertising via internet and radio. Women who express interest to participate in the clinical study will undergo the informed consent process administered by a trained investigational center staff member including information about the study objectives, design and procedures, and potential risks and benefits of study participation.

A signed and dated informed consent form will be obtained before screening procedures commence (see Section 11.1). Women who sign the informed consent form will be assigned a

participant number and have a screening interview to obtain the following: medical history and demographic information, breast examination, blood sample for hemoglobin and liver function, height, weight, and vital signs measurements (BP, pulse, and respiration), and an interview about mood. To be eligible for Part 1 of the study all participants must have had a normal mammogram within the last year. Participants without a normal mammogram in the last year or who have an undiagnosed mass detected by breast exam during the screening visit, will have to have mammography performed to rule out breast cancer. During the screening visit, the investigational center may conduct clinical procedures per site-specific standard of care that are not required by the study protocol (eg, cervical cytology, STI testing). A subject who is screened and does not meet study entry criteria may be rescreened 1 additional time if there is a change in the subject's medical background or there is a modification to study entry criteria. If the re-screening visit occurs more than 2 months apart from the original screening visit, all screening procedures including informed consent will be repeated and a new participant number assigned.

Eligible subjects will be scheduled to return to the clinic up to 6 times for serum progesterone and estradiol measurements to confirm their ovulatory cycle (approximately twice a week preferably 3 days apart during approximately the 2 to 3 weeks preceding their next expected menses). Subjects who present for screening approximately 2 weeks prior to their next expected menses, may have their first blood sample for serum progesterone and estradiol taken on the same day.

In summary, the following procedures will be performed at screening:

- explain study purpose and procedures
- obtain written informed consent before any other study-related procedures are performed
- perform screening interview to determine eligibility and collect demographics and baseline data, including medical history
- assign participant number
- measure vital signs (BP [systolic/diastolic], pulse, and respiration)
- measure body weight and height to estimate BMI
- perform breast examination
- refer for mammography, if necessary
- interview about mood (Part 2 only)
- obtain a blood sample for liver function testing (approximately 5 mL; Part 2 only)
- obtain a blood sample for hemoglobin measurement (approximately 4 mL)

3.14.2. Pretreatment

Subjects who meet the inclusion/exclusion criteria at screening visit will return to the clinic approximately twice a week (preferably 3 days apart) during the approximately 2 to 3 weeks preceding their next expected menses (ideally at least 4 times) for serum progesterone and estradiol measurements to confirm ovulation. They will also have a mammogram scheduled

during this time if they have not had a mammogram within the last 12 months during Part 1 only. During these visits, blood samples will be obtained for serum progesterone and estradiol evaluation. If progesterone is at or above 4.7 ng/mL in at least 2 consecutive samples, ovulation will be considered confirmed and the subject eligible for the study. Eligible subjects will be scheduled to return to the clinic for the enrollment/injection visit during the first 5 days of her next menstrual cycle.

3.14.3. Procedures During Study Drug Treatment

3.14.3.1. Enrollment (Injection) Visit (Day 0)

The enrollment visit should take place during the first 5 days of menses. During this visit, a urine pregnancy test will be performed. Participants with hemoglobin ≥10.5 g/dL measured at screening, confirmed ovulation and negative pregnancy test will be enrolled in the study. Medications that the subjects used over the last 30 days will be documented as concomitant medications; vital signs (BP [systolic/diastolic], pulse, and respiration), and body weight will be measured and blood samples will be collected for serum MPA, serum progesterone, and estradiol before the study drug injection.

Part 1 is open-label; therefore, subjects will be assigned without randomization. The study staff allocating the study drug assignments in Part 2 will open the next sequential randomization envelope, document treatment assignment in a secure log, store the opened envelope, and communicate the assigned treatment arm to the pharmacy and/or study staff preparing and administering the injection (unless s/he is the one administering the injection).

The Part 2 investigational center staff who assigns the study drug treatment, and study staff providing the injection, will not be blinded but they will keep the subject and the rest of the investigational center staff unaware of the study drug treatment assignment. The study staff member will prepare the assigned study drug for injection according to the dilution procedures, and, unless s/he is the one administering the injection, pass it to the study staff who will inject the study drug subcutaneously in the fatty tissue over the abdomen while shielding the study drug injection from the subject's sight, as described in Section 5.1. After the injection the unblinded study staff will provide feedback on the ease of the injection administration. On the injection day the injection site will be examined for ISRs twice: within 10 minutes after the injection (by the un-blinded provider) who performed the injection; and within 1st hour after the injection (between 10 and 60 minutes) (by the blinded investigational center staff). The subject will be interviewed for acceptability of the study injection by the blinded investigational center staff. Before leaving the investigational center during the injection visit, each subject will receive the schedule of their follow-up visits.

The following procedures/assessments will be performed during enrollment/injection:

- perform urine pregnancy test (and during the study, if indicated)
- confirm eligibility
- measure vital signs (BP [systolic/diastolic], pulse, and respiration)
- measure body weight and height and estimate BMI

- (prior to injection) obtain a blood sample (approximately 15 mL) for serum MPA, serum progesterone, and estradiol
- open next opaque envelope to reveal the treatment allocation, have the pharmacist prepare the indicated dose, and deliver the syringe to the study staff (Part 2 only)
- administer study drug injection
- evaluate site of injection for an ISR after the injection twice (within 10 minutes and within 1st hour)
- document concomitant medication in the last 30 days
- document adverse events reported after the injection
- assess subject's acceptability of the injection
- assess ease of study drug injection by the study staff

The subject will remain in the clinic for at least 15 minutes after the study drug injection for observation of possible anaphylactic reactions.

For logistical reasons, study drug injection may be administered the day after other enrollment procedures are completed. When the visit is split, the blood draw and injection will occur the day after other enrollment visit procedures are conducted. The date of injection is considered "day 0."

3.14.3.2. Follow-up (Day 1 to Week 78)

Regardless of ovulation status, all subjects should remain in follow-up for at least 52 weeks post-injection.

There are 2 types of follow-up visits in this study: scheduled follow-up visits and laboratory visits.

3.14.3.2.1. Scheduled Follow-up Visits (Day 7, Month 3, and Month 7.5)

Scheduled follow-up visits will occur on day 7, month 3 (week 13), and month 7.5 (week 32) from start of study drug treatment. During these visits, in addition to collection of blood samples for serum MPA, progesterone, and estradiol, the site of study drug injection will be examined for ISR and subjects will be asked about pain, itching, and sensitivity disturbances, or other complaints at the site of injection. Measurement of vital signs and body weight will be performed. Subjects will be asked if they experienced any medical problems or took any medications since the previous report. Menstrual bleeding patterns, mood (for Part 2 only) and acceptability will be evaluated through an interview questionnaire. For Part 2, in addition to the scheduled follow-up visits menstrual bleeding patterns will be evaluated weekly through on-line diaries. For the laboratory measurement schedule, see Table 1.

The following procedures/assessments will be performed during the 3 scheduled follow-up visits:

- measure vital signs (BP [systolic/diastolic], pulse, and respiration)
- measure body weight

- obtain blood sample (approximately 15 mL) for serum MPA, serum progesterone, and estradiol
- obtain blood sample (approximately 5 mL) for liver function tests (month 3 and month 7.5, Part 2 only)
- evaluate site of injection for ISRs
- inquire about adverse events
- inquire about concomitant medication(s)
- interview about mood (month 3 and month 7.5; Part 2 only)
- interview about menstrual bleeding pattern (month 3 and month 7.5)
- interview about acceptability

3.14.3.2.2. Laboratory Visits

During the laboratory visits, blood samples will be obtained for serum MPA, serum progesterone, and estradiol per the sampling schedule (see Sections 3.3 and 3.4, and Table 1). In addition, the injection site will be observed for ISRs on days 1, 2, 3, and 5; and thereafter, if indicated. Information on adverse events and concomitant medications will not be solicited but documented if reported by the subject.

The following procedures/assessments will be performed during laboratory visits:

- obtain blood sample (up to approximately 15 mL) for serum MPA, serum progesterone, and estradiol per the sampling schedule
- evaluate site of injection for ISRs (on days 1, 2, 3, and 5; and thereafter, if indicated)
- interview about menstrual bleeding pattern once monthly (Part 1 only)
- document adverse event (if reported)
- document concomitant medication (if reported)

Blood samples for MPA will be collected and stored for possible future MPA testing (if necessary) any time when samples are collected for serum progesterone and estradiol, except for pre-treatment visits and visits for confirmation of ovulation.

3.14.3.2.3. Laboratory Visits after Week 52

Additional laboratory visits will be scheduled at weeks 61, 62, 63, 64, and 65 for all subjects in whom ovulation did not return by week 52; and at weeks 74, 75, 76, 77, and 78 if ovulation has not returned by week 65. During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol (all visits) and serum MPA (weeks 61 and 74), but not past ovulation. Blood samples for MPA will be collected at all weekly visits after Week 52 and stored for possible future MPA testing (if necessary).

3.14.4. Procedures After Study Drug Treatment and Lost to Follow-up

3.14.4.1. Final Visit

Subjects will complete the study at 12 months after administration of TV-46046, or after ovulation returns (if after month 12) or at the week 78 laboratory visit (if ovulation does not return before then). If Part 2 is not initiated, subjects in Part 1 may be discontinued from the study as early as 26 weeks following study drug injection. If Part 2 is initiated, subjects will stay in the study for a minimum of 12 months (52 weeks) from start of TV-46046 treatment even if ovulation returns before then. All subjects will complete the study by 18 months (78 weeks) from the start of TV-46046 treatment even if ovulation does not return by then. Additional post-discontinuation follow-up may be considered for safety purposes until ovulation returns and/or MPA levels become undetectable.

For subjects in whom ovulation returns before month 12 post-injection, the final study visit will be scheduled at month 12. If ovulation occurs between months 12 and 18 (between weeks 52 and 78), at the time when the defining serum progesterone result becomes available, the study staff will inform the subject that she needs to return within 5 days to the investigational center for the final study visit. For subjects in whom ovulation does not return by month 18, the laboratory visit at week 78 will be considered the final study visit.

The following procedures/assessments will be performed during the final visit:

- obtain blood sample for serum MPA (approximately 5 mL)
- obtain blood sample for serum progesterone, estradiol (approximately 10 mL), if indicated; and liver function tests (Part 2 only, approximately 5 mL)
- measure body weight
- measure vital signs (BP [systolic/diastolic], pulse, and respiration)
- perform breast exam
- interview about acceptability
- evaluate site of injection for ISRs
- inquire about adverse events
- inquire about concomitant medications
- interviews about mood (Part 2 only) and menstrual bleeding pattern

If the subject cannot return to the investigational center in person, the final evaluation may be completed by telephone (to the extent possible) and documented in the CRF.

For subjects who withdraw prematurely from the study, the final visit will be performed at the time of discontinuation, if known.

3.14.4.2. Missed Visits

Visits will be scheduled using target visit windows, as detailed in the Study Manual. When a subject cannot return to the clinic within her visit window, missed procedures will be performed at her next clinic visit.

3.14.4.3. Lost to Follow-up

If a subject fails to appear for a scheduled visit, at least 3 attempts to contact the subject will be made. One additional attempt to contact the subject will be made after each subsequent missed study visit. These attempts will be documented in the subject's study file. If the subject does not return for the scheduled appointment, the subject will be considered "presumed lost to follow-up". The subject's file will remain open until study closeout. If the subject does not return to the study before the study is closed, the Final form will be completed at the end of the study (see Section 11.4 for definition). The form will indicate that the subject was lost to follow-up. The final "lost to follow-up" designation cannot be made for any subject until the closing date of the study.

3.14.5. Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained, if applicable (eg, adverse events, concomitant medications and treatments, and results from procedures or tests).

Procedures performed during unscheduled visits include the following:

- concomitant medication inquiry
- vital signs measurements (BP [systolic/diastolic], pulse, and respiration)
- adverse event inquiry

Other procedures may be performed at the discretion of the investigator.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Prospective waivers (exceptions) from study eligibility criteria to allow subjects to enter a study are not granted by Teva (see Section 10.1.2).

4.1. Subject Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria:

a. has regular menstrual cycle (24 to 35 days)

b. has confirmed ovulatory cycle during the pretreatment phase (serum progesterone ≥4.7 ng/mL in 2 consecutive samples)

c. is at low risk of pregnancy (ie, sterilized, in exclusively same-sex partnership, in monogamous relationship with vasectomized partner, or using non-hormonal IUD)

d. is in good general health as determined by a medical history

e. 18 to 40 years of age, inclusive

f. willing to provide informed consent and follow all study requirements

g. is not pregnant and does not have desire to become pregnant in the subsequent 36 months

h. has a BMI of 18 to 35, inclusive (unless included in subset of subjects with extreme obesity (BMI ≥40), 2 in each dose-range finding group from a single investigational center, in Part 2)

i. has hemoglobin ≥10.5 g/L

j. has had a normal mammogram within the last year (for Part 1 only)

4.2. Subject Exclusion Criteria

Subjects will be excluded from participating in this study if they meet any of the following criteria:

a. has hypertension:
   - systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg
   - vascular disease

b. has current or history of ischemic heart disease

c. has history of stroke

d. has history of thromboembolic event

e. has systemic lupus erythematosus
   - positive (or unknown) antiphospholipid antibodies
   - severe thrombocytopenia

f. has rheumatoid arthritis on immunosuppressive therapy

g. has migraine with aura

h. has unexplained vaginal bleeding

i. has diabetes

j. has strong family history of breast cancer (defined as one or more first degree relatives, breast cancer occurring before menopause in three or more family members, regardless of degree of relationship, and any male family member with breast cancer), or current or history of breast cancer, or undiagnosed mass detected by breast exam

k. has current or history of cervical cancer

l. has severe cirrhosis (decompensated) or liver tumors

m. has one or more baseline liver function test(s) outside the local laboratory's normal range (Part 2 only)

n. has known significant renal disease

o. history of diagnosed clinical depression or bipolar disorder, with or without suicidal ideation, and/or history of suicide attempt

p. in last 2 years, history of either hospitalization or medication management for psychiatric disorder that in the opinion of the investigator would make study participation unsafe, would interfere with adherence to study requirements or complicate data interpretation

q. used DMPA products (Depo-Provera CI or Depo-subQ Provera 104) in the past 12 months

r. used any of the following medications within 1 month prior to enrollment:

    - any investigational drug
    - prohibited drugs per protocol
    - oral contraceptives, contraceptive ring or patch
    - levonorgestrel intrauterine system (LNG IUS) or contraceptive implant

s. used a combined injectable contraceptive in the past 6 months

t. less than 3 months since the end of last pregnancy

u. currently lactating

v. is using or plans to use prohibited drugs per protocol in the next 18 months

w. has known sensitivity to MPA or inactive ingredient

x. has a plan to move to another location in the next 24 months

y. in the opinion of the investigator, potentially at elevated risk of HIV infection (eg, HIV-positive partner, IV drug use by self or by partner)

z. has any condition (social or medical), which in the opinion of the investigator would make study participation unsafe, would interfere with adherence to the clinical study requirements or complicate data interpretation

4.3. Justification for Key Inclusion and Exclusion Criteria

Due to uncertain risk of pregnancy, all necessary precautions will be taken to minimize the risk of pregnancy among study subjects. Therefore, only women who are not pregnant, not wanting to become pregnant in the next 36 months, and who are at low risk of pregnancy will be enrolled in the study. The study will recruit women of reproductive age with regulatory menstrual cycle and with confirmed ovulation to ensure that the lack of ovulation during the treatment can be attributed to the treatment effect rather than the preexisting ovulatory dysfunction.

The study will not enroll female subjects who have medical contraindications to DMPA nor medical or social conditions that may make study participation unsafe, interfere with drug absorption and metabolism, have a strong family history of breast cancer defined as one or more first degree relatives, breast cancer occurring before menopause in three or more family members, regardless of degree of relationship and any male family member with breast cancer or complicate data interpretation.

4.4. Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of intercurrent illness, adverse events, pregnancy (see Section 7.2), or other reasons concerning the health or well-being of the subject, or in the event of lack of cooperation. In addition, a subject may be withdrawn from the study as described in Sections 3.12 and 7.1.7 .

Should a subject decide to withdraw from the study, or should the investigator decide to withdraw the subject, every reasonable effort will be made to assess information relevant to the endpoints at the time of discontinuation. This may include but may not be limited to progesterone and MPA testing, pregnancy testing and assessment of ISRs, and/or acceptability. The final visit procedures should be followed for all subjects who withdraw, if possible (see Section 3.14.4.1).

The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed onto the CRF. If a subject withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the subject is referred to the care of a healthcare professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event or test result must be recorded on the source documentation and transcribed onto the CRF.

In addition, a blood sample will be obtained for the measurement of study drug concentration. The sample date and time will be recorded on the source documentation and transcribed to the CRF.

All assessments should be performed according to the protocol as soon as possible.

Since this is a single-dose study and the study product remains in the body months after injection, prompt withdrawal from the study treatment is not possible, and discontinuation from the study will not be the same as withdrawal from treatment. Study staff will explain to subjects who wish to discontinue from the study early that it is impossible to discontinue the treatment and that it is important to stay in the study at least until safety assessments are completed (including delayed return to ovulation [>12 months post-study drug injection]).

5. TREATMENT OF SUBJECTS

5.1. Drugs Administered During the Study

In Part 1 of the study after enrollment, 12 enrolled subjects will be sequentially assigned to a treatment group as presented below.

The first 6 subjects will be assigned to:

- Treatment group 1: 0.3 mL of 400 mg/mL of undiluted TV-46046 (120 mg)

The next 6 subjects will be assigned to:

- Treatment group 2: 0.6 mL of 200 mg/mL of saline-diluted TV-46046 (120 mg)

If warranted, an additional 6 subjects in Part 1 will be assigned to:

- Treatment group 3: 0.4 mL of 300 mg/mL of saline-diluted TV-46046 (120 mg)

In Part 2 of the study, subjects will be randomly assigned to 1 of up to 3 treatment groups (up to 3 additional dose levels of undiluted TV-46046 within the range of 80 to 300 mg).

5.1.1. Dilution Procedure of TV-46046

Diluted TV-46046 will be prepared by the investigational center pharmacist or other trained personnel. Dilution procedures for TV-46046 treatment group 2 in Part 1 and, potentially, treatment group 3 in Part 1, are provided in the Pharmacy Manual.

5.1.2. Subcutaneous Administration of TV-46046

In both parts of the study TV-46046 will be administered by a study staff member as a single subcutaneous injection in the abdomen during the first 5 days of the menstrual cycle using a 23 gauge 3/8 inch needle following the sponsor's instructions for administering a subcutaneous injection (see Appendix B).

Part 2 will be a subject-blinded study. The clinical staff providing the injections 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. For additional details, see Section 3.8.2.

Briefly, the provider will follow these steps:

1. Use alcohol pad to wipe the skin in the abdominal injection area and allow the skin to dry
2. Gently grasp and squeeze a large area of skin in the chosen injection area between the thumb and forefinger, pulling it away from the body
3. Insert the 23 gauge 3/8 inch needle at a 45° angle so that most of the needle is in the fatty tissue

4. Inject the medication slowly (over 5 to 7 seconds) until the syringe is completely empty
5. After withdrawing the needle, press a cotton pad lightly on the injection area (do not use Band-Aid®[4] taking care of not rubbing the site of injection

5.2. Restrictions

Medications prohibited before and/or during the study are described in Section 5.3. Subjects will remain at the investigational center for at least 15 minutes after the study drug injection for observation. The investigational center will have an EpiPen (epinephrine injection) available and easy access to emergency care necessary in the unlikely event of anaphylaxis or anaphylactoid reaction.

5.3. Prior and Concomitant Medication or Treatment

Any prior or concomitant therapy, medication, or procedure a subject has had within 30 days before study drug administration and up to the final visit will be recorded on the CRF. During the scheduled follow-up visits, the investigator will ask subjects whether they have taken any medications (other than study drug), including over the counter (OTC) medications, vitamins, or herbal or nutritional supplements, since the previous visit. During laboratory visits information of the use of concomitant medications will be documented only if reported by the subject. Generic or trade name, indication, route of study drug administration, dosage, and start and end dates will be recorded.

Any drugs that may interfere with metabolism of MPA or affect ovarian function will be prohibited during the study. The following medications should not be used during this study (unless medically indicated):

- rifampicin
- griseofulvin
- anticonvulsants
- barbiturates
- antiretroviral drugs (ARVs): non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine) and ritonavir-boosted protease inhibitors
- aminoglutethimide
- St. John’s wort
- selective cyclooxygenase-2 (COX-2) inhibitors (eg, meloxicam, celecoxib) for 5 or more consecutive days
- steroids (synthetic estrogens, progestins, androgens)

[4] Band-Aid is a registered trademark of Johnson & Johnson Corporation.

5.4. Procedures for Monitoring Subject Compliance

Given that a single injection of the study drug will be provided by the investigational center personnel in the clinic, monitoring of subject compliance will not be necessary.

5.5. Total Blood Volume

The total volume of blood to be collected for each subject in this study is approximately 909 mL, as provided in Table 2.

Table 2: Approximate Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Pharmacodynamics (serum P and E2) -before study drug injection -if ovulation by week 52 -if no ovulation by week 52	about 10 (for both P and E2)	 up to 7 up to 48 up to 58	 ~70 ~480 ~580
Pharmacokinetics (serum MPA) -before study drug injection -if ovulation by week 52 -if no ovulation by week 52	about 5	 1 up to 48 up to 50	 5 ~240 ~250
Hemoglobin	about 4	1	~4
Liver Function	about 5	4	~20
Total[a]		**~121**	**~924**

[a] These are maximum figures, assuming a subject does not ovulate before week 78. The sampling schedule for Part 2 may be reduced further based on assessment of Part 1 data.
~=approximately, P=progesterone, E2=estradiol.

6. ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

6.1. Pharmacokinetics

Pharmacokinetics of MPA will be evaluated based on individual and mean serum MPA concentration-time profiles and estimated noncompartmental pharmacokinetic parameters (see Section 8.5). All subjects will be assessed for nonzero MPA levels at baseline. The MPA results will not be known until later in the study and, therefore, will not be used as exclusion criteria. Subjects with nonzero MPA levels at baseline (ie, more than 5% of their individual C_{max}) will be excluded from the primary pharmacokinetic analyses (see Section 8.5.3). During the study MPA concentrations will be measured at pre-defined time points (see Table 1). In addition, subjects for whom ovulation has not returned by month 12 (week 52), blood samples for MPA will be collected and tested up to 2 more times (at week 61 and week 74), but not past return to ovulation. Based on accumulating data, additional sampling and testing for MPA in one or more study groups in Part 1 and/or Part 2 may be conducted for a more accurate characterization of the pharmacokinetic profile of TV-46046.

6.1.1. Part 1: Exploratory Pharmacokinetic Variables

The following non-exhaustive list of non-compartmental pharmacokinetic parameters will be calculated for MPA for each treatment group:

- C_{max}
- t_{max}
- C_{182} (week 26)
- $AUC_{0\text{-}182}$
- $AUC_{0\text{-}\infty}$
- apparent terminal half-life

6.1.2. Part 2: Dose-range Finding Variables

The following pharmacokinetic parameters will be calculated for MPA for each treatment and population:

- C_{max}
- t_{max}
- C_{182} (week 26)
- C_{210} (week 30)
- $AUC_{0\text{-}182}$
- $AUC_{0\text{-}210}$

- $AUC_{0-\infty}$
- apparent terminal half-life

6.1.3. Blood Sampling and Handling

Blood samples (~5 mL) for pharmacokinetic analysis will be obtained from all subjects via venipuncture at the time points detailed in Table 1.

The date and time of study drug administration and the date and time of each pharmacokinetic sample will be recorded on the source documentation and transcribed onto the CRF.

Blood specimen will be collected into one Vacutainer tube containing no anticoagulant and allowed to set at room temperature for at least 20 minutes, but no more than 40 minutes, to permit clot formation. Samples will be centrifuged at room temperature at 2500 to 3000 revolutions per minute (rpm) (approximately 650 to 1450 ×g) for 10 to 15 minutes to achieve a clear serum layer over the clotted red cells. Approximately equal portions of the sample will then be immediately transferred into 2 properly labeled polypropylene sample storage tubes. The prepared serum samples will be immediately frozen at -20ºC and stored in an upright position until shipment.

6.1.4. Shipment and Analysis of Samples

One aliquot will remain frozen on site, and another will be sent on dry ice in batches with other samples to PPD (Richmond, Virginia, United States of America) where MPA levels will be measured via a proprietary validated method utilizing sensitive and selective high-performance liquid chromatography coupled with mass spectrometry. This method is applicable to the quantitation of MPA within a nominal range between 0.02 to 5.00 ng/mL and requires a 250-µL aliquot of human serum. Timing of the initiation of sample analysis will be determined by the study monitor. The PPD staff performing the analysis will be blinded to the treatment assignment.

Source documentation for MPA will be maintained at PPD. The MPA results will be transferred electronically from PPD to FHI 360 for data management and analysis. The MPA results will not be documented on study CRFs or communicated to the study participants. No further testing of any remaining blood samples is planned; however, any remaining serum will be stored by PPD at least until the end of the study in the event of needed repeat testing or analysis of long-term stored sample stability. The PPD laboratory will discard remaining blood samples per PPD standard operating procedures (SOPs) upon receiving written approval from FHI 360. Any remaining aliquots stored on site will also be maintained until the end of the study, and only discarded after receiving written FHI 360 approval.

More detailed instructions on how to take, prepare, store, and send the serum samples for analysis in the central laboratory will be provided in the Study Manual.

6.2. Pharmacodynamics

Potential for contraceptive effect of TV-46046 when injected subcutaneously will be evaluated primarily based on its ability to suppress ovulation. While postovulatory maximum progesterone levels are usually greater than 16 nmol/L, progesterone levels used as a criterion of ovulation in contraceptive research usually range from 10 nmol/L to 16 nmol/L (approximately 3 to 5 ng/mL)

(Rahimy et al 1999, Brache et al 2012, Westhoff et al 2010, Jesam et al 2014). In addition, any rise in progesterone levels has to be sustained for at least 5 days to be consistent with ovulation. However, given the long-acting nature of TV-46046, anticipated irregular menstrual cycles, as well as the schedule of laboratory visits generally more than 5 days apart, it will not be possible to precisely define the timing within the luteal phase when elevated progesterone is detected. Therefore, measurement of sustained levels of progesterone for a presumption of ovulation will not be required in this study. The primary pharmacodynamics variable for this study will be ovulation defined as a single elevated serum progesterone ≥4.7 ng/mL. The same approach was used previously in pharmacokinetic/pharmacodynamic studies of Depo subQ 104 (Jain et al 2004, Toh et al 2004).

During the pre-treatment phase ovulation will be confirmed in all women by measuring progesterone approximately twice a week during the approximately 2 to 3 weeks preceding their expected menses. Only women with confirmed ovulation will be enrolled in the study. During the pre-treatment phase of the study, if progesterone is at or above 4.7 ng/mL in at least 2 consecutive samples, ovulation will be considered confirmed for the purposes of the study eligibility.

All enrolled subjects will provide blood for progesterone measurement before the injection to document the baseline level of progesterone. During the study, all subjects will return for serum progesterone testing according to the pre-defined schedule (see Table 1). Serum progesterone results will be available within approximately 24 to 48 hours of specimen collection. Any time during the study, all women with initial serum progesterone ≥3.0 ng/mL will be asked to return within 5 days for repeated progesterone measurement to ensure close monitoring of the potential post-ovulatory rise of progesterone. If the repeated measurement within 5 days is at or below 3.0 ng/mL, the subject will continue follow-up per her visit schedule.

During the treatment phase of the study if progesterone is at or above 4.7 ng/mL in a single sample, ovulation will be considered confirmed for the purpose of the primary analysis. At any time during the study, any subject with initial progesterone ≥4.7 ng/mL will be asked to return within 5 days for repeated progesterone measurement. Although repeated elevated progesterone is not needed for the primary definition of ovulation, this information will be used for more accurate ascertainment of ovarian function. Subjects with a single elevated progesterone measurement of ≥4.7 ng/mL will be considered to have their ovulation restored.

Estradiol, an additional pharmacodynamic indicator, will be measured every time progesterone is measured. It will be used to more accurately characterize ovarian function.

At the discretion of the center investigator and/or based on accumulating data, additional sampling and testing for progesterone and estradiol may be conducted to ensure accurate ascertainment of the primary pharmacodynamic endpoint.

Blood Sampling and Handling

Detailed instructions on how to draw and prepare serum samples for progesterone and estradiol analysis, and liver function analysis (Part 2 only) will be investigational center-specific and provided in the laboratory SOPs and/or Study Manual. Briefly, blood samples for progesterone and estradiol (up to 10 mL) will be collected via venipuncture, centrifuged, and then transferred into 2 aliquots. One aliquot will be sent to the investigational center laboratory for the same day testing; and the other one stored as a back-up sample at -20°C. Collection and movement of progesterone and estradiol samples will be recorded on appropriate study CRFs and/or tracking tools. In Part 2 blood samples for liver function analysis (up to 5 mL) will be collected via venipuncture, centrifuged and then transferred to one aliquot for analysis.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating the following: vital signs (BP [systolic/diastolic], pulse, and respiration), body weight, adverse events, concomitant medication usage, changes in menstrual bleeding patterns, mood, liver function tests, occurrence of ISRs, and return to ovulation after 12 months after the study drug injection.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

In this study, any adverse event occurring after signing the informed consent form should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended medical condition (eg, physical sign, symptom, disease, or laboratory parameter) that develops or worsens in severity during the course of this study, whether or not considered related to the study drug. The worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events. Irregular vaginal bleeding will not be recorded on the Adverse Event Form unless it requires medical intervention or meets the definition of a serious adverse event.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during this study should be recorded as an adverse event.)
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the subject from the study, are associated with clinical signs and symptoms or a serious adverse event, or require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant. (Note: Abnormal laboratory test results at the screening visit that preclude a subject from entering the study or receiving study treatment are not considered adverse events.)

7.1.2. Recording and Reporting Adverse Events

For adverse event recording, the study period is defined for each subject as that time period from signature of the informed consent form to the end of the follow-up period.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the Serious Adverse Event Form must also be completed and the serious adverse event must be reported immediately (see Section 7.1.5.3.1). The investigator does not need to actively monitor subjects for adverse events once the study has ended. Serious adverse events occurring to a subject after study discontinuation should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

At each of the 3 scheduled follow-up visits, the investigator or designee must question the subject about adverse events by asking an open-ended question such as, “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the Serious Adverse Event Form. During frequent laboratory visits adverse events will not be actively solicited but will be documented if reported by the subject.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to baseline, or until the subject is referred for continued care to a another healthcare professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the CRF.

The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.1.3. Severity of an Adverse Event

The severity of adverse events including ISRs and abnormal laboratory tests will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, November 2014 (see Appendix A).

7.1.4. Relationship of an Adverse Event to the Study Drug

The relationship of an adverse event to the study drug is characterized as follows and will be determined by Teva:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the study drug. • It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It does not follow a known pattern of response to the study drug. • It does not reappear or worsen when the study drug is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the study drug administration cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the study drug. • It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the study drug, yet a drug relationship clearly exists. • It follows a known pattern of response to the study drug.

7.1.5. Serious Adverse Events

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (ie, the subject was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event.

- Hospitalizations scheduled prior to study entry or hospitalization for elective surgery of pre-existing condition will not be considered serious adverse events, unless there was worsening of the preexisting condition during the subject's participation in this study.
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect
- important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event, although it may nonetheless be severe (see Appendix A).

7.1.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The reference safety information (RSI) for this study is the current IB for TV-46046.

This is a Phase 1 clinical study; to date, expected adverse reactions have not been identified for the study drug. However, the composition of TV -46046 including the active product ingredient (API) is similar to the approved contraceptive injectables Depo-Provera CI and Depo-subQ 104. A serious adverse event that is not included in the Appendix A - Reference Safety Information for Expedited Reporting Purposes in the IB is considered an unexpected adverse event.

Teva's Pharmacovigilance Department will determine the expectedness for all serious adverse events.

For the purpose of suspected unexpected serious adverse reaction (SUSAR) reporting, the version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.5.1) that occur during the study period (including the protocol-defined follow-up period, described in Section 7.1.2), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the

event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor subjects for adverse events once this study has ended.

Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) and FHI 360 (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's Global Patient Safety & Pharmacovigilance Department.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- participant number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility)

Additional information may include the following:

- age and sex of subject
- date of study drug injection
- date and amount of last administered dose of study drug
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- for an adverse event resulting in death:
  - cause of death (whether or not the death was related to study drug)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator, the study medical monitor at FHI 360, and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigational center within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's Global Patient Safety & Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO and FHI 360 for local submission to the regulatory authorities, IEC/IRBs, and investigators, according to regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Blinding will be maintained for the people who are involved directly in the study except for the pharmacist or other trained personnel administering the study drug injection. Therefore, in case of a SUSAR, only the LSO and FHI 360 medical monitor will receive the unblinded report for regulatory submission; the others will receive a blinded report.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.2).

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of TV-46046 and the appropriate regulatory authorities (and IEC/IRB, if appropriate).

In addition to notifying the investigators and regulatory authorities (and IEC/IRB, if appropriate), other measures may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- altering the process of informed consent by modifying the existing consent form and informing current study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to TV-46046

7.1.6. Protocol-Defined Adverse Events for Expedited Reporting

No protocol-defined adverse events for expedited reporting were identified for this study.

7.1.7. Withdrawal Due to an Adverse Event

Any subject who experiences an adverse event may be withdrawn from the study at any time at the discretion of the investigator. If a subject is withdrawn wholly or in part because of an adverse event, the adverse event CRF and the final status CRF will be completed at that time.

Given a single dose design and sustained nature of the study drug, withdrawal from the study is possible but withdrawal from treatment is not possible. Study staff will explain to participants who wish to discontinue the study early due to adverse event that the study product will remain in the body months after injection and the importance of staying in the study at least until resolution of an adverse event. Should the subject decide to withdraw from the study, every reasonable effort will be made to assess information relevant to the endpoints at the time of

discontinuation. This may include but may be not limited to progesterone and MPA testing, pregnancy testing and assessment of ISRs, and/or acceptability. The final visit procedures should be followed for all subjects who withdraw, if possible (see Section 3.14.4.1).

In addition, a blood sample will be obtained for the measurement of study drug concentrations. The subject will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the subject is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The investigator must inform the Clinical Project Physician/Clinical Lead as soon as possible of each subject who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a subject is withdrawn from the study for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event.

7.1.8. Overdose of Study Drug

Given the single-dose study design and provision of the study drug by a medical provider, overdose of study drug is not anticipated. In the unlikely event of administration error, relevant information will be documented and reported to the study medical monitor and sponsor promptly.

7.1.9. Protocol Deviations Because of an Adverse Event

If a subject experiences an adverse event or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment has been administered to ensure subject safety, the investigator or other physician in attendance must contact the individual identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the subject should continue to participate in the study with understanding that the study drug will remain in the body for an extended period of time.

7.2. Pregnancy

The risk of pregnancy is minimal due to the fact that only women who are at low risk of pregnancy will be enrolled in the study (see Section 4.1 for Inclusion Criteria). Only women who are not pregnant on the day of the study injection and do not want to become pregnant in the next 36 months will be enrolled in the study. During the study pregnancy test will be performed if the woman is experiencing any symptoms or signs of pregnancy, or thinks she may be pregnant. In the unlikely event of pregnancy, any participant becoming pregnant during the study will be withdrawn and pregnancy recorded as reason for discontinuation on appropriate study CRFs. Pregnancy will be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the LSO and FHI 360 medical monitor with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (see Section 7.1.5.3 for details). All subjects who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome, including spontaneous or voluntary termination, details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the study sponsor.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.
- For a spontaneous abortion, report as a serious adverse event.

7.3. Medication Error and Special Situations

Any administration of medication that is not in accordance with the study protocol should be reported on the CRF either as a violation, if it meets the violation criteria specified in the protocol (Section 10.1.2), or as a deviation, in the subject's source documents, regardless of whether an adverse event occurs as a result. All instances of incorrect medication administration should be categorized on the CRF as "Non-Compliance to investigational medicinal product (IMP)".

Types of medication errors and special situations:

- Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, subject, or consumer.
- Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.
- Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
- Abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
- Off-label use: Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
- Occupational exposure: Exposure to a medicinal product, as a result of one's professional or non-professional occupation.

7.4. Clinical Laboratory Tests

A clinical laboratory test for hemoglobin will be performed at the screening visit using the investigational center laboratory within 24 hours of blood collection. Liver function testing including, but not limited to, ALT and AST will be performed in Part 2 only by the investigational center laboratory at the screening visit, as well as at the month 3, month 7.5 and final visits. Detailed instructions on how to draw and prepare samples for liver function testing will be investigational center-specific and provided in the laboratory SOPs and/or Study Manual.

7.5. Vital Signs

Vital signs (BP [systolic/diastolic], pulse, and respiration) will be measured at the time points detailed in Table 1.

Before pulse and BP are measured, the subject must be in a supine or semi-erect/seated position and resting for at least 5 minutes. (The same position and arm should be used each time vital signs are measured for a given subject.) For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as a potentially clinically significant change (worsening) from a baseline value will be considered an adverse event, recorded on the source documentation, transcribed onto the CRF, and monitored as described in Section 7.1.2.

7.6. Body Weight

Body weight will be measured at the time points detailed in Table 1 and documented on appropriate study CRF. A standardized protocol for weight measurement will be provided in the study manual.

Weight gain or loss will be documented as an adverse event only if reported by the subject.

7.7. Injection Site Reactions

The tolerability of subcutaneous injection of different doses and volumes of TV-46046 will be assessed by evaluating ISRs after the injection during the enrollment/injection visit twice (within 10 minutes and within the 1st hour of post-injection), at days 1, 2, 3, and 5; during the scheduled follow-up visits at day 7, month 3, and month 7.5; at the final visit; and at other visits, if indicated. All ongoing ISRs will be examined during the next clinic visit, regardless of visit type, or more frequently at the discretion of the center investigator, until ISR resolution, or outcome. Subjects will be asked about pain, itching, and other problems at the site of injection. The site of injection will be examined for signs of redness, swelling, induration, etc. Most ISRs will be reported as adverse events and graded for severity similar to adverse events using the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, November 2014 (see Appendix A). Injection site reactions that do not meet the definition of site reaction or Grade 1 severity per the DAIDS table, "Adverse Event Severity Grading Table: Site Reactions to Injections and Infusions" will be considered minor and not reported adverse events. All other ISRs will be reported as adverse events. All findings will be recorded on the appropriate study CRFs. When feasible and with written consent from the study participant, photographs may be taken of the injection site to supplement documentation of ISRs.

7.8. Menstrual Bleeding Patterns

Study subjects will be asked about changes in their menstrual bleeding patterns, including no bleeding since last assessment, at monthly intervals (in Part 1 only) and during the scheduled follow-up visits in both Part 1 and Part 2 at week 13 (month 3) and week 32 (month 7.5), and at the final study visit. Interview items will include date of last bleeding, description of bleeding pattern since last visit, as well as frequency of bleeding, duration of episodes, pain/cramps, and volume, all compared with the pre-study period. The acceptability and tolerability of the bleeding pattern will be queried.

In addition, in Part 2, subjects will be trained to use and prompted to complete weekly menstrual diaries on-line. On these diaries, subjects will record daily occurrence of no flow, spotting (pantyliner or no protection needed), bleeding (tampons or sanitary pads needed), and pain (none/mild or moderate/severe) for the last seven days. These data will be automatically uploaded into the clinical data base using the OpenClinica Participate module.

7.9. Mood Changes

In Part 2, subjects will be interviewed about aspects of and changes in mood at screening and at the scheduled follow-up visits at month 3 and month 7.5, and at the final study visit. To measure depression or psychological distress, a selected validated scale, such as the 10-item Patient Health Questionnaire (PHQ-9) that screens for depression, will ascertain the frequency of a variety of somatic and emotional indicators of well-being and produce an overall score that can be compared at different time points in the study. The PHQ-9 includes items on pleasure in doing things, having little energy, feeling bad about yourself, and having trouble concentrating, among others. The frequency of each indicator is then summed to produce a single overall score for the severity of depression.

7.10. Concomitant Therapy or Medication

Concomitant therapy or medication usage will be monitored throughout the study. Details of prohibited medications are found in Section 5.3.

7.11. Methods and Time Points of Assessing, Recording, and Analyzing Safety Data

All adverse events will be reviewed on a periodic basis by the medical monitor according to the medical monitoring plan (eg, scheduled safety reviews for study drug) as interim/preliminary safety databases become available. Safety data will be reviewed at the time of the study interim analyses by the DSMB. Information about the DSMB used for this study is provided in Section 3.8.3. In addition, safety data will additionally be evaluated periodically and ad hoc (if necessary) in the Teva's Product Safety Group.

Methods and timing of assessing safety data are discussed in Section 3.14. Procedures for recording safety data are discussed in Section 12.1 and methods of analyses are discussed in Section 8.8.2.

7.12. ASSESSMENT OF ACCEPTABILITY

The acceptability of the different injection doses and volumes will be assessed and recorded on appropriate study CRFs at the end of the enrollment/injection visit, at the scheduled follow-up visits at day 7, month 3 (week 13), and month 7.5 (week 32), and at the final visit by blinded staff. During the enrollment/injection visit the subject will be asked about her perception of pain at injection. Other acceptability questions will include but not be limited to questions about acceptability of the bleeding patterns (only during month 3 and month 7.5 follow-up visits, and final visit) and other side effects, what she likes and dislikes most about this method, whether she would use this method in the future and/or recommend it to a friend, and whether the schedule of re-injections was acceptable. In addition, the study staff performing the injection during the

enrollment/injection visit will be asked about the ease of resuspension and performing the study drug injection.

8. STATISTICS

This section describes the statistical and pharmacokinetic analyses of primary and secondary objectives as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in a separate statistical analysis plan written and approved prior to study initiation. Any substantive changes made to the statistical analysis plan after study initiation, including changes made to address revisions to the protocol, will be documented in subsequent approved versions of the statistical analysis plan and fully disclosed in the clinical study report.

8.1. Sample Size and Power Considerations

Sample size for the exploratory pharmacokinetics component of the study (Part 1), 6 subjects in each of up to 3 additional treatment groups, is not intended to make definitive conclusions regarding the pharmacokinetics of TV-46046. Rather, it is intended to provide assurance that the half-life and other key pharmacokinetic properties of undiluted TV-46046 are consistent with a 6-month duration of use before moving into the dose-range finding component of the study (Part 2). It will also allow assessment of whether a diluted formulation may have a more favorable pharmacokinetic profile, in the event undiluted drug is not moved into Part 2. Likewise, the sample size for Part 2 (up to 20 subjects in each of up to 3 additional treatment groups) was not chosen to make definitive conclusions regarding the efficacy of TV-46046. However, on the basis of historical data of MPA delivered subcutaneously (eg, the variability of pharmacokinetic parameter estimates; Jain et al, 2004; Toh et al, 2004), the sample size should be sufficient to inform the selection of a dose of undiluted TV-46046 for further study as a 6-month contraceptive method, if warranted. 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 population pharmacokinetic parameter estimates and rates of return to ovulation observed in Part 1 or interim Part 2 data.

8.2. 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. Each analysis population and analysis set will be derived and analyzed separately for each component (Part 1 and Part 2) of the study unless otherwise noted. However, the definitions are assumed to be the same for both components.

8.2.1. Screened Population

All subjects who consent to be screened for a given part of the study, regardless of enrollment status.

8.2.2. Treated Population

All subjects who consent to participate in a given part of the study, are enrolled, and receive an injection of study drug. Analyses of this population will be based on the treatment received. In the event of Part 2 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. The corresponding Treated Analysis Set includes all baseline and follow-up data contributed by subjects in the Treated Population, up to and including applicable censoring times described elsewhere in this section.

8.2.3. 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 (including the 6 subjects purposefully enrolled with BMI ≥40); or use of drugs known to impact ovulation or the pharmacokinetics of MPA. The Primary Evaluable Analysis Set includes all time contributed by participants in the Primary Evaluable Population during which a pharmacokinetic or pharmacodynamic outcome is assessed, up to the initiation of any concomitant medication known to impact ovulatory function or the pharmacokinetics of MPA.

8.3. Data Handling Conventions

The primary pharmacodynamic outcome, time to serum progesterone ≥4.7 ng/mL, will be censored 12 months following initiation of treatment; no imputation of missing pharmacodynamic outcomes prior to month 12 will take place. Missing MPA concentrations at key time points (eg, start- and end-times of partial areas under the concentration-time curve) will be imputed, as appropriate, using methods specified in the detailed statistical analysis plan. Incomplete adverse event onset or concomitant medication use dates may also be imputed or adjudicated by the Medical Monitor (blinded to treatment group assignment and incorporated into the clinical database per FHI 360 SOPs) to assess safety or when censoring subjects from analyses due to excluded medication use. No other missing data will be imputed unless otherwise specified in the detailed statistical analysis plan.

8.4. Study Population

8.4.1. Subject Disposition

The numbers of subjects screened and enrolled to each treatment group in each part of the study will be tabulated by investigational center and pooled across sites. A flow diagram will be provided which presents the numbers and percentages of participants contributing to the Screened, 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 overall); and the numbers and percentages of subjects who complete the study, discontinue early (overall and by reason), or are lost to follow-up. Protocol deviations will be summarized in frequency tables, by investigational center and treatment group. Categories of deviations will include violations of study entry criteria (eg, age, BMI, or use of excluded medications), randomization errors, violation of study withdraw criteria, and other violations captured on CRFs.

8.4.2. Demographic and Baseline Characteristics

Summary statistics (frequencies, percentages, means, medians, inter-quartile range, minima, and maxima) appropriate to the measurement scale will be used to describe baseline demographic, behavioral, medical, and contraceptive use history data. Continuous variables may be described using categorical levels chosen based on previous experience with similar studies. Baseline data will be presented for the Screened Population, the Treated Population, and the Primary Evaluable Population. Summaries will be provided by treatment group, investigational center, and pooled across sites and regimens. No formal statistical testing will be performed to compare distributions of baseline characteristics between randomized method groups.

8.5. Pharmacokinetic Analysis

8.5.1. Primary Endpoints

8.5.1.1. Part 1 (Exploratory Pharmacokinetics)

Individual and mean serum MPA concentration-time profiles, and estimated noncompartmental pharmacokinetics parameters, including but not limited to C_{max}, t_{max}, C_{182} (week 26), $AUC_{0\text{-}182}$, $AUC_{0\text{-}\infty}$, and the apparent terminal half-life.

8.5.1.2. Part 2 (Dose-range Finding)

Individual and mean serum MPA concentration-time profiles, and estimated noncompartmental pharmacokinetic parameters, including but not limited to: C_{max}, t_{max}, C_{182}, C_{210} (week 30), $AUC_{0\text{-}182}$, $AUC_{0\text{-}210}$, $AUC_{0\text{-}\infty}$, and apparent terminal half-life.

8.5.2. Secondary Pharmacokinetic Endpoints

Release rates, relative bioavailability, and other pharmacokinetic parameters derived from non-linear mixed model compartmental analysis of serum MPA concentrations over time.

8.5.3. Planned Method of Analysis

There are 5 planned reviews of the interim data; 2 reviews in Part 1 and 3 reviews in Part 2, although their number and timing may change based on the findings. The 2nd interim data review in Part 1 is intended to inform the decision to move into, and the selection of doses for, Part 2. The timing of interim data reviews may change based on the findings. For details, see Section 8.10.

For both Part 1 and Part 2, individual MPA profiles will be displayed through month 12 following treatment initiation or earlier date of withdrawal from the study using the Primary Evaluable Analysis Set, with any 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 doses in Part 2, then subjects in that treatment group in Part 1 will be incorporated in the Part 2 pharmacokinetics analysis. Data from the subset of 6 subjects (2 per treatment 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. Pharmacokinetic parameters will be estimated for each subject in the Primary Evaluable Population using non-compartmental analysis.

Summaries of pharmacokinetics parameters and metrics will include means, medians, geometric means, minima, maxima, as well as standard deviation (SD), percent coefficient of variation (%CV) and 95% CIs for means and geometric means. The time to achieve MPA concentration greater than 0.2 ng/mL, and the number and percentage of subjects with MPA serum concentrations below 0.1 ng/mL and 0.2 ng/mL at days 182 and 210, will likewise be summarized by treatment group. Treatment group comparisons will be based on 90% confidence intervals for geometric mean ratios of pharmacokinetic parameters or analysis of covariance based on log-transformed responses. Specific variables included in covariate adjusted analyses (eg, age, BMI) will be specified in the separate statistical analysis plan.

In addition to assessing non-compartmental pharmacokinetic parameters by treatment group in Part 1, population pharmacokinetic effects modeling and simulation will be performed to inform dose selection and sample size for Part 2. [redacted]

8.5.3.1. Sensitivity Analysis

Sensitivity analyses will be performed excluding subjects determined to be outliers (eg, due to strong suspicion of injection on or near a blood vessel).

8.5.3.2. Exploratory Analysis

[redacted]

8.6. Pharmacodynamic Analysis

The primary pharmacodynamic objective in Part 2 will be assessed by estimating the cumulative probability of return to ovulation (occurrence of progesterone ≥4.7 ng/mL) through 52 weeks from start of study drug treatment in the Primary Evaluable Population; if 120 mg/mL is selected as one of the doses in Part 2, then subjects assigned to that treatment group in Part 1 will be incorporated in the analysis. Cumulative probabilities will be estimated for each treatment group based on the Kaplan Meier method and 95% CIs derived using the complementary log-log transformation. Differences in the distribution of return to ovulation between dose 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. Data from the subset of 6 subjects (2 per treatment group) with extreme obesity (BMI ≥40), and subjects with detectable MPA at baseline or who used drugs known to interfere with the pharmacokinetics or

pharmacodynamics of MPA prior to return to ovulation will be excluded from the primary analysis but will be described separately.

Nonlinear mixed effects pharmacokinetic/pharmacodynamic modeling and simulation will be used to explore the relationship between individual serum MPA concentrations and duration of ovulation suppression, with particular emphasis on characterizing the distribution of any apparent ovulatory suppression threshold and the lowest dose, which may reliably inhibit ovulation for 6 months.

8.7. Multiple Comparisons and Multiplicity

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

8.8. Safety Endpoints and Analysis

Safety analyses will be performed on the Treated Population.

8.8.1. Safety Endpoints

Safety measures and time points are provided in Section 3.5 and Table 1.

8.8.2. Safety Analysis

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by preferred term and system organ class (SOC). The number and percentage of participants experiencing adverse events will be presented by treatment group: overall, by severity grade, relatedness to treatment, and according to whether or not the event had an onset date within 7.5 months of initiation of study drug treatment (the intended dosing interval plus 1.5 months). Serious adverse events and adverse events leading to withdrawal from the study will be summarized separately. All relevant information on any deaths will be discussed in the subject narrative included in the clinical study report.

Summaries of ISR data will be provided by group in frequency tables and using subject-data listings, and the differences in proportions of subjects experiencing ISRs between treatment groups will be compared descriptively using Fisher's exact tests. The probability of return to ovulation more than 12 months after treatment initiation with TV-46046 will be estimated using Kaplan-Meier methods, with corresponding 95% CIs presented by group.

The percentage of women experiencing amenorrhea or other menstrual bleeding disturbances (irregular bleeding or spotting) will be assessed at monthly intervals during scheduled laboratory visits (in Part 1 only) and at follow-up visits at week 13 and week 32 only, and the final study visit. In addition, in Part 2 weekly self-reported menstrual data will be assessed, and compared between treatment groups using frequency tables; details are found in the Statistical Analysis Plan (SAP). In Part 2 only, liver function tests, including but not limited to ALT and AST, will be assessed by tabulating and graphing change from screening to week 13 (month 3), week 32 (month 7.5), and final study visit data. In Part 2 only mood will be assessed in frequency tables at screening and at week 13 (month 3), week 32 (month 7.5), and final study visits. Vital signs and body weight will be summarized graphically and using shift-tables, by investigational center and treatment group.

The use of concomitant medications during follow-up will be summarized by therapeutic class using descriptive statistics.

8.9. Acceptability Variables and Analysis

The responses to acceptability questions regarding menstrual patterns will be assessed at week 13, week 32, and the final study visit, and compared between treatment groups. 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 and descriptively compared between treatment groups.

8.10. Planned Interim Analyses

This Phase1 study has a data-driven, 2-part design. The purpose of Part 1 is to select an appropriate drug concentration and dose levels for further study. If undiluted TV-46046 has an appropriate pharmacokinetic profile based on the results of Part 1, then the study will move seamlessly into a dose-range finding component (Part 2). If the undiluted formulation does not have an appropriate pharmacokinetic profile, and/or one of the saline-diluted TV-46046 concentrations has a more acceptable profile, then a less concentrated formulation may be recommended for further development and testing in a separate protocol.

There are several planned reviews of the interim data, although their number and timing may change based on the findings. The 1st review will be performed after the 6 subjects in treatment group 1 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 (eg, whether or not the contraceptive threshold is likely to be achieved within 24 hours with a dose of no more than 300 mg). The 2nd review will be performed after the same 6 subjects in treatment group 1 of Part 1 have completed 4 months post-injection, and is intended to inform the decision to move into, and the selection of doses for, Part 2. At that time, available pharmacokinetics data from women in treatment group 2 (ie, the next 6 women receiving diluted TV-46046) will also be analyzed. Additional assessments will be made if warranted (eg, when the 12 women in both the undiluted and diluted groups complete 4 months (17 weeks)). Other features of the undiluted drug may also be considered in the decision-making process, including stability, re-suspendability, syringeability, and safety, although these will not be part of the formal analysis.

At least two interim reviews are planned to occur in Part 2 (after 50% of subjects have completed approximately 4 months and 7.5 months post-injection, respectively). These analyses are primarily intended to help inform the decision to move to and the dose selection for a Phase 3 clinical study. Additional interim analyses of Part 2 data may be conducted if needed to inform potential modifications to the Phase 1 study. The final planned data review will occur when 100% of subjects in Part 2 have completed 7.5 months post-injection (ie, the entire intended dosing interval plus 1.5 months); those data may be submitted to the FDA in the pre-Phase 3 submission.

The decision to move into Part 2 will be based on predicted pharmacokinetic parameters for a range of potential Part 2 doses, as informed by observed Part 1 pharmacokinetic data. Part 2 will only be implemented if the administration of undiluted TV-46046 (400 mg/mL) in Part 1 demonstrates an appropriate pharmacokinetic profile. Pharmacokinetic criteria considered before moving into Part 2 include predicted mean C_{max} less than 3 ng/mL, predicted time to achieve

0.2 ng/mL no more than 24 hours after study drug administration for all subjects, predicted 6-month concentration greater than 0.1 ng/mL in 95% of subjects, and predicted concentration 24 months after the last injection below 0.1 ng/mL in 90% of subjects for all treatment groups selected for Part 2.

As no formal hypothesis testing is being conducted in this study, no adjustment for multiple comparisons will be made to account for these interim analyses. Early evidence of unexpected, severe, or serious adverse events, including ISRs, could lead the DSMB to recommend termination of enrollment into one or more treatment groups, recognizing that enrollment may be completed before an informative interim analysis takes place. A schedule of planned reviews of the interim data, DSMB meetings, DSMB operation and responsibilities, and guidelines for premature discontinuation of the study will be provided in the statistical analysis plan and a separate DSMB operational plan.

8.11. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, amendments to the statistical analysis plan, the clinical study report, or any combination of these, as appropriate, and in accordance with applicable local and regional requirements and regulations.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The study monitors, auditors, IEC/IRB, and health authority inspectors (or their agents) will be given direct access to source data and documentation (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

The investigator must maintain the original records (ie, source documents) of each subject's data at all times. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, and CRFs that are used as the source (see Section 3.13).

The investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject. All study-related documents must be kept until notification by the sponsor.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Protocol Amendments and Protocol Deviations and Violations

10.1.1. Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the subjects or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

10.1.2. Protocol Violations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the subjects of the study and/or (b) the scientific value of the study will be considered a protocol violation. Protocol violations may include non-adherence on the part of the subject, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to study drug administration; or use of prohibited medications. Protocol violations will be identified and recorded by investigational center personnel in the CRF. All protocol violations will be reported to the responsible IEC/IRB, as required.

Changes in the inclusion and exclusion criteria of the protocol are not prospectively granted by the sponsor. If investigational center personnel learn that a subject who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol violation. If such subject has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded.

Lesser protocol deviations, i.e. those that do not significantly affect subject safety or scientific value of the data, will be recorded in a Protocol Deviation Log. The cumulative Log will be submitted to the responsible IEC/IRB at annual reviews.

10.2. Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting the study and during the course of the study (eg, when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the investigational center staff responsibility log, which includes a clear description of each staff member’s responsibilities. This list must be updated throughout the study, as necessary.

FHI 360 is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring they comply with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

10.3. Study Monitoring

Qualified FHI 360 or contract clinical monitors will conduct periodic study monitoring in accordance with FHI 360 policies. The monitor will make site visits as needed and as feasible, with a minimum of one initiation training visit, interim monitoring visits approximately every 6 months, and one close-out visit to assure that the study is being conducted and informed consent is being obtained according to the approved protocol, and to monitor recruitment and data accuracy. Before the study begins, FHI 360 will develop a detailed clinical monitoring plan. Briefly, the study clinical monitors will:

- Review informed consent forms and documentation
- Assess compliance with the study protocol, GCP guidelines, and applicable regulatory requirements (US and non-US)
- Verify that all serious adverse events in source documents have been reported on CRFs and in accordance with regulatory guidelines
- Perform source document verification to ensure the accuracy and completeness of study data
- Verify proper collection and storage of biological specimens
- Verify proper storage, dispensing, and accountability of study products
- Verify that current license/certification is available on site for study staff listed on the current Statement of Investigator Form, and Delegation of Responsibilities Log

During the course of this study, a qualified FHI 360 monitor or contract monitor will maintain regular contact with the investigational centers and regularly review clinical data received at FHI 360.

The center investigator or designee will securely maintain all source documents used to complete CRFs, including medical notes and laboratory reports. All study records will be retained following FHI 360 SOPs unless an exception is granted.

Investigators and study staff will allow the monitors to inspect the regulatory file, study documents (eg, consent forms, case report forms, other source documents) and pertinent clinic records for verification of the study data. Investigators and staff will allow clinical monitors to inspect study facilities and documentation.

As part of the supervision of study progress, other FHI 360 staff or representatives may, on request, accompany the study monitor on visits to the investigational center. The center investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits and/or provided in follow up written communication. Investigational centers will maintain a site visit log to document all visits.

10.4. Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies and/or clinical device supplies used in a

clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to the following:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc.)
- defective components
- missing or extra units (eg, primary container is received at the site with more or less than the designated number of units inside)
- incorrect packaging or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the Product Complaint Form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving a drug product, all relevant samples (eg, the remainder of the subject's drug supply) should be sent back to the sponsor for investigative testing whenever possible.

10.4.1. Product Complaint Information Needed from the Investigational Center

In the event that the Product Complaint Form cannot be completed, the investigator will obtain the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- subject identifier (subject study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- subject number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No
- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a complaint must not be delayed because not all the required information can be immediately obtained. Known information must be immediately reported. The sponsor will collaborate with the investigator to obtain any outstanding information.

10.4.2. Handling the Study Drug at the Investigational Center

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the study drug. Details may be found in the Pharmacy Manual.

If it is determined that the investigational center must return all of the study drug, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected subject.

10.4.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

10.4.4. Documenting a Product Complaint

The investigator will record a description of the product complaint in the source documentation as well as any actions taken to resolve the complaint and to preserve the safety of the subject. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

10.5. Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance department, independent of the Global Clinical Development department, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that regulatory authorities and sponsor representatives may conduct inspections to verify compliance with GCP guidelines.

11. ETHICS

Details of compliance with regulatory guidances and applicable laws are provided in Section 1.6.

11.1. Informed Consent

A participant will not be enrolled into this research study until the center investigator has obtained her legally effective (signed and/or witnessed) informed consent. The center investigator shall seek such consent under circumstances that provide the prospective participant with sufficient opportunity to learn about the study and consider whether or not to participate in it. Informed consent will be obtained without coercion, undue influence or misrepresentation of the potential benefits and risks that might be associated with participation in the research study. Informed consent encompasses all oral or written information given to the participant about the study and the study materials. This includes the consent form signed by the participant and any other information provided to the participant. All such information that is given to the participant will be in a language that is understandable to her. The participant must agree that she understands the investigational nature of the study, its inherent risks and benefits, other treatment alternatives, her rights to terminate participation in the study without affecting her health care at the site, whom to contact with questions regarding the study, and that she has freely given informed consent to participate in the study and to have her medical records reviewed as part of the study.

Informed consent will be documented by the use of a written consent form that is signed by the participant (or with the participant's mark if she cannot sign). A copy of the signed informed consent form will be given to her. The original signed consent form for each participant will be stored in a secure location separately from the study data forms. The consent form must include each of the basic and additional elements of informed consent described in 45 CFR Part 46.116 and must describe each of the risks or discomforts to the participant that have been identified by FHI 360 as reasonably foreseeable. The information will not include any language in which the participant is made to waive any of her rights or which releases or appears to release the center investigator, the center investigator's institution, or the sponsor from liability for negligence.

11.2. Health Authorities and Independent Ethics Committees/Institutional Review Boards

This protocol, the informed consent forms, and other documentation (as required) will be reviewed and approved by the PHSC at FHI 360 and the site IRBs. The center investigator at each research site is responsible for ensuring that all requirements of the local IEC/IRB are met. Before implementing any changes to the protocol, informed consent, or participant written materials, the center investigator must have the changes approved by FHI 360's PHSC and the local IEC/IRB, and applicable health regulatory agencies, except where necessary to eliminate immediate hazards to human participants. If the local IEC/IRB withdraws its approval of this research at any time before its completion, the investigator must notify FHI 360 as soon possible, but no later than within 48 hours.

The center investigator is responsible for making progress reports to the local IEC/IRB and to FHI 360 annually and within 3 months of study termination or completion. The reports should

include at a minimum the total number of participants enrolled, the numbers and reason(s) for discontinuation, a description of all serious adverse events, the number of participants completing the study, all changes in the research activity, and all unanticipated problems involving risks to human participants or others. Copies of all study-related correspondence with the local IEC/IRB must be sent to FHI 360.

11.3. Confidentiality Regarding Study Subjects

The investigator must ensure that the privacy of the subjects, including their identity and all personal medical information, will be maintained at all times. All study visit procedures will be conducted in private. In CRFs and other documents or image material submitted to the sponsor, subject s will be identified not by their names, but by a subject identification number.

Personal medical information may be reviewed for the purpose of subject safety and/or verifying data in the source and transcribed onto the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

11.4. Declaration of the End of the Clinical Study

The definition of the end of study is the date of the last visit of the last subject.

11.5. Registration of the Clinical Study

In compliance with local regulations and in accordance with Teva standard procedures, this clinical study will be registered on ClinTrials.gov.

12. DATA HANDLING, DATA QUALITY CONTROL, AND RECORD KEEPING

12.1. Data Collection

Most data will be collected using 1-ply CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users who require access to the system will receive training on the system and study-specific training. After they are trained, those users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each subject who provided informed consent. Subject identity should not be discernible from the data provided on the CRF. Data will be verified using the data source by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

In Part 2 only, data on menstrual bleeding will be collected weekly using the validated, Part 11-compliant on-line Participate application module of OpenClinica, the CDMS. Women will be prompted by text message and/or e-mail to open a unique link, with access code, to access the application and submit answers to a brief question set. These data will be automatically uploaded in real-time into the OpenClinica clinical database.

If data are processed from other sources, (eg, central laboratory, bioanalytical laboratory, central image center, electronic patient-reported outcome [ePRO] Tablet), the results will be sent to the investigational center, where they will be retained but not entered into the CRF unless otherwise specified in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management) for direct entry into the clinical database. Laboratory test results will not be entered into the CRF unless otherwise noted in the protocol. All data from other sources will be available to the investigators.

For subjects who enter a study but do not meet entry criteria, at a minimum, data for screen failure reason, demography, and adverse events from the time of informed consent will be entered into the CRF.

12.2. Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality control, will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality control, will be described in a data management plan.

Case report forms received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS. Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS functionality. In compliance with 21 CRF Part 11, the system requires a reason for each change and keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

12.3. Archiving of Case Report Forms and Source Documents

12.3.1. Sponsor Responsibilities

All data management tasks for this study are delegated to FHI 360; these functions will be carried out as described in FHI 360 SOPs. The original CRFs will be stored at the respective investigational centers until the end of the study. FHI 360 will maintain electronic files of the scanned CRFs.

Ultimately, the sponsor will have final responsibility for the processing and quality control of the data.

12.3.2. Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports and data related to the study and any additional records required to be maintained under country, state/province, or other local laws, including, but not limited to, the following:

- full case histories
- signed informed consent forms
- subject identification lists
- case report forms for each subject on a per-visit basis
- data results from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the study drug
- copies of all correspondence with sponsor, the IRB/IEC, and any regulatory authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the contract research organization (CRO) or sponsor sends written notification that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. Upon receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor and FHI 360 of any accidental loss or destruction of study records.

13. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be entered into between each principal investigator and FHI 360 before the study drug is delivered.

This clinical study is insured in accordance with the corresponding local legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are inter alia, damages to health, and worsening of previous existing disease that would have occurred or continued if the subject had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete Form FDA 3454. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

14. REPORTING AND PUBLICATION OF RESULTS

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements and regulations for registration and posting of results, and to requirements outlined in any current or future agreements between sponsor and FHI 360.

FHI 360 will prepare the clinical study report, in cooperation with the sponsor. The final report is signed by the sponsor and by the FHI 360 Coordinating Investigator.

When the sponsor generates reports from the data collected in this study for presentation to regulatory authorities, drafts will be circulated to the FHI 360 coordinating investigator for comments and suggestions.

No unpublished information shall be published or disclosed to a third party without the prior written consent of the sponsor and FHI 360. The primary publication from this study will report the results of the study in accordance with the current "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. Authorship will be based on meeting all the following 4 criteria:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

A joint publications committee will be established by the sponsor and FHI 360 to oversee this process. Additional publications may follow upon the agreement of the committee. Policies regarding the publication of the study results are further defined in a collaboration agreement between Teva and FHI 360. Any disputes or issues about publication will be referred to the Executive Committee, as described in that agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

15. REFERENCES

Abel K, Rourke T, Lu D, Bost K, McChesney MB, Miller CJ. Abrogation of attenuated lentivirus-induced protection in rhesus macaques by administration of depo-provera before intravaginal challenge with simian immunodeficiency virus mac239[published erratum appears in J Infect Dis 2005;191(6):1028]. J Infect Dis. 2004;190(9):1697-1705.

Baumgartner JN, Morroni C, Mlobeli RD, Otterness C, Myer L, Janowitz B, et al. Timeliness of contraceptive reinjections in South Africa and its relation to unintentional discontinuation. International family planning perspectives. 2007;33(2):66-74.

Brache V, Sitruk-Ware R, Williams A, Blithe D, Croxatto H, Kumar N, et al. Effects of a novel estrogen-free, progesterone receptor modulator contraceptive vaginal ring on inhibition of ovulation, bleeding patterns and endometrium in normal women. Contraception. 2012;85(5):480-8.

Castle WM, Sapire KE, Howard KA. Efficacy and acceptability of injectable medroxyprogesterone. A comparison of 3-monthly and 6-monthly regimens. S Afr Med J. 1978;53(21):842-5.

Centers for Disease Control and Prevention. Update to CDC's U.S. medical eligibility criteria for contraceptive use, 2010: revised recommendations for the use of contraceptive methods during the postpartum period. MMWR. 2011;60(26):869-905.

Depo-Provera Contraceptive Injection [package insert]. New York, NY: Pfizer Inc; 2016.

Depo subQ Provera 104 [package insert]. New York, NY: Pfizer Inc; 2016.

Genesca M, Li J, Fritts L, Chohan P, Bost K, Rourke T, et al. Depo-Provera abrogates attenuated lentivirus-induced protection in male rhesus macaques challenged intravenously with pathogenic SIVmac239. J Med Primatol. 2007;36(4-5):266-75.

Halpern V, Stalter RM, Owen DH, Dorflinger LJ, Lendvay A, Rademacher KH. Towards the development of a longer-acting injectable contraceptive: past research and current trends. Contraception. 2015;92:3-9.

Hild-Petito S, Veazey RS, Larner JM, Reel JR, Blye RP. Effects of two progestin-only contraceptives, Depo-Provera and Norplant-II, on the vaginal epithelium of rhesus monkeys. AIDS Res Hum Retroviruses. 1998;14(Suppl 1):S125-S130.

Jain J, Dutton C, Nicosia A, Wajszczuk C, Bode FR, Mishell DRJr. Pharmacokinetics, ovulation suppression and return to ovulation following a lower dose subcutaneous formulation of Depo-Provera. Contraception. 2004;70(1):11-8.

Jesam C, Salvatierra AM, Schwartz JL, Fuentes A, Croxatto HB. Effect of oral administration of a continuous 18 day regimen of meloxicam on ovulation: experience of a randomized controlled trial. Contraception. 2014;90(2):168-73.

Jordan A. Toxicology of depot medroxyprogesterone acetate. Contraception. 1994;49(3):189-201.

Kaunitz AM, Darney PD, Ross D, Wolter KD, Speroff L. Subcutaneous DMPA vs. intramuscular DMPA: a 2-year randomized study of contraceptive efficacy and bone mineral density. Contraception. 2009;80:7-17.

Kaunitz AM, Grimes DA. Removing the black box warning for depot medroxyprogesterone acetate. Contraception. 2011;84(3):212-3.

Kaushic C, Ashkar AA, Reid LA, Rosenthal KL. Progesterone increases susceptibility and decreases immune responses to genital herpes infection. J Virol. 2003;77(8):4558-65.

Lakha F, Henderson C, Glasier A. The acceptability of self-administration of subcutaneous Depo-Provera. Contraception. 2005; 72(1):14-8.

Lee NC, Rosero-Bixby L, Oberle MW, Grimaldo C, Whatley AS, Rovira EZ. A case-control study of breast cancer and hormonal contraception in Costa Rica. JNCL. 1987;79(6):1247-54.

Li CI, Beaber EF, Tang MTC, Porter PL, Daling JR, Malone KE. Effect of depo-medroxyprogesterone acetate on breast cancer risk among women 20 to 44 years of age. Cancer Res. 2012;72(8):2028-35.

Mackay EV, Khoo SK, Adam RR. Contraception with a six-monthly injection of progestogen. Part 1. Effects on blood pressure, body weight and uterine bleeding pattern, side-effects, efficacy, and acceptability. Aust N Z J Obstet Gynaecol. 1971;11(3):148-55.

McDaniel EB, Pardthaisong T. Use-effectiveness of six-month injections of DMPA as a contraceptive. Am J of Obstet and Gynecol. 1974; 119(2):175-80.

MHRA. SAYANA PRESS 104 mg/0.65 mL suspension for injection. Public Assessment Report, Mutual Recognition Decentralised Procedure. UK/H/0960/002/DC: Pfizer Limited;2015. Available at: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con126147.pdf.

Morrison CS, Chen P-L, Kwok C, Baeten JM, Brown J, Crook AM, et al. Hormonal contraception and the risk of HIV acquisition: An individual participant data meta-analysis. PLoS medicine. 2015;12(1):e1001778.

Paul C, Skewgg DCG, Spears GFS. Depot medroxyprogesterone (Depoi-Provera) and risk of breast cancer. BMJ 1989:299(6702);759-62.

Polis CB, Curtis KM, Hannaford PC, Phillips SJ, Chipato T, Kiarie JN, etc. An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women. AIDS. 2016 Nov 13;30(17):2665-2683.

[PR]DEPO-PROVERA and [PR]DEPO-PROVERA-SC [product monograph]. Kirkland, Quebec: Pfizer Canada, Inc;2013.

Rahimy MH, Ryan KK, Hopkins NK. Lunelle monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension): steady-state pharmacokinetics of MPA and E_2 in surgically sterile women. Contraception. 1999;60(4):209-14.

Ralph LJ, McCoy SI, Shiu K, Padian NS. Hormonal contraceptive use and women's risk of HIV acquisition: a meta-analysis of observational studies. Lancet. 2015;15(2):181-9.

Schwallie PC, Assenzo JR. Contraceptive use--efficacy study utilizing Depo-Provera administered as an injection once every six months. Contraception. 1972;6(4):315-27.

Shapiro S, Rosenberg L, Hoffman M, Truter H, Cooper D, Rao S, et al. Risk of breast cancer in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen contraceptives. Am J Epidemiol 2000;151(4);396-403.

Stanback J, Spieler J, Shah I, Finger WR. Community-based health workers can safely and effectively administer injectable contraceptives: conclusions from a technical consultation. Contraception. 2010;81(3):181-4.

Toh YC, Jain J, Rahimy MH, Bode FR, Ross D. Suppression of ovulation by a new subcutaneous depot medroxyprogesterone acetate (104 mg/0.65 mL) contraceptive formulation in Asian women. Clinical therapeutics. 2004;26(11):1845-54.

United Nations Department of Economic and Social Affairs, Population Division. World Contraceptive Use, 2011.

Westhoff CL, Torgal AH, Mayeda ER, Stanczynk FZ, Lerner JP, Benn EKT, et al. Ovarian suppression in normal-weight and obese women during oral contraceptive use: a randomized controlled trial. Obstet and Gynecol. 2010;116(No. 2 Part 1):275-83.

World Health Organization. Breast cancer and depot-medroxyprogesterone acetate: a multinational study. Lancet. 1991;338(8771):833-8.

World Health Organization. Depot-medroxyprogesterone acetate (DMPA) and cancer: Memorandum from a WHO meeting. Bull World Health Organ. 1993;71(6):669-76.

World Health Organization Department of Reproductive Health and Research. Hormonal contraceptive eligibility for women at high risk of HIV: 2017 guidance statement (WHO/RHR/17.04). Geneva: World Health Organization; 2017. Available at: http://www.who.int/reproductivehealth/publications/family_planning/HC-and-HIV-2017/en/. Accessed on March 8, 2017.

Williams DL, Hagen AA, Runyan JW, Jr. Chromosome alterations produced in germ cells of dogs by progesterone. J Lab Clin Med. 1971;77(3):417-29.

Williams DL, Runyan JW, Jr, Hagen AA. Progesterone-induced alterations of oogenesis in the Chinese hamster. J Lab Clin Med. 1972;79(6):972-77.

Wright CE III, Antal EJ, Gillespie WR, Albert KS. Effect of injection volume on the bioavailability of sterile medroxyprogesterone acetate suspension. Clin Pharmacy. 1983;(2):435-8.

16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Protocol Amendment 04 Dated 09 August 2017

The primary reasons for this amendment are additions, corrections and clarifications. These revisions are considered to be substantial by the sponsor's Authorized Representative. Changes made within the text of the protocol were also made within the synopsis.

Original text with changes shown	**New wording**	**Reason/Justification for change**
Clinical Laboratory And Other Departments And Institutions		
Comité Ético Científico del Servicio de Salud Metropolitano Central Victoria Subercaseaux #381 Santiago, Chile Comité de Ética de PROFAMILIA Clínica Abreu, Calle Beller #42 esq. Ave. Independencia Santo Domingo, Dominican Republic	Comité Ético Científico del Servicio de Salud Metropolitano Central Victoria Subercaseaux #381 Santiago, Chile Comité de Ética de PROFAMILIA Clínica Abreu, Calle Beller #42 esq. Ave. Independencia Santo Domingo, Dominican Republic	Addition. A new Investigational Center Ethics Committee was added.
Clinical Laboratoriesy University of Pennsylvania Endocrinology Laboratory 8th Floor 3701 Market Street Philadelphia, Pennsylvania 19104 United States of America	**Clinical Laboratories** University of Pennsylvania Endocrinology Laboratory 8th Floor 3701 Market Street Philadelphia, Pennsylvania 19104 United States of America	Correction.
Jones Institute for Reproductive Medicine Endocrinology Laboratory 601 Colley Avenue Norfolk, VA 23507 United States of America	Jones Institute for Reproductive Medicine Endocrinology Laboratory 601 Colley Avenue Norfolk, VA 23507 United States of America	Correction.
Laboratorios Clinicos PUC - Centro Medico San Joaquin Vicuna Mackenna 4686 Macul Santiago, Chile Referencia Laboratorio Clínico Avenida Independencia 202, 3er piso Edificio Santa Ana Santo Domingo, Dominican Republic	Laboratorios Clinicos PUC - Centro Medico San Joaquin Vicuna Mackenna 4686 Macul Santiago, Chile Referencia Laboratorio Clínico Avenida Independencia 202, 3er piso Edificio Santa Ana Santo Domingo, Dominican Republic	Addition. A new clinical lab was added.

Original text with changes shown	New wording	Reason/Justification for change
Instituto Chileno de Medicina Reproductiva [redacted] Jose Victorino Lastarria 29 of 101 Santiago Centro, Santiago Chile Asociación Dominicana Pro Bienestar de la Familia, Inc. (PROFAMILIA) Nicolas de Ovando esq. Calle 16 Ens. Luperon Santo Domingo, Dominican Republic	Instituto Chileno de Medicina Reproductiva [redacted] Jose Victorino Lastarria 29 of 101 Santiago Centro, Santiago Chile Asociación Dominicana Pro Bienestar de la Familia, Inc. (PROFAMILIA) Nicolas de Ovando esq. Calle 16 Ens. Luperon Santo Domingo, Dominican Republic	Addition. A new investigational center was added.
Clinical Study Personnel Contact Information		
[redacted] - FHI 360 Medical Monitor Tel: [redacted] Tel: [redacted] Fax: [redacted]	[redacted], FHI 360 Medical Monitor Tel: [redacted] Tel: [redacted] Fax: [redacted]	Correction.
Clinical Study Protocol Synopsis		
Countries Planned: United States (US), Chile, and the Dominican Republic ~~other Latin American countries pending~~	**Countries Planned:** United States (US), Chile, and the Dominican Republic	Addition. The Dominican Republic added to the list of countries.
Section 1.2. Name and Description of Investigational Product (Sections 5.1.1 and 7.1.5.3.1)		
The 300 and 200 mg/mL concentrations will be achieved by diluting the original 400 mg/mL formulation with sterile saline by a pharmacist or other trained personnel prior to injection.	The 300 and 200 mg/mL concentrations will be achieved by diluting the original 400 mg/mL formulation with sterile saline by a pharmacist or other trained personnel prior to injection.	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.7. Study Population and Justification		
The study will enroll healthy women 18 to 40 years of age, inclusive, who are at low risk of pregnancy (ie, ~~eg,~~ sterilized, in exclusively same-sex partnership, in monogamous relationship with vasectomized partner, using non-hormonal IUD), and who are confirmed to have ovulated during the pre-treatment phase of the study.	The study will enroll healthy women 18 to 40 years of age, inclusive, who are at low risk of pregnancy (ie, sterilized, in exclusively same-sex partnership, in monogamous relationship with vasectomized partner, using non-hormonal IUD), and who are confirmed to have ovulated during the pre-treatment phase of the study.	Correction.
Section 1.8.Location and Duration of Study		
For Part 2, up to 3 more investigational centers will be added (at least two ~~tentatively all~~ in Latin America).	For Part 2, up to 3 more investigational centers will be added (at least two in Latin America).	Clarification.
Section 3.1.General Design and Study Schematic Diagram		
Prior to injection, ovulation will be confirmed in all subjects by measuring serum progesterone approximately twice a week during the approximately 2 to 3 weeks preceding expected menses.	Prior to injection, ovulation will be confirmed in all subjects by measuring serum progesterone approximately twice a week during the approximately 2 to 3 weeks preceding expected menses.	Clarification.
During the pre-treatment phase ovulation will be confirmed in all subjects who are otherwise eligible for the study by measuring serum progesterone approximately twice a week (preferably 3 days apart) during the approximately 2 to 3 weeks preceding expected menses.	During the pre-treatment phase ovulation will be confirmed in all subjects who are otherwise eligible for the study by measuring serum progesterone approximately twice a week (preferably 3 days apart) during the approximately 2 to 3 weeks preceding expected menses.	Clarification.
In addition to frequent laboratory visits to collect blood samples, there will be 3 scheduled follow-up visits: at day 7, month 3 (13 weeks), and month 7.5 (32 weeks) after start of study drug treatment, during which subjects will be weighed and evaluated for ISRs, vital signs, and acceptability~~including responses to questions about injection pain, ISR complaints, and menstrual bleeding patterns~~.	In addition to frequent laboratory visits to collect blood samples, there will be 3 scheduled follow-up visits: at day 7, month 3 (13 weeks), and month 7.5 (32 weeks) after start of study drug treatment, during which subjects will be weighed and evaluated for ISRs, vital signs, and acceptability.	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
The subject's menstrual bleeding patterns will be obtained by an interview questionnaire at monthly intervals (in Part 1 only), by weekly diary completed by the subjects on-line (in Part 2 only), and at follow-up visits (month 3 and month 7.5 only), and the final study visit. In Part 2 only, liver function will be assessed by tabulating and graphing change in liver function tests including but not limited to ALT and AST, from screening to week 13 (month 3), week 32 (month 7.5), and final study visit. In Part 2 only, mood will be assessed in frequency tables at screening and at week 13 (month 3), week 32 (month 7.5), and final study visits.	The subject's menstrual bleeding patterns will be obtained by an interview questionnaire at monthly intervals (in Part 1 only), by weekly diary completed by the subjects on-line (in Part 2 only), and at follow-up visits (month 3 and month 7.5 only), and the final study visit. In Part 2 only, liver function will be assessed by tabulating and graphing change in liver function tests including but not limited to ALT and AST, from screening to week 13 (month 3), week 32 (month 7.5), and final study visit. In Part 2 only, mood will be assessed in frequency tables at screening and at week 13 (month 3), week 32 (month 7.5), and final study visits.	Clarification.
Up to 4 additional investigational centers will be added for Part 2 including Eastern Virginia Medical School in the US, and Instituto Chileno de Medicina Reproductiva (ICMER) in Chile and the Biomedical Research Department with Profamilia in the Dominican Republic (Profamilia).	Up to 4 additional investigational centers will be added for Part 2 including Eastern Virginia Medical School in the US, Instituto Chileno de Medicina Reproductiva (ICMER) in Chile and the Biomedical Research Department with Profamilia in the Dominican Republic (Profamilia).	Addition. Investigational site added.
Section 3.3. Pharmacokinetic Measures and Time Points		
For Part 1, blood samples for measurement of serum concentrations will be obtained on days 0 (baseline), 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, 0, 28, 35, and 42; weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52, regardless of ovulation status.	For Part 1, blood samples for measurement of serum concentrations will be obtained on days 0 (baseline), 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, 28, 35, and 42; weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52, regardless of ovulation status.	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
Among s~~S~~ubjects in~~for~~ whom ovulation has not returned by month 12 (week 52), blood samples for MPA will be tested ~~collected~~ up to 2 more times (once at week 61 and once at week 74), but not past return to ovulation. The sampling schedule and duration of MPA testing may be modified based on ~~the interim results of Part 1 to ensure that~~ accumulating data for a more accurate characterization of the pharmacokinetic profile of TV-46046 ~~primary and secondary outcomes are precisely measured in both parts of the study~~.	Among subjects in whom ovulation has not returned by month 12 (week 52), blood samples for MPA will be tested up to 2 more times (once at week 61 and once at week 74), but not past return to ovulation. The sampling schedule and duration of MPA testing may be modified based on accumulating data for a more accurate characterization of the pharmacokinetic profile of TV-46046.	Clarification.
In addition, blood samples will also be collected and stored for possible future MPA testing (if necessary) at all weekly visits ~~up to 12 months~~ when samples are collected for serum progesterone and estradiol, except for pre-treatment visits and visits for confirmation of ovulation.	In addition, blood samples will also be collected and stored for possible future MPA testing (if necessary) at all weekly visits when samples are collected for serum progesterone and estradiol, except for pre-treatment visits and visits for confirmation of ovulation.	Clarification.
Section 3.4. Pharmacodynamic Measures and Time Points		
Blood samples for measurement of progesterone and estradiol will be obtained as follows: on day 0 (baseline); then at day 7~~weeks 1~~ and~~, 2, 4, 6, 8, 10, and 12;~~ then weekly through week 32, regardless of ovulation status.	Blood samples for measurement of progesterone and estradiol will be obtained as follows: on day 0 (baseline); then at day 7 and then weekly through week 32, regardless of ovulation status.	Addition. Estradiol levels will be measured for pharmacodynamics analysis.
If there is no ovulation by week 52, then blood samples for serum progesterone and estradiol will be collected weekly between weeks 61 through 65 and between weeks 74 through 78, ~~until ovulation (~~but not past return to ovulation~~)~~.	If there is no ovulation by week 52, then blood samples for serum progesterone and estradiol will be collected weekly between weeks 61 through 65 and between weeks 74 through 78, but not past return to ovulation.	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
At any time point during follow-up, a subject with progesterone ≥3.0 ng/mL will be asked to return within 5 days for repeated progesterone measurement to ensure close monitoring of the potential post-ovulatory rise of progesterone. If the repeated measurement within 5 days is at or below 3.0 ng/mL, the subject will continue follow-up per her visit schedule. At any time point during follow-up, a subject with initial progesterone ≥4.7 ng/mL will be asked to return within 5 days for repeated progesterone measurement for more accurate ascertainment of ovarian function.	At any time point during follow-up, a subject with progesterone ≥3.0 ng/mL will be asked to return within 5 days for repeated progesterone measurement to ensure close monitoring of the potential post-ovulatory rise of progesterone. If the repeated measurement within 5 days is at or below 3.0 ng/mL, the subject will continue follow-up per her visit schedule. At any time point during follow-up, a subject with initial progesterone ≥4.7 ng/mL will be asked to return within 5 days for repeated progesterone measurement for more accurate ascertainment of ovarian function.	Addition. Statement added to describe requirements for the repeated measurement of progesterone.
Estradiol will be measured at the same time points as progesterone as a supporting pharmacodynamics measure. ~~For a detailed description of progesterone sampling, see Table 1 and Section 3.14.3.2.2.~~	Estradiol will be measured at the same time points as progesterone as a supporting pharmacodynamics measure.	Correction.
Section 3.6.Acceptability Measures and Time Points		
Acceptability of the menstrual bleeding patterns will be assessed through responses by subjects obtained by an interview questionnaire at monthly intervals during scheduled laboratory visits (in Part 1 only); at scheduled~~ nd or~~follow-up visits (except day 7); and at the final study visit.	Acceptability of the menstrual bleeding patterns will be assessed through responses by subjects obtained by an interview questionnaire at monthly intervals during scheduled laboratory visits (in Part 1 only); at scheduled follow-up visits (except day 7); and at the final study visit.	Clarification.
Section 3.13. Source Data Recorded on the Case Report Form		
The CRFs are filed in the clinical sites'~~ponsor's central~~ files and CRFs will be shipped to the sponsor at the end of the trial.	The CRFs are filed in the clinical sites' files and CRFs will be shipped to the sponsor at the end of the trial.	Process clarification.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.14. Study Procedures		
Participants will come to the study clinic for 1 screening visit, up ~~4~~ to 6 pre-treatment visits, 1 enrollment/injection visit, 3 scheduled follow-up visits, a final visit, and frequent laboratory visits to draw blood samples for progesterone, estradiol, and/or MPA.	Participants will come to the study clinic for 1 screening visit, up to 6 pre-treatment visits, 1 enrollment/injection visit, 3 scheduled follow-up visits, a final visit, and frequent laboratory visits to draw blood samples for progesterone, estradiol, and/or MPA.	Clarification.
Table 1. Study Procedures and Assessments (Parts 1 and 2)		
Row: Mammogram ~~mo~~ **Screening (x), ~~Pretreatment (x)~~**	Mammogram [m] Screening (x)	Correction. Mammogram at pretreatment removed.
c Day 0; within the 1st 5 days of the start of subject's menstrual cycle.	c Day 0; within the 1st 5 days of the start of subject's menstrual cycle.	Clarification
~~d At any time during the study, subjects with initial serum progesterone ≥3.0 ng/mL will be asked to return within 5 days for repeated progesterone measurement. If repeated progesterone is at 3 ng/mL or below, the subject will continue follow up per their visit schedule.~~ ~~e In addition, at any time during the study, if the serum progesterone level is equal to or greater than 4.7 ng/mL, subjects in all treatment groups will be asked to return to repeat the serum progesterone measurement within 5 days.~~ ~~f~~ d ~~During pretreatment, b~~Blood samples for serum progesterone and estradiol will be collected approximately twice weekly during the approximately 2 to 3 weeks preceding the subject's expected menses for confirmation of ovulation (ideally at least 4 measurements).	d Blood samples for serum progesterone and estradiol will be collected approximately twice weekly during the approximately 2 to 3 weeks preceding the subject's expected menses for confirmation of ovulation (ideally at least 4 measurements).	Clarification

Original text with changes shown	New wording	Reason/Justification for change
e ~~gDuring the follow-up laboratory visits, b~~Blood samples for serum progesterone and estradiol will be collected on day 0 (baseline); then at day 7 and then weekly through week 32, regardless of ovulation status. If ovulation does not return by week 32, then weekly blood samples for serum progesterone and estradiol will continue to be collected until ovulation or ~~at weeks 1, 2, 4, 6, 8, 10, and 12; then weekly~~ through week 52, whichever is earlier. If there is no ovulation by week 52, then blood samples for progesterone and estradiol will be collected~~additional laboratory visits for these subjects will be scheduled~~ at weeks 61, 62, 63, 64, and 65; and at weeks 74, 75, 76, 77, and 78, if ovulation has not returned by week 65. During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol at ~~(~~all visits~~)~~, but not past return to ovulation.	e Blood samples for serum progesterone and estradiol will be collected on day 0 (baseline); then at day 7 and then weekly through week 32, regardless of ovulation status. If ovulation does not return by week 32, then weekly blood samples for serum progesterone and estradiol will continue to be collected until ovulation or through week 52, whichever is earlier. If there is no ovulation by week 52, then blood samples for progesterone and estradiol will be collected at weeks 61, 62, 63, 64, and 65; and at weeks 74, 75, 76, 77, and 78, if ovulation has not returned by week 65. During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol at all visits, but not past return to ovulation.	Clarification
f At any time during follow-up, subjects with initial serum progesterone ≥3.0 ng/mL will be asked to return within 5 days for repeated progesterone and estradiol measurement. If repeated progesterone is at 3 ng/mL or below, the subject will continue follow-up per their visit schedule.	f At any time during follow-up, subjects with initial serum progesterone ≥3.0 ng/mL will be asked to return within 5 days for repeated progesterone and estradiol measurement. If repeated progesterone is at 3 ng/mL or below, the subject will continue follow-up per their visit schedule.	Addition. Details included to describe the follow-up process for subjects with initial serum progesterone greater than 3.0 ng/mL.

Original text with changes shown	**New wording**	**Reason/Justification for change**
g At any time during follow-up, if the serum progesterone level is ≥4.7 ng/mL, subjects will be asked to return within 5 days for repeated progesterone and estradiol measurement ~~within 5 days. and serum MPA at (weeks 61 and 74). Estradiol will be measured at all of the same time points as progesterone as a supporting pharmacodynamics measure.h If the estradiol level is at or greater than 75 pg/mL during weeks 2 to 12 or weeks 52 to 78, then blood samples for progesterone and estradiol will be collected weekly.~~	g At any time during follow-up, if the serum progesterone level is ≥4.7 ng/mL, subjects will be asked to return within 5 days for repeated progesterone and estradiol measurement.	Clarification.
h ~~i During the follow-up visits, b~~ Blood samples for MPA will be collected on day 0; then on ~~at~~ days 1, 2, 3, 5, 7, 10, 12, 14, 18, 2~~0~~1, 28, 35, and 42; then at weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52, regardless of ovulation status.	h Blood samples for MPA will be collected on day 0; then on days 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, 28, 35, and 42; then at weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52, regardless of ovulation status.	Clarification.
i ~~j A blood sample will be collected if the last MPA sample was taken more than 2 weeks ago.~~ Injection site reactions will be recorded on day 0 immediately after the injection (within 10 minutes) and within the 1st hour after injection; at days 1, 2, 3, 5, and 7; week 13 and week 32 visits; at the final visit; and at other visits, if indicated	i Injection site reactions will be recorded on day 0 immediately after the injection (within 10 minutes) and within the 1st hour after injection; at days 1, 2, 3, 5, and 7; week 13 and week 32 visits; at the final visit; and at other visits, if indicated	Clarification.
j ~~k~~ During laboratory visits, information on adverse events and concomitant medications will not be solicited, but will be documented if reported by the subject.	j During laboratory visits, information on adverse events and concomitant medications will not be solicited, but will be documented if reported by the subject.	Clarification.
k ~~m~~Liver function testing and mood evaluation will be evaluated at the ~~screening,~~ week 13 and~~,~~ week 32 follow-up visits~~and the final visit only~~.	k Liver function testing and mood evaluation will be evaluated at the week 13 and week 32 follow-up visits.	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
l ~~n In Part 1, m~~Menstrual bleeding patterns will be obtained by an interview questionnaire approximately monthly; at scheduled follow-up visits (weeks 13 and 32 only); and the final study visit. In addition, in Part 2 menstrual data will be collected weekly via an on-line diary.	l Menstrual bleeding patterns will be obtained by an interview questionnaire approximately monthly; at scheduled follow-up visits (weeks 13 and 32 only); and the final study visit. In addition, in Part 2 menstrual data will be collected weekly via an on-line diary.	Clarification.
~~o~~ m Part 1 only, prior to enrollment.	m Part 1 only, prior to enrollment.	Clarification.
Section 3.14.1. Procedures Before Study Drug Treatment		
Eligible subjects will be scheduled to return to the clinic up to ~~4 to~~ 6 times for serum progesterone and estradiol measurements to confirm their ovulatory cycle (approximately twice a week preferably 3 days apart during approximately the 2 to 3 weeks preceding their next expected menses).	Eligible subjects will be scheduled to return to the clinic up to 6 times for serum progesterone and estradiol measurements to confirm their ovulatory cycle (approximately twice a week preferably 3 days apart during approximately the 2 to 3 weeks preceding their next expected menses).	Clarification.
Section 3.14.2. Pretreatment		
Subjects who meet the inclusion/exclusion criteria at screening visit will return to the clinic approximately twice a week (preferably 3 days apart) during the approximately 2 to 3 weeks preceding their next expected menses (ideally at least 4 ~~to 6~~ times) for serum progesterone and estradiol measurements to confirm ovulation.	Subjects who meet the inclusion/exclusion criteria at screening visit will return to the clinic approximately twice a week (preferably 3 days apart) during the approximately 2 to 3 weeks preceding their next expected menses (ideally at least 4 times) for serum progesterone and estradiol measurements to confirm ovulation.	Clarification.
Section 3.14.3.2. Follow-up (Day 1 to Week 78)		
Regardless of ovulation status, all subjects should remain in follow-up for at least 52 weeks post-injection. There are 2 types of follow-up visits in this study: scheduled follow-up visits and laboratory visits.	Regardless of ovulation status, all subjects should remain in follow-up for at least 52 weeks post-injection. There are 2 types of follow-up visits in this study: scheduled follow-up visits and laboratory visits.	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.14.3.2.1. Scheduled Follow-up Visits (Day 7, Month 3, and Month 7.5)		
~~In Part 1, m~~Menstrual bleeding patterns, mood (for Part 2 only) and acceptability will be evaluated through an interview questionnaire.	Menstrual bleeding patterns, mood (for Part 2 only) and acceptability will be evaluated through an interview questionnaire.	Clarification.
For Part 2, in addition to the scheduled follow-up visits menstrual bleeding patterns will be evaluated weekly through on-line diaries~~; mood and acceptability will be evaluated through an interview administered questionnaire~~.	For Part 2, in addition to the scheduled follow-up visits menstrual bleeding patterns will be evaluated weekly through on-line diaries.	Clarification.
• interview about menstrual bleeding pattern (month 3 and month 7.5~~; Part 1 only~~)	• interview about menstrual bleeding pattern (month 3 and month 7.5)	Clarification.
Section 3.14.3.2.2. Laboratory Visits		
During the laboratory visits, blood samples will be obtained for serum MPA, serum progesterone, and estradiol per the sampling schedule (see Sections 3.3 and 3.4, and Table 1).	During the laboratory visits, blood samples will be obtained for serum MPA, serum progesterone, and estradiol per the sampling schedule (see Sections 3.3 and 3.4, and Table 1).	Clarification.
• obtain blood sample (up to approximately 15 mL) for serum MPA, serum progesterone, and estradiol per the sampling schedule	• obtain blood sample (up to approximately 15 mL) for serum MPA, serum progesterone, and estradiol per the sampling schedule	Clarification.
Blood samples for MPA will be collected and stored for possible future MPA testing (if necessary) any time when samples are collected for serum progesterone and estradiol ~~up until month 12~~, except for pre-treatment visits and visits for confirmation of ovulation.	Blood samples for MPA will be collected and stored for possible future MPA testing (if necessary) any time when samples are collected for serum progesterone and estradiol, except for pre-treatment visits and visits for confirmation of ovulation.	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
3.14.3.2.3. Laboratory Visits after Week 52		
During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol (all visits) and serum MPA (weeks 61 and 74), <u>but not past ovulation. Blood samples for MPA will be collected at all weekly visits after Week 52 and stored for possible future MPA testing (if necessary).</u>	During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol (all visits) and serum MPA (weeks 61 and 74), but not past ovulation. Blood samples for MPA will be collected at all weekly visits after Week 52 and stored for possible future MPA testing (if necessary).	Clarification.
Section 3.14.4.1. Final Visit		
• obtain blood sample for serum MPA (approximately 5 mL) ~~(if previous MPA was completed more than 2 weeks ago)~~ • obtain blood sample for serum progesterone, estradiol (approximately 10 mL), <u>if indicated;</u> and liver function tests (Part 2 only, approximately 5 mL)	• obtain blood sample for serum MPA (approximately 5 mL) • obtain blood sample for serum progesterone, estradiol (approximately 10 mL), if indicated; and liver function tests (Part 2 only, approximately 5 mL)	Clarification.
Section 4.2. Subject Exclusion Criteria		
m. has one or more baseline liver function test(s) outside the local laboratory's normal range <u>(Part 2 only)</u>	m. has one or more baseline liver function test(s) outside the local laboratory's normal range (Part 2 only)	Clarification.
Section 5.3. Prior and Concomitant Medication or Treatment		
• aminoglutethimide • ~~chronic use of systemic glucocorticoids~~ • St. John's wort	• aminoglutethimide • St. John's wort	Correction.

Original text with changes shown	New wording	Reason/Justification for change
Section 6.2.Pharmacodynamics		
During the pre-treatment phase ovulation will be confirmed in all women by measuring progesterone approximately twice a week during the approximately 2 to 3 weeks preceding their expected menses.	During the pre-treatment phase ovulation will be confirmed in all women by measuring progesterone approximately twice a week during the approximately 2 to 3 weeks preceding their expected menses.	Clarification.
Estradiol, an additional pharmacodynamic indicator, will be measured every time progesterone is measured. It will be used to more accurately characterize ovarian function. ~~Before the time period when progesterone is measured weekly, subjects in any group who have an estradiol result of 75 pg/mL or higher (ie, during weeks 2 to 12 or weeks 52 to 78) will be asked to return for weekly progesterone and estradiol testing.~~	Estradiol, an additional pharmacodynamic indicator, will be measured every time progesterone is measured. It will be used to more accurately characterize ovarian function.	Correction.
Section 7. Assessment Of Safety		
In this study, safety will be assessed by qualified study personnel by evaluating the following: vital signs (BP [systolic/diastolic], pulse, and respiration), body weight, adverse events, concomitant medication usage, changes in menstrual bleeding patterns, mood, liver function tests, occurrence of ISRs, and return to ovulation after 12 months after the study drug injection.	In this study, safety will be assessed by qualified study personnel by evaluating the following: vital signs (BP [systolic/diastolic], pulse, and respiration), body weight, adverse events, concomitant medication usage, changes in menstrual bleeding patterns, mood, liver function tests, occurrence of ISRs, and return to ovulation after 12 months after the study drug injection.	Clarification.
Section 7.8.Menstrual Bleeding Patterns		
Study subjects will be asked about changes in their menstrual bleeding patterns, including no bleeding~~,~~ since last assessment, at monthly intervals (in Part 1 only) and during the scheduled follow-up visits in both Part 1 and Part 2 at week 13 (month 3) and week 32 (month 7.5), and at the final study visit.	Study subjects will be asked about changes in their menstrual bleeding patterns, including no bleeding since last assessment, at monthly intervals (in Part 1 only) and during the scheduled follow-up visits in both Part 1 and Part 2 at week 13 (month 3) and week 32 (month 7.5), and at the final study visit.	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
Section 7.12. Assessment Of Acceptability		
Other acceptability questions will include but not be limited to questions about acceptability of the bleeding patterns (only during month 3 and, month 7.5 follow-up visits, and final visits) and other side effects, what she likes and dislikes most about this method, whether she would use this method in the future and/or recommend it to a friend, and whether the schedule of re-injections was acceptable.	Other acceptability questions will include but not be limited to questions about acceptability of the bleeding patterns (only during month 3 and, month 7.5 follow-up visits, and final visit) and other side effects, what she likes and dislikes most about this method, whether she would use this method in the future and/or recommend it to a friend, and whether the schedule of re-injections was acceptable.	Clarification.
Section 8.1.Sample Size and Power Considerations		
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 population pharmacokinetic parameter estimates and rates of return to ovulation observed in Part 1 or interim Part 2 data.	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 population pharmacokinetic parameter estimates and rates of return to ovulation observed in Part 1 or interim Part 2 data.	Clarification.
Section 8.10. Planned Interim Analyses		
There are several planned reviews of the interim data, although their number and timing may change based on the findings.	There are several planned reviews of the interim data, although their number and timing may change based on the findings.	Clarification.
At least ~~The 3rd and 4th~~ two interim reviews are planned to occur in Part 2 (after 50% of subjects ~~in Part 2~~ have completed approximately 4 months and 7.5 months post-injection, respectively). These analyses, ~~and~~ are primarily intended to help inform the decision to move to and the dose selection for a Phase 3 clinical study.. Additional interim analyses of Part 2 data may be conducted if needed to inform potential modifications to the Phase 1 study. The ~~5th and~~ final planned data review will occur when 100% of subjects in Part 2 have completed 7.5 months post-injection (ie, the entire intended dosing interval plus 1.5 months); those data may be	At least two interim reviews are planned to occur in Part 2 (after 50% of subjects have completed approximately 4 months and 7.5 months post-injection, respectively). These analyses are primarily intended to help inform the decision to move to and the dose selection for a Phase 3 clinical study. Additional interim analyses of Part 2 data may be conducted if needed to inform potential modifications to the Phase 1 study. The final planned data review will occur when 100% of subjects in Part 2 have completed 7.5 months post-injection (ie, the	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
submitted to the FDA in the pre Phase 3 submission.	entire intended dosing interval plus 1.5 months); those data may be submitted to the FDA in the pre-Phase 3 submission.	
Section 10.1.2. Protocol Violations		
Protocol violations may include non-adherence on the part of the subject, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to study drug administration; or use of prohibited medications.	Protocol violations may include non-adherence on the part of the subject, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to study drug administration; or use of prohibited medications.	Correction.
~~When a protocol violation is reported, the sponsor will determine whether to discontinue the subject from the study or permit the subject to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the subject and preserving the integrity of the study.~~ Changes in the inclusion and exclusion criteria of the protocol are not prospectively granted by the sponsor. If investigational center personnel learn that a subject who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol violation. If such subject has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded. Lesser protocol deviations, i.e. those that do not significantly affect subject safety or scientific value of the data, will be recorded in a Protocol Deviation Log. The cumulative Log will be submitted to the responsible IEC/IRB at	Changes in the inclusion and exclusion criteria of the protocol are not prospectively granted by the sponsor. If investigational center personnel learn that a subject who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol violation. If such subject has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded. Lesser protocol deviations, i.e. those that do not significantly affect subject safety or scientific value of the data, will be recorded in a Protocol Deviation Log. The cumulative Log will be submitted to the responsible IEC/IRB at annual reviews.	Correction.

Original text with changes shown	New wording	Reason/Justification for change
annual reviews.		
Section 12.3.1. Sponsor Responsibilities		
The original CRFs will be stored at ~~archived by~~ the respective investigational centers until the end of the study.	The original CRFs will be stored at the respective investigational centers until the end of the study.	Clarification.
Section 14 Reporting and Publication of Results		
FHI 360 will prepare the ~~The sponsor is responsible for the preparation of~~ a clinical study report, in cooperation with the sponsor ~~the FHI 360 coordinating investigator~~. The final report is signed by the sponsor and by the FHI 360 Coordinating Investigator**.**	FHI 360 will prepare the clinical study report, in cooperation with the sponsor. The final report is signed by the sponsor and by the FHI 360 Coordinating Investigator.	Clarification.
When the sponsor generates reports from the data collected in this study for presentation to regulatory authorities ~~or the DSMB~~, drafts will be circulated to the FHI 360 coordinating investigator for comments and suggestions. ~~An endorsement of the final report will be sought from the FHI 360 coordinating investigator.~~	When the sponsor generates reports from the data collected in this study for presentation to regulatory authorities, drafts will be circulated to the FHI 360 coordinating investigator for comments and suggestions.	Clarification.

16.2. Protocol Amendment 03 Dated 27 March 2017

The primary reasons for this amendment are additions. These revisions are considered to be substantial by the sponsor's Authorized Representative. Changes made within the text of the protocol were also made within the synopsis.

Original text with changes shown	**New wording**	**Reason/Justification for change**
Clinical Laboratory and Other Departments and Institutions		
Investigational Center Ethics ~~Committee~~Committees	**Investigational Center Ethics Committees**	Correction.
Chesapeake IRB 6940 Columbia Gateway Drive, Suite 110 Columbia, Maryland 21046 United States of America Comité Ético Científico del Servicio de Salud Metropolitano Central Victoria Subercaseaux #381 Santiago Chile	Chesapeake IRB 6940 Columbia Gateway Drive, Suite 110 Columbia, Maryland 21046 United States of America Comité Ético Científico del Servicio de Salud Metropolitano Central Victoria Subercaseaux #381 Santiago Chile	Addition. Text includes names and addresses of recently added Investigational Center Ethics Committees.
Clinical Laboratory		
Jones Institute for Reproductive Medicine Endocrinology Laboratory 601 Colley Avenue Norfolk, VA 23507 Laboratorios Clinicos PUC - Centro Medico San Joaquin Vicuna Mackenna 4686 Macul Santiago, Chile	Jones Institute for Reproductive Medicine Endocrinology Laboratory 601 Colley Avenue Norfolk, VA 23507 Laboratorios Clinicos PUC - Centro Medico San Joaquin Vicuna Mackenna 4686 Macul Santiago, Chile	Addition. Text includes names and addresses of recently added Central Labs.
Investigational ~~Center~~Centers	**Investigational Centers**	Correction.
Conrad Clinical Research Center Eastern Virginia Medical School [redacted] 601 Colley Avenue Norfolk, VA 23507 Unites States of America Instituto Chileno de Medicina Reproductiva	Conrad Clinical Research Center Eastern Virginia Medical School [redacted] 601 Colley Avenue Norfolk, VA 23507 Unites States of America Instituto Chileno de Medicina Reproductiva	Addition. Text includes names and addresses of recently added Investigational Centers.

Original text with changes shown	New wording	Reason/Justification for change
[redacted] Jose Victorino Lastarria 29 of 101 Santiago Centro, Santiago Chile	[redacted] Jose Victorino Lastarria 29 of 101 Santiago Centro, Santiago Chile	
Clinical Study Protocol		
Countries Planned: United States (US) ~~and~~, Chile, other Latin ~~America~~ (~~American~~ countries pending~~)~~	**Countries Planned:** United States (US) , Chile, other Latin American countries pending	Addition. Text lists the location of additional study sites.
Section 1.4.2. Risks of TV-46046		
While some observational data have suggested an association between the use of Depo-Provera CI and increased risk of HIV acquisition (Morrison et al 2015; Ralph et al 2015; Polis 2016) the data are inconsistent and causality has not been established.	While some observational data have suggested an association between the use of Depo-Provera CI and increased risk of HIV acquisition (Morrison et al 2015; Ralph et al 2015; Polis 2016) the data are inconsistent and causality has not been established.	Reference added.
In light of the inconclusive evidence, the WHO recently revised their Medical Eligibility Criteria for contraceptive use (WHO 2017); per the revised criteria, women at low risk of HIV can continue using all hormonal methods of contraception including DMPA without restriction. Women who are at high risk of HIV, however, can use DMPA if they are informed of the possible increased risk of HIV acquisition among DMPA users, the uncertainty over a causal relationship, and how to minimize their risk of acquiring HIV. ~~The World Health Organization (WHO) and CDC recommend that women at high risk of HIV who choose to use Depo-Provera CI or any other hormonal product should be counseled to use condoms consistently and correctly (WHO 2014).~~	In light of the inconclusive evidence, the WHO recently revised their Medical Eligibility Criteria for contraceptive use (WHO 2017); per the revised criteria, women at low risk of HIV can continue using all hormonal methods of contraception including DMPA without restriction. Women who are at high risk of HIV, however, can use DMPA if they are informed of the possible increased risk of HIV acquisition among DMPA users, the uncertainty over a causal relationship, and how to minimize their risk of acquiring HIV.	Text revised to include the updated WHO Medical Eligibility Criteria for contraceptive use.

Original text with changes shown	New wording	Reason/Justification for change
This FIH study will not recruit women at high risk for HIV, but the information on how to minimize risk of acquiring HIV as well as the ~~However,~~ recommendation to use condoms for protection against HIV and sexually transmitted infections (STIs) will be provided to all subjects in this study.	This FIH study will not recruit women at high risk for HIV, but the information on how to minimize risk of acquiring HIV as well as the recommendation to use condoms for protection against HIV and sexually transmitted infections (STIs) will be provided to all subjects in this study.	Text revised to state that this study will not recruit women at high risk for HIV.
Section 1.8 Location and Duration of Study		
For Part 1, the study is planned to be conducted at 1 to 2 investigational ~~center~~ centers in the US. An additional US-based investigational center ~~may~~ will only be considered if necessary to accomplish enrollment in a timely fashion.	For Part 1, the study is planned to be conducted at 1 to 2 investigational centers in the US. An additional US-based investigational center will only be considered if necessary to accomplish enrollment in a timely fashion.	Addition. The number of study centers increased.
Section 2.2.1 Primary Endpoints (also Sections 2.2.2, 3.1, 3.9, 5.1, and 8.1)		
The primary objective of Part 2 is to evaluate the pharmacodynamics of MPA after a single subcutaneous injection in the abdomen of undiluted TV-46046 at up to 3 dose levels (where pharmacodynamics response is defined as suppression of ovulation determined through serum progesterone concentrations).	The primary objective of Part 2 is to evaluate the pharmacodynamics of MPA after a single subcutaneous injection in the abdomen of undiluted TV-46046 at up to 3 additional dose levels (where pharmacodynamics response is defined as suppression of ovulation determined through serum progesterone concentrations).	Clarification. Text added to state that up to 3 additional dose levels may be evaluated in this study.
Section 2.3.3 Safety Endpoints		
• change in menstrual bleeding patterns • change in mood (Part 2 only) • change in liver function tests (Part 2 only) • use of concomitant medications	• change in menstrual bleeding patterns • change in mood (Part 2 only) • change in liver function tests (Part 2 only) • use of concomitant medications	Safety endpoints added to Part 2 of study.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.1 General Design and Study Schematic Diagram		
An interim pharmacokinetic analysis is planned to inform the decision to move into Part 2 and will be performed after all subjects in treatment group 1 (ie, the first six women receiving undiluted TV-46046) in Part 1 have had a chance to complete at least 4 months (17 weeks) of treatment ~~with additional~~ At that time, available PK data from women in treatment group 2 (ie, the next six women receiving diluted TV-46046) will also be analyzed. Additional assessments will be made if warranted (eg, when 12 women [in both the undiluted and diluted groups] complete 4 months [17 weeks]).	An interim pharmacokinetic analysis is planned to inform the decision to move into Part 2 and will be performed after all subjects in treatment group 1 (ie, the first six women receiving undiluted TV-46046) in Part 1 have had a chance to complete at least 4 months (17 weeks) of treatment. At that time, available PK data from women in treatment group 2 (ie, the next six women receiving diluted TV-46046) will also be analyzed. Additional assessments will be made if warranted (eg, when 12 women [in both the undiluted and diluted groups] complete 4 months [17 weeks]).	Addition. Text added to describe the collection of PK data.
Part 2 will only be implemented if the administration of undiluted TV-46046 (400 mg/mL) in Part 1 demonstrates an appropriate pharmacokinetic profile. Other features of the undiluted drug may also enter the decision-making, including stability, re-suspendability, syringeability and safety.	Part 2 will only be implemented if the administration of undiluted TV-46046 (400 mg/mL) in Part 1 demonstrates an appropriate pharmacokinetic profile. Other features of the undiluted drug may also enter the decision-making, including stability, re-suspendability, syringeability and safety.	Addition. Text added to describe factors that will impact the decision to move into Part 2 of the study.
Enrolled subjects will receive an injection of the study drug and then be followed for at least 12 months (52 weeks) to characterize pharmacodynamics and pharmacokinetics of MPA (ie, 6 months of treatment plus 6 months of post-treatment follow-up), regardless of earlier return to ovulation. ~~Medroxyprogesterone acetate sampling will be extended to 52 weeks from study drug administration among participants with earlier return of ovulation to properly characterize the~~	Enrolled subjects will receive an injection of the study drug and then be followed for at least 12 months (52 weeks) to characterize pharmacodynamics and pharmacokinetics of MPA (ie, 6 months of treatment plus 6 months of post-treatment follow-up), regardless of earlier return to ovulation.	Correction. Text no longer applicable.

Original text with changes shown	New wording	Reason/Justification for change
~~apparent terminal half life of TV-46046.~~		
In addition to frequent laboratory visits to collect blood samples, there will be 3 scheduled follow-up visits: at day 7, month 3 (13 weeks), and month 7.5 (32 weeks) after start of study drug treatment, during which subjects will be weighed and evaluated for ISRs, vital signs, and acceptability ~~(eg,.~~ including responses to questions about injection pain, ISR complaints, and menstrual bleeding patterns~~).~~	In addition to frequent laboratory visits to collect blood samples, there will be 3 scheduled follow-up visits: at day 7, month 3 (13 weeks), and month 7.5 (32 weeks) after start of study drug treatment, during which subjects will be weighed and evaluated for ISRs, vital signs, and acceptability. including responses to questions about injection pain, ISR complaints, and menstrual bleeding patterns.	Correction.
The subject's menstrual bleeding patterns will be obtained by an interview questionnaire at monthly intervals ~~during scheduled laboratory or~~(in Part 1 only), at follow-up visits (~~weeks 13~~month 3 and ~~32~~month 7.5 only~~);~~), and the final study visit.	The subject's menstrual bleeding patterns will be obtained by an interview questionnaire at monthly intervals (in Part 1 only), at follow-up visits (month 3 and month 7.5 only), and the final study visit.	Correction. Text edited to state that an interview questionnaire will be given in Part 1 and weeks changed to months.
In Part 2 only: liver function will be assessed by tabulating and graphing change in liver function tests including but not limited to ALT and AST, from screening to week 13 (month 3), week 32 (month 7.5), and final study visit. In Part 2 only: mood will be assessed in frequency tables at screening and at week 13 (month 3), week 32 (month 7.5), and final study visits. Information on adverse events and concomitant medicines will be collected throughout the study. The study staff will provide assessment on the ease of the injection.	In Part 2 only: liver function will be assessed by tabulating and graphing change in liver function tests including but not limited to ALT and AST, at screening to week 13 (month 3), week 32 (month 7.5), and final study visit. In Part 2 only: mood will be assessed in frequency tables at screening and at week 13 (month 3), week 32 (month 7.5), and final study visits. Information on adverse events and concomitant medicines will be collected throughout the study. The study staff will provide assessment on the ease of the injection.	Added to describe the addition of liver function and mood test in Part 2 of the study.
Up to 4 additional investigational centers will be added for Part 2 including Eastern Virginia Medical School in the US and Instituto Chileno	Up to 4 additional investigational centers will be added for Part 2 including Eastern Virginia Medical School in the US and Instituto	Addition. Text added to list additional investigational centers.

Original text with changes shown	New wording	Reason/Justification for change
de Medicina Reproductiva (ICMER) in Chile.	Chileno de Medicina Reproductiva (ICMER) in Chile.	
Figure 2 Overall Study Schematic Diagram		
X.X=will be determined on the basis of Part 1 results. Part 2 will include from 1 to 3 groups, depending on Part 1 results.	X.X=will be determined on the basis of Part 1 results. Part 2 will include up to 3 additional groups, depending on Part 1 results.	Addition. Text added to state Part 2 will include up to 3 additional groups.
Section 3.5 Safety Measures and Time Points		
• data on menstrual bleeding pattern by interview monthly~~,~~ (in Part 1 only), as well as at the week 13 (month 3~~)and~~), week 32 (month 7.5~~)~~), and final visits • in Part 2 only: – in addition to the scheduled and final visits, menstrual bleeding data weekly via an on-line diary – data on mood at the week 13 (month 3), week 32 (month 7.5), and final study ~~visit~~visits – liver function testing at the week 13 (month 3), week 32 (month 7.5), and final study visits	• data on menstrual bleeding pattern by interview monthly (in Part 1 only), as well as at the week 13 (month 3), week 32 (month 7.5), and final visits • in Part 2 only: – in addition to the scheduled and final visits, menstrual bleeding data weekly via an on-line diary – data on mood at the week 13 (month 3), week 32 (month 7.5), and final study visits – liver function testing at the week 13 (month 3), week 32 (month 7.5), and final study visits	Addition. Text added to detail measures recorded in Part 1 and Part 2.
Section 3.7. Randomization		
In Part 2 (dose-range finding), from 1 to 3 doses will be studied, depending on the interim results of Part 1.	In Part 2 (dose-range finding), from up to 3 additional doses will be studied, depending on the interim results of Part 1.	Addition. Text added to state the number of doses to be included in Part 2.
The treatment allocation ratio will depend on the number of doses selected for study, and whether or not	The treatment allocation ratio will depend on the number of doses selected for study, and whether or not	Addition. Text added to detail treatment allocation.

Original text with changes shown	New wording	Reason/Justification for change
the 120 mg dose of undiluted TV-46046 is selected for inclusion.	the 120 mg dose of undiluted TV-46046 is selected for inclusion.	
~~If yes~~If only one dose is selected for Part 2, no randomization will be done. If more than one dose is selected, including the 120 mg dose, then up to 12 subjects will be randomized to ~~the 120 mg dose~~ that group, and up to 18 subjects will be randomized to each of the other ~~2~~ selected treatment groups ~~in a 2:3:3 allocation ratio.~~.	If only one dose is selected for Part 2, no randomization will be done. If more than one dose is selected, including the 120 mg dose, then up to 12 subjects will be randomized to that group, and up to 18 subjects will be randomized to each of the other selected treatment groups.	Addition. Text added to describe randomization.
If the 120 mg dose is not selected for inclusion in Part 2 then the allocation ratio will be ~~1:1:~~balanced (1:1 or 1:1:1) at each investigational center, with up to 18 subjects randomized to each treatment group.	If the 120 mg dose is not selected for inclusion in Part 2 then the allocation ratio will be balanced (1:1 or 1:1:1) at each investigational center, with up to 18 subjects randomized to each treatment group.	Addition. Text added to describe randomization.
In addition, 2 subjects with a body mass index (BMI) ≥40 ~~(preferably in a single investigational center)~~ will be separately randomized into each treatment group (equaling a total of 20 subjects in each treatment group in Part 2) for exploratory analyses of the effect of extreme obesity on pharmacokinetics of MPA.	In addition, 2 subjects with a body mass index (BMI) ≥40 will be separately randomized into each treatment group (equaling a total of 20 subjects in each treatment group in Part 2) for exploratory analyses of the effect of extreme obesity on pharmacokinetics of MPA.	Correction. Text no longer applicable.
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.	However, enrollment 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.	Correction. Enrollment may be expanded in Part 1 or 2.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.11. Duration of Subject Participation and Justification		
~~Minimal~~If Part 2 of the study is not initiated, minimal participation in Part 1 of the study may be as short as ~~is~~ approximately ~~13~~7 months ~~(56~~ , or 30 weeks~~)~~ (approximately 1 month of pre-treatment and ~~approximately 12~~6 months of treatment~~), if Part 2 of the study is not initiated.~~).	If Part 2 of the study is not initiated, minimal participation in Part 1 of the study may be as short as approximately 7 months, or 30 weeks (approximately 1 month of pre-treatment and 6 months of treatment).	Clarification. Minimal time for study participation is defined.
Section 3.12. Stopping Rules and Discontinuation Criteria		
This determination is intended to be made after all subjects enrolled in treatment group 1 of Part 1 (ie, 6 subjects receiving undiluted TV-46046) have had a chance to complete at least 4 months (17 weeks) of follow-up, but the timing may be modified based on accumulating data~~.~~ (eg, additional review of the data for all 12 women [in both undiluted and diluted groups] when they complete 4 months [17 weeks] may be needed).	This determination is intended to be made after all subjects enrolled in treatment group 1 of Part 1 (ie, 6 subjects receiving undiluted TV-46046) have had a chance to complete at least 4 months (17 weeks) of follow-up, but the timing may be modified based on accumulating data (eg, additional review of the data for all 12 women [in both undiluted and diluted groups] when they complete 4 months [17 weeks] may be needed).	Addition. Text added to explain that an additional review of the data may occur after all 12 subjects have completed 4 months of treatment.
Section 3.13. Source Data Recorded on the Case Report Form		
Subject data should have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF; data will not be recorded directly on the CRF and considered as source data unless ~~the sponsor~~FHI 360 provides written instructions specifying which data are permitted to be recorded directly to the CRF (eg, subject's responses to interview questions about menstrual bleeding patterns and acceptability).	Subject data should have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF; data will not be recorded directly on the CRF and considered as source data unless FHI 360 provides written instructions specifying which data are permitted to be recorded directly to the CRF (eg, subject's responses to interview questions about menstrual bleeding patterns and acceptability).	Correction. Change to text indicates that FHI 360 will provide instructions for adding data to the CRF.
If data are processed from other institutions or means (eg, clinical laboratory, central image center, or	If data are processed from other institutions or means (eg, clinical laboratory, central image center, or	Correction. Text changed to reflect the use of an online data diary. Data may be

Original text with changes shown	New wording	Reason/Justification for change
~~electronic~~ on-line diary data), the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically ~~to the sponsor (or organization performing data management)~~ FHI 360 for direct entry into the clinical database (see Section 12.1).	on-line diary data), the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to FHI 360 for direct entry into the clinical database (see Section 12.1).	forwarded to FHI 360.
Hemoglobin, liver function testing, progesterone, and estradiol testing will be conducted at the local laboratories and made available to source verify.	Hemoglobin, liver function testing, progesterone, and estradiol testing will be conducted at the local laboratories and made available to source verify.	Addition. Liver function testing included with testing to be performed at local labs.
Table 1. Study Procedures and Assessment (Parts 1 and 2)		
Demographics and baseline characteristics ~~Physical examination~~ Height	Demographics and baseline characteristics Height	Row removed from table.
Liver Function Testing (Part 2 only)	Liver Function Testing (Part 2 only)	Test added to table.
Mood evaluation (Part 2 only)	Mood evaluation (Part 2 only)	Evaluation added to table.
[i]During the follow-up visits, blood samples for MPA will be collected at days 1, 2, 3, 5, 7, 10, 12, 14, 18, 20, 28, 35, and 42; then at weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52 ~~(in Part 1).~~.	[i]During the follow-up visits, blood samples for MPA will be collected at days 1, 2, 3, 5, 7, 10, 12, 14, 18, 20, 28, 35, and 42; then at weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52.	Correction. Footnote corrected to indicate that blood sampling is not limited to Part 1.
[m]Liver function testing and mood evaluation will be evaluated at screening, week 13, week 32 and the final visit only	[m]Liver function testing and mood evaluation will be evaluated at screening, week 13, week 32 and the final visit only	Addition. Footnote added to clarify that liver function testing and mood evaluation will be evaluated at t screening, week 13, week 32 and the final visit only

Original text with changes shown	New wording	Reason/Justification for change
[n]In Part 1, m~~M~~enstrual bleeding patterns will be obtained by an interview questionnaire ~~at~~ monthly; ~~intervals (during Part 1 only),~~ at scheduled ~~laboratory or~~ follow-up visits (weeks 13 and 32 only); and the final study visit. In addition, in Part 2 menstrual data will be collected weekly via an on-line diary.	[n]In Part 1, menstrual bleeding patterns will be obtained by an interview questionnaire monthly; at scheduled follow-up visits (weeks 13 and 32 only); and the final study visit. In addition, in Part 2 menstrual data will be collected weekly via an on-line diary.	Addition. Text added to footnote to indicate that an on-line diary will be used to reflect menstrual data.
Section 3.14.1 Procedures Before Study Drug Treatment		
Women who sign the informed consent form will be assigned a participant number and have a screening interview to obtain the following: medical history and demographic information, breast examination, blood sample for hemoglobin and liver function, height, weight, and vital signs measurements (BP, pulse, and respiration) and an interview about mood.	Women who sign the informed consent form will be assigned a participant number and have a screening interview to obtain the following: medical history and demographic information, breast examination, blood sample for hemoglobin and liver function, height, weight, and vital signs measurements (BP, pulse, and respiration) and an interview about mood.	Addition. Mood change interview and liver function testing added.
~~• perform physical examination to:~~ • measure vital signs (BP~~,~~ ~~heart rate~~ [systolic/diastolic], pulse, and respiration)	• measure vital signs (BP [systolic/diastolic], pulse, and respiration)	Addition. Vital signs measured before treatment listed.
• interview about mood (Part 2 only) • obtain a blood sample for liver function testing (approximately 5 mL; Part 2 only)	• interview about mood (Part 2 only) • obtain a blood sample for liver function testing (approximately 5 mL; Part 2 only)	Addition. Mood change interview and liver function testing added.
Section 3.14.3.1. Enrollment (injection) Visit (Day 0)		
The ~~pharmacist~~study staff member will prepare the assigned study drug for injection according to the dilution procedures, and, unless s/he is the one	The study staff member will prepare the assigned study drug for injection according to the dilution procedures, and, unless s/he is the one	Correction.

Original text with changes shown	New wording	Reason/Justification for change
administering the injection, pass it to the study staff who will inject the study drug subcutaneously in the fatty tissue over the abdomen while shielding the study drug injection from the subject's sight, as described in Section 5.1.	administering the injection, pass it to the study staff who will inject the study drug subcutaneously in the fatty tissue over the abdomen while shielding the study drug injection from the subject's sight, as described in Section 5.1.	
• confirm eligibility • ~~perform physical examination to:~~ • measure vital signs (BP [systolic/diastolic], pulse, and respiration)	• confirm eligibility • measure vital signs (BP [systolic/diastolic], pulse, and respiration)	Correction.
• (prior to injection) obtain a blood sample (approximately 15 mL) for serum MPA, serum progesterone and, estradiol	• (prior to injection) obtain a blood sample (approximately 15 mL) for serum MPA, serum progesterone and, estradiol	Addition. Volume of blood sample collected in Part 2 added.
Section 3.14.3.2.1. Scheduled Follow-up Visits (Day 7, Month 3 and Month 7.5)		
~~A physical examination will be performed including measurement~~ Measurement of vital signs and body weight will be performed. Subjects will be asked if they experienced any medical problems or took any medications since the previous report.	Measurement of vital signs and body weight will be performed. Subjects will be asked if they experienced any medical problems or took any medications since the previous report.	Correction.
In Part 1, m~~M~~enstrual bleeding patterns and acceptability will be evaluated through an interview questionnaire. For Part 2, menstrual bleeding patterns will be evaluated through on-line diaries; mood and acceptability will be evaluated through an interview administered questionnaire.	In Part 1, menstrual bleeding patterns and acceptability will be evaluated through an interview questionnaire. For Part 2, menstrual bleeding patterns will be evaluated through on-line diaries; mood and acceptability will be evaluated through an interview administered questionnaire.	Addition. Details describing evaluation of menstrual bleeding patterns added to section.

Original text with changes shown	New wording	Reason/Justification for change
• ~~perform physical examination to:~~ • measure vital signs (BP [systolic/diastolic], pulse, and respiration)	• measure vital signs (BP [systolic/diastolic], pulse, and respiration)	Correction.
• obtain blood sample (approximately 15 mL) for serum MPA, serum progesterone, and estradiol	• obtain blood sample (approximately 15 mL) for serum MPA, serum progesterone, and estradiol	Addition. Volume of blood sample collected in Part 2
• obtain blood sample (approximately 5 mL) for liver function tests (month 3 and month 7.5, Part 2 only)	• obtain blood sample (approximately 5 mL) for liver function tests (month 3 and month 7.5, Part 2 only)	Addition. Liver function test added
• interview about mood (month 3 and month 7.5, Part 2 only)	interview about mood (month 3 and month 7.5, Part 2 only)	Addition. Interview about mood will be conducted during visit.
• interview about menstrual bleeding pattern (month 3 and month 7.5 only; Part 1 only)	• interview about menstrual bleeding pattern (month 3 and month 7.5 only; Part 1 only)	Addition. Interview about menstrual bleeding patterns will be conducted during visit in Part 1 only.
• interview about menstrual bleeding pattern ~~(~~once monthly (Part 1 only)	• interview about menstrual bleeding pattern once monthly (Part 1 only)	Addition. Interview about menstrual bleeding patterns will be conducted during visit in Part 1 only.
Section 3.14.4.1 Final Visit		
• obtain blood sample for serum progesterone~~and,~~ estradiol (approximately 10 mL), and liver function tests (Part 2 only, approximately 5 mL)	• obtain blood sample for serum progesterone, estradiol (approximately 10 mL), and liver function tests (Part 2 only, approximately 5 mL)	Addition. Volume of blood sample collected in Part 2 and liver function test added.
• interviews about mood	• interviews about mood	Addition. Interview about mood will be

Original text with changes shown	New wording	Reason/Justification for change
(Part 2 only) and menstrual bleeding pattern.	(Part 2 only) and menstrual bleeding pattern.	conducted during visit.
Section 4.2. Subject Exclusion Criteria		
b. has current ~~and~~ or history of ischemic heart disease	b. has current or history of ischemic heart disease	Correction.
l. has severe cirrhosis (decompensated) or liver tumors m. has one or more baseline liver function test(s) outside the local laboratory's normal range	l. has severe cirrhosis (decompensated) or liver tumors m. has one or more baseline liver function test(s) outside the local laboratory's normal range	Exclusion criteria added
k. has current or history of cervical cancer ~~l. has severe cirrhosis (decompensated)~~ ~~m. has liver tumors~~	k. has current or history of cervical cancer	Exclusion criteria removed
o. history of diagnosed clinical depression or bipolar disorder, with or without suicidal ideation, and/or history of suicide attempt p. in last two years, history of either hospitalization or medication management for psychiatric disorder that in the opinion of the investigator would make study participation unsafe, would interfere with adherence to study requirements or complicate data interpretation	o. history of diagnosed clinical depression or bipolar disorder, with or without suicidal ideation, and/or history of suicide attempt p. in last two years, history of either hospitalization or medication management for psychiatric disorder that in the opinion of the investigator would make study participation unsafe, would interfere with adherence to study requirements or complicate data interpretation	Exclusion criteria added
~~o. has history of medical treatment for clinical depression~~ p.used DMPA products (Depo-Provera CI or Depo-subQ Provera 104) in the past 12 months	q.used DMPA products (Depo-Provera CI or Depo-subQ Provera 104) in the past 12 months	Exclusion criteria removed
y. in the opinion of the investigator, potentially at elevated risk of HIV infection (eg, HIV-positive	y. in the opinion of the investigator, potentially at elevated risk of HIV infection (eg, HIV-positive partner,	Exclusion criteria added

Original text with changes shown	New wording	Reason/Justification for change
partner, IV drug use by self or by partner)	IV drug use by self or by partner)	
Section 5.1.1 Dilution Procedure of TV-46046		
Diluted TV-46046 will be prepared by the investigational center pharmacist or other trained study staff member	Diluted TV-46046 will be prepared by the investigational center pharmacist or other trained study staff member	Addition. Other trained staff can now prepare diluted TV-46046.
Table 2 Approximate Blood Volume		
Liver Function	Liver Function	Addition. Liver function test added to table listing total blood volumes collected.
about 5	about 5	Addition. Approximate volume of blood collected for liver function test.
4	4	Addition. Approximate number of samples collected liver function tests.
~20	~20	Addition. Approximate total volume of blood collected for liver function tests.
~~117~~**121**	~**121**	Addition. Increase in total number of samples collected.
~~909~~**924**	~**924**	Addition. Increase in total volume of blood collected.
Section 6.1.4. Shipment and Analysis of Samples		
~~Computer print outs will serve as source~~ Source documentation for ~~the~~MPA ~~data and~~ will be ~~stored by~~ maintained at PPD ~~and available for clinical monitoring if needed.~~.	Source documentation for MPA will be maintained at PPD.	Clarification. Location of source documentation stated.
Section 6.2 Pharmacodynamics		
Detailed instructions on how to draw and prepare serum samples for	Detailed instructions on how to draw and prepare serum samples for	Addition. Text added to describe progesterone and estradiol sampling

Original text with changes shown	New wording	Reason/Justification for change
progesterone and estradiol analysis and liver function analysis (Part 2 only) will be investigational center-specific and provided in the laboratory SOPs and/or Study Manual.	progesterone and estradiol analysis and liver function analysis (Part 2 only) will be investigational center-specific and provided in the laboratory SOPs and/or Study Manual.	and liver function analysis.
Briefly, blood samples for progesterone and estradiol (up to 10 mL) will be collected via venipuncture, centrifuged, and then transferred into 2 aliquots.	Briefly, blood samples for progesterone and estradiol (up to 10 mL) will be collected via venipuncture, centrifuged, and then transferred into 2 aliquots.	Addition. Text added to state how much blood will be collected for progesterone and estradiol sampling.
Collection and movement of progesterone and estradiol samples will be recorded on appropriate study CRFs and/or tracking tools.	Collection and movement of progesterone and estradiol samples will be recorded on appropriate study CRFs and/or tracking tools.	Addition. Text added to state how estradiol sampling will be recorded.
In Part 2 blood samples for liver function analysis (up to 5 mL) will be collected via venipuncture, centrifuged and then transferred to one aliquot for analysis.	In Part 2 blood samples for liver function analysis (up to 5 mL) will be collected via venipuncture, centrifuged and then transferred to one aliquot for analysis.	Addition. Liver function analysis detailed.
Section 7.1.4. Relationship of an Adverse Event to the Study Drug		
The relationship of an adverse event to the study drug is characterized as follows and will be determined by Teva:	The relationship of an adverse event to the study drug is characterized as follows and will be determined by Teva:	Clarification. Text added to explain that Teva will determine the relationship of an adverse event to the study drug.
Section 7.4 Clinical Laboratory Tests		
Liver function testing including, but not limited to, ALT and AST will be performed in Part 2 only by the investigational center laboratory at the screening visit, as well as at the month 3, month 7.5 and final visits. Detailed instructions on how to draw and prepare samples for liver function testing will be investigational center-specific and provided in the laboratory SOPs and/or Study Manual.	Liver function testing including, but not limited to, ALT and AST will be performed in Part 2 only by the investigational center laboratory at the screening visit, as well as at the month 3, month 7.5 and final visits. Detailed instructions on how to draw and prepare samples for liver function testing will be investigational center-specific and provided in the laboratory SOPs and/or Study Manual.	Addition. Liver function testing details included.

Original text with changes shown	New wording	Reason/Justification for change
Section 7.6 Body Weight		
7.6 ~~Physical examinations, including height (to be obtained at the screening and enrollment visits only), body~~ Body Weight	7.6 Body Weight	Correction. Section heading updated.
Body weight~~, and vital signs (see Section 7.5)~~ will be ~~performed~~measured at the time points detailed in Table 1~~,~~ and documented on appropriate study CRF. A standardized protocol for weight measurement will be provided in the study manual.	Body weight will be measured at the time points detailed in Table 1 and documented on appropriate study CRF. A standardized protocol for weight measurement will be provided in the study manual.	Correction. Measurement of vital signs removed from body weight section.
Weight gain or loss will be ~~document~~documented as an adverse event only if reported by the subject.	Weight gain or loss will be documented as an adverse event only if reported by the subject.	Correction.
Section 7.8 Menstrual Bleeding Patterns		
~~Subjects~~Study subjects will be asked about changes in their menstrual bleeding patterns, including no bleeding, since last assessment at monthly intervals (in Part 1 only) and during the scheduled ~~laboratory or~~ follow-up visits at week 13 (month 3) and week 32 (month 7.5), and at the final study visit.	Study subjects will be asked about changes in their menstrual bleeding patterns, including no bleeding, since last assessment at monthly intervals (in Part 1 only) and during the scheduled follow-up visits at week 13 (month 3) and week 32 (month 7.5), and at the final study visit.	Addition. Text added to describe how subjects will record changes in their menstrual bleeding patterns.
Interview items will include date of last bleeding, description of bleeding pattern since last visit, as well as frequency of bleeding, duration of episodes, pain/cramps, and volume, all compared with the pre-study period. The acceptability and tolerability of the bleeding pattern will be queried.	Interview items will include date of last bleeding, description of bleeding pattern since last visit, as well as frequency of bleeding, duration of episodes, pain/cramps, and volume, all compared with the pre-study period. The acceptability and tolerability of the bleeding pattern will be queried.	Addition. Interview topics to describe menstrual bleeding patterns.

Original text with changes shown	New wording	Reason/Justification for change
In addition, in Part 2, subjects will be trained to use and prompted to complete weekly menstrual diaries on-line. On these diaries, subjects will record daily occurrence of no flow, spotting (pantyliner or no protection needed), bleeding (tampons or sanitary pads needed), and pain (none/mild or moderate/severe) for the last seven days. These data will be automatically uploaded into the clinical data base using the OpenClinica Participate module.	In addition, in Part 2, subjects will be trained to use and prompted to complete weekly menstrual diaries on-line. On these diaries, subjects will record daily occurrence of no flow, spotting (pantyliner or no protection needed), bleeding (tampons or sanitary pads needed), and pain (none/mild or moderate/severe) for the last seven days. These data will be automatically uploaded into the clinical data base using the OpenClinica Participate module.	Addition. Text added to describe how subjects will record changes in their menstrual bleeding patterns.
Section 7.9 Mood Changes		
In Part 2, subjects will be interviewed about aspects of and changes in mood at screening and at the scheduled follow-up visits at month 3 and month 7.5, and at the final study visit. To measure depression or psychological distress, a selected validated scale, such as the 10-item Patient Health Questionnaire (PHQ-9) that screens for depression, will ascertain the frequency of a variety of somatic and emotional indicators of well-being and produce an overall score that can be compared at different time points in the study. The PHQ-9 includes items on pleasure in doing things, having little energy, feeling bad about yourself, and having trouble concentrating, among others. The frequency of each indicator is then summed to produce a single overall score for the severity of depression.	In Part 2, subjects will be interviewed about aspects of and changes in mood at screening and at the scheduled follow-up visits at month 3 and month 7.5, and at the final study visit. To measure depression or psychological distress, a selected validated scale, such as the 10-item Patient Health Questionnaire (PHQ-9) that screens for depression, will ascertain the frequency of a variety of somatic and emotional indicators of well-being and produce an overall score that can be compared at different time points in the study. The PHQ-9 includes items on pleasure in doing things, having little energy, feeling bad about yourself, and having trouble concentrating, among others. The frequency of each indicator is then summed to produce a single overall score for the severity of depression.	Addition. Text added to describe the evaluation of mood changes over the course of the study.
Section 8.1 Sample Size and Power Considerations		
Scientific judgment will be used to determine if the sample size in Part 2 can be reduced from 20 subjects per	Scientific judgment will be used to determine if the sample size in Part 2 can be reduced from 20 subjects per	Correction. Text no longer applicable.

Original text with changes shown	New wording	Reason/Justification for change
group~~to 12 or 15 subjects per treatment group~~, depending on the variability of population pharmacokinetic parameter estimates observed in Part 1.	group, depending on the variability of population pharmacokinetic parameter estimates observed in Part 1.	
Section 8.5.3. Planned Method of Analysis		
There are 5 planned reviews of the interim data; 2 reviews in Part 1 and 3 reviews in Part 2,although their number and timing may change based on the findings	There are 5 planned reviews of the interim data; 2 reviews in Part 1 and 3 reviews in Part 2, although their number and timing may change based on the findings	Addition. Text added to explain that the timing of interim data reviews may change over the course of the study.
Section 8.8.2. Safety Analysis		
The percentage of women experiencing amenorrhea or other menstrual bleeding disturbances (irregular bleeding or spotting) will be assessed at monthly intervals during scheduled laboratory ~~or~~visits (in Part 1 only) and at follow-up visits ~~(~~at week 13 and week 32 only~~)~~, and the final study visit.	The percentage of women experiencing amenorrhea or other menstrual bleeding disturbances (irregular bleeding or spotting) will be assessed at monthly intervals during scheduled laboratory visits (in Part 1 only) and at follow-up visits at week 13 and week 32 only, and the final study visit.	Clarification. Text edited to state when assessments for amenorrhea or other menstrual bleeding disturbances will occur.
In addition, in Part 2 weekly self-reported menstrual data will be assessed, and compared between treatment groups ~~for the Treated Populations in Part 1 and Part 2. Likewise, vital~~ using frequency tables; details are found in the Statistical Analysis Plan. In Part 2 only, liver function tests, including but not limited to ALT and AST, will be assessed by tabulating and graphing change from screening to week 13 (month 3), week 32 (month 7.5), and final study visit data. In Part 2 only mood will be assessed in frequency tables at screening and at week 13 (month 3), week 32 (month 7.5), and final study visits.	In addition, in Part 2 weekly self-reported menstrual data will be assessed, and compared between treatment groups using frequency tables; details are found in the Statistical Analysis Plan. In Part 2 only, liver function tests, including but not limited to ALT and AST, will be assessed by tabulating and graphing change from screening to week 13 (month 3), week 32 (month 7.5), and final study visit data. In Part 2 only mood will be assessed in frequency tables at screening and at week 13 (month 3), week 32 (month 7.5), and final study visits.	Addition. Text added to describe additional safety assessments.

Original text with changes shown	New wording	Reason/Justification for change
Vital signs and body weight will be summarized graphically and using shift-tables, by investigational center and treatment group.	Vital signs and body weight will be summarized graphically and using shift-tables, by investigational center and treatment group.	Correction.
Section 8.10. Planned Interim Analysis		
At that time, available PK data from women in treatment group 2 (ie, the next six women receiving diluted TV-46046) will also be analyzed. Additional assessments will be made if warranted (eg, when the 12 women in both the undiluted and diluted groups complete 4 months (17 weeks)). Other features of the undiluted drug may also be considered in the decision-making process, including stability, re-suspendability, syringeability, and safety, although these will not be part of the formal analysis.	At that time, available PK data from women in treatment group 2 (ie, the next six women receiving diluted TV-46046) will also be analyzed. Additional assessments will be made if warranted (eg, when the 12 women in both the undiluted and diluted groups complete 4 months (17 weeks)). Other features of the undiluted drug may also be considered in the decision-making process, including stability, re-suspendability, syringeability, and safety, although these will not be part of the formal analysis.	Addition. Text added to describe other formulation features that may impact the decision-making process.
Section 9. Direct Access To Source Data/Documents		
Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, ~~diary data, protocol required worksheets,~~ and CRFs that are used as the source (see Section 3.13).	Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, and CRFs that are used as the source (see Section 3.13).	Correction. Text no longer applicable.
Section 12.1. Data Collection		
~~Data~~Most data will be collected using 1-ply CRFs that are specifically designed for this study.	Most data will be collected using 1-ply CRFs that are specifically designed for this study.	Clarification. Text edited to describe collection of data.
In Part 2 only data on menstrual bleeding will be collected weekly using a validated, Part 11-compliant on-line application of OpenClinica, the clinical	In Part 2 only data on menstrual bleeding will be collected weekly using a validated, Part 11-compliant on-line application of OpenClinica,	Addition. Text added to describe collection of weekly bleeding data.

Original text with changes shown	New wording	Reason/Justification for change
data management system. Women will be prompted by text message or e-mail to access the website and submit answers to a brief question set. These data will be entered automatically uploaded into the OpenClinica clinical database.	the clinical data management system. Women will be prompted by text message or e-mail to access the website and submit answers to a brief question set. These data will be entered automatically uploaded into the OpenClinica clinical database.	
If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center~~, electronic diary data,~~ electronic patient-reported outcome [ePRO] Tablet), the results will be sent to the investigational center, where they will be retained but not entered into the CRF unless otherwise specified in the protocol.	If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic patient-reported outcome [ePRO] Tablet), the results will be sent to the investigational center, where they will be retained but not entered into the CRF unless otherwise specified in the protocol.	Correction.
Section 12.3.1. Sponsor Responsibilities		
All data management tasks for this study are delegated to FHI 360; these functions will be carried out as described in FHI 360 SOPs. ~~These SOPs will be reviewed by the sponsor before the start of data management activities.~~	All data management tasks for this study are delegated to FHI 360; these functions will be carried out as described in FHI 360 SOPs.	Correction.
Section 12.3.2. Investigator Responsibilities		
• data results from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary~~data~~)	• data results from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary)	Correction.
References		
Depo-Provera Contraceptive Injection [package insert]. New York, NY: Pfizer Inc; 201~~5~~6. Depo subQ Provera 104 [package insert]. New York, NY: Pfizer Inc; 201~~5~~6.	Depo-Provera Contraceptive Injection [package insert]. New York, NY: Pfizer Inc; 2016. Depo subQ Provera 104 [package insert]. New York, NY: Pfizer Inc; 2016.	Most recent Prescribing Information referenced.

16.3. Protocol Amendment 02 Dated 04 November 2016

The primary reasons for this amendment are corrections. These changes are unlikely to affect to a significant degree the safety or rights (physical or mental integrity) of the subjects in the clinical study or the scientific value of the clinical study. Changes made within the text of the protocol were also made within the synopsis.

Original text with changes shown	New wording	Reason/Justification for change
Clinical Laboratory And Other Departments And Institutions		
[redacted], ~~Global Clinical Development~~ [redacted], Women's Health Teva Pharmaceutical Industries, Ltd.	[redacted], Women's Health Teva Pharmaceutical Industries, Ltd.	Correction. Study personnel updated.
[redacted] Global Patient Safety & Pharmacovigilance Teva Branded Pharmaceutical Products R&D, Inc. ~~41 Moores Road~~ ~~Frazer~~ 2 West Liberty Blvd, Suite 300 Malvern, Pennsylvania 19355 United States of America	[redacted] Global Patient Safety & Pharmacovigilance Teva Branded Pharmaceutical Products R&D, Inc. 2 West Liberty Blvd, Suite 300 Malvern, Pennsylvania 19355 United States of America	Correction. Study personnel updated.
Clinical Study Protocol Synopsis		
Planned Study Period: ~~July~~ November 2016 (first subject screened) to November 2019 (last subject last visit).	Planned Study Period: November 2016 (first subject screened) to November 2019 (last subject last visit).	Date Corrected
Section 1.1 Introduction		
When compared to Depo-Provera CI, Depo-subQ 104 exhibited a lower average maximum observed ~~plasma/~~ serum drug concentration (C_{max}) (1.56 ng/mL compared to 3.73 ng/mL), a longer mean half-life (43 days compared to 13 days), and lower overall drug exposure (area under the ~~plasma/~~serum drug concentration by-time curve from time 0 to infinity [$AUC_{0-\infty}$] of 92.84 ng•day/mL compared to 134 ng•day/mL) (Jain et al 2004).	When compared to Depo-Provera CI, Depo-subQ 104 exhibited a lower average maximum observed serum drug concentration (C_{max}) (1.56 ng/mL compared to 3.73 ng/mL), a longer mean half-life (43 days compared to 13 days), and lower overall drug exposure (area under the serum drug concentration by-time curve from time 0 to infinity [$AUC_{0-\infty}$] of 92.84 ng•day/mL compared to 134 ng•day/mL) (Jain et al 2004).	Correction. Text updated to reflect literature.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.3.1 Nonclinical Studies		
Published nonclinical pharmacological and toxicological studies from literature, including nonclinical ~~biological~~ pharmacology and toxicology/toxicokinetic activities of DMPA/MPA support the contraception indication, nonclinical pharmacokinetics, and expected safety profile of TV-46046.	Published nonclinical pharmacological and toxicological studies from literature, including nonclinical pharmacology and toxicology/toxicokinetic activities of DMPA/MPA support the contraception indication, nonclinical pharmacokinetics, and expected safety profile of TV-46046.	Correction.
Section 1.3.1.1 Nonclinical Studies Conducted by Teva		
Teva's current nonclinical safety program consists of 4 in vivo nonclinical studies: a Good Laboratory Practice (GLP) female rabbit subcutaneous local tolerance/distant target organ tissue evaluation with long term toxicokinetic study (Study DS-2015-009); a GLP murine local lymph node assay study (Study ~~DS-2014-064)~~DS-2015-017); a non-GLP murine local lymph node assay study (Study DS-2014-064); and a non-GLP female rabbit subcutaneous pharmacokinetic and gross tolerability study (Study DP-2014-135).	Teva's current nonclinical safety program consists of 4 in vivo nonclinical studies: a Good Laboratory Practice (GLP) female rabbit subcutaneous local tolerance/distant target organ tissue evaluation with long term toxicokinetic study (Study DS-2015-009); a GLP murine local lymph node assay study (Study DS-2015-017); a non-GLP murine local lymph node assay study (Study DS-2014-064); and a non-GLP female rabbit subcutaneous pharmacokinetic and gross tolerability study (Study DP-2014-135).	Correction. Text updated to reflect previous studies.
However, the slight increase in the magnitude of effects in the TV-46046 group correlates with the higher MPA exposure levels observed on study, as measured by C_{max} (8.6 ng/mL), area under the ~~plasma/serum~~ plasma drug concentration by time curve from time 0 to day 6 (AUC_{0-6}) (42.6 ng•day/mL), and area under the ~~plasma/serum~~ plasma drug concentration by time curve from time 0 to day 89 (AUC_{0-89}) (504.3 ng•day/mL). No toxic effects were associated with TV-46046 excipients.	However, the slight increase in the magnitude of effects in the TV-46046 group correlates with the higher MPA exposure levels observed on study, as measured by C_{max} (8.6 ng/mL), area under the plasma drug concentration by time curve from time 0 to day 6 (AUC_{0-6}) (42.6 ng•day/mL), and area under the plasma drug concentration by time curve from time 0 to day 89 (AUC_{0-89}) (504.3 ng•day/mL). No toxic effects were associated with TV-46046 excipients.	Correction. Text updated to reflect previous studies.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.3.1.2 Nonclinical Literature		
~~Depo~~ In in vitro genotoxicity studies, ~~Depomedroxyprogesterone acetate (~~DMPA~~)~~/MPA was negative in ~~bacteria~~ bacterial and mammalian somatic ~~cells using a large series of in vitro and in vivo genotoxicity studies~~cell lines.	In in vitro genotoxicity studies, DMPA/MPA was negative in bacterial and mammalian somatic cell lines.	Correction. Text corrected to reflect literature.
Based on the published literature and results of Teva's GLP-compliant nonclinical studies, subcutaneous administration of TV-46046 in humans should have a safety profile similar to that of the FDA-approved Depo-subQ 104.	Based on the published literature and results of Teva's GLP-compliant nonclinical studies, subcutaneous administration of TV-46046 in humans should have a safety profile similar to that of the FDA-approved Depo-subQ 104.	Clarification.
Section 1.8 Location and Duration of Study		
The expected duration of the 2-part study is from ~~July~~ November 2016 (first subject screened) to November 2019 (last subject last visit).	The expected duration of the 2-part study is from November 2016 (first subject screened) to November 2019 (last subject last visit).	Date Corrected
Section 2.3.1 Primary Endpoints (also Sections 2.3.2, 3.3, and 3.4)		
In Part 1 (exploratory pharmacokinetics), the primary endpoints are individual and mean serum MPA concentration-time profiles measured during follow-up visits, and estimated noncompartmental pharmacokinetics parameters, including but not limited to C_{max}, t_{max}, ~~maximum~~ observed ~~plasma/~~serum drug concentration at day 182 (C_{182}), area under the ~~plasma/~~serum drug concentration by time curve from time 0 to day 182 (AUC_{0-182}), $AUC_{0-\infty}$, and apparent terminal half-life.	In Part 1 (exploratory pharmacokinetics), the primary endpoints are individual and mean serum MPA concentration-time profiles measured during follow-up visits, and estimated noncompartmental pharmacokinetics parameters, including but not limited to C_{max}, t_{max}, observed serum drug concentration at day 182 (C_{182}), area under the serum drug concentration by time curve from time 0 to day 182 (AUC_{0-182}), $AUC_{0-\infty}$, and apparent terminal half-life.	Text corrected to indicate that only serum levels will be used to estimate pharmacokinetic and pharmacodynamic parameters.
Section 2.3.2 Secondary Endpoints		
In Part 2, secondary endpoints include pharmacokinetics of MPA based on individual and mean serum MPA concentration-time profiles ~~measured during follow up visits~~ and estimated noncompartmental pharmacokinetics	In Part 2, secondary endpoints include pharmacokinetics of MPA based on individual and mean serum MPA concentration-time profiles and estimated noncompartmental pharmacokinetics parameters,	Correction. Text corrected to indicate that only serum will be collected.

Original text with changes shown	New wording	Reason/Justification for change
parameters, including but not limited to C_{max}, t_{max}, C_{182}, ~~maximum~~ observed ~~plasma~~/serum drug concentration at day 210 (C_{210}), AUC_{0-182}, area under the ~~plasma~~/serum drug concentration by time curve from time 0 to day 210 (AUC_{0-210}), $AUC_{0-\infty}$, and apparent terminal half-life.	including but not limited to C_{max}, t_{max}, C_{182}, observed serum drug concentration at day 210 (C_{210}), AUC_{0-182}, area under the serum drug concentration by time curve from time 0 to day 210 (AUC_{0-210}), $AUC_{0-\infty}$, and apparent terminal half-life.	
Section 3.3 Pharmacokinetic Measures and Time Points		
For Part 1, blood samples for measurement of serum concentrations will be obtained on days 0 (baseline), 1, 2, 3, 5, 7, 10, 12, 14, 18, ~~21~~20; 28, 35, and 42; weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52.	For Part 1, blood samples for measurement of serum concentrations will be obtained on days 0 (baseline), 1, 2, 3, 5, 7, 10, 12, 14, 18, 20; 28, 35, and 42; weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52.	Correction. The 21 day collection time changed to 20.
~~In addition, s~~Subjects for whom ovulation has not returned by month 12 (week 52), blood samples for MPA will be collected up to 2 more times (once at week 61 ~~and 65~~ and once at~~more~~ week 74 ~~and78~~), but not past return to ovulation.	Subjects for whom ovulation has not returned by month 12 (week 52), blood samples for MPA will be collected up to 2 more times (once at week 61 and once at week 74), but not past return to ovulation.	Clarification to explain when sampling will occur in subjects for whom ovulation has not returned by month 12 (week 52)
In addition, blood samples will also be collected and stored for possible future MPA testing (if necessary) ~~any time~~ at all weekly visits up to 12 months when samples are collected for serum progesterone and estradiol, except for pre-treatment visits and visits for confirmation of ovulation.	In addition, blood samples will also be collected and stored for possible future MPA testing (if necessary) a at all weekly visits up to 12 months when samples are collected for serum progesterone and estradiol, except for pre-treatment visits and visits for confirmation of ovulation.	Correction
Section 3.11 Duration of Subject Participation and Justification		
Minimal participation in the study is approximately ~~7~~13 months (~~30~~56 weeks) (approximately 1 month of pre-treatment and approximately ~~6~~12 months of treatment), if Part 2 of the study is not initiated.	Minimal participation in the study is approximately 13 months (56 weeks) (approximately 1 month of pre-treatment and approximately 12 months of treatment), if Part 2 of the study is not initiated	Corrected to lengthen minimal participation period.
Section 3.12 Stopping Rules and Discontinuation Criteria		
Others reasons the study may be stopped include: • The sponsor decides to reduce the scope (eg, reduce sample size, drop one or more study	Others reasons the study may be stopped include: • The sponsor decides to reduce the scope (eg, reduce sample size, drop one or more study	Text added to clarify the role of the sponsor and FHI 360 and present reasons for early termination of the study.

Original text with changes shown	New wording	Reason/Justification for change
groups) or discontinue the study (eg, due to noncompliance with protocol or regulatory requirements, feasibility, etc.). • FHI 360's Protection of Human Subjects Committee (PHSC) recommends to terminate the study • Local IRB(s) recommend to terminate the study • The FDA requests that the study be discontinued or placed on hold	groups) or discontinue the study (eg, due to noncompliance with protocol or regulatory requirements, feasibility, etc.). • FHI 360's Protection of Human Subjects Committee (PHSC) recommends to terminate the study • Local IRB(s) recommend to terminate the study • The FDA requests that the study be discontinued or placed on hold	
Section 3.14.1. Procedures Before Study Drug Treatment		
• perform physical examination to: measure BP, heart rate, and respiration measure body weight and height to estimate BMI	• perform physical examination to: measure BP, heart rate, and respiration measure body weight and height to estimate BMI	Revision to presentation.
Section 3.14.2 Pretreatment		
Subjects who meet the inclusion/exclusion criteria at screening visit will return to the clinic twice a week (preferably 3 days apart) during the 2 to 3 weeks preceding their next expected menses (4 to 6 times) for serum progesterone and estradiol measurements to confirm ovulation. They will also have a mammogram scheduled during this time if they have not had a mammogram within the last 12 months during Part 1 only.	Subjects who meet the inclusion/exclusion criteria at screening visit will return to the clinic twice a week (preferably 3 days apart) during the 2 to 3 weeks preceding their next expected menses (4 to 6 times) for serum progesterone and estradiol measurements to confirm ovulation. They will also have a mammogram scheduled during this time if they have not had a mammogram within the last 12 months during Part 1 only.	Text added to state that subjects will have a mammogram scheduled if they have not had one within the last 12 months.
Section 3.14.3.1. Enrollment (Injection) Visit (Day 0) (also Section 3.14.3.2.1, Section 3.14.4.1)		
•perform physical examination to: •~~perform~~ measure vital signs ~~measurement~~(BP [systolic/diastolic], pulse, and respiration)	•perform physical examination to: measure vital signs measurement (BP [systolic/diastolic], pulse, and respiration)	Typo.
Section 3.14.3.2.1. Scheduled Follow-up Visits (Day 7, Month 3, and Month 7.5)		
•perform physical examination to: measure vital signs ~~measurement~~ (BP	• perform physical examination to: measure vital signs measurement	Typo

Original text with changes shown	New wording	Reason/Justification for change
[systolic/diastolic], pulse, and respiration) measure body weight	(BP [systolic/diastolic], pulse, and respiration) measure body weight	
•interview about menstrual bleeding pattern (month 3 and month 7.5 only)	• interview about menstrual bleeding pattern (month 3 and month 7.5 only)	Clarification to explain when interviewing will occur.
Section 3.14.3.2.2. Laboratory Visits		
Blood samples for MPA will be collected and stored for possible future MPA testing (if necessary) any time when samples are collected for serum progesterone and estradiol up until Month 12, except for pre-treatment visits and visits for confirmation of ovulation.	Blood samples for MPA will be collected and stored for possible future MPA testing (if necessary) any time when samples are collected for serum progesterone and estradiol up until Month 12, except for pre-treatment visits and visits for confirmation of ovulation.	Text moved to month 12 section.
Section 3.14.3.2.3. Laboratory Visits after Week 52		
During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol (all visits) and serum MPA (weeks 61~~5~~ and 74~~8~~).~~Blood samples for MPA will be collected and stored for possible future MPA testing (if necessary) any time when samples are collected for serum progesterone and estradiol.~~	During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol (all visits) and serum MPA (weeks 61 and 74).	Text revised to replicate collection times in similar studies.
Table 1: Study Procedures and Assessments (Parts 1 and 2)		
Mammogram[n]	Mammogram[n]	Added
g. During the follow-up laboratory visits, blood samples for serum progesterone and estradiol will be collected at weeks 1, 2, 4, 6, 8, 10, and 12; then weekly through week ~~32~~52. ~~If ovulation does not return by week 32, then weekly blood samples for serum progesterone and estradiol will continue to be collected until ovulation or through week 52, whichever is earlier.~~	g. During the follow-up laboratory visits, blood samples for serum progesterone and estradiol will be collected at weeks 1, 2, 4, 6, 8, 10, and 12; then weekly through week 52.	Correction. Text revised to replicate collection times in similar studies.
g. During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol (all visits) and serum MPA	g. During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol (all visits) and serum MPA	Correction. Text revised to replicate collection times in similar studies.

Original text with changes shown	New wording	Reason/Justification for change
(weeks ~~65~~61 and ~~78~~74).	(weeks 61 and 74).	
i. During the follow-up visits, blood samples for MPA will be collected at days 1, 2, 3, 5, 7, 10, 12, 14, 18, 20~~1~~, 28, 35, and 42; then at weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52 (in Part 1). Among subjects in whom ovulation does not return by week 52, blood samples for MPA will be collected up to 2 more times (at weeks 61~~5~~ and 74~~8~~), but not past return to ovulation. Blood samples will also be collected and stored for possible future MPA testing (if necessary) at all weekly visits up to 12 months ~~any time~~ when samples are collected for serum progesterone and estradiol, except for pre-treatment visits and visits for confirmation of ovulation.	i. During the follow-up visits, blood samples for MPA will be collected at days 1, 2, 3, 5, 7, 10, 12, 14, 18, 20, 28, 35, and 42; then at weeks 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days until week 52 (in Part 1). Among subjects in whom ovulation does not return by week 52, blood samples for MPA will be collected up to 2 more times (at weeks 61 and 74), but not past return to ovulation. Blood samples will also be collected and stored for possible future MPA testing (if necessary) at all weekly visits up to 12 months when samples are collected for serum progesterone and estradiol, except for pre-treatment visits and visits for confirmation of ovulation.	Correction. Text revised to replicate collection times in similar studies.
n. Part 1 only	n. Part 1 only	Footnote added to state that subjects will have a mammogram scheduled if they have not had one within the last 12 months during Part 1 only.
Section 3.14.3.2.1 Scheduled Follow-up Visits (Day 7, Month 3, and Month 7.5)		
interview about menstrual bleeding pattern (month 3 and month 7.5 only)	interview about menstrual bleeding pattern (month 3 and month 7.5 only)	Clarification. Text added to indicate that this interview will only take place during the 3 and 7.5 month visit.
Section 3.14.3.2.2 Laboratory Visits		
Blood samples for MPA will be collected and stored for possible future MPA testing (if necessary) any time when samples are collected for serum progesterone and estradiol up until Month 12, except for pre-treatment visits and visits for confirmation of ovulation.	Blood samples for MPA will be collected and stored for possible future MPA testing (if necessary) any time when samples are collected for serum progesterone and estradiol up until Month 12, except for pre-treatment visits and visits for confirmation of ovulation.	Clarification. Text moved from Section 3.14.3.2.3 and added to define the amount of time blood samples will be stored for MPA testing.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.14.3.2.3 Laboratory Visits after Week 52		
During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol (all visits) and serum MPA (weeks 61~~5~~ and 74~~8~~).~~Blood samples for MPA will be collected and stored for possible future MPA testing (if necessary) any time when samples are collected for serum progesterone and estradiol.~~	During these additional laboratory visits, blood samples will be collected and tested for serum progesterone and estradiol (all visits) and serum MPA (weeks 61 and 74).	Correction. Text revised to replicate collection times in similar studies.
Section 3.14.4.1. Final Visit		
• <u>perform physical examination to:</u> measure body weight ~~perform~~ measure vital signs ~~measurement~~ (BP [systolic/diastolic], pulse, and respiration)	• perform physical examination to: measure body weight measure vital signs (BP [systolic/diastolic], pulse, and respiration)	Correction.
Section 4.1 Subject Inclusion		
h. has a BMI of 18.~~0~~ to ~~30.0~~ 35, inclusive, (unless included in subset of subjects with extreme obesity (BMI ≥40), 2 in each dose-range finding group from a single investigational center, in Part 2)	h. has a BMI of 18 to 35, inclusive, (unless included in subset of subjects with extreme obesity (BMI ≥40), 2 in each dose-range finding group from a single investigational center, in Part 2)	Correction. BMI range expanded for consistency with similar studies.
Section 4.2 Subject Exclusion		
j. has <u>strong</u> family history of breast cancer (<u>defined as one or more first degree relatives, breast cancer occurring before menopause in three or more family members, regardless of degree of relationship, and any male family member with breast cancer</u>), or current or history of breast cancer, or undiagnosed mass detected by breast exam	j. has strong family history of breast cancer (defined as one or more first degree relatives, breast cancer occurring before menopause in three or more family members, regardless of degree of relationship, and any male family member with breast cancer), or current or history of breast cancer, or undiagnosed mass detected by breast exam	Clarification. Text added to describe a “strong” family history of breast cancer.
Section 4.3 Justification for Key Inclusion and Exclusion Criteria		
The study will not enroll female subjects who have medical contraindications to DMPA nor medical or social conditions that may make study participation unsafe, interfere with drug absorption and metabolism, <u>have a strong family</u>	The study will not enroll female subjects who have medical contraindications to DMPA nor medical or social conditions that may make study participation unsafe, interfere with drug absorption and metabolism, have a strong family	Clarification. Text added to describe a “strong” family history of breast cancer.

Original text with changes shown	New wording	Reason/Justification for change
history of breast cancer defined as one or more first degree relatives, breast cancer occurring before menopause in three or more family members, regardless of degree of relationship and any male family member with breast cancer or complicate data interpretation.	history of breast cancer defined as one or more first degree relatives, breast cancer occurring before menopause in three or more family members, regardless of degree of relationship and any male family member with breast cancer, or complicate data interpretation.	
Section 5.3 Prior and Concomitant Medication or Treatment		
•selective cyclooxygenase-2 (COX-2) inhibitors (eg, meloxicam, celecoxib) for 5 or more consecutive days	•selective cyclooxygenase-2 (COX-2) inhibitors (eg, meloxicam, celecoxib) for 5 or more consecutive days	Added. Text added to indicate that co-administration of selective cyclooxygenase-2 (COX-2) inhibitors are prohibited for if taken for more than 5 days.
Section 5.5 Total Blood Volume		
~~by week 52~~ Pharmacokinetics (serum MPA) -before study drug injection -if ovulation by week 52 -if no ovulation by week 52 ~~week 52~~	Pharmacokinetics (serum MPA) -before study drug injection -if ovulation by week 52 -if no ovulation by week 52	Typo
about 10 (for both P and E2)	about 10 (for both P and E2)	Clarification. Added to indicate that volumes are approximate.
about 5	about 5	Clarification. Added to indicate that volumes are approximate.
about 4	about 4	Clarification. Added to indicate that volumes are approximate.
6.1. Pharmacokinetics		
The MPA results will not be known until later in the study and, therefore, will not be used as exclusion criteria. Subjects with nonzero MPA levels at baseline (ie, more than 5% of their individual C_{max}) will be excluded from the primary pharmacokinetic analyses (see Section 8.5.3).	The MPA results will not be known until later in the study and, therefore, will not be used as exclusion criteria. Subjects with nonzero MPA levels at baseline (ie, more than 5% of their individual C_{max}) will be excluded from the primary pharmacokinetic analyses (see Section 8.5.3).	Clarification of concentration.

Original text with changes shown	New wording	Reason/Justification for change
In addition, subjects for whom ovulation has not returned by month 12 (week 52), blood samples for MPA will be collected and tested up to 2 more times (at week ~~65 [month 15]~~61 and week ~~78 [(month 18]),~~74), but not past return to ovulation.	In addition, subjects for whom ovulation has not returned by month 12 (week 52), blood samples for MPA will be collected and tested up to 2 more times (at week 61 and week 74), but not past return to ovulation.	Clarification of testing for MPA for subjects for whom ovulation has not returned by month 12.
Section 6.2.Pharmacodynamics		
Although repeated elevated progesterone is not needed for the primary definition of ovulation, this information will be used for more accurate ascertainment of ovarian function. Subjects with a single elevated progesterone measurement of ≥4.7 ng/mL will be considered to have their ovulation restored. ~~Women in whom ovulation returns before month 12 (week 52) will continue weekly sampling for progesterone and estradiol until the month 12 visit. The subjects will then be asked to return for their final visit within 5 days to complete confirmatory progesterone measurement and final visit procedures.~~	Although repeated elevated progesterone is not needed for the primary definition of ovulation, this information will be used for more accurate ascertainment of ovarian function. Subjects with a single elevated progesterone measurement of ≥4.7 ng/mL will be considered to have their ovulation restored.	Correction. Deleted as this section addresses PK.
Section 7.8.Menstrual Bleeding Patterns		
Subjects will be asked about changes in their menstrual bleeding patterns, including ~~amenorrhea~~,no bleeding, since last assessment ~~since last study visit~~ at monthly intervals and during the scheduled laboratory or follow-up visits at week 13 (month 3) and week 32 (month 7.5), and at the final study visit.	Subjects will be asked about changes in their menstrual bleeding patterns, including no bleeding, since last assessment at monthly intervals and during the scheduled laboratory or follow-up visits at week 13 (month 3) and week 32 (month 7.5), and at the final study visit.	Clarification. Question regarding changes in menstrual bleeding patterns will be asked monthly.
Section 8.2.3 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	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	Clarification. Added to define “detectable MPA”.

Original text with changes shown	New wording	Reason/Justification for change
pre-treatment period; BMI outside the eligible range (including the 6 subjects purposefully enrolled with BMI ≥40); or use of drugs known to impact ovulation or the pharmacokinetics of MPA.	confirmed ovulation in the pre-treatment period; BMI outside the eligible range (including the 6 subjects purposefully enrolled with BMI ≥40); or use of drugs known to impact ovulation or the pharmacokinetics of MPA.	
The Primary Evaluable Analysis Set includes all time contributed by participants in the Primary Evaluable Population during which a pharmacokinetic or pharmacodynamic outcome is assessed, (up to the initiation of any concomitant medication) known to impact ovulatory function or the pharmacokinetics of MPA~~.~~	The Primary Evaluable Analysis Set includes all time contributed by participants in the Primary Evaluable Population during which a pharmacokinetic or pharmacodynamic outcome is assessed, (up to the initiation of any concomitant medication) known to impact ovulatory function or the pharmacokinetics of MPA.	Typo.
Appendix B		
Insert the ~~26g~~ 23g x 3/8” needle at a 45 degree angle so that most of the needle is in the fatty tissue.	Insert the 23g x 3/8” needle at a 45 degree angle so that most of the needle is in the fatty tissue.	Correction. Gauge of needle updated.

16.4. Protocol Amendment 01 Dated 29 May 2016

The primary reasons for this amendment are corrections. These revisions are considered to be substantial by the sponsor's Authorized Representative. These changes are unlikely to affect to a significant degree the safety or rights (physical or mental integrity) of the subjects in the clinical study or the scientific value of the clinical study.

Original text with changes shown	New wording	Reason/Justification for change
Title page, Investigator Agreement, and Coordinating Investigator Agreement		
FHI 360 Study Number: 780861~~-1~~	FHI 360 Study Number: 780861	Correction
Section 3.9 Drugs Used in the Study		
Each TV-46046 dose will be presented in a 3 mL United States Pharmacopeia (USP) Type 1 clear glass vial, 13-mm rubber stopper, and 13-mm aluminum seal covered with a green cap (STERI-TAMP®[3] single-use tamper evident sticker)~~13 mm aluminum seal with green color flip-off disc~~.	Each TV-46046 dose will be presented in a 3 mL United States Pharmacopeia (USP) Type 1 clear glass vial, 13-mm rubber stopper, and 13-mm aluminum seal covered with a green cap (STERI-TAMP® single-use tamper evident sticker).	Correction
Not Applicable	[3]STERI-TAMP is a registered trademark of STERI-TAMP, LLC.	Added
Section 3.10.2 Drug Accountability		
~~Empty and unused units of study product will be disposed of, retained, or returned to the sponsor per FHI 360 instructions.~~ Empty and partially used containers of study drug will be destroyed at the investigational center in accordance with investigational center SOPs, with sponsor approval. In the event the investigational center is unable to destroy the empty and/or unused units of study drug, the study drug will be disposed of, retained, or returned to the sponsor or designee per FHI 360 instructions.	Empty and partially used containers of study drug will be destroyed at the investigational center in accordance with investigational center SOPs, with sponsor approval. In the event the investigational center is unable to destroy the empty and/or unused units of study drug, the study drug will be disposed of, retained, or returned to the sponsor or designee per FHI 360 instructions.	Correction

APPENDIX A. DAIDS TABLE FOR GRADING ADULT AND PEDIATRIC ADVERSE EVENTS

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[13] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*
≤15 years of age	Same as for **Injection Site Erythema or Redness**, *≤15 years of age*	Same as for **Injection Site Erythema or Redness**, *≤15 years of age*	Same as for **Injection Site Erythema or Redness**, *≤15 years of age*	Same as for **Injection Site Erythema or Redness**, *≤15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[13] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Notes: According to the DAIDS Grading Table, Grade 5 indicates death; however, this grade is not specifically presented in the table.
Refer to the full source for complete information: US Department of Health and Human Services. National Institute of Allergy and Infectious Diseases. National Institutes of Health. Division of AIDS (DAIDS) Table for grading the severity of adult and pediatric adverse events. Version 2.0; November 2014.
US=United States; AIDS=acquired immune deficiency syndrome.

APPENDIX B. INJECTION INSTRUCTIONS

FOR SUBCUTANEOUS ADMINISTRATION ONLY

Please read these instructions carefully. It is very important that the indicated dose of TV-46046 is given accurately.

Step 1: Getting ready

Subjects enrolled in Part 1 of this study will be assigned to 1 of the following 2 treatment groups comprising of 6 women in each:

1. Treatment group 1: 0.3 mL of 400 mg/mL of undiluted TV-46046
2. Treatment group 2: 0.6 mL of 200 mg/mL of saline-diluted TV-46046

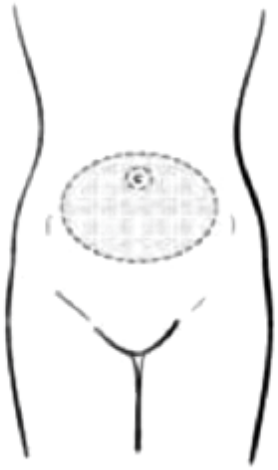
If warranted, Part 1 treatment group 3 will be enrolled subsequently (N=6), receiving 0.4 mL of 300 mg/mL of saline-diluted TV-46046.

Do not refrigerate the study product. Ensure that the vial is at room temperature prior to injection (to ensure appropriate viscosity of the suspension). Inspect the vial visually for particulate matter and discoloration prior to administration. (If particulate matter and/or discoloration are noted, do not use the vial. Collect the vial for return to the manufacturer. Refer to the Pharmacy Manual for return instructions.)

Details of product administration are found in the Pharmacy Manual. Briefly, at the time of product administration, disperse the product by shaking the vial vigorously until a homogeneous suspension is observed. Withdraw the indicated volume of the study drug from the vial using the provided 23G x 3/8” needle. Expel extra air and adjust the volume if necessary.

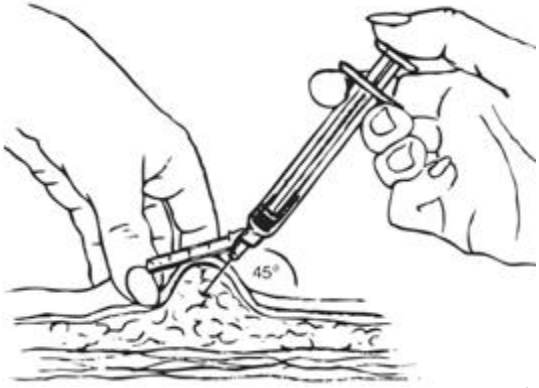
If not administered within a few minutes, shake the syringe vigorously prior to administration. Administer the subcutaneous injection using the same 23G x 3/8” needle.

Step 2: Choosing & preparing the injection area

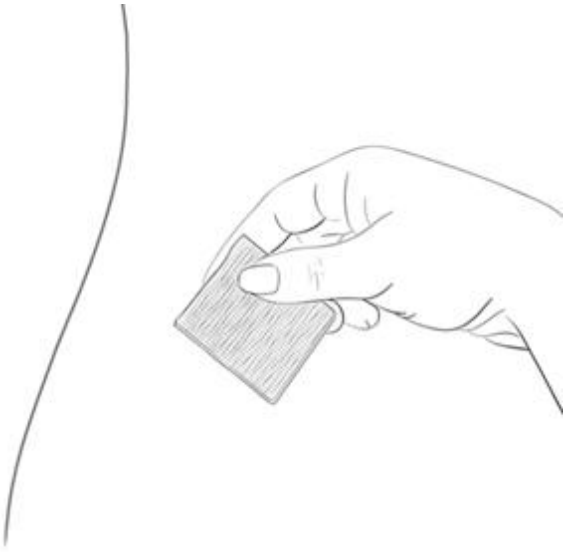
Choose the injection area. • **The abdomen is the selected injection site for this clinical study. Avoid bony areas and the umbilicus.**	**Preferred injection area:**
Use an alcohol pad to wipe the skin in the abdominal injection area. • **Allow the skin to dry**	 **Use Abdomen area only**

Step 3: Injecting the dose

Gently grasp and squeeze a large area of skin in the chosen injection area between the thumb and forefinger, pulling it away from the body.	

Insert the 23g x 3/8" needle at a 45 degree angle so that most of the needle is in the fatty tissue. • The plastic hub of the needle should be nearly or almost touching the skin	
Inject the medication slowly until the syringe is empty. • This should take about 5 to 7 seconds • It is important that the entire dose is given	**Inject slowly (5 to 7 seconds)** 

Step 4: Disposing the needle and syringe

Use a clean cotton pad to **press lightly on the injection area** for a few seconds. **Do NOT rub the area** **Do NOT use Band Aid®** **Subject should stay in the clinic for at least 15 minutes after the injection for observation of possible post-injection problems including anaphylactic reaction.**	
Following the administration of each dose, **the used syringe should be discarded in a safe and proper manner**.	