Clinical Study Protocol

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

Study Number TV46046-WH-10159

NCT04682353

Protocol with Amendment 02 Approval Date: 16 March 2021

Clinical Study Protocol with Amendment 02

Study Number TV46046-WH-10159

FHI 360 Study Number 1449048

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

Phase 1

IND number: 126249

EudraCT number: Not applicable

Clinical Study Protocol with Amendment 02 Version Date: 16 March 2021

Sponsor
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Global Patient Safety &
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Teva Branded Pharmaceutical
Products R&D, Inc.
Tel: [redacted]

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

Confidentiality Statement

DOCUMENT HISTORY

Amendment 02	16 March 2021 10 subjects enrolled to date
Amendment 01	02 July 2020 0 subjects enrolled to date.
Original Protocol	04 March 2020

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 17.

SPONSOR PROTOCOL APPROVAL

Clinical Study Protocol with Amendment 02

Study TV46046-WH-10159

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

Version Date: 16 March 2021

I have read the protocol with Amendment 02 and approve the design of this study.

Sponsor's Authorized Representative	**Signature**	**Date**
[redacted]		

Executed signature pages are maintained within the Trial Master File

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 02

Study TV46046-WH-10159

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

Version Date: 16 March 2021

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 02 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 agreement with 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 national or local legal and regulatory requirements and applicable regulations and guidelines.

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

Principal Investigator	**Signature**	**Date**

Executed signature pages are maintained within the Investigator Site File and the Trial Master File

CLINICAL STUDY PROTOCOL SYNOPSIS

With Amendment 02

Study: TV46046-WH-10159

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

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

Investigational New Drug (IND) Number: 126249

Name of Test Investigational Medicinal Product (IMP): depot medroxyprogesterone acetate (DMPA [TV-46046])

Active Substance: medroxyprogesterone acetate (MPA)

EudraVigilance (EV) code for the IMP: Not Applicable

Type of Study: Pharmacokinetic (PK) Study

Phase of Clinical Development: 1

Number of Investigational Centers Planned: 3 investigational centers

Countries Planned: United States of America, Dominican Republic

Planned Study Period: The study is expected to start in Quarter 04 2020 (first subject screened) and have a duration period of approximately 26 months (through last subject out).

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

Secondary Objective(s): The secondary objectives of the study are to evaluate and compare the safety, local tolerability, and acceptability of a subcutaneous injection of 3 doses of TV-46046 300 mg/mL (120 mg/0.4mL; 180 mg/0.6mL; 240 mg/0.8mL) and 104 mg/0.65 mL of Depo-subQ Provera in healthy female subjects.

General Study Design and Methodology: This is a randomized, partially-blinded dose-range finding study to evaluate and compare the pharmacokinetics of MPA, safety, local tolerability, and acceptability of the single subcutaneous administration of 3 doses of TV-46046 300 mg/mL (120 mg/0.4 mL, 180 mg/0.6 mL or 240 mg/0.8 mL), and 104 mg/0.65 mL of Depo-subQ Provera in healthy female subjects of reproductive age. The ultimate goal is to select for further investigation a dose of TV-46046 that is both safe and well tolerated, and has a PK profile consistent with contraceptive protection when injected subcutaneously every 6 months.

Study participation will consist of a screening period (approximately 1.5 months, or 6 weeks), treatment initiation (Day 0) and follow-up (up to 18 months or 78 weeks).

Investigational Medicinal Products (IMPs): Dose, Pharmaceutical Form, Route of Administration, and Administration Rate

Test IMP: TV-46046 (Medroxyprogesterone acetate injectable suspension 300 mg/mL)

Reference IMP: Depo –subQ Provera 104® (Medroxyprogesterone acetate injectable suspension [104 mg/0.65mL for sc use])

Study Population and Number of Subjects Planned: Approximately sixty (60) healthy female subjects of reproductive age at low risk of pregnancy with no contraindications for MPA-containing products will be randomized to 1 of 3 doses of TV-46046 300 mg/mL (120, 180, 240 mg) or 1 dose of Depo-subQ Provera (104 mg/0.65mL) (approximately 15 women per group).

Duration of Subject Participation: Total duration of the study for each subject is expected to be approximately 19.5 months, including approximately 1.5 months of screening and up to 18 months of follow-up after study treatment initiation.

Main Criteria for Inclusion: Subjects may be included in the study only if they meet all of the study inclusion criteria. The main inclusion criteria are:

a. willing and capable of giving signed informed consent
b. female of 18 to 45 years of age (inclusive)
c. healthy based on results of physical examination, medical history, vital signs tests, and Pap smear results
d. has regular menstrual cycle (21 to 35 days)
e. has a low risk of pregnancy (ie, sterilized, in exclusively same-sex partnership, abstinent, in monogamous relationship with vasectomized partner, using non-hormonal intrauterine device (IUD), or consistently using barrier methods of contraception)
f. had a normal mammogram within the last year, if 40 years of age or older
g. has a body mass index (BMI) of 18 to 35, inclusive
h. has hemoglobin ≥10.5 g/dL
i. is willing and able to comply with all study requirements and return to the investigational center for the follow-up procedures and assessments as specified in this protocol

Main Criteria for Exclusion: Subjects will be excluded from participating in this study if they meet any of the study exclusion criteria. The main exclusion criteria are:

a. has hypertension with:
    - systolic blood pressure (BP) ≥160 mm Hg or diastolic BP ≥100 mm Hg
    - vascular disease
b. has an abnormal Pap result that requires treatment or in the opinion of an investigator would make study participation unsafe or complicate data interpretation

c. has multiple risk factors for cardiovascular disease (eg, smoking, obesity, hypertension, known low high density lipoprotein [HDL], high low density lipoprotein [LDL], or high triglyceride levels)

d. has current or history of ischemic heart disease

e. has active thrombophlebitis, current or past history of thromboembolic disorders, cerebral vascular disease or stroke

f. has systemic lupus erythematosus

g. has rheumatoid arthritis on immunosuppressive therapy

h. has unexplained vaginal bleeding

i. has diabetes

j. has strong family history of breast cancer (defined as one or more first degree relatives with breast cancer, 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

k. has current or history of breast cancer, or undiagnosed mass detected by breast exam

l. has current or history of cervical cancer

m. has cirrhosis or liver tumors

n. has one or more baseline liver function test(s) outside the local laboratory's normal range

o. has known osteoporosis or osteopenia

p. has history of diagnosed clinical depression or bipolar disorder, with or without suicidal ideation, and/or history of suicide attempt, except short-lived situational depression that did not require medication and has not recurred in last five years

q. has history of 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

r. used MPA-containing injectable products in the past 12 months

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

t. 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

u. is participating in another clinical trial

v. is pregnant

w. desires to become pregnant in subsequent 24 months

x. has been pregnant in last 3 months

y. is currently lactating

z. is using or planning to use prohibited drugs per protocol in the next 12 months

aa. has known sensitivity to MPA or inactive ingredients

bb. plans to move to another location in the next 12 months

cc. 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

Study Evaluations

Pharmacokinetic Assessments: Blood samples (approximately 5 mL) will be collected before and up to 52 weeks (365 days) after IMP administration for the determination of serum MPA.

Safety Assessments: Safety and local tolerability evaluation will be based on the following:

- occurrence of adverse events
- use of concomitant medication
- change in vital signs and body weight
- vaginal bleeding pattern
- change in mood
- change in liver function tests
- Estradiol (E2) levels
- delayed return to ovulation (>12 months after treatment initiation) where ovulation is defined as a single progesterone (P) ≥4.7 ng/mL
- occurrence of injection site reactions (ISRs)

Acceptability assessments: Acceptability will be evaluated based on the subject's responses to acceptability questions.

Statistical Methods

Sample Size Determination: The goal of the study is to select a dose of TV-46046 that is safe and well tolerated, and has a PK profile consistent with contraceptive protection when injected every 6 months. Recognizing that there is no formal hypothesis test on which to base sample size calculations, 15 subjects per treatment group (approximately 60 in total) are expected to be sufficient to inform dose selection based on data from recent PK studies of MPA delivered subcutaneously. [redacted]

The intent of the study is to have a minimum of 54 subjects with evaluable data complete 32 weeks per protocol. Additional subjects may be enrolled to complete the minimum number of evaluable subjects at the discretion of the Sponsor.

Pharmacokinetic Measures/Parameters:

The following primary pharmacokinetic parameters will be calculated from concentration-time data:

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

Analyses

Pharmacokinetic Analysis: Non-compartmental methods will be used to estimate AUC values and $t_{½}$. The other estimates (t_{max}, C_{max}, C_{91}, C_{182}, and C_{210}) will be based on observed values where possible. No formal hypothesis tests of pharmacokinetic data are planned. Parameter estimates will be summarized by treatment group for each dose level using descriptive statistics, including number (n), mean, standard deviation (SD), geometric mean, geometric coefficient of variation, harmonic mean (for $t_{½}$), median, minimum, maximum, and associated 95% confidence intervals (CIs). Graphical displays will include individual and geometric mean pharmacokinetics profiles on un-transformed and semi-log (base 10) data. Descriptive comparisons of PK parameters between test and reference groups will be based on geometric mean ratios and 90% CIs.

Safety Measurements:

The safety measurements for this study include:

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

The acceptability parameters are:

- subject's responses to acceptability questions

Safety Analysis: No formal hypothesis tests of safety data are planned. All safety data will be summarized by treatment group using descriptive statistics (n, mean, SD, standard error, median,

minimum, and maximum for continuous variables, and frequency and percentage for categorical variables). Specifically, the number and percentage of subjects experiencing treatment-emergent adverse events will be presented by treatment group, overall, by severity grade, and by relatedness to treatment. Adverse events will be further summarized in listings or frequency tables according to system organ class and preferred term. Serious adverse events and adverse events leading to withdrawal from the study will be listed separately. Concomitant medication use will be summarized by treatment group in frequency tables, by therapeutic class and medicine category. Change in vital signs (BP [systolic/diastolic], pulse, body temperature and respiration) and body weight from Day 0 to Day 7, Weeks 13, 26, and 52 will be described in shift tables. The percentage of women experiencing amenorrhea or vaginal bleeding disturbances (irregular vaginal bleeding or spotting) will likewise be summarized descriptively and compared between treatment groups. Mood data will be summarized over time using frequency tables and graphical displays. Liver function will be assessed by tabulating change in liver function tests from baseline to Day 7, Weeks 13, 26, and 52. Rates of return to ovulation by 12 months (Week 52), where ovulation is defined as a single P $\geq$4.7 ng/mL, will be provided by treatment group. Estradiol concentrations will be summarized for each group using means, standard deviations, and graphical displays through Week 52. The ISR data will be provided by group in frequency tables (if applicable) and using subject-data listings. The responses to acceptability questions will be descriptively compared between treatment groups.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum drug concentration-time curve
AUC_{0-182}	area under the serum concentration-time curve from time 0 to day 182
AUC_{0-210}	area under the serum concentration-time curve from time 0 to day 210
$AUC_{0-\infty}$	area under the serum concentration-time curve extrapolated to infinity
BP	blood pressure
BMI	body mass index
CDMS	clinical data management system
CFR	Code of Federal Regulations (US)
CI	contraceptive injection
C_{91}	serum MPA concentration at day 91
C_{182}	serum MPA concentration at day 182
C_{210}	serum MPA concentration at day 210
C_{max}	maximum observed serum drug concentration
CRF	case report form
DMPA	depot medroxyprogesterone acetate
E2	estradiol
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HDL	high density lipoprotein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
ISR	Injection site reaction
IUD	intrauterine device

Abbreviation	Term
LDL	low density lipoprotein
MPA	medroxyprogesterone acetate
P	progesterone
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetics
SD	standard deviation
SOP	standard operating procedure
SMP	Serious Adverse Event Management Plan
SRC	Study Review Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	apparent terminal half-life
t_{max}	time to maximum serum observed drug concentration
ULN	upper limit of the normal range
US(A)	United States (of America)

1. BACKGROUND INFORMATION

1.1. Introduction

Teva and FHI 360 are in collaboration to develop TV-46046, a formulation of depot medroxyprogesterone acetate (DMPA), for the prevention of pregnancy when injected every 6 months. Depo-subQ Provera 104 and Depo Provera Contraceptive Injection (CI) are the 2 proposed listed drugs for the TV-46046 development program. More detailed information is provided in the current version of the Investigator's Brochure (IB).

The objective of this study is to evaluate and compare the pharmacokinetic profile of medroxyprogesterone acetate (MPA), safety and local tolerability, and acceptability following subcutaneous administration of one of 3 doses of TV-46046 or Depo-subQ Provera 104 in healthy female subjects.

1.2. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetic, toxicology, and clinical studies are provided in the following sections. More detailed information is provided in the current version of the IB.

1.2.1. 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 evaluating nonclinical biological and toxicological/toxicokinetic activities of DMPA are summarized in the current version of the IB to support the contraception indication for TV-46046.

Teva's current nonclinical toxicology program consists of 5 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); a single dose non-GLP feasibility study of subcutaneous injection (Study DS-2018-008); and a non-GLP female rabbit subcutaneous pharmacokinetic and gross tolerability study (Study DP-2014-135). The results of these studies are summarized in the current version of IB.

1.2.2. Clinical Studies

1.2.2.1. Clinical Pharmacology Studies

The pharmacokinetics (PK) of MPA following a single subcutaneous injection of undiluted and saline diluted 120 mg TV-46046 has been evaluated in a single Phase 1 study which included 12 healthy subjects (Study TV46046-WH-10075). All subjects, except 1 in the undiluted TV-46046 group, had serum MPA levels greater than 0.20 ng/mL 24 hours after treatment initiation. Maximum observed serum drug concentration (C_{max}) in the undiluted TV-46046 group and the

saline-diluted TV-46046 group were 0.53 ng/mL and 0.97 ng/mL, respectively. Areas under the concentration curve ($AUC_{0-\infty}$) of the undiluted TV-46046 group and the saline-diluted TV-46046 group were 94.56 days*ng/mL and 114.13 days*ng/mL, respectively. All evaluable subjects in the undiluted
TV-46046 group and all except 1 subject in the saline-diluted TV-46046 group had serum MPA concentrations exceeding 0.10 ng/mL on Day 182. The apparent half-lives of the undiluted TV-46046 group and the saline-diluted TV-46046 group were 82.87 and 42.34 days, respectively.

1.2.2.2. Clinical Efficacy and Safety Studies

The efficacy of TV-46046 has not been evaluated.

Safety was evaluated in Study TV46046-WH-10075. The safety data indicated that treatment with 120 mg TV-46046 was well tolerated. No death, treatment related serious adverse event (SAE), or withdrawal due to adverse event (AE) occurred in this study. Twelve (100%) of the 12 subjects reported at least one AE during the course of the study. A total of 51 AEs occurred throughout the study, the majority of which (80.4%) occurred within 7.5 months of treatment initiation. Injection site reaction (ISR) was the most frequently reported AE (9 [75.0%] subjects). The rate of ISRs associated with subcutaneous injection of TV-46046 appeared to be higher compared to historical data on the approved DMPA products. However, most of the ISRs in the study were mild, transient, and resolved without sequelae. Two subjects developed skin discoloration (hypopigmentation) at the site of injection. One subject developed hypopigmentation approximately 4 months after the injection which was still present at study exit approximately one year after onset; the other subject developed hypopigmentation approximately 3 months after the injection which completely resolved approximately one year after onset.

Vital signs of all but one subject were within normal ranges and remained largely unchanged during the study compared to the baseline. With the exception of one subject in the undiluted TV-46046 group who was lost to follow-up on Day 201, all subjects in both groups returned to ovulation within 15 months of treatment initiation.

1.3. Known and Potential Benefits and Risks

1.3.1. Overall Potential Benefits and Risks

The study will be conducted in healthy subjects. Subjects will undergo a physical exam, Pap smear evaluation and hemoglobin testing at screening. Liver enzymes testing will be conducted at screening and during the study. Mood evaluation will be conducted at enrollment and during the study. Women 40 years of age or older will have a mammogram performed unless they have had one in the last year prior to enrollment. No other direct health benefits are expected in this study population. The study design, inclusion/exclusion criteria, and procedures have been developed in a manner to protect subject safety. The results of this study may facilitate the development of a new longer-acting injectable contraceptive.

1.3.2. Known and Potential Risks of TV-46046

Specific risks for TV-46046 include the risk of possible skin discoloration (including hypopigmentation). Additional information regarding risks to subjects may be found in the IB.

1.4. Study Design Rationale

1.4.1. General Study Design Rationale

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

Study participation will consist of a screening period (approximately 1.5 months, or 6 weeks), treatment initiation (Day 0), and at least 52 weeks of follow-up. Subjects with unresolved ISR(s) at Week 52 will be followed every 3 months through the resolution of ISR(s) or Week 78, whichever comes first. Approximately 60 eligible subjects will be enrolled into the study and randomly assigned in a 1:1:1:1 ratio to receive one of the 4 study treatments: 120 mg/0.4 mL, 180 mg/0.6 mL or 240 mg/0.8 mL of TV-46046, or 104 mg/0.65 mL of Depo-subQ Provera 104 (approximately 15 women per group). After treatment initiation, subjects will be followed for 52 weeks and provide blood samples for MPA, progesterone (P, and estradiol (E2) as shown in Table 1.

In addition to frequent laboratory visits there will be four scheduled follow-up visits at Week 1 (Day 7), Week 13, Week 26, and Week 52, during which subjects will be evaluated for vital signs, body weight, liver enzymes, and ISRs. Vaginal bleeding pattern, acceptability, and mood will be assessed throughout the study at predefined time points. Urine pregnancy test will be performed periodically and information on adverse events and concomitant medicines will be collected throughout the study.

The study schematic diagram is shown in Figure 1. Study procedures and assessments with scheduled time points are shown in Table 1.

1.4.2. Dosage Rationale

This study is designed to evaluate and compare the pharmacokinetics of MPA, safety and local tolerability, and acceptability of the single subcutaneous administration of one 3 doses of TV-46046 300 mg/mL (120 mg/0.4 mL, 180 mg/0.6 mL or 240 mg/0.8 mL) or 104 mg/0.65 mL of Depo-subQ Provera 104 in healthy female subjects of reproductive age. The goal is to select a dose of TV-46046 that is both safe and has PK profile consistent with contraceptive protection when injected subcutaneously every 6 months.

The selected dose range of TV-46046 was chosen to have a high probability of bracketing the dose necessary to 1) to achieve a comparable geometric mean 6-month trough concentration as the 3-month trough of the reference drug (0.35 to 0.40 ng/mL), and 2) to ensure a low (eg, 5% or less) risk of return to ovulation within 7 months of treatment injection. Both criteria are expected to be met for by a dose of TV-46046 between 120 mg/0.4 mL and 240 mg/0.8 mL based on results of Study TV46046-WH-10075 (NCT02817464), Study 702179 (NCT02456584), and the

PK/PD studies which informed the label for Depo-subQ Provera 104 (Jain et al 2004, Toh et al 2004). A dose of TV-46046 in the selected range is also expected to be safe when injected subcutaneously every 6 months.

2. STUDY OBJECTIVES AND MEASURES/PARAMETERS

2.1. Primary and Secondary Study Objectives and Measures/Parameters

Objectives	Measures/Parameters
The **primary objective** of this study is to evaluate and compare the pharmacokinetic profile of medroxyprogesterone acetate (MPA) following subcutaneous administration of 3 doses of TV-46046 300 mg/mL (120 mg/0.4mL; 180 mg/0.6mL; 240 mg/0.8mL), and 104 mg/0.65 mL of Depo-subQ Provera 104 in healthy female subjects.	The following non-exhaustive list of pharmacokinetic parameters will be evaluated to support the primary objective of the study: • C_{max} (maximum observed serum concentration) • T_{max} (time to C_{max}) • Serum MPA concentrations at treatment days 91, 182, and 210 (C_{91}, C_{182}, C_{210}) • $AUC_{0\text{-}182}$ (area under the serum drug concentration-time curve from time 0 to day 182); $AUC_{0\text{-}210}$ (AUC from time 0 to day 210); and $AUC_{0\text{-}\infty}$ (AUC extrapolated to infinity) • Apparent terminal half-life ($t_{½}$)
The **secondary objectives** of the study are: 1) to evaluate and compare the safety and local tolerability of a subcutaneous injection of 3 doses of TV-46046 300 mg/mL (120 mg/0.4mL; 180 mg/0.6mL; 240 mg/0.8mL) and 104 mg/0.65 mL of Depo-subQ Provera 104 in healthy female subjects. 2) to evaluate the acceptability of a subcutaneous injection of TV-46046 over the range of different doses.	The safety and local tolerability measures/parameters are: • occurrence of adverse events • use of concomitant medication • vital signs and body weight measurement • vaginal bleeding pattern • assessment of mood by Patient Health Questionnaire-9 (PHQ-9) • liver function tests • estradiol (E2) measurements throughout the study • progesterone (P) measurements at Weeks 48, 49, 50, 51, and 52 • occurrence of injection site reactions (ISRs) The acceptability parameters are: • subject's responses to acceptability questions

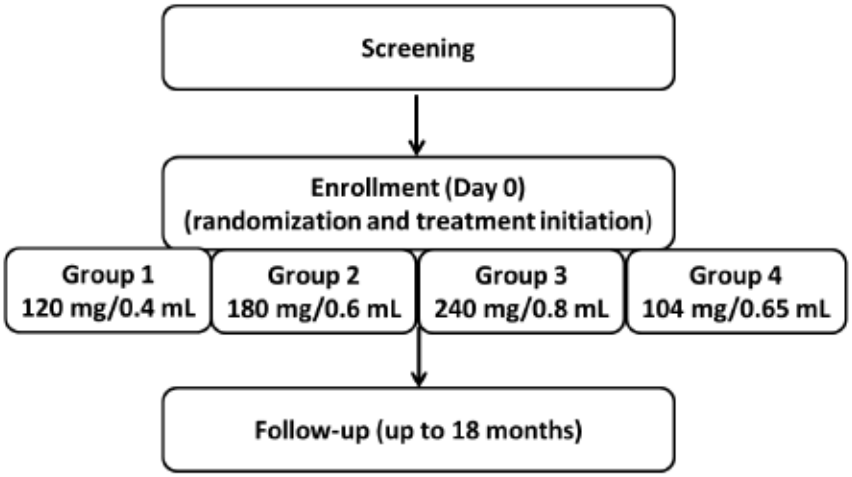
3. INVESTIGATIONAL PLAN

3.1. General Study Design

The assessments and procedures performed during each study visit are detailed in Table 1 and Section 3.4.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



3.2. Subject Eligibility

Prospective waivers (exceptions) from study eligibility criteria to allow subjects to enter a study are not granted by Teva (see Section 11.1.2).

3.2.1. Subject Inclusion Criteria

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

a. willing and capable of giving signed informed consent

b. female of 18 to 45 years of age (inclusive)

c. healthy based on results of physical examination, medical history, vital signs tests, and Pap smear results

d. has regular menstrual cycle (21 to 35 days)

e. has a low risk of pregnancy (ie, sterilized, in exclusively same-sex partnership, abstinent, in monogamous relationship with vasectomized partner, using non-hormonal intrauterine device (IUD), or consistently using barrier methods of contraception)

f. had a normal mammogram within the last year, if 40 years of age or older

g. has a body mass index (BMI) of 18 to 35, inclusive

h. has hemoglobin ≥10.5 g/dL

i. is willing and able to comply with all study requirements and return to the investigational center for the follow-up procedures and assessments as specified in this protocol

3.2.2. Subject Exclusion Criteria

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

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

b. has an abnormal Pap result that requires treatment or in the opinion of an investigator would make study participation unsafe or complicate data interpretation

c. has multiple risk factors for cardiovascular disease (eg, smoking, obesity, hypertension, known low high density lipoprotein (HDL), high low density lipoprotein (LDL), or high triglyceride levels)

d. has current or history of ischemic heart disease

e. has active thrombophlebitis, current or past history of thromboembolic disorders, cerebral vascular disease or stroke

f. has systemic lupus erythematosus

g. has rheumatoid arthritis on immunosuppressive therapy

h. has unexplained vaginal bleeding

i. has diabetes

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

k. has current or history of breast cancer, or undiagnosed mass detected by breast exam

l. has current or history of cervical cancer

m. has cirrhosis or liver tumors

n. has one or more baseline liver function test(s) outside the local laboratory's normal range

o. has known osteoporosis or osteopenia

p. has history of diagnosed clinical depression or bipolar disorder, with or without suicidal ideation, and/or history of suicide attempt, except short-lived situational depression that did not require medication and has not recurred in last five years

q. has history of 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

r. used MPA-containing injectable products in the past 12 months

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

t. 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 or contraceptive implant

u. is participating in another clinical trial

v. is pregnant

w. desires to become pregnant in subsequent 24 months

x. has been pregnant in last 3 months

y. is currently lactating

z. is using or planning to use prohibited drugs per protocol in the next 12 months

aa. has known sensitivity to MPA or inactive ingredients

bb. plans to move to another location in the next 12 months

cc. 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

3.3. Duration of Subject Participation

Total duration of the study for each subject is expected to be approximately 19.5 months, including approximately 1.5 months of screening and up to 18 months of follow-up after study treatment initiation. All subjects will be followed for at least 52 weeks after treatment initiation. If subjects have unresolved ISR(s) at Week 52, they will be followed until ISR resolution or Week 78, whichever comes first. Therefore, the minimal duration of subject participation is 52 weeks and the maximum 78 weeks after treatment initiation.

See Section 12.4 for the definition of the end of the study.

3.4. Study Procedures

Study procedures and assessments with their timing are summarized in Table 1. Detailed descriptions of each assessment are provided in Section 5 (safety assessments) and Section 6 (pharmacokinetic assessments).

Table 1: Study Procedures and Assessments

Procedures and assessments	Screening	Enrollment	Follow-Up		
	(6 Weeks before Randomization)	Day 0	Day 1 to Week 52 (Day 365)		Weeks 65 and 78
			Scheduled Follow-up (Day 7, Weeks 13, 26, and 52)	Lab visits [a]	
Informed consent	X				
Medical history	X				
Inclusion and exclusion criteria	X	X			
Demographics, contraceptive and reproductive history	X				
Height	X				
Vital signs measurement	X	X	X		
Body weight	X	X	X		
Physical exam	X				
Urine pregnancy test [b]		X	X	X	X
Randomization		X			
Study drug administration		X			
E2 [c]		X	X	X	
P [c]		X	X	X	
Serum MPA [d]		X	X	X	
Injection site reactions [e]		X	X		X
Adverse event inquiry [f]		X	X		X

Procedures and assessments	Screening	Enrollment	Follow-Up		
	(6 Weeks before Randomization)	Day 0	Day 1 to Week 52 (Day 365)		Weeks 65 and 78
			Scheduled Follow-up (Day 7, Weeks 13, 26, and 52)	Lab visits [a]	
Concomitant medication inquiry [f]		X	X		X
Hemoglobin	X				
Liver function testing [g]	X		X		
Mood evaluation [h]		X	X	X	
Vaginal bleeding pattern [i]			X		
Mammogram [j]	X				
Pap smear [k]	X				
Acceptability [l]			X		

[a] Subjects will return for laboratory visits at pre-defined time points: Days 0, 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, and 28; Weeks 6, 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days through Week 52.

[b] An urine pregnancy test will be performed on Day 0; Weeks 26, 32, 36, 40, 44, 48, and 52; and at Weeks 65 and 78 if applicable, and at any other times when indicated.

[c] Blood samples for P and E2 will be collected at Day 0 and at Weeks 48, 49, 50, 51, and 52. Blood samples for E2 will be collected at all visits when MPA or P is tested starting on Day 28.

[d] Blood samples for MPA will be collected on Days 0, 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, and 28; Weeks 6, 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days through Week 52.

[e] ISRs will be evaluated on Day 0 immediately (ie, as soon as possible but no later than 10 minutes upon removing the needle) and 1 hour (±5 minutes) after injection; Day 7; at Weeks 13, 26, and 52 and at other visits, if indicated. Subjects who have ISR(s) at Week 52 will be followed every 3 months (at Weeks 65 and 78) until ISR resolution or Week 78, whichever is earlier. If the subject does not have any ISRs at Week 52 it will be her final visit. All subjects will be instructed to return to the clinic if any ISRs develop after their final visit.

[f] During laboratory visits, information on adverse events and concomitant medications will not be solicited, but will be documented if self-reported by the subject. Adverse events and use of concomitant medications will also be evaluated during additional ISR follow up at Weeks 65 and 78.

[g] Liver function testing will be done at Screening, Day 7 and at the Weeks 13, 26, and 52.

[h] Mood will be evaluated on Days 0 and 28; Weeks 8, 13, 17, 21, 26, 32, 36, 40, 44, 48, and 52.

[i] Vaginal bleeding pattern will be assessed at Weeks 13, 26, and 52.

[j] Normal mammogram results from within the last year must be presented prior to enrollment for women 40 years of age or older.

[k] Pap test will be completed for women who do not have results of their previous Pap test that are within American College of Obstetricians and Gynecologists (ACOG) Pap test standard of care requirements. If additional testing is

required based on Pap results, this should be completed prior to enrollment (in accordance with Committee on Practice Bulletins Gynecology 2016).

[1] Acceptability data will be collected at Weeks 26 and 52.

E2= Estradiol; ISR=injection site reaction; Lab = laboratory; MPA = medroxyprogesterone acetate; P= Progesterone

3.4.1. Procedures for Screening

A signed and dated informed consent form (ICF) will be obtained before screening procedures commence (see Section 12.2).

After informed consent is obtained, subjects will be assigned a subject identification number in consecutive order within each investigational center.

Demographic data as well as contraceptive and reproductive history will be collected and documented. Screening for eligibility will include, review of eligibility criteria and medical history, measurement of hemoglobin and liver enzymes, and physical examination that will include, at minimum: head/neck, ears, eyes, nose, throat, chest and lungs, cardiovascular, abdomen, skin, lymph nodes and breast assessments. BMI will be calculated based on the measured weight and height. [redacted] In addition, a mammogram will be performed for women 40 years of age or older if mammogram results from within the last year are not available. A Pap test will be performed if required, following American College of Obstetricians and Gynecologists Pap test guidelines (Committee on Practice Bulletins Gynecology 2016). In addition, investigational centers may perform additional screening procedures per their standard of care procedures (eg, STI testing, urine drug screening). All screening procedures and tests will be completed within 6 weeks before randomization.

3.4.2. Procedures for Enrollment (Day 0)

Enrollment visits will be scheduled to occur during the first 5 days of the menstrual cycle. On that day, a urine pregnancy test will be completed in all subjects to rule out pregnancy. In addition, an assessment of vital signs, body weight and BMI, mood, E2 and P, and MPA will be performed. Adverse events and concomitant medications will be evaluated.

All eligibility criteria will be verified prior to randomization.

Eligible subjects will be enrolled into the study and randomly assigned in a 1:1:1:1 ratio to receive one of the 4 study treatments: 120 mg/0.4 mL, 180 mg/0.6 mL or 240 mg/0.8 mL of TV-46046, or 104 mg/0.65 mL of Depo-subQ Provera 104. Each study treatment will consist of a single subcutaneous injection in the abdomen. The injection site location will be marked and photographed for reference. The injection site will be observed for ISRs immediately (ie, as soon as possible but no later than 10 minutes upon removing the needle) and 1 hour (±5 minutes) after the injection.

3.4.3. Procedures for Follow-Up

Study follow-up will last for at least 52 weeks from treatment initiation. There will be four scheduled follow-up visits at Week 1 (Day 7), Week 13, Week 26, and Week 52, during which subjects will be evaluated for vital signs, body weight, liver enzymes, ISRs, adverse events and

use of concomitant medications. Vaginal bleeding pattern, acceptability and mood will be evaluated throughout the study at pre-defined time points (See Table 1). Urine pregnancy tests will be administered periodically starting at Week 26 through the end of the study.

In addition to the scheduled follow-up visits, subjects will return for laboratory visits to provide blood samples for MPA, P, and E2 at pre-defined time points (see Table 1).

If the subject has new or ongoing ISRs at Week 52, she will be followed every 3 months (at Weeks 65 and 78) until ISR resolution or Month 18 (Week 78), whichever is earlier. If the subject does not have any ISRs at Week 52 it will be her final visit. However, all subjects will be instructed to return to the clinic if any ISRs develop after their final visit. In that case, their status will change from completed the study to active and they will be followed per the schedule above until ISR resolution or Week 78, whichever is earlier.

Follow up visits should be scheduled using the target window periods below. However, if a subject cannot attend a visit within the target window below, the visit procedures should be conducted as soon as possible regardless of timing.

Table 2: Target Time Windows for Follow-up Visits

Target visit date	Target time window
Days 1, 2	± 1 hour
Days 3, 5, 7	± 3 hours
Days 10, 12, 14, 18	± 24 hours
Any scheduled clinic or laboratory visit past Day 21	± 48 hours

3.4.4. Unscheduled Procedures and Visits

An unscheduled procedure or visit may be performed at any time during the study at the subject's request or as deemed necessary by the investigator.

Unscheduled procedures may include the following:

- concomitant medication review
- vital signs measurements
- adverse event inquiry
- study compliance review
- urine pregnancy test

Other procedures may be performed at the discretion of the investigator and in consult with the sponsor.

4. TREATMENT OF SUBJECTS

4.1. Investigational Medicinal Products Administered During the Study

The IMPs used in this study are described in Table 3.

4.1.1. Test Investigational Medicinal Product

Approximately 60 subjects will be randomized in a 1:1:1:1 ratio to receive one of the 4 study treatments: 120 mg/0.4 mL, 180 mg/0.6 mL or 240 mg/0.8 mL of TV-46046, or 104 mg/0.65 mL of Depo-subQ Provera 104, stratified by site.

4.1.2. Reference Investigational Medicinal Product

Depo-subQ Provera 104 is the reference investigational medicinal product (IMP). For this study, Depo-subQ Provera 104 will be supplied as a single-unit dose of 104 mg/0.65 mL prefilled glass syringes pre-packaged with 26 gauge 3/8" needle. Detailed composition and injection instructions are contained in the Depo-subQ Provera 104 Prescribing Information (Depo-subQ Provera 104 US Prescribing Information 2016).

4.2. Treatment of Subjects

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. The clinical staff preparing the dose and providing the injections will be trained to shield the syringe from view of the subject and any blinded study staff prior to and at the time of injection.

Table 3: Investigational Medicinal Products Used in the Study

IMP name	TV-46046		Reference IMP	
Trade name and INN, if applicable, or company assigned number	Medroxyprogesterone acetate injectable suspension 300mg/mL		Depo –SubQ Provera 104® Medroxyprogesterone acetate injectable suspension (104 mg/0.65mL for sc use)	
Formulation	Medroxy-progesterone Acetate	300 mg	Medroxy-progesterone acetate	104 mg
	Docusate sodium	0.60 mg	Methylparaben	1.040 mg
	Polyethylene glycol 3350	20.00 mg	Propylparaben	0.098 mg
	Sodium sulfate anh.	13.00 mg	Sodium Chloride	5.200 mg
	Monobasic sodium phosphate anh.	0.60 mg	Polyethylene Glycol	18.688 mg
	Dibasic Sodium phosphate anh.	0.23 mg	Polysorbate 80	1.950 mg
	L-Methionine	1.50 mg	Monobasic Sodium Phosphate · H_2O	0.451 mg
	Water for Injection (up to 1 mL)	qs	Dibasic Sodium Phosphate · $12H_2O$	0.382 mg
	NA	NA	Methionine	0.975 mg
	NA	NA	Povidone	3.250 mg
	NA	NA	Water for injection (up to 0.65 mL)	qs
Unit dose strength(s)/Dosage level(s)	120 mg/0.4 mL 180 mg/0.6 mL 240 mg/0.8 mL		104 mg/0.65 mL	
Route of administration	SC injection		SC injection	

anh=anhydrous; H_2O =water; IMP= investigational medicinal product; INN= international nonproprietary name; NA=not applicable; qs=quantity sufficient; SC=subcutaneous

4.3. Blinding/Unblinding

This study will be partially-blinded due to differences in appearance and volume of the treatments. Designated unblinded study staff will conduct randomization procedures. The staff preparing and administering study injections will be unblinded but will be trained to shield the syringe prior to and at the time of injection from view of the subject and any other blinded study staff. FHI 360 and sponsor project team members involved in assessment of adverse events, data analysis or results interpretation will be blinded to treatment assignment until the planned interim analysis, after which only investigational center staff performing subject interviews and

assessing safety outcomes will remain blinded. Lab personnel performing MPA testing will remain blinded to treatment assignment throughout the study.

4.3.1. Unblinding During the Study

A description of the emergency unblinding procedures will be included in the study pharmacy manual.

For adverse events that are defined as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (ie, reasonable possibility that adverse event is related to treatment; Section 5.2.5), Global Patient Safety and Pharmacovigilance will request that the treatment code be revealed to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. In the case of a SUSAR, only the sponsor and a designated unblinded FHI 360 staff will receive the unblinded report for regulatory submission; other staff will receive a blinded report in accordance with sponsor's current procedures.

All cases of inadvertent unblinding will be handled per FHI 360's standard operating procedures (SOPs).

4.4. Stopping Rules and Discontinuation Criteria

If, at any time one of the following occurs: two or more ISRs graded as severe adverse events, 15 cases of skin discoloration at injection site (eg, hypopigmentation) ongoing for more than 7 days, or two serious and related adverse events in the study across all treatment groups, an unplanned review of interim data by a Study Review Committee (SRC), will occur, at which time a recommendation may be made to pause enrollment or halt the study. Other planned reviews will take place as scheduled (see Section 9.8), at which time the SRC could advise that the study stop or be modified based on concerns for safety of subjects or definitive conclusions.

Since most of the study drugs are 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 until safety assessments are completed. 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. All subjects who discontinue early will be followed according to Subject Withdrawal Criteria and Procedures (Section 4.9.1). Reasons for discontinuation from the study will be recorded on the appropriate electronic case report form (eCRF)

Others reasons the study may be stopped include:

- Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) recommend terminating the study
- The Food and Drug Administration (FDA) requests that the study be discontinued or placed on hold.
- The sponsor decides to reduce the scope (eg, reduce sample size, drop one or more study groups) or terminate the study. The sponsor may terminate the study at any time for any reason.

If the whole study is stopped, the subjects that are terminated early will be followed according to Subject Withdrawal Criteria and Procedures (Section 4.9.1).

4.5. Interim Data Reviews

The study will be overseen by an internal SRC, the composition and responsibilities of which will be detailed in a separate SRC Operational Plan. External consultants with relevant specialties may also be engaged as part of this SRC.

The SRC will convene for at least one review of interim data after at least 80% of subjects have had a chance to complete 7.5 months after treatment initiation. This analysis is intended to help inform the decision to move to, and select the dose for, a pivotal study. In addition, unplanned reviews may be triggered by the occurrence of ISRs, injection site discoloration (hypopigmentation) events and/or serious and related adverse events. At the time of any planned or unplanned interim review of data, the SRC may recommend that the trial be modified or halted to ensure the safety and well-being of study subjects. There will be no adjustment to type I error to account for any interim reviews of study data.

4.6. Prior and Concomitant Therapy or Medication

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

The following medications should not be used during this study: aminoglutethimide; steroid hormones (estrogens, progestins and androgens); and antiretroviral drugs including non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine) and ritonavir-boosted protease inhibitors. The use of prohibited drugs will be documented as an important protocol deviation. In addition, application of bandages to injection sites will be discouraged.

4.7. Procedures for Monitoring Subject Compliance

All IMPs will be injected by the investigator or other clinical personnel at the investigational center; therefore, monitoring of subject compliance will not be necessary.

4.8. Total Blood Volume

The total volume of blood to be collected for each subject in this study is approximately 345 mL as detailed in Table 4.

Table 4: Approximate Blood Volumes

Assessments	Volume per sample (mL)	Total number of samples	Total volume (mL)
Pharmacokinetics	MPA: about 5 mL	32	160 mL
Clinical laboratory	Hemoglobin: about 5 mL Liver enzymes: about 5 mL P: about 5 mL E2: about 5 mL	Hemoglobin: 1 Liver enzymes: 5 P: 6 E2: 25	Hemoglobin: 5 mL Liver enzymes: 25 mL P: 30 mL E2: 125 mL
Approximate Total		**69**	**345 mL**

MPA: Medroxyprogesterone acetate

4.9. Withdrawal of Subjects

4.9.1. Subject Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki, 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 5.1) or other reasons concerning the health or well-being of the subject, or in the event of lack of cooperation.

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 MPA testing, pregnancy testing, assessment of ISRs and/or acceptability. The final visit procedures will be followed for all subjects who withdraw, if possible (see Section 3.4).

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 investigator determines that an adverse event is related to the test IMP, monitoring will continue until the adverse event has resolved or stabilized, the subject exited the study or the subject has reached the end of the follow-up period. The investigator must inform FHI 360 as soon as possible of all subjects who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

The study product remains in the body months after the injection, therefore, 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 until safety assessments are completed.

4.9.2. 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. If she does not return to clinic while the study is ongoing then she will be considered "presumed lost to follow-up", but her file will remain open until study closeout. If the subject

does not return before the study is closed, she will be classified as lost to follow-up. The lost to follow-up designation will not be made for any subject until the closing date of the study.

5. SAFETY MEASUREMENTS AND ASSESSMENTS

5.1. Safety and Tolerability Measurements

The following safety and local tolerability measures will be implemented throughout the study at the time points listed in Table 1:

- occurrence of adverse events
- use of concomitant medication
- vital signs and body weight measurements
- vaginal bleeding pattern
- assessment of mood by Patient Health Questionnaire-9 (PHQ-9)
- liver function tests
- E2 levels throughout the study
- P measurements at Weeks 48, 49, 50, 51, and 52
- occurrence of ISRs

5.1.1. Adverse Events

Information on adverse events will be monitored throughout the study as detailed in Table 1.

During scheduled follow-up visits, study staff will proactively ask study subjects about any new or worsening medical issues since the previous visit. At all other visits information on adverse events will be recorded if self-reported by study subjects.

See Section 5.2 for details on adverse event recording and reporting.

5.1.2. Concomitant Medication Use

Concomitant therapy or medication usage will be monitored throughout the study as detailed in Table 1.

During scheduled follow-up visits, study staff will proactively ask study subjects about any new medication since the previous visit. At all other visits information on concomitant medication use will be recorded if self-reported by study subjects. Details of prohibited medications are found in Section 4.6.

5.1.3. Vital Signs and Body Weight Measurement

Vital signs (BP [systolic/diastolic], temperature, pulse and respiration rate) and weight will be measured as 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. Any vital sign value that is judged by the investigator as a

potentially clinically significant change (worsening) from Day 0 will be considered an adverse event.

Weight gain or loss will be documented as an adverse event if considered clinically significant by the site investigator.

5.1.4. Assessment of Vaginal Bleeding

Study subjects will be asked about their vaginal bleeding pattern since last assessment during the scheduled follow-up visits at Weeks 13, 26, and 52. Interview items will include date of last bleeding, description of bleeding pattern since last visit, and its acceptability.

5.1.5. Assessment of Mood

Subjects will be interviewed about aspects of and changes in mood at enrollment and at pre-defined timepoints throughout the study (Table 1). To measure depression or psychological distress, a selected validated scale based on the 10-item PHQ-9 (Kroenke et al 2001) will be used to ascertain the frequency of a variety of somatic and emotional indicators of well-being and produce an overall score for the severity of depression that will be compared between Day 0 and different time points in the study.

5.1.6. Liver Function Tests

Liver function testing will be performed by the investigational center laboratory as detailed in Table 1.

The following tests will be included in the liver panel:

- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Total protein
- Albumin
- Total and direct bilirubin

All occurrences of possible drug induced liver injury that meet Hy's law criteria, defined as all of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- ALT or AST increase of >3x the upper limit of normal (ULN)
- total bilirubin increase of >2x ULN
- absence of initial findings of cholestasis (ie, no substantial increase of ALP)

5.1.7. Estradiol Measurement

All enrolled subjects will provide blood for E2 measurement before the injection to document the baseline level. During the study, all subjects will return for serum E2 testing according to the pre-defined schedule (Table 1).

5.1.8. Assessment of Return to Ovulation at 52 Weeks

All enrolled subjects will provide blood for P measurement before the injection. During the study, all subjects will return for serum P testing according to the pre-defined schedule (Table 1).

During the treatment phase of the study, if P is ≥4.7 ng/mL in a single sample ovulation will be considered confirmed for the purpose of the analysis.

5.1.9. Injection Site Reactions

Injection site reaction (ISR) will be evaluated as detailed in Table 1.

Local tolerability will be assessed by occurrence of ISRs including but not limited to erythema (redness), swelling, pruritus (itching), bleeding, bruising, injection site discoloration (eg, hypopigmentation), atrophy (ie, dimple) or injection site pain. For the purpose of this protocol, injection site pain will include pain associated with injection and any pain or tenderness at/around the injection site.

The site of injection will be evaluated for possible ISRs after the injection at least twice during the injection visit immediately (ie, as soon as possible but no later than 10 minutes upon removing the needle) and 1 hour (±5 minutes) after the injection. Injection sites will be monitored for the progress of ongoing and/or occurrence of new ISRs. If the subject has new or ongoing ISR at Week 52, she will be followed every 3 months (at Weeks 65 and 78) until ISR resolution or Week 78, whichever is earlier. All ongoing ISRs will be examined during the next clinic visit, regardless of visit type, or more frequently at the discretion of the investigator, until ISR resolution, or the final visit, whichever occurs first.

ISRs will be evaluated at all study timepoints listed in Table 1 by subject's self-reports and visual examination of the site of injection by blinded study staff. The study staff will be instructed to use non-leading questions (eg, "Do you have any new medical issues since previous visit?") for ISR ascertainment. If the subject reports injection site pain at any time during the study, she will be asked to assess the pain using an 11-point Numeric Rating Scale (NRS) by indicating a number between 0 (no pain) and 10 (worst pain).

All findings will be recorded on the appropriate study CRFs and clinical notes. Photos of the injection site may be taken to supplement documentation of ISRs any time during the study. All cases of injection site discoloration (hypopigmentation) will be photographed. If necessary, a consultation with an appropriate clinical expert may be scheduled.

The following ISRs will be documented as adverse events:

- Injection site pain with an NRS score of 7 to 10
- Injection site pruritus/itching if itching localized to the injection site requiring ≥48 hours of treatment OR generalized itching causing inability to perform usual social and functional activities
- Injection site erythema/redness of ≥5 cm in diameter (or ≥ 25 cm^2 surface area) or greater than minimal interference with usual social and functional activities
- Injection site induration/swelling of ≥5 cm in diameter (or ≥ 25 cm^2 surface area) or greater than minimal interference with usual social and functional activities

- Any ISR that meets the definition of "serious adverse event"

5.1.10. Physical Examinations

Physical examination will be performed at screening to define inclusion/exclusion.

5.2. Safety Assessments

5.2.1. 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 the treatment.

In this study, any adverse event occurring after the clinical study subject has signed the ICF through the end of the follow-up period should be recorded and reported as an adverse event. An adverse event occurring during or after study injection is referred to as a treatment emergent adverse event

A new condition or 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.

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 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
- 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.)
- all events of possible drug induced liver injury (Section 5.1.6)
- any physical examination, vital signs measurement, electrocardiogram, or other safety assessment finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event

- For the purpose of this study, irregular vaginal bleeding will not be considered an adverse event unless it requires medical intervention or meets the definition of "serious adverse event" (See Section 5.2.5).

5.2.2. 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 ICF through the end of the follow-up period. For this study, the follow-up period is defined as up to 78 weeks after the last dose of IMP.

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 IMP. For serious adverse events, a Serious and Protocol Defined Adverse Event Form must also be completed and must be reported immediately. The investigator does not need to actively monitor subjects for adverse events once their follow-up period has ended. Serious adverse events occurring in a subject after study discontinuation will be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 5.2.5.3.

At the scheduled visits, the investigator will 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." At all other visits information on adverse events will be recorded if self-reported by study subjects. All observed or reported 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 or protocol defined adverse event, on the Serious Adverse Event Form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to baseline, through the subject's final study visit.

The onset and end dates and times, action taken regarding IMP, 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 IMP and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described in Section 5.2.3, Section 5.2.4, and Section 5.2.5.

5.2.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the choices on the following scale:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

5.2.4. Relationship of an Adverse Event to the IMP

The relationship of an adverse event to the IMP is characterized as follows:

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 IMP.	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 IMP. • 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 IMP. • It does not reappear or worsen when the IMP 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 IMP 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 IMP. • 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 IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

5.2.5. Serious Adverse Events

5.2.5.1. 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 will not be considered serious adverse events, unless there was worsening of the preexisting condition during the subject's participation in this study

- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical 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.

5.2.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction Section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study is the current IB for TV-46046, and US prescribing information for Depo-SubQ Provera104, Depo-Provera CI and Depo Provera 400 mg/mL (Depo-subQ Provera104 US prescribing information 2016, Depo-Provera CI US prescribing information 2016, and Depo-Provera Sterile Aqueous Suspension US prescribing information 2017).

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

For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.

5.2.5.3. Serious Adverse Event Management Plan

The objective of the Serious Adverse Event Management Plan (SMP) is to establish the responsibilities and procedures for receiving, processing, reporting, reconciliation and following up of serious adverse events. The SMP will be finalized prior to study initiation.

5.2.5.3.1. Investigator Responsibility

All serious adverse events that occur during the study period (including the protocol defined follow-up period, regardless of judged relationship to treatment with the study drug), must be reported to the sponsor by the investigator per the procedures specified in the SMP. The event must be reported within 24 hours of when the investigator learns about it. Completing the Serious and Protocol Defined Adverse Event Form and reporting the event must not be delayed, even if not all the information is available.

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

- study number
- investigator and investigational center identification

- subject identification 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
- 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)

The investigator does not need to actively monitor subjects for adverse events once their follow-up period has ended. Serious adverse events occurring after study discontinuation will be reported to the sponsor within 24 hours from when the investigator becomes aware of them, following the procedures described in Section 5.2.5.3.

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, and study procedures.

If additional (follow-up) information about a serious adverse event becomes available, the investigator will forward it to the sponsor within 24 hours.

Blinding will be maintained for the people who are directly involved in the study except for authorized unblinded staff. In the case of a SUSAR, only the sponsor and a designated unblinded FHI 360 staff will receive the unblinded report for regulatory submission; other staff will receive a blinded report.

5.2.5.3.2. 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 health authorities and IRB/IEC, if appropriate.

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

- amending the protocol
- discontinuing or suspending the study
- informing current study subjects of new findings by amending the existing ICF and re-consenting all subjects
- modifying listings of expected toxicities to include adverse events newly identified as related to TV-46046

5.2.6. Protocol Defined Adverse Events for Expedited Reporting

No protocol-defined adverse events for expedited reporting to Teva are identified for this study.

5.2.7. Medication Error and Special Situations Related to the Investigational Medicinal Products

Any administration of IMP that is not in accordance with the study protocol will be recorded as a deviation. If it meets the important protocol deviation criteria, the incorrect IMP administration will be categorized as "Non-Compliance to Investigational Medicinal Product (IMP)."

The following are 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, patient, 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. Any dose of IMP (whether the test IMP, reference IMP, or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.
- Misuse: Any intentional therapeutic use of a drug product in an inappropriate way or opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects. Examples: under usage, erratic or disorganized use, inappropriate use (for anxiety), in conjunction with alcohol or illegal substances, overuse.
- Abuse: Any intentional, nontherapeutic use of a drug product or substance, even once, for the purpose of achieving a desirable psychological or physiological effect, or intentional use of the opioid for a nonmedical purpose, such as euphoria or altering one's state of consciousness.
- Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.
- Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.

- Breastfeeding: Suspected adverse events which occur in infants following exposure to a medicinal product from breast milk.

5.2.8. 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 physician identified in the Clinical Study Personnel Contact Information section of this protocol (Appendix A) 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.

5.2.9. 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 3.2.1 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 24 months will be enrolled in the study. During the study, a pregnancy test will be performed as detailed in Table 1, and at any time the woman is experiencing any symptoms or signs of pregnancy, or thinks she may be pregnant. In the unlikely event of pregnancy, any subject 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 sponsor with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form. The investigator is not required to report subjects who are found to be pregnant between screening and enrollment.

All subjects who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

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

- For a spontaneous abortion, report as a serious adverse event.
- 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.

6. PHARMACOKINETIC MEASUREMENTS AND ASSESSMENTS

6.1. Timing of Pharmacokinetic Sampling

Blood samples (approximately 5 mL) will be obtained via venipuncture or indwelling catheter before and through 52 weeks (365 days) after TV-46046 administration for determination of serum concentration of MPA at the time points detailed in Table 1. Specimen collection, processing, and handling requirements are detailed in Appendix B. When the pharmacokinetic blood sample collection coincides with vital sign assessment, assessment of vital signs should precede pharmacokinetic blood sampling.

6.2. Pharmacokinetic Parameters

The following pharmacokinetic parameters will be calculated from concentration-time data using non-compartmental methods, when possible:

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

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

7. PHARMACODYNAMIC MEASUREMENTS AND ASSESSMENTS

7.1. Pharmacodynamics

Please refer to Section 5 for a description of E2 and P assessments.

8. ACCEPTABILITY ASSESSMENTS

The acceptability of the different injection doses and treatment groups will be assessed and recorded on appropriate study CRFs at Weeks 26 and 52 by blinded staff. Acceptability questions will include but not be limited to questions about what she likes and dislikes most about this method, and whether she would use this method in the future and/or recommend it to a friend.

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan. Any subsequent additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report.

9.1. Sample Size Determination and Rationale

The goal of the study is to select a dose of TV-46046 that is safe and well tolerated, and has a PK profile consistent with contraceptive protection when injected every 6 months. Recognizing that there is no formal hypothesis test on which to base same size calculations, 15 subjects per treatment group (approximately 60 in total) are expected to be sufficient to inform dose selection based on data from recent PK studies of MPA delivered subcutaneously. [redacted]

The intent of the study is to have a minimum of 54 subjects with evaluable data complete 32 weeks per protocol. Additional subjects may be enrolled to complete the minimum number of evaluable subjects at the discretion of the Sponsor. SRC will provide guidance regarding the value of expanding enrollment and size of such expansion to help ensure that at least 54 subjects complete 32 weeks per protocol.

9.2. Method of Randomization and Blinding

This is a randomized, partially-blinded study. Approximately 60 subjects will be randomized in a 1:1:1:1 ratio to the 4 treatment groups, stratified by site. The randomization sequence will be developed by an FHI 360 Randomization Statistician not otherwise involved in the study using a validated program written in SAS®.

FHI 360 and sponsor project team members involved in assessment of adverse events, data analysis or results interpretation will be blinded to treatment assignment until the planned interim analysis, after which only site staff performing subject interviews and assessing safety outcomes will remain blinded.

A description of emergency unblinding procedures will be described in the study pharmacy manual.

9.3. Analysis Sets

9.3.1. Screened Analysis Set

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

9.3.2. Randomized Analysis Set

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

9.3.3. Safety Analysis Set

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

9.3.4. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set will be a subset of the Safety Analysis Set, excluding any subjects who had a baseline MPA concentration that exceeded 5% of their individual C_{max}, had an important protocol deviation that may affect interpretation of the MPA data, or failed to provide at least one evaluable post-treatment MPA specimen. The analysis set will exclude MPA data collected during time periods when subjects used a concomitant medication known to impact the pharmacokinetics of MPA. In this analysis set, subjects will be analyzed according to treatment received, regardless of any allocation errors.

9.4. Data Handling Conventions

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 statistical analysis plan.

9.4.1. Handling Withdrawals and Missing Data

Incomplete adverse event onset or concomitant medication use dates may also be imputed or adjudicated to assess safety or when censoring subjects from analyses due to prohibited medication use.

No other missing data will be imputed unless specified in the detailed statistical analysis plan.

9.5. Study Population

This study will recruit healthy subjects to eliminate confounding factors (comorbidities, comedications) with potential impact on study outcome. Since TV-46046 is a hormonal

contraceptive, only women will be enrolled in the study. Since the contraceptive dose and duration of TV-46046 is unknown, we will enroll women who are not pregnant, not wanting to become pregnant in the next 24 months, and who are at low risk of pregnancy because they are sterilized, in exclusively same-sex partnership, abstinent, in monogamous relationship with vasectomized partner, using non- hormonal IUD, consistent use of condoms or other barrier methods of contraception.

9.5.1. Subject Disposition

Data from subjects screened, subjects screened but not randomized and reason not randomized, subjects who are randomized/enrolled, subjects randomized/enrolled but not treated and reason, pharmacokinetic, and safety analysis sets, subjects who complete the study, and subjects who withdraw from the study will be summarized using descriptive statistics. Data from subjects who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

9.5.2. Demographics, Contraceptive and Reproductive History

Subject demographics, contraceptive and reproductive history will be examined to assess the comparability of the treatments and will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation (SD), median, minimum, and maximum) will be provided. For categorical variables, subject counts and percentages will be provided. Categories for missing data will be presented if necessary.

9.6. Safety Analysis

Safety analyses will be performed on the safety analysis set. Safety measures and time points are provided in Table 1.

Safety and local tolerability evaluation will be based on the following:

- occurrence of adverse events
- use of concomitant medication
- change in vital signs and body weight
- vaginal bleeding pattern
- change in mood
- change in liver function tests
- E2 levels
- delayed return to ovulation (>12 months after treatment initiation) where ovulation is defined as a single P $\geq$4.7 ng/mL
- occurrence of ISRs

No formal hypothesis tests of safety data are planned. All safety data will be summarized by treatment group using descriptive statistics (n, mean, SD, SE, median, minimum, and maximum for continuous variables, and frequency and percentage for categorical variables). Specifically, the number and percentage of subjects experiencing treatment-emergent adverse events will be

presented by treatment group, overall, by severity grade, and by relatedness to treatment. Adverse events will be further summarized in listings or frequency tables according to system organ class and preferred term. Serious adverse events and adverse events leading to withdrawal from the study will be listed separately. Concomitant medication use will be summarized by treatment group in frequency tables, by therapeutic class and medicine category. Change in vital signs (BP [systolic/diastolic], pulse, body temperature and respiration) and body weight from Day 0 to Day 7, Week 13, Week 26, and Week 52 will be described in shift tables. The percentage of women experiencing amenorrhea or vaginal bleeding disturbances (irregular vaginal bleeding or spotting) will likewise be summarized descriptively and compared between the test and reference groups. Mood data will be summarized over time from Day 0 using frequency tables and graphical displays. Liver function will be assessed by tabulating change in liver function tests from baseline to Day 7, Weeks 13, 26, and 52. Rates of return to ovulation by 12 months (Week 52), where ovulation is defined as a single P $\geq$4.7 ng/mL, will be provided by treatment group. Estradiol concentrations will be summarized for each group using means, standard deviations, and graphical displays through Week 52. The ISR data will be provided by group in frequency tables (if applicable) and using subject-data listings.

9.7. Pharmacokinetic Analysis

The following primary pharmacokinetic parameters will be calculated from concentration-time data based on the Pharmacokinetic Analysis Set:

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

Among these primary pharmacokinetics parameters, non-compartmental methods will be used to estimate AUC values and $t_{½}$. The other estimates (t_{max}, C_{max}, C_{91}, C_{182}, and C_{210}) will be based on observed values where possible. No formal hypothesis tests of pharmacokinetic data are planned. Parameter estimates will be summarized by treatment group for each dose level using descriptive statistics, including n, mean, SD, standard error, geometric mean, geometric coefficient of variation, harmonic mean (for $t_{½}$), median, minimum, maximum, and 95% confidence intervals (CIs) for means. Graphical displays will include individual and geometric mean pharmacokinetics profiles.

PK comparisons between each dose of test formulation (TV46046) and the reference product (Depo-subQ Provera 104) will be made based on geometric mean ratios (test/reference) and 90% CIs with the following MPA exposure parameters: C_{max}, C_{91}, C_{182}, C_{210}, $AUC_{0\text{-}182}$, $AUC_{0\text{-}210}$, and $AUC_{0\text{-}\infty}$.

Other pharmacokinetic parameters (eg, steady-state trough concentrations) may be calculated using non-compartmental methods or non-linear mixed effects models to inform dose selection.

Effects of subject characteristics (eg, BMI) on pharmacokinetics of MPA will likewise be explored using non-linear mixed effects models as the data permits.

9.8. Acceptability Analysis

The responses to acceptability questions at Weeks 26 and 52, including likes and dislikes of the method and willingness to use the product in the future will be tabulated in frequency tables and compared between the test and the reference groups using descriptive Chi-squared tests.

9.9. Planned Interim Analysis

At least one interim review is planned to occur after at least 80% of subjects have had a chance to complete 7.5 months after treatment initiation. This analysis is intended to help inform the decision to move to, and select the dose for, a pivotal study. These interim data may be used to inform the end of Phase 1 meeting with the FDA.

10. INVESTIGATIONAL MEDICINAL PRODUCT INFORMATION

10.1. Investigational Medicinal Product Storage and Security

All IMPs 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. TV-46046 should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F).

The investigator must confirm appropriate temperature conditions have been maintained for all IMPs received. The investigator must report and resolve any discrepancies before use of the IMPs.

10.2. Investigational Medicinal Product Accountability

Each IMP shipment will include a packing slip listing the contents of the shipment and any applicable forms. The investigator is responsible for ensuring that deliveries of IMP and other study materials from the sponsor are correctly received, recorded, handled and stored safely and properly in accordance with the CFR or local regulations, and used in accordance with this protocol.

A record of IMP accountability (ie, IMP and other materials received, used, retained, returned, or destroyed) must be prepared and signed by the investigator, with an account given for any discrepancies. Empty and partially used containers of IMP 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 IMP, the IMP will be disposed of, retained, or returned to the sponsor or designee per FHI 360 instructions.

IMP accountability includes maintaining accurate records of 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 responsible for daily temperature monitoring and safe storage of the study products.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol Amendments, Protocol Deviations, and Important Protocol Deviations

11.1.1. 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 IRB/IEC and local health 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 investigator, coordinating investigator and the sponsor will sign the protocol amendment.

11.1.2. Important Protocol Deviations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the subjects in the study and/or (b) the scientific value of the study will be considered an important protocol deviation. Important protocol deviations 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; or noncompliance to IMP administration. Important protocol deviations will be identified and recorded by study staff on a CRF and will be reported to the responsible IRB/IEC, as required.

When an important protocol deviation is reported, FHI 360 in consultation with the sponsor will determine whether to discontinue the subject from the study or permit the subject to continue in the study. 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 study staff learn that a subject who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform FHI 360 of the important protocol deviation. If such a subject has already completed the study or has withdrawn early, no action will be taken but the important protocol deviation will be recorded.

FHI 360 will record minor protocol deviations, ie those that do not significantly affect subject safety or scientific value of the data, on a Protocol Deviation Log. The cumulative log will be submitted to the responsible IRB/IEC at annual reviews, if/as required.

11.2. Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that subjects have signed the ICF and the study is conducted in accordance with applicable SOPs, the protocol, and other written instructions and regulatory guidelines. Details of the monitoring procedures are outlined in the study's clinical monitoring plan which is maintained by FHI 360.

The main responsibilities of the study monitor are to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all subjects before they participate in the study and when changes to the consent

form are warranted, in accordance with IRB/IEC approvals. The study monitor will be permitted to check and verify the various records (CRFs and other pertinent source data records), including specific electronic source documentation (see Section 13.1) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of study progress, other sponsor or FHI 360 personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected during these monitoring visits and/or provided in follow-up written communication.

11.3. Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical IMP supplies and/or clinical device supplies used in a sponsor's clinical research study. 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 investigational center 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 the sponsor and emailing it to [redacted] 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 an IMP, all relevant samples (eg, the remainder of the subject's IMP supply) should be sent back to the sponsor for investigative testing upon sponsor's request.

11.3.1. 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 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 in accordance with the 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 even if 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.

11.3.2. Handling the Product Complaint IMP at the Investigational Center

The investigator is responsible for retaining the IMP related to the product complaint 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 IMP.

If it is determined that the investigational center must return all IMP, 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.

11.3.3. Documenting a Product Complaint

The investigator will record a description of the product complaint in the source documentation, along with 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.

11.4. Data Quality Control

The investigator 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 International Council for Harmonisation (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.

Data will be verified by the study monitor using the data source, and reviewed by Data Management using both automated logical checks and manual review. Data identified as erroneous, or data that are missing, will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed.

Case report forms 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.

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. All data collected will be approved by the investigator at the investigational center.

11.5. Audit and Inspection

The sponsor or FHI 360 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 health authorities and sponsor representatives may conduct inspections to verify compliance with GCP guidelines.

12. ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) 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, Directive 2001/20/EC of the European Parliament and of the Council 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 studies on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator has the overall responsibility for the conduct and administration of the clinical study and for contacts with study management, with the IRB/IEC, and with health authorities.

The investigator is responsible for performing the clinical 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 clinical study in accordance with the protocol will be documented in separate clinical study agreements with FHI 360 and other forms as required by national health 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 clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the IMPs as described in the IB or prescribing information.

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 study (eg, when new staff become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific responsibilities. These study personnel must be listed on the center's staff delegation log, which includes a clear description of each staff member's responsibilities and appropriately delegated significant study-related responsibilities. This list must be updated throughout the study, as necessary.

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

Before this study starts, the protocol will be submitted to health authorities, if required, and to each IRB/IEC for review. As required, the study will not start at the investigational centers before the IRB/IEC and health authority (as applicable) for the center give written approval or a favorable opinion.

12.2. Informed Consent

The investigator, or a qualified person designated by the investigator, will fully inform the subject of all pertinent aspects of the study, including the written information approved by the IRB/IEC. All written and oral information about the study will be provided in a language as

nontechnical as practical and understood by the subject. The subject will be given ample time and opportunity to inquire about details of the study and to decide whether to participate in the study. The above will be detailed in the source documentation.

Written informed consent will be obtained from each subject before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, in accordance with applicable regulatory requirements. The subject's willingness to participate in the study will be documented in an ICF, which will be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The investigator will keep the original consent forms, and copies will be given to the subject. It will also be explained to the subject that the subject is free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

12.3. Subject Confidentiality

The investigator must ensure that the privacy of the subjects, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, subjects will be identified not by their names, but by an identification code (ie, subject number).

Personal medical information may be reviewed for subject safety and for 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 or FHI 360, Global Quality Assurance (GQA), or health authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of the Clinical Study

Local regulations will be followed to determine the end of the study.

12.5. Registration of the Clinical Study

In compliance with local regulations and in accordance with the sponsor's standard procedures, this clinical study will be registered on clinicaltrials.gov.

13. STUDY DOCUMENTATION

13.1. Source Data and Case Report Forms

Data will be collected at the investigational center by appropriately designated and trained personnel. The investigator must maintain the original records (ie, source documents) of each subject's data at all times. The investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject. Subject identity will not be discernible from the data provided on CRFs.

Examples of source documents are hospital records, office visit records, examining physician's finding or notes, laboratory reports, drug inventory, IMP label records, and worksheets that are used as the source.

Some data may be recorded directly onto the CRF, if instructed by FHI 360; the investigational center will generate a document specifying which data are recorded directly onto CRFs. "Case report form" means any CRF, whether paper or electronic.

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

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.

The data collected on CRFs will be entered in a CDMS that meets the technical requirements described in 21CFR Part 11 (USA) and documents of other concerned health authorities. 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 will receive training on the system and study specific training. After they are trained, users will be provided with individual system access rights.

For subjects who sign an ICF but do not meet eligibility criteria, at a minimum, data for screen failure reason, demography, and adverse events from the time of informed consent will be entered onto a CRF.

13.2. Archiving of Study Documentation

13.2.1. FHI 360 Responsibilities

All data management tasks for this study are delegated to FHI 360. The original CRFs will be stored at the respective investigational centers until the end of the study.

13.2.2. 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 national and local laws, including, but not limited to:

- full case histories
- signed ICFs
- subject identification lists
- case report forms for each subject on a per-visit basis
- data from other sources (eg, external laboratory)
- safety reports
- reports of receipt, use, and disposition of the IMPs
- copies of all correspondence with FHI 360, the IRB/IEC, and any health 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 FHI 360 or sponsor notifies the institution in writing 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 FHI 360 has not provided written notification of destruction, then the investigator may submit a written request to FHI 360 at least 60 days before any planned disposition of study records. After receipt of such request, FHI 360 may arrange for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor or FHI 360. The investigator shall notify FHI 360 of any accidental loss or destruction of study records.

14. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be entered into between each 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.

15. 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 the 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 FHI 360.

When the sponsor generates reports from the data collected in this study for presentation to health authorities, drafts will be circulated to FHI 360 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 the sponsor 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.

16. REFERENCES

Committee on Practice Bulletins Gynecology. Practice Bulletin No. 168: Cervical Cancer Screening and Prevention. Obstet Gynecol 2016;128(4):e111-30.

Depo-Provera Contraceptive Injection US prescribing information. New York, NY: Pfizer Inc; 2016.

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Depo-subQ Provera 104 US prescribing information. New York, NY: Pfizer Inc; 2016.

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

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606-13.

Toh YC, Jain J, Rahnny 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.

17. SUMMARY OF CHANGES TO PROTOCOL

17.1. Protocol Amendment 02 Dated 16 March 2021

The primary reasons for this amendment are to update the assessment timepoints in Table 1 and to modify the definition of irregular vaginal bleeding as an adverse event. In addition, information was added on enrollment expansion and on collection of contraceptive and reproductive history during the screening phase.

A table showing the changes from the Protocol with Amendment 01 to Amendment 02 is provided below. All major changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. Previous text with changes indicated is presented in the column titled "Original text with changes shown", and the final text is presented in the column titled "New wording." Added text is shown in underline and deletions are shown in strike-through.

Table 1 (Study Procedures and Assessments) has been revised to reflect changes described below.

Minor editorial changes (typos, punctuation, replacing text with abbreviations, etc) have been made to the protocol and protocol synopsis, as appropriate.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.3.1 Overall Potential Benefits and Risks		
Mood evaluation will be conducted at <u>enrollment</u> ~~**baseline**~~ and during the study.	Mood evaluation will be conducted at enrollment and during the study.	Update. Timing of assessments updated.
Section 1.4.1 General Study Design Rationale		
Study participation will consist of a screening period (~~up to~~ <u>approximately</u> 1.5 months, or 6 weeks),	Study participation will consist of a screening period (approximately 1.5 months, or 6 weeks),	Update. Description of screening phase period updated
Section 2.1 Primary and Secondary Study Objectives and Measures/Parameters		

Original text with changes shown	New wording	Reason/Justification for change
The safety and local tolerability measures/parameters are: • ~~change in~~ vital signs ~~(blood pressure, respiratory rate, body temperature, and pulse)~~ and body weight measurement • ~~change in body weight~~ • ~~change in~~ vaginal bleeding pattern • ~~change in mood~~ assessment of mood by Patient Health Questionnaire-9 (PHQ-9) • ~~change in~~ liver function tests • ~~change in~~ estradiol (E2) ~~levels~~ measurements throughout the study • ~~delayed return to ovulation (>12 months after treatment initiation) where ovulation is defined as a single P≥4.7 ng/mL~~ progesterone (P) measurements at Weeks 48, 49, 50, 51, and 52	The safety and local tolerability measures/parameters are: • vital signs and body weight measurement • vaginal bleeding pattern • assessment of mood by Patient Health Questionnaire-9 (PHQ-9) • liver function tests • estradiol (E2) measurements throughout the study • progesterone (P) measurements at Weeks 48, 49, 50, 51, and 52	Update. Definition of the safety and local tolerability measures/parameters updated.
Section 3.3 Duration of Subject Participation		
Total duration of the study for each subject is expected to be ~~up to~~ approximately19.5 months, including ~~up to~~ approximately 1.5 months of screening and up to 18 months of follow-up after study treatment initiation.	Total duration of the study for each subject is expected to be approximately 19.5 months, including approximately 1.5 months of screening and up to 18 months of follow-up after study treatment initiation.	Update. Description of screening phase period updated
Section 3.4 Study Procedures		
Table 1. Study Procedures and Assessments		
See New wording column	Table 1 (Study Procedures and Assessments) has been revised as described below: • Medical history removed from enrollment phase day 0)in Table 1 • Demographics, contraceptive and reproductive history removed from enrollment phase (Day 0) in Table 1 • Mood evaluation removed from screening phase (6 weeks before Randomization) in Table 1 • Vaginal bleeding pattern removed from screening phase (6	Update. Assessments removed from the specified timepoints in Table 1.

Original text with changes shown	New wording	Reason/Justification for change
	weeks before Randomization) and lab visits (Follow-Up) in Table 1	
Demographics, ~~c~~contraceptive and ~~r~~reproductive h~~h~~istory ~~and baseline characteristics~~	Demographics, contraceptive and reproductive history	Update. Description of procedure updated.
Section 3.4.1 Procedures for Screening		
Demographic data as well as contraceptive and reproductive history will be collected and documented. Screening for eligibility will include review of eligibility criteriaand medical history ~~demographics, review of medical history~~, measurement of hemoglobin and liver enzymes, and physical examination that will include, at minimum: head/neck, ears, eyes, nose, throat, chest and lungs, cardiovascular, abdomen, skin, lymph nodes and breast assessments.	Demographic data as well as contraceptive and reproductive history will be collected and documented. Screening for eligibility, will include review of eligibility criteria and medical history, measurement of hemoglobin and liver enzymes, and physical examination that will include, at minimum: head/neck, ears, eyes, nose, throat, chest and lungs, cardiovascular, abdomen, skin, lymph nodes and breast assessments.	Addition and update. Requirement for demographic data and contraceptive and reproductive history collection was added to screening phase. Screening for eligibility updated.
BMI will be calculated based on the measured weight and height. [redacted]	BMI will be calculated based on the measured weight and height. [redacted]	Addition. [redacted]
Section 3.4.2. Procedures for Enrollment (Day 0)		
Section 3.4.2. Procedures for ~~Treatment Initiation~~ Enrollment (Day 0)	**Section 3.4.2. Procedures for Enrollment (Day 0)**	Title of Section 3.4.2 updated
In addition, an assessment of vital signs, body weight and BMI, mood, E2 and P, and MPA will be performed. ~~Relevant medical history including pre-existing conditions will be reviewed and documented.~~ Adverse events and concomitant medications will ~~also~~ be evaluated. All eligibility criteria will be verified ~~and confirmed~~ prior to randomization	In addition, an assessment of vital signs, body weight and BMI, mood, E2 and P, and MPA will be performed. Adverse events and concomitant medications will be evaluated. All eligibility criteria will be verified prior to randomization	Addition. BMI added to vital sign assessment for enrollment phase. Medical history added for reviewed documents for this phase.

Original text with changes shown	New wording	Reason/Justification for change
The injection site location will be marked and photographed for reference. [redacted] The injection site will be observed for injection site reactions (ISRs) immediately (ie, as soon as possible but no later than 10 minutes upon removing the needle) and 1 hour (±5 minutes) after the injection.	The injection site location will be marked and photographed for reference. The injection site will be observed for injection site reactions (ISRs) immediately (ie, as soon as possible but no later than 10 minutes upon removing the needle) and 1 hour (±5 minutes) after the injection.	Deletion. [redacted]
Section 5.1 Safety and Tolerability Measurements		
The following safety and local tolerability measures will be implemented throughout the study at the time points listed in Table 1: • ~~incidence~~ occurrence of adverse events • use of concomitant medication ~~use~~ • ~~change in body weight~~ • ~~assessment of~~ vaginal bleeding pattern • assessment of mood by Patient Health Questionnaire-9 (PHQ-9) • E2 ~~concentration~~ levels throughout the study • ~~assessment of return to ovulation at 52 weeks as measured by~~ P measurements at Weeks 48, 49, 50, 51, and 52 • ~~incidence~~ occurrence of injection site reactions (ISRs)	The following safety and local tolerability measures will be implemented throughout the study at the time points listed in Table 1: • occurrence of adverse events • use of concomitant medication • vaginal bleeding pattern • assessment of mood by Patient Health Questionnaire-9 (PHQ-9) • E2 levels throughout the study • P measurements at Weeks 48, 49, 50, 51, and 52 • occurrence of injection site reactions (ISRs)	Update. Definition of the safety and local tolerability measures updated.
Section 5.1.5 Assessment of Mood		
Subjects will be interviewed about aspects of and changes in mood at enrollment ~~screening~~ and at pre-defined timepoints throughout the study (Table 1).	Subjects will be interviewed about aspects of and changes in mood at enrollment and at pre-defined timepoints throughout the study (Table 1).	Update. Timing of subjects' interview on mood changes updated
Section 5.2.1 Definition of an Adverse Event		
• For the purpose of this study, irregular vaginal bleeding will not be considered an adverse event unless it requires medical intervention or meets the definition of "serious adverse event" (See Section 5.2.5)	• For the purpose of this study, irregular vaginal bleeding will not be considered an adverse event unless it requires medical intervention or meets the definition of "serious adverse event" (See Section 5.2.5)	Addition. Clarification on irregular vaginal bleeding as an adverse event added.
Section 9.1 Sample Size Determination and Rationale		

Original text with changes shown	New wording	Reason/Justification for change
The intent of the study is to have a minimum of 54 subjects with evaluable data complete 32 weeks per protocol. Additional subjects may be enrolled to complete the minimum number of evaluable subjects at the discretion of the Sponsor. SRC will provide guidance regarding the value of expanding enrollment and size of such expansion to help ensure that at least 54 subjects complete 32 weeks per protocol.	The intent of the study is to have a minimum of 54 subjects with evaluable data complete 32 weeks per protocol. Additional subjects may be enrolled to complete the minimum number of evaluable subjects at the discretion of the Sponsor. SRC will provide guidance regarding the value of expanding enrollment and size of such expansion to help ensure that at least 54 subjects complete 32 weeks per protocol.	Addition. Statement on enrollment expansion added.
9.5.2 Demographics, Contraceptive and Reproductive History ~~and Baseline Characteristics~~	**9.5.2 Demographics, Contraceptive and Reproductive History**	**Title of section 9.5.2 updated**
Subject demographics, contraceptive and reproductive history ~~and baseline characteristics~~ will be examined to assess the comparability of the treatments and will be summarized using descriptive statistics.	Subject demographics, contraceptive and reproductive history will be examined to assess the comparability of the treatments and will be summarized using descriptive statistics.	**Update. Subject's characteristics required for assessment of treatment comparability updated**
Section 9.6 Safety Analysis		

Original text with changes shown	New wording	Reason/Justification for change
Safety and local tolerability evaluation will be based on the following: • occurrence ~~incidence~~ of adverse events • use of concomitant medication ~~use~~ • change in vital signs and body weight ~~measurement~~ • change in ~~assessment of~~ mood • change in liver function tests • ~~change in~~ E2 levels ~~concentration measurement~~ • delayed ~~assessment of~~ return to ovulation (>12 months after treatment initiation) where ovulation is defined as a single P ≥4.7 ng/mL ~~at 52 weeks as measured by P ≥ 4.7 ng/mL~~ • occurrence of ~~incidence of~~ ISRs	Safety and local tolerability evaluation will be based on the following: • occurrence of adverse events • use of concomitant medication • change in vital signs and body weight • change in mood • change in liver function tests • E2 levels • delayed return to ovulation (>12 months after treatment initiation) where ovulation is defined as a single P ≥4.7 ng/mL • occurrence of ISRs	Update. Clarification on definition of safety and local tolerability evaluation measurements.
Serious adverse events and adverse events leading to withdrawal from the study will be listed separately. Concomitant medication use will be summarized by treatment group in frequency tables, by therapeutic class and medicine category.	Serious adverse events and adverse events leading to withdrawal from the study will be listed separately. Concomitant medication use will be summarized by treatment group in frequency tables, by therapeutic class and medicine category.	Addition. Clarification on summaries classification of concomitant medication use added.
Mood data will be summarized over time from ~~in tables at~~ Day 0 using frequency tables and graphical displays ~~at follow-up visits~~.	Mood data will be summarized over time from Day 0 using frequency tables and graphical displays.	Update. Clarification on display of mood data over time.
Appendix A STUDY RESPONSIBILITIES		

Original text with changes shown	New wording	Reason/Justification for change
Institutional Review Boards ~~Midlands~~ WCG IRB 1019 39th Ave., SE Suite 120 Puyallup, WA 98374 ~~8207 Melrose Drive, Suite 205~~ ~~Lenexa, Kansas 66214~~ United States of America	**Institutional Review Boards** WCG IRB 1019 39th Ave., SE Suite 120 Puyallup, WA 98374 United States of America	Updated address
Appendix B SPECIMEN SAMPLING AND HANDLING		
Sample processing (serum): 1. Collect samples (approximately 5 mL) into Vacutainer® tubes (tube red top, 13 x 75 mm, silicone coated interior) containing no anticoagulant 2. Immediately after the sample is drawn, gently invert the tube 5 times. Allow tubes to sit at room temperature for ~~15 to 30~~ at least 20 minutes (no more than 40 minutes) 3.Centrifuge ~10-15 minutes (at room temperature at 2500 to 3000 rpm [approximately 650 to 1450 x g] ~~4°C to 8°C, 2000g~~) to achieve a clear serum layer over the clotted red cells (the speed and time may be varied according to the make and model of centrifuge used)	Sample processing (serum): 1. Collect samples (approximately 5 mL) into Vacutainer® tubes (tube red top, 13 x 75 mm, silicone coated interior) containing no anticoagulant 2. Immediately after the sample is drawn, gently invert the tube 5 times. Allow tubes to sit at room temperature for at least 20 minutes (no more than 40 minutes) 3. Centrifuge ~10-15 minutes (at room temperature at 2500 to 3000 rpm [approximately 650 to 1450 x g]) to achieve a clear serum layer over the clotted red cells (the speed and time may be varied according to the make and model of centrifuge used)	Addition and update. Information added on type of sample tube, tube handling and centrifuge.
Storage: Samples will be stored at a temperature of –2~~7~~0°C in an upright position until they are shipped to the bioanalytical laboratory.	Storage: Samples will be stored at a temperature of –20°C in an upright position until they are shipped to the bioanalytical laboratory.	Update. Storage temperature of serum sample updated
Storage: For every MPA blood draw, batch one aliquot ("aliquot 1") for eventual shipment to PPD store, and one aliquot ("aliquot 2") to be stored on site during the study as back up in case additional testing is needed. ~~Storage at -15°C to -25°C without any freeze/thaw is acceptable for a period of up to 4 days if a freezer with a temperature of ≤ -65°C is not available.~~	Storage: For every MPA blood draw, batch one aliquot ("aliquot 1") for eventual shipment to PPD store, and one aliquot ("aliquot 2") to be stored on site during the study as back up in case additional testing is needed.	Update. Statement on sample aliquots added and information on acceptable period of freeze/thaw removed.

17.2. Protocol Amendment 01 Dated 02 July 2020

The primary reason for this amendment is to extend the duration of this study.

A table showing the changes from the Protocol to Amendment 01 is provided below. All major changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. Previous text with changes indicated is presented in the column titled "Original text with changes shown", and the final text is presented in the column titled "New wording." Added text is shown in underline and deletions are shown in strike-through.

The Schedule of Procedures and Assessments table (Table 1) has been revised to reflect the changes described below as applicable. Listings of individual collection or assessment times have been replaced with a reference to Table 1. Only the title of an additional table added to the body of the protocol has been included in the summary of changes.

Minor editorial changes (typos, punctuation, replacing text with abbreviations, etc) have been made to the protocol and protocol synopsis, as appropriate.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.4.1. General Study Design Rationale		
Study participation will consist of a screening period (up to 1.5 months, or 6 weeks), treatment initiation (Day 0), and at least 52 weeks of follow-up	Study participation will consist of a screening period (up to 1.5 months, or 6 weeks), treatment initiation (Day 0), and at least 52 weeks of follow-up	Update. Study duration extended.
Subjects with unresolved ISR(s) at Week 52 will be followed every 3 months through the resolution of ISR(s) or Week 78, whichever comes first.	Subjects with unresolved ISR(s) at Week 52 will be followed every 3 months through the resolution of ISR(s) or Week 78, whichever comes first.	Update. Study duration extended.
After treatment initiation, subjects will be followed for 52 weeks and provide blood samples for MPA ~~at the following time points: Days 0, 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, and 28; Weeks 6, 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days through Week 52. Blood samples for progesterone, (P,) will be collected at Weeks 48, 49, 50, 51 and 52. In addition, starting on Day 28 blood samples for~~ and estradiol (E2) as shown in Table 1 ~~will be collected every time MPA or P is measured.~~	After treatment initiation, subjects will be followed for 52 weeks and provide blood samples for MPA, P, and estradiol (E2) as shown inTable 1.	Update. Timepoints removed and reference made to Table 1.
Vaginal bleeding pattern, acceptability, and mood will be assessed throughout the study at predefined time points. ~~and acceptability will be assessed at Weeks 13, 26, and 52. Mood will be evaluated using a brief standardized questionnaire every 28 days throughout the study.~~	Vaginal bleeding pattern, acceptability, and mood will be assessed throughout the study at predefined time points.	Update. Timepoints removed and reference made to predefined time points.

Original text with changes shown	New wording	Reason/Justification for change
Urine pregnancy test will be performed ~~every 28 days starting at the Week 26 visit through the end of the study~~ periodically and ~~.~~ Information on adverse events and concomitant medicines will be collected throughout the study.	Urine pregnancy test will be performed periodically and information on adverse events and concomitant medicines will be collected throughout the study.	Update. Timing of assessments updated.
~~The study staff will provide assessment on the ease of drug re-suspension and injection.~~ The study schematic diagram is shown in Figure 1.	The study schematic diagram is shown in Figure 1.	Update. Statement regarding assessment of drug re-suspension and injection removed.
Section 3.1. General Study Design (Figure 1)		
Follow-up (~~12 months~~ up to 18 months)	Follow-up (up to 18 months)	Update. Duration of study extended.
Section 3.2.2. Subject Exclusion Criteria		
aa. has known sensitivity to MPA or inactive ingredients ~~bb. has skin disorders or skin allergies which in the opinion of the investigator would make study participation unsafe or complicate data interpretation~~ cc. plans to move to another location in the next 12 months	aa. has known sensitivity to MPA or inactive ingredients bb. plans to move to another location in the next 12 months	Clarification. This is not the primary objective of the study.
Section 3.3. Duration of Subject Participation		
Total duration of the study for each subject is expected to be up to ~~13~~19.5 months, including up to 1.5 months of screening and ~~12~~-18 months of follow-up after study treatment initiation. All subjects will be followed for at least 52 weeks after treatment initiation. If subjects have unresolved ISR(s) at Week 52, they will be followed until ISR resolution or Week 78, whichever comes first. Therefore, the minimal duration of subject participation is 52 weeks and the maximum 78 weeks after treatment initiation.	Total duration of the study for each subject is expected to be up to 19.5 months, including up to 1.5 months of screening and 18 months of follow-up after study treatment initiation. All subjects will be followed for at least 52 weeks after treatment initiation. If subjects have unresolved ISR(s) at Week 52, they will be followed until ISR resolution or Week 78, whichever comes first. Therefore, the minimal duration of subject participation is 52 weeks and the maximum 78 weeks after treatment initiation.	Update. Duration of study extended.
Section 3.4. Study Procedures (Table 1)		
[a] Subjects will return for laboratory visits at pre-defined time points: Days 0, 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, and 28; Weeks 6, 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days through Week 52.	[a] Subjects will return for laboratory visits at pre-defined time points: Days 0, 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, and 28; Weeks 6, 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days through Week 52.	Update. Footnote adding timepoints for lab visits updated.

Original text with changes shown	New wording	Reason/Justification for change
[a,b] A urine pregnancy test will be performed on Day 0; Weeks 26, 32, 36, 40, 44, 48, and 52; and at Weeks 65 and 78 if applicable, and at any other times when indicated. ~~A urine pregnancy test will be performed at Day 0; every 28 days starting at Week 26 and at any other times when indicated.~~	[b] A urine pregnancy test will be performed on Day 0; Weeks 26, 32, 36, 40, 44, 48, and 52; and at Weeks 65 and 78 if applicable, and at any other times when indicated.	Update. Footnote describing timing of pregnancy tests updated.
[c,d]ISRs will be evaluated on Day 0 immediately (ie, as soon as possible but no later than 10 minutes upon removing the needle) and 1 hour (±5 minutes) after injection; Day 7; at Weeks 13, 26, and 52 and at other visits, if indicated. Subjects who have ISR(s) at Week 52 will be followed every 3 months (at Weeks 65 and 78) until ISR resolution or Week 78, whichever is earlier. If the subject does not have any ISRs at Week 52 it will be her final visit. All subjects will be instructed to return to the clinic if any ISRs develop after their final visit.	[e]ISRs will be evaluated on Day 0 immediately (ie, as soon as possible but no later than 10 minutes upon removing the needle) and 1 hour (±5 minutes) after injection; Day 7; at Weeks 13, 26, and 52 and at other visits, if indicated. Subjects who have ISR(s) at Week 52 will be followed every 3 months (at Weeks 65 and 78) until ISR resolution or Week 78, whichever is earlier. If the subject does not have any ISRs at Week 52 it will be her final visit. All subjects will be instructed to return to the clinic if any ISRs develop after their final visit.	Update. Footnote describing assessment of ISRs during the follow-up period updated.
[e,f]During laboratory visits, information on adverse events and concomitant medications will not be solicited, but will be documented if self-reported by the subject. Adverse events and use of concomitant medications will also be evaluated during additional ISR follow up at Weeks 65 and 78.	[f]During laboratory visits, information on adverse events and concomitant medications will not be solicited, but will be documented if self-reported by the subject. Adverse events and use of concomitant medications will also be evaluated during additional ISR follow up at Weeks 65 and 78.	Update. Footnote describing the documentation of adverse events and concomitant medications during the follow-up period updated.
[g,h]Mood will be evaluated on Days 0 and 28; Weeks 8, 13, 17, 21, 26, 32, 36, 40, 44, 48, 52. ~~Mood will be evaluated at Day 0 and every 28 days throughout the study.~~	[h]Mood will be evaluated on Days 0 and 28; Weeks 8, 13, 17, 21, 26, 32, 36, 40, 44, 48, and 52.	Update. Timing of mood assessments updated.
[i,j]Vaginal bleeding pattern ~~data~~ will be assessed ~~collected at Screening, and~~ at Weeks 13, 26, and 52.	[i]Vaginal bleeding pattern will be assessed at Weeks 13, 26, and 52.	Update. Timing of vaginal bleeding pattern assessments updated.
Section 3.4.3. Procedures for Follow-Up		
Study follow-up will last for at least 52 weeks from treatment initiation.	Study follow-up will last for at least 52 weeks from treatment initiation.	Update. Duration of follow-up period extended.
Vaginal bleeding pattern ~~and~~, acceptability and mood will be evaluated throughout the study at pre-defined time points. ~~at Weeks 13, 26, and 52. Mood will be evaluated using a brief standardized questionnaire every 28 days throughout the study.~~ Urine pregnancy tests will be administered ~~every 28 days~~ periodically starting at Week 26 through the end of the study.	Vaginal bleeding pattern, acceptability and mood will be evaluated throughout the study at pre-defined time points (See Table 1). Urine pregnancy tests will be administered periodically starting at Week 26 through the end of the study.	Update. Assessment of mood added to follow-up period.

Original text with changes shown	New wording	Reason/Justification for change
In addition to the scheduled follow-up visits, subjects will return for laboratory visits to provide blood samples for MPA, P and E2 ~~at the following time points: Days 0, 1, 2, 3, 5, 7, 10, 12, 14, 18, 21, and 28; Weeks 6, 8, 10, 12, 13, 15, 17, 19, 21, 23, 25, 26, 28, 30, and 32; and then every 28 days through Week 52. Blood samples for P will be collected at Weeks 48, 49, 50, 51 and 52. In addition, starting on Day 28 blood samples for E2 will be collected every time MPA or P is measured.~~ at pre-defined time points (see Table 1).	In addition to the scheduled follow-up visits, subjects will return for laboratory visits to provide blood samples for MPA, P and E2 at pre-defined time points (see Table 1).	Update. Collection times removed and replace with a reference to Table 1.
If the subject has new or ongoing ISR at Week 52, she will be followed every 3 months (at Weeks 65 and 78) until ISR resolution or Month 18 (Week 78), whichever is earlier. If the subject does not have any ISRs at Week 52 it will be her final visit. However, all subjects will be instructed to return to the clinic if any ISRs develop after their final visit. In that case, their status will change from completed the study to active and they will be followed per the schedule above until ISR resolution or Week 78, whichever is earlier.	If the subject has new or ongoing ISRs at Week 52, she will be followed every 3 months (at Weeks 65 and 78) until ISR resolution or Month 18 (Week 78), whichever is earlier. If the subject does not have any ISRs at Week 52 it will be her final visit. However, all subjects will be instructed to return to the clinic if any ISRs develop after their final visit. In that case, their status will change from completed the study to active and they will be followed per the schedule above until ISR resolution or Week 78, whichever is earlier.	Update. Procedures for reporting and recording ISRs during the follow-up period.
Follow up visits should be scheduled using the target window periods below. However, if a subject cannot attend a visit within the target window below, the visit procedures should be conducted as soon as possible regardless of timing.	Follow up visits should be scheduled using the target window periods below. However, if a subject cannot attend a visit within the target window below, the visit procedures should be conducted as soon as possible regardless of timing.	Addition. A description of the table including the target time windows.
Table 2. Target Time Windows for Follow-up Visits	Table 2. Target Time Windows for Follow-up Visits	Addition. Table 2 was added to include the target time windows for follow-up visits
Section 4.5. Interim Data Reviews		
The SRC will convene for at least ~~single planned~~one review of interim data after at least 80% of subjects have had a chance to complete 7.5 months after treatment initiation.	The SRC will convene for at least one review of interim data after at least 80% of subjects have had a chance to complete 7.5 months after treatment initiation.	Clarification. Timing of interim data review updated.
Section 5.1.5. Assessment Of Mood		
Subjects will be interviewed about aspects of and changes in mood at screening and at pre-defined ~~on a regular basis~~ timepoints throughout the study (Table 1).	Subjects will be interviewed about aspects of and changes in mood at screening and at pre-defined timepoints throughout the study (Table 1).	Clarification. Time of assessments updated to pre-defined timepoints
Section 5.1.9. Injection Site Reactions (ISRs)		

Original text with changes shown	New wording	Reason/Justification for change
Injection site reaction (ISR) will be evaluated ~~measured~~ as detailed in Table 1.	Injection site reaction (ISR) will be evaluated as detailed in Table 1.	Clarification.
For the purpose of this protocol, injection site pain will include pain associated with injection and any pain or tenderness at/around the injection site. ~~For the purpose of this protocol, injection site pain will include pain associated with insertion of the needle, injecting of the drug, and any pain or tenderness at/around the injection site.~~	For the purpose of this protocol, injection site pain will include pain associated with injection and any pain or tenderness at/around the injection site.	Update. Injection site description updated.
Injection sites will be monitored for the progress of ongoing and/or occurrence of new ISRs. If the subject has new or ongoing ISR at Week 52, she will be followed every 3 months (at Weeks 65 and 78) until ISR resolution or Week 78, whichever is earlier.	Injection sites will be monitored for the progress of ongoing and/or occurrence of new ISRs. If the subject has new or ongoing ISR at Week 52, she will be followed every 3 months (at Weeks 65 and 78) until ISR resolution or Week 78, whichever is earlier.	Update. Procedures related to ISR monitoring updated.
ISRs will be evaluated at all study timepoints listed in Table 1 by subject's self-reports and visual examination of the site of injection by blinded study staff.	ISRs will be evaluated at all study timepoints listed in Table 1 by subject's self-reports and visual examination of the site of injection by blinded study staff.	Clarification. Table 1 is listed as a reference for timepoints.
The study staff will be instructed to use non-leading questions (eg, "Do you have any new medical issues since previous visit?") ~~how does the injection site feel, do you have any new complaints about the injection site since last visit)~~ for ISR ascertainment. ~~Injection site pain will be evaluated by self reports.~~	The study staff will be instructed to use non-leading questions (eg, "Do you have any new medical issues since previous visit?") for ISR ascertainment.	Update. Questions regarding ISRs removed. Statement regards self-reports of ISRs removed.
~~If necessary, a consultation with an appropriate clinical expert may be scheduled.~~ All cases of injection site discoloration (hypopigmentation) will be photographed ~~and consulted by a dermatologist.~~ If necessary, a consultation with an appropriate clinical expert may be scheduled.	All cases of injection site discoloration (hypopigmentation) will be photographed. If necessary, a consultation with an appropriate clinical expert may be scheduled.	Update. Details describing ISR documentation and evaluation updated.
Section 5.2.2. Recording and Reporting Adverse Events		
For this study, the follow up period is defined as up to 78 ~~52~~-weeks after the last dose of IMP.	For this study, the follow up period is defined as up to 78 weeks after the last dose of IMP.	Update. The follow-up period of the study updated.
At the scheduled ~~Week 1 (Day 7) and Week 13, 26, and 52~~ visits, the investigator will 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."	At the scheduled visits, the investigator will 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."	Update. Days removed.
Section 5.2.5.3.1. Investigator Responsibility		

Original text with changes shown	New wording	Reason/Justification for change
~~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 will be reported to the sponsor, within 24 hours, from when the investigator becomes aware of them.~~ The investigator does not need to actively monitor subjects for adverse events once their follow-up period has ended. Serious adverse events occurring after study discontinuation will be reported to the sponsor within 24 hours from when the investigator becomes aware of them, following the procedures described in Section 5.2.5.3.	The investigator does not need to actively monitor subjects for adverse events once their follow-up period has ended. Serious adverse events occurring after study discontinuation will be reported to the sponsor within 24 hours from when the investigator becomes aware of them, following the procedures described in Section 5.2.5.3.	Update. Investigator responsibilities after a subject's follow-up period updated.
Section 5.2.9. Pregnancy		
During the study, a pregnancy test will be performed ~~if the woman is experiencing any symptoms or signs of pregnancy, or thinks she may be pregnant, and every 28 days between Weeks 26 and 52.~~ as detailed in Table 1, and at any time the woman is experiencing any symptoms or signs of pregnancy, or thinks she may be pregnant.	During the study, a pregnancy test will be performed as detailed in Table 1, and at any time the woman is experiencing any symptoms or signs of pregnancy, or thinks she may be pregnant.	Update. Additional times for pregnancy tests included.
Section 8. ACCEPTABILITY ASSESSMENTS		
The acceptability of the different injection doses and treatment groups will be assessed and recorded on appropriate study CRFs at Weeks ~~13,~~ 26~~,~~ and 52 by blinded staff. Acceptability questions will include but not be limited to questions about ~~acceptability of the bleeding patterns and other side effects,~~ what she likes and dislikes most about this method, and whether she would use this method in the future and/or recommend it to a friend.	The acceptability of the different injection doses and treatment groups will be assessed and recorded on appropriate study CRFs at Weeks 26 and 52 by blinded staff. Acceptability questions will include but not be limited to questions about what she likes and dislikes most about this method, and whether she would use this method in the future and/or recommend it to a friend.	Update. Timing of acceptability assessments updated. Questions included in the assessment updated.
Section 9.3.4. Pharmacokinetic Analysis Set		
~~Follow-up time will also be censored after a subject initiates use of a concomitant medication known to impact the pharmacokinetics of MPA.~~ The analysis set will exclude MPA data collected during time periods when subjects used a concomitant medication known to impact the pharmacokinetics of MPA.	The analysis set will exclude MPA data collected during time periods when subjects used a concomitant medication known to impact the pharmacokinetics of MPA.	Update. Data excluded from the analysis set updated.
Section 9.5.2. Demographic and Baseline Characteristics		

Original text with changes shown	New wording	Reason/Justification for change
Subject demographic and baseline characteristics, ~~including medical history, and prior medications~~ will be examined to assess the comparability of the treatments and will be summarized using descriptive statistics.	Subject demographic and baseline characteristics, will be examined to assess the comparability of the treatments and will be summarized using descriptive statistics.	Update. Demographics data collected updated.
Section 9.6. Safety Analysis		
The percentage of women experiencing amenorrhea or vaginal bleeding disturbances (irregular vaginal bleeding or spotting) will likewise be summarized descriptively and compared between the test and reference ~~treatment~~ groups. Mood data will be summarized in tables at ~~approximately monthly~~ Day 0 and at follow-up visits.	The percentage of women experiencing amenorrhea or vaginal bleeding disturbances (irregular vaginal bleeding or spotting) will likewise be summarized descriptively and compared between the test and reference groups. Mood data will be summarized in tables at Day 0 and at follow-up visits.	Update. "Test and reference" group added. Timing of mood data summaries updated.
Section 9.8. Acceptability Analysis		
The responses to acceptability questions at Weeks 26 and 52, including likes and dislikes of the method and willingness to use the product in the future will be tabulated in frequency tables and compared between the test and the reference groups using descriptive Chi-squared tests.	The responses to acceptability questions at Weeks 26 and 52, including likes and dislikes of the method and willingness to use the product in the future will be tabulated in frequency tables and compared between the test and the reference groups using descriptive Chi-squared tests.	Addition. Acceptability analysis added.
Section 9.9. Planned Interim Analysis		
At least ~~O~~one interim review is planned to occur after at least 80% of subjects have had a chance to complete 7.5 months after treatment initiation. This analysis is intended to help inform the decision to move to, and select the dose for, a pivotal study. These interim data may be used to inform the end of Phase 1 meeting with the FDA.	At least one interim review is planned to occur after at least 80% of subjects have had a chance to complete 7.5 months after treatment initiation. This analysis is intended to help inform the decision to move to, and select the dose for, a pivotal study. These interim data may be used to inform the end of Phase 1 meeting with the FDA.	Update. Frequency of planned interim review updated.
APPENDIX A. Study Responsibilities		
Site Investigators	Site Investigators	Update. Multiple site investigators added.

Original text with changes shown	New wording	Reason/Justification for change
[redacted] Asociación Dominicana Pro Bienestar de la Familia, Inc. (PROFAMILIA) [redacted] ICON [redacted] WCCT [redacted]	[redacted] Asociación Dominicana Pro Bienestar de la Familia, Inc. (PROFAMILIA) [redacted] ICON [redacted] [redacted]tigator WCCT [redacted]	Update. Additional investigators included.
[redacted] FHI 360 [redacted]	[redacted] FHI 360 [redacted]	Update. Title changed.
~~Central~~ Institutional Review Boards	Institutional Review Boards	Update. Central IRB removed.
Midlands IRB 8207 Melrose Drive, Suite 205 Lenexa, Kansas 66214 United States of America Ethical Committee of Profamilia Clínica Abreu, Calle Beller #42 esq. Ave. Independencia Santo Domingo, Dominican Republic CONABIOS Ave. Bolívar #902, La Julia Santo Domingo, Dominican Republic ~~Protection of Human Subjects Committee FHI 360~~ [redacted]	Midlands IRB 8207 Melrose Drive, Suite 205 Lenexa, Kansas 66214 United States of America Ethical Committee of Profamilia Clínica Abreu, Calle Beller #42 esq. Ave. Independencia Santo Domingo, Dominican Republic CONABIOS Ave. Bolívar #902, La Julia Santo Domingo, Dominican Republic	Update. IRBs added.

APPENDIX A. STUDY RESPONSIBILITIES

Sponsor's Authorized Representative	[redacted]
Sponsor's Medical Expert	[redacted] Nuventra, Inc.™ [redacted]
Sponsor's Safety Representative	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. [redacted]
Site Investigators	[redacted] Asociación Dominicana Pro Bienestar de la Familia, Inc. (PROFAMILIA) [redacted] ICON [redacted] WCCT [redacted]
Coordinating Investigator	[redacted] FHI 360 [redacted]
Monitor	FHI 360 [redacted]
Trial Supply Management (TSM) Vendor	Actavis Laboratories UT, Inc 577 Chipeta Way Salt Lake City, UT 84108, USA

Institutional Review Boards	WCG IRB 1019 39th Ave., SE Suite 120 Puyallup, WA 98374 United States of America Ethical Committee of Profamilia Clínica Abreu, Calle Beller #42 esq. Ave. Independencia Santo Domingo, Dominican Republic CONABIOS Ave. Bolívar #902, La Julia Santo Domingo, Dominican Republic

APPENDIX B. SPECIMEN SAMPLING AND HANDLING

Pharmacokinetic Serum Collection and Processing Instructions	
Venipuncture and transfer tube label information	Study number, subject randomization number, sample type (eg, PK), study period (if applicable), nominal collection time, sample set (A or B)
Sample processing (serum)	1. Collect samples (approximately 5 mL) into Vacutainer® tubes (tube red top, 13 x 75 mm, silicone coated interior) containing no anticoagulant 2. Immediately after the sample is drawn, gently invert the tube 5 times. Allow tubes to sit at room temperature for at least 20 minutes (no more than 40 minutes) 3. Centrifuge ~10-15 minutes (at room temperature at 2500 to 3000 rpm [approximately 650 to 1450 x g]) to achieve a clear serum layer over the clotted red cells (the speed and time may be varied according to the make and model of centrifuge used) 4. Transfer approximately equal portions of separated serum (at least 1 mL) into 2 labeled, polypropylene transfer tubes (sets A and B)
Storage	Samples will be stored at a temperature of –20°C in an upright position until they are shipped to the bioanalytical laboratory. For every MPA blood draw, batch one aliquot ("aliquot 1") for eventual shipment to PPD store, and one aliquot ("aliquot 2") to be stored on site during the study as back up in case additional testing is needed.
Shipping	The bioanalytical laboratory will be notified prior to the shipment of the samples. Primary and backup samples are not to be sent in the same shipment. An electronic file containing sample collection dates will be emailed to the bioanalytical laboratory and the sponsor's bioanalytical department representative for each shipment.