ACTG A5338

An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)

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FINAL

Statistical Analysis Plan

Version 2.0

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1 Study design

ACTG A5338 is a phase II, open-label, single-arm, multicenter, steady-state pharmacokinetic (PK) study of drug-drug interactions in HIV and TB co-infected women treated with DMPA while receiving an efavirenz (EFV)-based combination anti-retroviral therapy (cART), rifampicin (RIF) and isoniazid (INH).

The study population is premenopausal women, 18 to 46 years of age, who are co-infected with HIV and TB. To be eligible to enroll in the study, participants must be on EFV plus two or more nucleoside reverse transcriptase inhibitors (NRTIs) for at least 28 days prior to study entry with no plans to change therapy for the 12 weeks of the study. Women must be on the continuation phase of active TB treatment taking RIF and INH on a 5-day or more per week schedule.

Additional entry criteria include:

- Premenopausal women with presumed normal ovarian function based on normal menstrual history and absence of previous ovarian dysfunction diagnosis.
- Last menstrual period $\leq$35 days prior to study entry. If last menstrual period >35 days prior to study entry, serum follicle-stimulating hormone (FSH) must be checked and be $\leq$40 mIU/mL to be eligible for enrollment. NOTE: Enrollment after the start of monthly menstrual flow is preferred, but not required.
- Negative serum or urine-HCG pregnancy test.
- No receipt of DMPA or any other injectable contraceptives within 180 days prior to study entry.
- No receipt of other hormonal contraceptives within 30 days prior to study entry.

This is a limited-site study. The sites were selected based on the availability of potentially eligible participants, close proximity to a TB clinic, integrated HIV/TB programs and interest in the study according to responses to a site feasibility survey. The approved sites are listed on the protocol-specific Web page.

1.1 Study Treatment

DMPA is the only drug provided by the study. cART and TB treatment medications are not provided by this study.

DMPA 150 mg is administered intramuscularly as a single-dose at study entry.

An optional dose of DMPA will be available at no cost to all study participants (after confirmation of a negative pregnancy test) who successfully complete all 12 weeks of the study, experience no adverse events (AEs) from the first injection, and are interested in continuing with DMPA outside of the protocol.

1.2 Evaluations

A single PK blood sample will be collected for assay of MPA at entry (day 0), just prior to DMPA injection and at weeks 2, 4, 6, 8, 10 and 12 after DMPA injection. The proportion of participants with sub-therapeutic MPA levels (<0.1 ng/mL) will be estimated based on the participants who complete the PK sampling at 12 weeks after DMPA administration.

After entry, a participant who misses 2 or more doses of RIF or EFV within the one-week prior to a scheduled PK sampling visit will have the visit rescheduled to one week later.

Other assessments include plasma progesterone levels (weeks 2, 4 6, 8, 10 and 12); clinical assessments for safety (including blood chemistry and hematology tests) at each study visit and at premature

discontinuation; CD4+/CD8+ (entry only), plasma HIV-1 RNA (entry and week 12); stored whole blood for drug metabolism genotype;and stored serum for bone metabolism biomarkers and others.

1.3 Definition of PK and safety populations, and about replacements

The **PK population** ("evaluable for primary endpoint" per protocol language) consists of participants who complete the MPA PK sampling and are compliant with study dosing and evaluations. Specifically, participants are excluded from the PK population, and are replaced in accrual for noncompliance with protocol (stated in protocol section 8.1) if:

- Participant fails to attend 2 consecutive visits at week 2, 4, 6, or 8.
- Participant fails to attend either the week 10 or week 12 visit.
- Participant misses 2 or more RIF and/or EFV doses within one week prior to PK sampling at week 2, 4, 6, or 8 and did not return with acceptable adherence for the rescheduled PK sampling visit for 2 consecutive study weeks.
- Participant misses 2 or more RIF and/or EFV doses within one week prior to PK sampling at week 10 or 12 and did not return with acceptable adherence for the rescheduled PK sampling.

Participants are also excluded from the PK population and replaced in accrual for certain changes to the cART or TB regimen during the 12 weeks on study (stated in protocol section 8.2); specifically:

- Addition of another NNRTI or any PI.
- Any substitution within the NNRTI class.
- Addition of an integrase inhibitor or entry inhibitor to the regimen.
- NOTE: Participants may stay on study if they change or discontinue one or more of their NRTIs, since this class of medications is not thought to affect the metabolism of DMPA or EFV. See section 5.4.2 for the NRTI combinations that are not allowed in this study.
- Stopping RIF secondary to toxicity or resistance.
- Addition of TB medications, to the study TB regimen of RIF and INH, of TB meds known to induce or inhibit the cytochrome p450 enzyme system, as identified by having study chairs review the complete list of all such meds. (When guidelines at the Botswana site changed to include Ethambutol, the team allowed the use of this drug.) Study chairs and pharmacologist will review a list of such medications, identifying those of concern and not.

The **safety population** (participants to be included in toxicity summaries) consists of participants to whom the DMPA injection was administered and had evaluations conducted during at least one post-baseline visit.

1.4 Accrual target, duration of study and anticipated time to meet accrual target

The accrual target is a total of 46 evaluable participants.

The duration of the study is 12 weeks from entry through the final clinic visit.

Accrual to A5338 was anticipated to take approximately 12 months (anticipate 3-4 participants to enroll per month). The study team anticipated enrolling approximately 4 participants per month, in which case the accrual target was expected to be met about 12 months after the first participant enrolled.

1.5 SAP version history

Version	Changes Made	Effective Date
1	Original Version	9/25/2017
2	Requirements for program validation and results verification were removed (to Analysis Implementation Plan). Minor clarifications were made.	4/30/2018

2 Study hypothesis and objectives

2.1 Hypothesis

Concurrent use of efavirenz (EFV) and rifampicin (RIF) will increase the clearance of medroxyprogesterone acetate (MPA) in HIV and TB coinfected women, resulting in reduced plasma MPA concentrations and reduced contraceptive efficacy.

2.2 Primary objectives

2.2.1 To estimate the optimal dosing frequency of DMPA for HIV and TB coinfected women taking EFV-based combination antiretroviral therapy (cART) and RIF-containing TB treatment, based on a target MPA concentration >0.1 ng/mL.

2.2.2 To determine whether a 150 mg DMPA IM injection will be adequate to suppress ovulation through 12 weeks in women taking EFV-based cART and RIF-containing TB treatment based on serial plasma progesterone concentrations.

2.3 Secondary objectives

2.3.1 To estimate the area under the concentration-time curve (AUC), trough concentration (Cmin), maximum concentration (Cmax), apparent clearance (CL/F), and half-life (t1/2) of MPA in HIV and TB coinfected women taking EFV-based cART and RIF-containing TB treatment.

2.3.2 To estimate time and variability in time to MPA Cmin reaching 0.1ng/mL or less in HIV and TB coinfected women taking EFV-based cART and RIF-containing TB treatment.

2.3.3 To estimate the proportion of participants who maintain MPA levels above the minimum level thought to suppress ovulation (MPA 0.1ng/mL) through 12 weeks after DMPA administration.

2.3.4 To evaluate the toxicity and safety of concurrent RIF, EFV, and DMPA use.

2.4 Exploratory objectives

2.4.1 To explore whether pharmacokinetic (PK) interactions between EFV, RIF, and/or DMPA are affected by human genetic polymorphisms that have been reported to affect metabolism of these drugs.

2.4.2 To explore body mass index (BMI) and body fat content over time and correlate with DMPA levels.

2.4.3 To explore relationship between DMPA and bone metabolism in the HIV and TB coinfected women.

3 Sample size considerations

A5338 is a phase II, open-label, single-arm, PK study to estimate the optimal dosing frequency of DMPA for HIV- and TB-coinfected women taking EFV-based combination antiretroviral therapy (cART) and RIF-containing TB treatment, based on MPA and plasma progesterone concentrations measured at week 12 (end of the dosing interval). The primary analysis consists of reporting proportions (and associated confidence intervals) of participants with MPA concentrations below 0.1 ng/mL (the threshold below which ovulation is no longer expected to be suppressed) and with plasma progesterone above 5 ng/mL (indicating the return of luteal activity and ovulation).

For the primary analysis outcome, of women with sub-therapeutic MPA levels (<0.1 ng/mL) at week 12, a one-sided binomial test with significance level 0.05 of the null hypothesis will be conducted. The null hypothesis is that the proportion of women with sub-therapeutic MPA concentration is 6% or less. If the true proportion of women with sub-therapeutic MPA levels at week 12 is at least 21% (15% or more above the null 6% threshold), the sample size of 42 women provides 90% power to reject the null. Based on the results from a PK study of oral contraceptives containing ethinyl estradiol (estrogen) and norethindrone (progestin) which are metabolized by CYP3A4 enzyme, the study team considers that the underlying proportion of women with sub-therapeutic MPA levels of 21% or higher (15% or higher increase from the 6% threshold) is plausible in the setting of coadministration with EFV and RIF.

To protect against 10% loss of data contributing to the primary outcome measures after accrual is closed (eg, loss of sample or inability to assay), the accrual target is a total of 46 women.

Appendix 1 shows sample size considerations as stated in the protocol.

4 Planned analyses

4.1 General statistical methods

See definitions of PK and safety populations in Section 1.3 herein.

Statistical tests are considered significant if the p-value is at/below 0.05. Confidence intervals (CIs) are calculated to have 95% coverage probability. No adjustments are made for multiple comparisons.

PK parameters will be determined using standard non-compartmental approach, using validated SAS 9.4 code (SAS Institute Inc., Cary, NC, USA).

4.2 Accrual, study disposition, and demographic and baseline clinical characteristics

Accrual counts by month and site will be tabulated.

A CONSORT diagram will be used to account for all participants who enrolled in the study, showing early study discontinuations and losses from the safety and PK populations.

Counts and percentages of participants by off-treatment reason and by off-study reason will be tabulated.

Listings of premature off-treatment and off-study participants will give details about the discontinuation.

Demographic and baseline clinical characteristics will be summarized for all participants who enrolled, and for the PK population participants. Categorical characteristics will be summarized by counts and percentages. Continuous characteristics will be summarized by mean, standard deviation (SD), median, 25 and 75th percentiles (interquartile range, IQR) and minimum and maximum (range). Categorical characteristics include race, ethnicity. Continuous baseline characteristics include height, weight, BMI, plasma HIV-1 RNA, and CD4+ and CD8+ counts and percentages. Percentages of participants with plasma HIV-1 RNA viral load <400 and <50 copies/mL at study entry will also be tabulated.

4.3 MPA and progesterone concentrations at week 12 (primary) and other weeks (secondary)

Apart from week 0 measurements, MPA and progesterone concentrations reported as below the lower limit of the assay will be assigned values of half the lower limit, respectively. Week 0 MPA

concentrations reported as below the lower limit of the assay will be assigned a value of zero (as MPA is not an endogenous chemical).

Participant-specific concentration-time plots of MPA and progesterone will be created. Separately for MPA and progesterone, plots of mean concentration, ± SD, by scheduled week (2, 4, 6, 8, 10, and 12) will be generated. Similarly, plots of median concentration, ± IQR, concentrations by scheduled week will be generated.

The primary endpoints are the percentages of participants with MPA concentrations below 0.1 ng/mL and with progesterone concentrations above 5, 3 and 1 ng/mL. (Serum progesterone of 5 ng/mL or above indicates a return of ovulation.) We will also report % with progesterone above 3 and above 1 ng/mL. The week 12 values are those obtained closest to 84 days after DMPA administration, within ±7 days (as stated in protocol Section 6.2.3; all data will be included in population PK modeling). Counts, percentages and 95% confidence intervals (CIs) around the percentages will be tabulated. (Note that protocol specified that CIs would have 90% coverage, but this was stated in error.) For calculation of CIs, Clopper-Pearson exact methods for binomial measurements will be used. (Note that this analysis also addresses secondary objective 2.3.3)

For completeness, proportions below the MPA and above the progesterone thresholds at other visits (weeks 2, 4, 6, 8, and 10) will also be tabulated. Week-specific summary statistics for MPA and progesterone concentrations will also be tabulated (mean, SD, median, IQR, and range).

4.4 MPA PK parameters (secondary objective 2.3.1), using noncompartmental analysis

Using standard non-compartmental methods, the following participant-specific MPA PK parameters will be calculated: AUC over the 12 weeks ($AUC_{0\text{-}12wk}$, defined as the sum of trapezoids), C_{min} (minimum observed concentration), C_{max} (maximum observed concentration), apparent clearance (CL/F, dose amount divided by $AUC_{0\text{-}12wk}$), and half-life ($t_{1/2}$, assuming exponential decay, estimated by fitting a log-linear regression to the 3 or more observed concentrations that occur <u>after</u> [not including] Cmax; if 3 such concentrations are not available, half-life will not be calculated, but population PK modeling will yield estimates for all participants). Descriptive statistics of these PK parameters will be tabulated, where descriptive statistics consist of mean, SD, median, IQR and range; for CL/F and $t_{1/2}$, descriptive statistics consist of median, IQR and range only.

4.5 Time and variability in time to MPA C_{min} falling below 0.10 ng/mL (secondary objective 2.3.2), using nonlinear mixed-effect population PK modeling

Estimation of time to MPA < 0.10 ng/mL is best addressed via nonlinear mixed-effects modeling, which (pending funding) will be performed by Paolo Denti in Helen McIlleron's pharmacology laboratory. Output of such modeling will produce the time (with 95%CI) for a typical individual to reach a concentration of 0.1 ng/mL, as well as the typical concentration (with 95%CI) at 84 days. Section 6/Appendix 2 herein shows protocol Section 10, Pharmacology Plan.

4.6 Safety and tolerability of concurrent RIF, EFV and DMPA (secondary objective 2.3.4)

Signs/symptoms, blood chemistry values and hematology values of grade 3 and higher will be summarized for participants in the safety population. Counts and proportions of participants (with Clopper-Pearson 95% CIs around the proportions) exhibiting grade 3 toxicities, grade 4 toxicities and death (if any; not expected) will be tabulated, overall, by MedDRA system organ class (SOC) and by

MedDRA preferred term. DMPA-related side effects such as vaginal bleeding, cramping, and vaginal candidiasis, of grades 1 and 2 will also be summarized[1]. A listing of such toxicities will also be provided, showing onset and resolution day (if resolved) relative to first dose of study drug. In the listings, events will be flagged with indicators for (a) "grade is higher than that for the same event/finding present at baseline (if present as baseline)" and (b) whether or not the team deemed the event related to study drug.

To provide information on tolerability, counts and proportion of participants prematurely discontinuing study drug and study participation will be tabulated, with Clopper-Pearson 95% CIs around the proportions).

The number of pregnancies believed to have begun while on study treatment (if any) will be reported.

4.7 Concomitant medications

A list of reported concomitant medications will be prepared for review by the study chairs. If concomitant medications are identified that have the potential for pharmacokinetic interactions with the study drugs, a listing of participants taking these drugs will be included in the Final Analysis Report (FAR),showing study days on which the concomitant medications of concern were started and stopped. This listing provides context for the estimated PK parameters.

4.8 Week 12 plasma HIV-1 RNA

Percentages of participants with plasma HIV-1 RNA viral load <400 and <50 copies/mL at the week 12 visit will be tabulated.

4.9 Exploratory objectives to be address in primary analysis report

Among secondary objectives, the primary analysis report will summarize changes in plasma HIV-1 RNA, body mass index[2], and waist-to-height ratio [3] over time, and in relation to MPA concentrations.

4.10 Exploratory objectives to be address in later analysis report

A secondary analysis report will summarize: (1) relationships between EFV, RIF and MPA PK parameters and human genetic polymorphisms that have been reported to affect metabolism of these drugs (pharmacogenomics); and (2) relationships between DMPA administration and biomarkers of bone metabolism.

[1] Statisticians will collaborate with Chairs to identify the MedDRA codes that correspond to DMPA-related side effects.

[2] Body mass index, BMI: if wtkgs eq . then wtkgs = round(wtlbs/2.2, .1); if htcm eq . then htcm = htin / 0.39; htmeter = htcm/100; * BMI = weight (in kg) / height squared (in meters).; bmi = wtkgs / (htmeter**2);

[3] Waist-to-height ratio, WHtR, is a measure of body fat content, calculated as 100*waist circumference/height, after converting waist circumference and height to common units.

5 Appendix 1, sample size considerations as stated in protocol

It is known that DMPA, EFV, and RIF drugs share some common metabolic pathways via the CYP3A4 enzyme system: MPA is metabolized by and induces CYP3A4 activity; RIF is primarily metabolized by CYP2B6 system but also by CYP3A4 and induces CYP3A4 and CYP2B6 enzyme activities; EFV is primarily metabolized by CYP2B6 and both induces and inhibits CYP3A4 enzyme activity (mixed and unpredictable activity). Therefore, it is anticipated that co-administration with EFV and RIF will induce clearance of MPA concentration, resulting in lower MPA concentrations during the elimination phase, compared to those seen when DMPA is administered alone. Thus, DMPA may need to be administered more frequently when used together with EFV and RIF.

The study hypothesis is that concurrent use of EFV and RIF increases the clearance of MPA, resulting in reduced MPA concentrations. The study will evaluate whether more frequent DMPA dosing is needed when DMPA is administered in combination with EFV and RIF in HIV- and TB-infected women. The evaluation of dosing frequency will be conducted by estimating the proportion of women with MPA levels <0.1 ng/mL 12 weeks post-dose (at the end of the dosing cycle). The critical value 0.1 ng/mL for MPA levels was chosen based on published papers including studies by Mishell et al (1996) and Smit et al. (2004). These studies indicate that when MPA level falls below 0.1 ng/mL, serum progesterone level rises and the probability of ovulation increases.

In ACTG DMPA studies A5093 and A5283 in HIV-infected women, of the 79 PK evaluable participants, 5 women had MPA levels <0.1 ng/mL at 12 weeks after a single dose of DMPA was administered. None of these 5 women, however, had any evidence of ovulation (serum progesterone levels remained below 5 ng/mL). In a study by Smit et al. (2004), in 94 women, all but one woman had MPA levels above 0.1 ng/mL at 12 weeks after DMPA administration. These 94 women had received either a single dose or multiple doses of DMPA. Therefore, based on the single dose studies, the proportion of women with MPA levels <0.1 ng/mL (sub-therapeutic MPA levels) 12 weeks post-dose is thought to be about 6% in normal DMPA use, although a study conducted by Trussell et al. (2011)showed that there is a contraceptive failure rate of about 0.3% when DMPA is used correctly.

The primary analysis outcome will be the proportion of women with sub-therapeutic MPA levels (<0.1 ng/mL) at 12 weeks. A one-sided binomial test with significance level 0.05 will be used to test the null hypothesis that the proportion of women with sub-therapeutic MPA level is 6% or less. A sample size of 42 women provides 90% power to reject the null hypothesis if the proportion of women with sub-therapeutic MPA levels in this study is at least 21% (this is 15% or higher increase from the 6% threshold). With a sample size of 42 women, the underlying true proportion will be declared as statistically significant increase if 6 or more women have sub-therapeutic MPA levels at 12 weeks (this is equivalent to saying that 90% CI for the underlying proportion is entirely above the 6% threshold). Based on the results from a PK study of oral contraceptives containing ethinyl estradiol (estrogen) and norethindrone (progestin) which are metabolized by CYP3A4 enzyme(LeBel et al, 1998), the study team considers that the underlying proportion of women with sub-therapeutic MPA levels of 21% or higher (15% or higher increase from the 6% threshold) is plausible in the setting of coadministration with EFV and RIF.

The statistical power was also examined to see if the sample size will achieve a plausible power to detect a clinically meaningful decrease (30%) in MPA concentration at 12 weeks (MPA C_{min}) as one of the secondary objectives. With a significance level of 0.05, a one-sided t-test showed about 91% and 84% power to detect a 30% decline when the coefficient of variation (CV) is 60% and 70%, respectively (in the ACTG study A5093, CV of MPA C_{min} was approximately 57% when coadministered with EFV). We note that this power was examined in log_e-scale since it is known that PK parameter C_{min} has a *log*-normal distribution.

To protect against 10% loss of the primary outcomes after study accrual is closed, the study will enroll a total of 46 women. (In the ACTG DMPA study, A5093, the loss of the primary outcomes of week 12 was 9.8% [6 of 61 participants] due to either sample specimen loss or assay results not available.)

6 Appendix 2, "Pharmacology Plan" (Section 10) as stated in protocol

Women stable on an EFV and 2 NRTIs-based regimens, who are on RIF and INH, and who have not received DMPA within the last 180 days, received one dose of DMPA at study entry. An optional dose of DMPA wad made available at no cost to all study participants, after all week 12 study evaluations are completed. Refer to section 5.1.1 for the allowed NRTIs and section 5.4.2 for the prohibited NRTI combinations.

The primary PK analysis is described in section 9.6. The secondary PK analysis employing a population approach and nonlinear mixed effects modelling is described in this section.

10.1 Pharmacology Objectives

Using nonlinear mixed-effects (NLME) modeling, the population PK of MPA will be described in the population in order:

10.1.1 To describe the structural PK model for MPA given in the DMPA formulation.

10.1.2 To identify and quantify the effects of covariates influences on PK (eg, weight [including total, fat and lean components], age, time on TB treatment, time on ART, adherence to ART and TB treatments, CYP2B6 genotype, etc.).

10.1.3 To characterize between subject and random unexplained components of the PK variability.

10.1.4 To predict the time at which the proportion of women with MPA <0.1 ng/L matches that at 12 weeks from historical data.

10.2 Pharmacology Study Design

Doses of all ARV and TB medications taken for 48 hours prior to PK will be collected on the CRF at weeks 2, 4, 6, 8, 10, and 12. The participant should be contacted one week prior to the scheduled visit to reinforce the importance of 100% adherence to RIF and EFV and of her upcoming appointment. A participant who misses 2 or more doses of RIF and EFV within one week prior to the scheduled PK sampling at weeks 2, 4, 6, 8, 10, and 12 will have the visit rescheduled to one week later. For the week 10 and week 12 visits, the rescheduled PK sampling should be strictly within the original visit window for that visit. The schedule for the remaining visit weeks should not be changed. The rules for replacing participants who do not complete the PK are described in sections 8.1 and 9.5.

A single 4 mL blood sample for PK will be collected just prior to DMPA injection at week 0 and at the scheduled visits at weeks 2, 4, 6, 8, 10, and 12. The blood sample will be centrifuged within 1 hour of collection to separate the plasma which will be stored at -70°C or colder until assay for MPA and progesterone.

The ACTG Pharmacology Specialty Laboratory at the University of Cape Town will use liquid chromatography-tandem mass spectrometry (LC MS/MS) to measure MPA and progesterone in the plasma. The assay methods will be validated and submitted to Clinical Pharmacology Quality Assurance (CPQA) for review.

10.3 Primary and Secondary Data, Modeling, and Data Analysis

The concentration vs. time data for DMPA will be analyzed using NLME modelling using the software NONMEM (Version 7.2) [see protocol for reference].

The modelling approach will follow a stepwise procedure to first identify the structural model best describing the data, and then incorporate the effect of the study covariates such as weight, age, and effect of concomitant anti-retroviral and anti-tuberculosis treatment.

Various structural pharmacokinetic models will be evaluated, focusing on correctly characterizing the absorption after intra-muscular injection. The tested models will include one, two, and three compartments disposition with first-order elimination and zero-, first-order, or saturable absorption.

Statistically significant variability and correlation estimates for the PK parameters will be included and the covariates of interest will be evaluated with respect to their impact on the PK parameters and their variability.

Allometric scaling [see protocol for reference] will be used to account for the effect of body size on the PK parameters, using total body weight or fat-free mass. Other covariate effects will be evaluated and included if they significantly improve the ability of the model to describe the data. The effect of adherence to and time on ART and TB regimens, and CYP2B6 genotype (if available), will be investigated on clearance.

Concentrations below the limit of quantification will be included in the analysis and handled with established methods [see protocol for reference].

The tools used for model development and graphical and statistical diagnostics will include Xpose, and Perl Speaks NONMEM, and Pirana [see protocol for reference].

The PK profiles will be analyzed using post-hoc Bayesian methods to extract information such as peak concentration, overall exposure (AUC), and time above target concentration. Simulations will be employed to explore the pharmacokinetic profiles, their variability in a population, and how they are affected by weight, concomitant anti-retroviral or anti-tuberculosis treatment, other covariates found significant, and possibly under different dosing scenarios, and to predict the time at which the proportion of women with MPA <0.1 ng/L matches that at 12 weeks from historical data.

10.4 Anticipated Outcomes

The anticipated outcomes are described in the section above. They are the model outputs: firstly the population PK of MPA will be described using the primary model parameters and secondary measure estimates. Covariate effects on the model parameters will be identified and quantified. The model will ascribe variability (due to fixed effects, inter individual and random unexplained variability) with accuracy. Secondly, simulations will predict the optimal dosing frequency to achieve a target trough concentration of >0.1 ng/mL in the target proportion of women.

10.5 Pharmacogenomics – Host Genetic Analysis

Inter-individual differences in host genes (eg, those that encode drug-metabolizing and transporter proteins) have been associated with inter-individual differences in plasma PK of EFV [see protocol for references] and RIF [see protocol for reference]. The study will therefore evaluate human genetic polymorphisms that are known to affect steady-state plasma PK of EFV and RIF. Among study

participants that receive EFV and RIF, analyses of PK data will take into consideration such polymorphisms. If additional polymorphisms are reported to affect sex hormones, these may also be studied.

7 References

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Smit J, Botha J, McFadyen L, Beksinska M. Serum medroxyprogesterone acetate levels in new and repeat users of depot medroxyprogesterone acetate at the end of the dosing interval. Contraception. 2004 Jan;69(1):3-7.

Trussell J (2011). "Contraceptive efficacy". In Hatcher RA.; Trussell J; Nelson AL.; Cates W Jr.; Kowal D; Policar MS (eds.). Contraceptive technology (20th revised ed.). New York: Ardent Media. pp. 779–863. ISBN 978-1-59708-004-0. ISSN 0091-9721. OCLC 781956734. (Tables 26–1 = Table 3–2 Percentage of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception, and the percentage continuing use at the end of the first year.)