A Study to Evaluate the Effectiveness, Pharmacokinetics, Safety, and Acceptability of Sayana® Press when Injected Every Four Months

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1 Study Synopsis

Protocol Title	A Study to Evaluate the Effectiveness, Pharmacokinetics, Safety, and Acceptability of Sayana® Press when Injected Every Four Months
Clinicaltrials.gov Identifier	Clinicaltrials.gov Study Identifier NCT03154125
Study Sponsor	FHI 360
Study Funder	USAID and The Bill & Melinda Gates Foundation
Investigational Drug	Sayana® Press (medroxyprogesterone acetate injectable suspension, 104 mg/0.65 mL)
Phase	3
Study Countries	Brazil, Chile, and Dominican Republic
Population	A total of 750 healthy, sexually active women between 18 and 35 years of age who are willing to use Sayana® Press injected every 4 months as their only means of contraception for 12 months.
Primary Objective	To evaluate the effectiveness of Sayana® Press injected subcutaneously every 4 months in the abdomen or upper thigh for 12 months (3 treatment cycles) of use.
Primary Endpoint	Pregnancy
Secondary Objectives	1) To assess trough concentrations, accumulation and apparent terminal half-life of MPA, and the impact of subcutaneous injection site (abdomen, upper thigh, or upper arm) on these parameters, when Sayana® Press is injected every 4 months for 12 months of use; 2) to evaluate the safety of Sayana® Press when injected every 4 months for 12 months of use; 3) to evaluate the acceptability of Sayana® Press when injected every 4 months for 12 months of use.
Secondary Endpoints	1) Serum MPA concentrations on day 0 (baseline), months 2, 3, 4, 8, and 12 after treatment initiation (subset of 120 participants, only); 2) serious adverse events and adverse events leading to product withdrawal; injection site reactions, bleeding patterns, blood pressure, and body weight; and 3) responses to acceptability questions.
Exploratory Objective	To evaluate return to ovulation among a subset of study participants who received month 4 and month 8 injections and plan to use non-hormonal methods of contraception, or no contraception, for up to a maximum of 12 months from the last study injection.
Exploratory Endpoint	Return to ovulation, where ovulation is defined as a single elevated serum progesterone (P ≥4.7 ng/mL) or a confirmed pregnancy test.
Contact for Questions	Vera Halpern, vhalpern@fhi360.org Jen Deese, jdeese@rti.org

2 Study Design and Methodology

2.1 Overview

This study will evaluate the effectiveness, PK, safety, and acceptability of Sayana® Press when injected every 4 months (17-18 weeks) for 12 months (3 treatment cycles), rather than every 3 months (12-14 weeks) per current prescribing information. A total of 750 healthy, sexually active women aged 18 to 35 years with regular menstrual cycles and at risk of pregnancy will be enrolled at 3 sites: Biomedical Research Department at Profamilia in the Dominican Republic (Profamilia); Universidade Estadual de Campinas in Brazil (UNICAMP), and Instituto Chileno de Medicina Reproductiva in Chile (ICMER). One cohort of N=630 women will be randomized 1:1 to receive injections of Sayana® Press in the abdomen or upper thigh, and a second PK cohort of N=120 women who, in addition to pregnancy testing, agree to blood draws for MPA testing at 6 time points during their study participation, will be randomized 1:1:1 to receive injections in the abdomen, upper thigh, or back of the upper arm. The N=710 women receiving injections in the abdomen or thigh, per Sayana® Press package insert instructions, will constitute the primary population for assessing contraceptive efficacy. Analyses will be done to compare PK across the three injection sites.

Treatment will begin in the first 5 days of menses. All participants will have a single serum sample collected at enrollment for possible MPA testing. Participants will receive re-injections in their randomly assigned SC injection site at month 4 (17 weeks after treatment initiation) and at month 8 (35 weeks after treatment initiation) and complete their scheduled follow-up at month 12 (53 weeks after treatment initiation). There will be a plus 7-day grace period for re-injections, but women who are up to 28 days late may continue treatment if they have a negative urine pregnancy test (participants who are more than 28 days late for re-injection will be discontinued from the study). Participants will be asked to provide information on adverse events, prohibited concomitant medication and other contraceptive use, vaginal bleeding, and method acceptability at months 4, 8, and 12; information on adverse events and concomitant medications will be recorded if self-reported by participants at the month 2 and 3 PK visits, and any unscheduled visits. Urine pregnancy testing will be performed for all women at month 4 and month 12/study exit, if a participant is more than 7 days late for her month 8 visit and at any other time it is clinically indicated. An additional pregnancy test will be completed at month 8 for women enrolled in BC-BMD sub-study in Brazil. Participants will be advised to return to the clinic for unscheduled visits any time they think they may be pregnant or have a medical problem that may be related to their study participation. In addition to pregnancy testing, participants in the PK cohort will provide blood specimens for serum MPA testing on day 0 (baseline) and months 2, 3, 4, 8, and 12.

A subset of approximately 20 participants at select study sites who received both month 4 and month 8 injections and plan to use a non-hormonal contraceptive method, or no contraception, after study discontinuation will be invited to be in the extended follow-up subset and monitored until resumption of ovulation or up to a maximum of 12 months after the last study injection, whichever comes first. At predetermined time points (specified in Table 2 and Table 3), blood will be collected for progesterone, estradiol, MPA and other synthetic steroids (e.g., levonorgestrel, etonorgestrel and ethinyl estradiol); urine pregnancy testing will be performed; and blood pressure and weight will be measured.

2.2 Randomization, Allocation Concealment and Blinding

All participants will receive the same study drug, Sayana® Press. However, women will be randomized to receive their injections in the abdomen, back of the upper arm, or upper thigh to control for potential confounding when assessing relationships between SC injection site, efficacy, and PK. One cohort of N=630 women will be randomized 1:1 to receive their injections in the abdomen or thigh, and a separate PK cohort of N=120 women agreeing to MPA testing will be randomized 1:1:1 to receive their injections in the abdomen, upper thigh, or back of the upper arm. Randomization will be stratified by cohort and site using appropriate randomly permuted block sizes. Randomization sequences will be created for each combination of site and

cohort by an FHI 360 randomization statistician using a validated program written in SAS® version 9.4 or higher.

Sequentially numbered, opaque randomization envelopes matching the randomization sequences will be provided to each clinic site. Each envelope will have the randomization number printed on the outside, with the corresponding SC injection site assignment concealed within. The randomization envelopes will be maintained in a secure office, with access limited to designated study staff. The next available randomization number will be assigned to the next study participant only after she has been confirmed to be eligible, consented to participate, and undergone all other enrollment procedures, including having a blood sample collected for MPA testing among women agreeing to participate in the PK cohort.

Neither participants nor site staff will be blinded to SC injection sites. However, laboratory staff analyzing serum MPA specimens and staff at FHI 360 responsible for adjudicating pregnancy outcomes and coding adverse events will be blinded to individual participant injection site assignments for the duration of each participant's follow up. In addition, the FHI 360 may review interim PK data, including MPA concentrations of any women who become pregnant, to inform other FHI 360 MPA projects.

2.3 Study Drug Dose and Mode of Administration

Sayana® Press (MPA injectable suspension, 104 mg/0.65 mL), injected subcutaneously in the abdomen, upper thigh, or back of the upper arm using the pre-filled Uniject™ delivery device.

2.4 Criteria for Inclusion

Women may be included in the study if, at enrollment, they meet all of the following criteria:

- not pregnant and no desire to become pregnant in the next 18 months
- regular menstrual cycles (25 to 35 days in length when not using hormonal contraception, pregnant, or lactating)
- at risk of pregnancy (no diagnosis of infertility, no history of tubal ligation or hysterectomy, and an average of 1 or more unprotected acts of vaginal intercourse per month)
- in good general health as determined by a medical history
- 18 to 35 years of age, inclusive
- willing to provide informed consent, follow all study requirements, and rely on Sayana® Press injected every 4 months as the only means of contraception for 12 months
- has only one sexual partner and expects to have that same sexual partner for the next 12 months

2.5 Criteria for Exclusion

Women will be excluded from this study if they meet any of the following criteria at enrollment:

- has a primary partner who has received a vasectomy or is otherwise sterile
- medical contraindications to depot medroxyprogesterone acetate (DMPA) per World Health Organization medical eligibility criteria for contraceptive use
- known HIV-infection (for her or her partner)
- diagnosis or treatment for a sexually transmitted infection in the past month (for her or a partner), excluding recurrent herpes or condyloma
- received an injection of a progestin-only containing contraceptive (DMPA or norethisterone enanthate) in the past 12 months
- received an injection of a combined injectable contraceptive in the past 6 months
- known or suspected allergic reaction to DMPA
- used a levonorgestrel-releasing intrauterine system, NuvaRing, contraceptive patch, oral contraceptives or a contraceptive implant in the 7 days prior to enrollment (PK cohort only)

- previous (within 1 month prior to enrollment), current or planned (in the next 12 months) use of an investigational drug, prohibited drug per protocol or other drug which in the opinion of the site investigator could complicate study findings
- has been pregnant in the past month
- is lactating
- plans to move to another location in the next 12 months
- has a social or medical condition which in the opinion of the site investigator would make study participation unsafe or interfere with adherence to protocol requirements.

2.6 Study Size and Statistical Analysis

The 710 women receiving injections in the abdomen or upper thigh will constitute the primary efficacy population. This study size is sufficient to ensure that the difference between the estimated Pearl Index (pregnancies per 100 woman-years of use) and the corresponding upper 95% confidence bound does not exceed 1.0, so long as the observed index is less than 0.75 and at least 80% of participants complete 12 months of follow-up. The PK cohort of 120 women (40 receiving injections in each the abdomen, upper thigh, and back of the upper arm) is sufficient to provide 85% power to detect 30% relative differences in PK parameters between injection sites, assuming the coefficient of variation is no more than 40% and using two-sided 0.05 significance tests.

2.7 Duration of Study Participation

This study will consist of a screening period (up to 1 month prior to enrollment) and a 12-month treatment period, for approximately 13 months of study participation per subject. A subset of approximately 20 participants will be followed until the resumption of ovulation or a maximum of 12 months from the last study injection, whichever comes first.

2.8 Participant Discontinuation

A participant may discontinue participation at any time for any reason without loss of other benefits or services to which she may be entitled. A participant may also be discontinued early from the study if the site investigator considers it to be in the participant's best interest. Final visit procedures should be completed for all participants who discontinue early, if possible. Reasons for discontinuation from the study will be recorded on the appropriate Case Report Form (CRF).

2.9 Source Data

Some CRF fields will have data directly recorded into them and will be considered source. Other source documents will include, but will not be limited to, clinical notes, laboratory results, dispensing records and consent forms. Source for all study data will be defined and documented in site-specific source documentation guides.

2.9.1 Table 1: CRF Completion Schedule

CRF/checklist	Screening	Enrollment	M1	M 2 & 3[a]	M4	M8	M12/Final
Screening eligibility checklist	X						
Medical eligibility checklist[b]		X					
ACCEPT		X			X	X	X
AE[c]				(X)	(X)	(X)	(X)

CRF/checklist	Screening	Enrollment	M1	M 2 & 3[a]	M4	M8	M12/Final
BSL	X						
BODY (*UNICAMP only*)		X				X	X
CONMED[d]				(X)	(X)	(X)	(X)
ELIG		X					
ENROL		(X)[j]					
FINAL	(X)	(X)		(X)	(X)	(X)	X
FU				X	X	X	X
INJECT		X			X	X	
INJECTSITE		X			X	X	
ISR		X			X	X	X
MPALOG[e]		X		X	X	X	X
PREG[f]				(X)	(X)	(X)	(X)
PREGOUT[g]				(X)	(X)	(X)	(X)
PV[h]	(X)	(X)		(X)	(X)	(X)	(X)
SHARM[i]				(X)	(X)	(X)	(X)
VI (*UNICAMP only*)	X		X	X[k]	X	X	X

(X) conditional completion, see corresponding footnotes

[a] Only for the PK cohort

[b] Depending on site clinic flow may be completed at screening and enrollment, or at enrollment only

[c] Only serious adverse events, adverse events leading to product withdrawal, and injection site reactions that are Grade 1 or higher

[d] Only other contraceptives and protocol-prohibited medications

[e] For all participants at enrollment. At follow-up visits only for PK cohort and for women who test positive for pregnancy during follow-up

[f] If pregnancy identified

[g] At time of any pregnancy outcome

[h] At time of any occurrence of a protocol-defined reportable protocol violation

[I] At time of any occurrence of a protocol-defined social harm

[j] Only for women who are enrolled

[k] Participants who consent to the collection of genital and blood specimens for the Vaginal Immunity Study will be asked to come to the clinic approximately 1 and 3 months after enrollment for specimen collection only.

2.10 Study Procedures

All participants will come to the study clinic for a screening visit, an enrollment visit (when treatment initiation occurs), re-injection visits at month 4 and month 8 post-treatment initiation, and a final visit at month 12. Participants in the PK cohort will attend additional visits at months 2 and 3 to provide blood specimens for MPA testing. Participants in the extended follow-up subset will return at predetermined time points (specified in Table 3) until return to ovulation or up to a maximum of 12 months from the last study injection, whichever comes first. See Table 2 and Table 3 for timing of study procedures.

2.10.1 Screening Visit

Women will be recruited through various channels which may include, but not be limited to, searches of internal participant databases, informing women seeking contraception at the study sites about the study, referrals from local clinics and use of advertisements. Women expressing interest in participating in the study will be given the informed consent form to review and trained site personnel will review the consent information including the study objectives, design and procedures, and potential risks of participation. Potentially eligible women will be asked if they are willing to be in the PK cohort, and provide blood specimens for MPA testing, until enrollment into the PK cohort is complete. Those that sign the informed consent form will be assigned a participant number and have a screening interview, including collection of medical history and demographic

information. Each site may also conduct clinical procedures per site-specific standard of care that are not required per the study protocol (e.g., STI testing, Pap smear, and breast exam).

Each potentially eligible woman will be scheduled to return to clinic for enrollment procedures during the first 5 days of her next menses, but if she is currently in the first 5 days of menses then enrollment procedures can begin immediately (this does not apply to women who also consent to participate in the Vaginal Immunity Study). In summary, the following will be done during the screening visit:

- Study purpose and procedures explained
- Written informed consent obtained
- Participant number assigned
- Assess study eligibility and collect baseline data
- Enrollment visit scheduled for first 5 days of next menses
- Appropriate CRFs completed

2.10.2 Enrollment Visit (Day 0)

The enrollment visit will take place during the first 5 days of menses. During this visit a urine pregnancy test will be performed and other eligibility criteria verified. Height, weight and BP measurements will be recorded. Vaginal bleeding information will be collected. Approximately 5 mL of blood for MPA testing will be collected before randomization.

After a participant is confirmed eligible and had all other enrollment procedures completed, the study site's randomization manager will open the next sequentially numbered randomization envelope from the appropriate stream of envelopes (PK cohort or non-PK cohort). Each participant will receive an injection of Sayana® Press in her assigned SC injection site, be monitored for at least 15 minutes for possible anaphylactic reactions and/or ISRs, and be scheduled to return to the clinic 4 months later for re-injection on study day 119 (17 weeks after enrollment) (participants who are unable to return precisely on study day 119 may have their re-injection scheduled to take place up to 7-days late, on or before study day 126). Participants in the PK cohort will be scheduled to return for additional blood draw visits at month 2 (study day 61) and month 3 (study day 91), allowing for a plus/minus 7-day grace period.

In summary, the following will be done during the enrollment visit:

- Urine pregnancy test performed
- Study eligibility confirmed and baseline data collected
- Coital frequency and condom use assessed
- Vaginal bleeding assessed
- BP, height, and weight measured
- Blood drawn for MPA assessment (MPA testing will only be done on specimens from participants in the main cohort if MPA is detected above the threshold defined in the Statistical Analysis Plan among baseline specimens from the PK cohort)
- Randomization completed
- Study drug administered and site of injection evaluated for possible ISRs
- Study visit schedule provided
- Appropriate CRFs completed

2.10.3 Regularly Scheduled Follow-up Visits

Month 4 re-injection

The first re-injection visit is scheduled to occur on study day 119, 4 months (17 weeks) after treatment initiation. Participants will be asked if they have experienced any medical problems or have taken any

medications since the previous visit (serious adverse events, adverse events leading to product withdrawal, ISRs and use of any study prohibited concomitant medications and other contraceptives , will be recorded on CRFs); asked to report on coital frequency and condom use since the last injection of study drug; have vaginal bleeding and product use acceptability evaluated; have BP and weight measured; and complete a urine pregnancy test. Any participants who are determined to be pregnant will have a blood specimen collected for MPA testing. Participants in the PK cohort will also provide approximately 5 mL of blood for MPA testing. Otherwise, participants who have a negative urine pregnancy test will receive a re-injection of Sayana® Press and be reminded to return for the next scheduled visit on study day 245, 8 months (35 weeks) after treatment initiation.

Participants who are up to 28 days late for the month 4 visit may continue treatment if they have a negative urine pregnancy test result. If a participant is more than 7 days late, however, then her month 8 and final study visits will be re-scheduled to occur at 18-week (126 day) intervals over the next 36 weeks in order to avoid shortening the effective lengths of subsequent treatment intervals. Participants who are more than 28 days late will undergo final visit procedures (see Section 3.14.3.3) and be discontinued from the study.

Month 8 re-injection

The second re-injection visit is schedule to occur on study day 245, 8 months (35 weeks) after treatment initiation. Participants will be asked if they have experienced any medical problems or have taken any medications since the previous visit (serious adverse events and adverse events leading to product withdrawal, ISRs, and use of any study prohibited concomitant medications and other contraceptives , will be recorded on CRFs); asked to report on coital frequency and condom use since the last injection of study drug; have vaginal bleeding and product use acceptability evaluated; and have BP and weight measured. A urine pregnancy test will not be performed unless the participant is more than 7 days late for her month 8 visit, she is enrolled in the BC-BMD sub-study, or if testing is clinically indicated. Any participants who are determined to be pregnant will have a blood specimen collected for MPA testing. Participants in the PK cohort will also provide approximately 5 mL of blood for MPA testing. Otherwise, participants who are not pregnant will receive a re-injection of Sayana® Press and be reminded to return for a final visit on study day 371, 12 months (53 weeks) after treatment initiation.

Participants who are 8 to 28 days late for the month 8 visit may continue treatment if the urine pregnancy test result is negative. If a participant is more than 7 days late, however, then the final study visit will be re-scheduled to occur 18 weeks (126 days) later. Participants who are more than 28 days late will undergo final visit procedures (see Section 3.14.3.3) and be discontinued from the study.

2.10.4 Final visit

The final visit is scheduled to occur on study day 371, 12 months (53 weeks) after treatment initiation. Participants will be asked if they have experienced any medical problems or have taken any medications since the previous visit; asked to report on coital frequency and any condom use since the last injection of study drug; have final vaginal bleeding and product use acceptability evaluated; have BP and weight measured; and complete a urine pregnancy test. Any participants who are determined to be pregnant will have a blood specimen collected for MPA testing. Interested participants who meet qualifications will be consented to the extended follow-up subset. Participants in the PK cohort and extended follow-up subset will also provide approximately 5 mL of a blood for MPA testing. Participants will be offered contraception of their choice from methods available at the study clinic and will be provided referrals as need for ongoing services. Final visit procedures should be done at the time of any early discontinuation.

In summary, the following will be done during regularly scheduled re-injection and final study visits:

- Participant asked about adverse events and concomitant medication use (serious adverse events, adverse events leading to product withdrawal, ISRs, and use of any study prohibited concomitant medications and other contraceptives, will be recorded on CRFs)
- Coital frequency and condom use assessed
- Vaginal bleeding and product use acceptability assessed
- BP and weight measured
- Consented to the extended follow-up subset*
- Blood drawn for MPA assessment (PK cohort, extended follow-up subset*, or if pregnant, only)
- Urine pregnancy test performed (at month 8 visit, only if more than 7 days late, or enrolled in the BC-BMD sub-study)
- Study drug administered (month 4 and month 8, only; contraception [locally available] offered at final visit)
- Site of the previous and new injection(s) evaluated for possible ISRs, as appropriate
- Appointment reminders provided (month 4, month 8, and extended follow-up subset only)
- Appropriate CRFs completed

*May occur after the Final/Month 12 visit so long as the participant meets the eligibility criteria for the extended cohort and the timetable for extended follow-up procedures.

2.10.5 Final Visit Procedural Changes due to COVID-19

Operational procedures were modified in March 2020, near the end of trial follow-up, due to the COVD-19 pandemic as follows:

Effective March 18, 2020 centers were instructed to conduct the remaining Month 12 visits as quickly as possible independent of target visit windows. At this visit, pregnancy tests were conducted in the clinic as per protocol and record the result on the appropriate CRF(s). Women who returned prior to their target date were provided with a pregnancy test to use at home on their Month 12 target date. Participants were instructed to send an image of the home pregnancy test result (e.g., by email, text message). The pregnancy test result image was printed and attached to an In- Home Pregnancy Test Results Log maintained at the clinical centers.

Month 12 visits were conducted by phone with local guidelines and/or participant preference precluded in person visits. Participants were provided pregnancy tests through the mail for conducting in-home pregnancy tests and instructed to follow the procedures above.

2.10.6 Additional Blood Draw Visits (Months 2 and 3)

Participants in the PK cohort will complete additional clinic visits to provide blood specimens for MPA testing at month 2 (study day 61) and month 3 (day 91). Blood pressure and weight will be measured; information on AEs and concomitant medication use will not be solicited; however, if reported by the participant, serious adverse events and adverse events leading to product withdrawal and use of any study prohibited concomitant medications and other contraceptives, will be recorded on CRFs. Additional blood draw visits will be scheduled to allow for a plus or minus 7-day grace period, but women returning outside the window will still have blood drawn for MPA testing.

2.10.7 Extended Follow-Up Subset Procedures

At select sites, consenting participants will be scheduled to return for two 5-week intervals at 10 and 12 months from the last study injection to monitor for return to ovulation. The first 5-week interval will be scheduled to occur 38 weeks from the date of the last injection (i.e., month 8 re-injection date + 38 weeks) with subsequent weekly visits occurring up to 42 weeks or return to ovulation, whichever comes first. If ovulation does not return within the 42 weeks from last injection, participants will be scheduled to return for a second 5-week interval scheduled to occur 46 weeks from the date of their last injection (i.e., month 8 re-injection date + 46 weeks) with subsequent weekly visits occurring up to 50 weeks (12 months from last injection). At predetermined time

points (specified in Table 3), blood will be collected for progesterone, estradiol, MPA and other synthetic steroids (e.g., levonorgestrel, etonogestrel and ethinyl estradiol); urine pregnancy testing will be performed; and blood pressure and weight will be measured. Participants will be discontinued when ovulation is confirmed (i.e., defined as a single elevated serum progesterone [P ≥4.7 ng/mL] or confirmed pregnancy test) or at 50 weeks from last injection, whichever comes first.

2.10.8 Table 2: Extended Follow-Up Subset CRF Schedule (for Profamilia and UNICAMP sites only)

CRF	Enroll-ment	Week 38[c, d]	Week 39[c, d]	Week 40[c, d]	Week 41[c, d]	Week 42[c, d]	Week 46[c, d]	Week 47[c, d]	Week 48[c, d]	Week 49[c, d]	Week 50[c, d]
AEX[a]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
CONMEDX[b]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
ENRFUX	X[e]	X	X	X	X	X	X	X	X	X	X
FINALX		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
LNG/ENG/EE LOG		X					X				
MPALOGX	X	X					X				
P/E2LOG		X	X	X	X	X	X	X	X	X	X

(X) conditional completion, see corresponding footnotes

[a] Only SAEs will be recorded on study CRFs and reported to FHI 360

[b] Use of prohibited concomitant medications and other contraceptives will be recorded on CRFs

[c] Weeks from last injection

[d] Participants will be discontinued from the study at the visit in which ovulation is confirmed (defined as a single elevated serum progesterone [P ≥4.7 ng/mL] or confirmed pregnancy test) or she does not ovulate by week 50 (from last injection), whichever occurs first

[e] Eligible participants will be offered the option to take part in the Extended Follow-up subset during their Final/Month 12/Final study visit. Eligible participants who have already completed the study and are still within the 38-week target window, may be re-contacted and invited to return to the clinic to enroll.

2.10.9 Missed and Unscheduled Visits

Re-injection and final visits will be scheduled to occur based on specific days since treatment initiation, allowing for up to a plus 7-day grace period. If a participant cannot return to the clinic within this visit window, the study staff will attempt to have the participant return as soon as possible. However, treatment will be stopped and the participant discontinued from the study if she is more than 28 days late for a re-injection visit. Sites will also ask participants to return to clinic for unscheduled visits if they suspect that they may be pregnant or if they have any other problems or concerns with study participation.

2.10.10 Loss to Follow Up

If a participant does not appear for a scheduled visit, at least three attempts to contact her will be made. If she does not return to clinic while the study is ongoing then she will be considered potentially lost to follow up, but her file will remain open until study closeout. If the participant does not return before the study is closed, she will be classified as lost to follow up. The lost to follow up designation cannot be made for any participant until the closing date of the study.

2.10.11 Prior and Concomitant Therapy or Medication

Study staff must record on the corresponding CRF use of any study prohibited concomitant medications and other contraceptives the participant takes during the study. Indication, dosage, and start and end dates will be entered on the corresponding CRF. Use of the following medications is an exclusion criterion at enrollment, and participants should not initiate their use during study participation unless prescribed by a physician:

- Rifampicin
- Griseofulvin
- Anticonvulsants
- Barbiturates
- Non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine) and ritonavir-boosted protease inhibitors
- Aminoglutethimide
- St. John's wort
- Steroids (synthetic estrogens, progestins, androgens)
- Use of selective COX-2 inhibitors (e.g., meloxicam, celecoxib) for 5 or more consecutive days

2.10.12 Table 2: Study Procedures and Assessments

Procedures	Screening [a]	Enrollment (Day 0)	Month 1	Months 2 and 3 [b]	Months 4 and 8	Final/ Month 12 [k]
Informed consent	X					X [l]
Inclusion/exclusion criteria	X	X				
Baseline characteristics	X	X				
Height		X				
Body weight		X		X	X	X
Blood pressure		X		X	X	X
Urine pregnancy test	X [c]	X			X [d]	X
Randomization		X				
Drug administration		X			X	
Serum MPA		X		X[e]	X[e]	X[e,l]
AE documentation [f]				X	X	X
ISR documentation		X			X	X
Concomitant medication documentation [g]				X	X	X
Vaginal bleeding		X			X	X
Acceptability					X	X
Coital frequency and condom use		X			X	X
Specimens for vaginal immunity study [h]	X		X	X	X	X
DXA for BC and BMD sub-study [i]		X			X [j]	X

[a] May coincide with enrollment visit if participant is in the first 5 days of her menses (this does not apply to women also participating in the Vaginal Immunity Study)
[b] Only for the PK cohort
[c] If clinically indicated
[d] Participants will only be tested at month 8 if they are more than 7 days late for their visit or are enrolled in the BC-BMD sub-study
[e] For all participants at enrollment. At follow-up visits only for the PK cohort and for any participant in the full cohort who has a positive pregnancy test during follow-up
[f] Serious adverse events, adverse events leading to product withdrawal, and injection site reactions that are Grade 1 or higher will be recorded on the AE CRF
[g] Use of prohibited concomitant medications and other contraceptives, will be recorded on CRFs
[h] Participants who consent to the collection of genital and blood specimens for the Vaginal Immunity Study will also be asked to come to the clinic approximately 1 and 3 months after enrollment for specimen collection only.
[i] Only for Brazilian participants who consent to measurement of BC and BMD by DXA scan. Does not need to be done in the case of early discontinuation.

[j] Only at month 8 for BC-BMD participants.
[k] Procedures to be done at the Month 12 visit, or at any visit of early discontinuation.
[l] Only for the extended follow-up subset; may occur after the Final/Month 12 visit so long as the participant meets the eligibility criteria for the extended cohort and the timetable for extended follow-up procedures.

2.10.13 Table 3: Study Procedures and Assessments (Extended Follow-Up Subset)

Procedures [a]	**Week 38** [d]	**Week 39** [d]	**Week 40** [d]	**Week 41** [d]	**Week 42** [d]	**Week 46** [d]	**Week 47** [d]	**Week 48** [d]	**Week 49** [d]	**Week 50** [d]
Body weight	X					X				
Blood pressure	X					X				
Urine pregnancy test [b]	X	X [c]	X [c]	X [c]	X	X	X [c]	X [c]	X [c]	X
Serum MPA	X					X				
Serum Estradiol	X	X	X	X	X	X	X	X	X	X
Serum Progesterone	X	X	X	X	X	X	X	X	X	X
Plasma levonorgestrel, etonogestrel, ethinyl estradiol	X					X				
AE documentation [e]										
Concomitant medication documentation [f]										

[a] Participants will be discontinued from the study at the visit in which ovulation is confirmed (defined as a single elevated serum progesterone [P ≥4.7 ng/mL] or confirmed pregnancy test) or she does not ovulate by week 50 (from last injection), whichever occurs first
[b] If positive at any time, discontinue
[c] If clinically indicated
[d] Weeks from last injection
[e] Only SAEs will be recorded on study CRFs and reported to FHI 360
[f] Use of prohibited concomitant medications and other contraceptives, will be recorded on CRFs

3 Open Data User Notes

In addition to this summary, the following documents are provided as part of the open data package:

- Annotated CRFs - The annotated CRFs contain variable names and codelist names.
- Data Dictionary – Contains variable names and description/label, data type and length, options lists/codelists names and values, comments
- Data sets in CSV files - The data sets are in csv format. The data sets contain data for eligible and consented participants only. Identifying information have been removed/dropped from the data set(s) to maintain participant confidentiality. The following datasets are available:

  - ***Effectiveness Trial:***

    1. Eligibility - EL
    2. Baseline - BA
    3. Enrollment – EN
    4. Follow-up – FU
    5. Acceptability Questionnaire - AC
    6. Injection - IN
    7. Injection Site – IJ
    8. Injection Site Reactions – IS
    9. Follow-up - FU
    10. Adverse Events – AE
    11. Concomitant Medications – CM
    12. MPA Log – MP
    13. MPA Results - MPADATA
    14. Pregnancy Diagnosis– PR
    15. Pregnancy Outcome – PO
    16. Protocol Violations – PV
    17. Social Harm – SH
    18. Final Status – FI
    19. Body Composition – BO
    20. Vaginal Immunity – VI
    21. Home Pregnancy Test Tracker - HMTSTRAC

  - ***Extended Follow-up Subset****

    1. Enrollment and Follow-up – EF
    2. MPA Log – MX
    3. MPA Results - EXMPADATA
    4. LNG log – LN
    5. EE Results - EXEEDATA
    6. ENG Results - EXENGDATA
    7. LNG Results - EXNORDATA
    8. PE2 log – PE
    9. Final Status – FX

Clarifications

The HMTSTRAC dataset contains pregnancy tests that were collected by participants at home due to final visits that could not be completed in clinic due to the COVID-19 pandemic. Any records with RESRECEV = “Yes” were included in the primary efficacy analysis. The later of PRTS1DTE or PRTS2DTE (from HMTSTRAC), or last recorded pregnancy test in clinic recorded on the FU CRF was used as the date of last pregnancy test result.

*No adverse events or concomitant medications were reported during the extended follow-up period, therefore there are no corresponding datasets.