APPROVALS

ACTG A5375

Primary Statistical Analysis Plan

Version 3.0

An Open-Label, Phase II Pharmacokinetic Study to Evaluate Double-Dose Levonorgestrel Emergency Contraception in Combination with Efavirenz-Based Antiretroviral Therapy or Rifampicin-Containing Anti-Tuberculosis Therapy

Protocol Version 2.0

ClinicalTrials.gov Identifier: NCT03819114

May 24, 2021

This is the ACTG A5375 SAP Version 3.0 with names of authors, names of publication writing team members, and analysis timelines redacted.

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures and any additional outcome measures of the ACTG A5375 study that will be included in the primary manuscript, and which address, at a minimum, the major primary and secondary objectives of the study. The Primary SAP outlines the general statistical approaches that will be used in the analysis of the study. It has been developed to facilitate discussion of the statistical

analysis components among the study team, and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented in the Primary Analysis Report. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov.

Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Analysis Report are included in the Analysis Implementation Plan (AIP).

Analyses for the Primary Analysis Report will be finalized once the last participant has completed the study, all queries have been resolved, and the study database closure/data lock has been completed.

1.2 Version History Table

Version	Changes Made	Rationale	Effective Date
1	Original Version		09/10/2019
2	Addition of SMC letter recommendation about PK replacement and edits based on team discussion/consensus Edits to PK data imputations based on assay limits	Review/update of SAP done in preparation for study closure based on said timeline	07/24/2020
3.0	Minor formatting changes, correction of typo, and other minor updates to align with protocol version 2. Attachment 2 : timeline was updated to reflect current forecasting near time of primary analysis initiation Removal of contingency language to perform primary analysis in 2 stages based on observed prompt completion of accrual. Reversing ratio for secondary comparison of groups A versus B so that Group A is in the denominator of the GMR. Refining definition of other outcome measure – single timed concentration of RIF and associated metabolites, to reflect testing of earlier post RIF dose samples due to accelerated clearance of RIF. And updating the thresholds for exclusion of participants in secondary analyses due to inadequate perpetrator drug concentrations.	Review triggered by finalization and release of protocol version 2 (dated 10/30/2020)	05/24/2021

	Addition of sensitivity analysis to the primary PK (for the assumption of equal variance between groups), as well as supplementary analyses to explore the robustness of primary PK analyses: a) exclusion of participants with inadequate measured exposure to perpetrator drug , and b) calculation of adjusted GMRs to account for imbalance in prognostic factors between comparison groups.		

2 Study Overview

2.1 Study Design

Copied from v2 (10/30/2020) Protocol Schema:

DESIGN — *A5375 is a phase II, open-label, four parallel group, partially randomized, pharmacokinetic (PK) study to evaluate if a double dose of levonorgestrel (LNG) emergency contraception (EC) overcomes known drug-drug interactions (DDIs) with efavirenz (EFV)-based antiretroviral therapy (ART) or rifampicin (RIF)-containing tuberculosis (TB) therapy. The safety of double-dose LNG EC versus standard-dose will also be compared.*

Participants will be volunteers who do not currently require EC for contraception. Eligible participants will receive a single dose (1.5 mg) or a double dose (3.0 mg) of LNG EC based on their group assignment, which will be determined by their infection (HIV or TB; participants cannot be coinfected), and, for those who are living with HIV, by their ART regimen at enrollment (see Schema Figure 1). Women living with HIV who are taking EFV-based ART will be randomized to Group A or B (1:2 ratio). Women taking dolutegravir (DTG)-based ART will be assigned to Group C. Women who are HIV-negative and in the continuation phase of TB treatment taking RIF and isoniazid (INH) will be assigned to Group D.

DURATION — *All participants will be followed for 4 weeks.*

SAMPLE SIZE — *116 participants; 17 in Group A, 33 in each of Groups B, C, and D.*

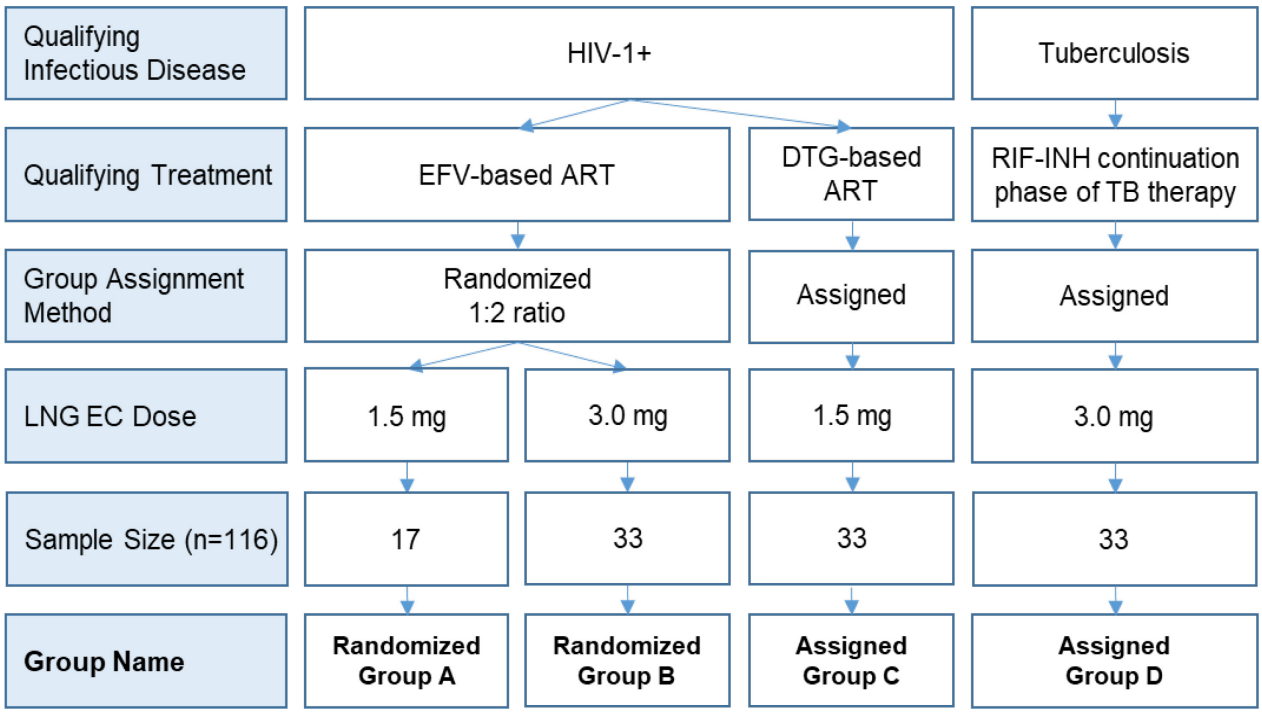
POPULATION — *Women who are 16 years of age or older, and who are either HIV+ and on stable ART, or who are HIV- and in the continuation phase of anti-TB therapy on daily INH/RIF.*

STRATIFICATION — *At entry, women with body mass index (BMI) ≥30 kg/m^2 will be limited to no more than five within Groups B-D and no more than three within Group A.*

REGIMEN *Women in Groups A and C will receive 1.5 mg LNG EC once at study entry.*

Women in Groups B and D will receive 3.0 mg LNG EC once at study entry.

Schema Figure 1: Study Design



Hypotheses *(copied from protocol v2):*

2.1.1 Primary Hypotheses:

1) Women receiving double-dose levonorgestrel (LNG) emergency contraception (EC) with efavirenz (EFV)-based antiretroviral therapy (ART) will achieve similar LNG concentrations compared to women receiving standard-dose LNG EC on dolutegravir (DTG)-based ART.

2) Women receiving double-dose LNG EC with rifampicin (RIF)-containing tuberculosis (TB) therapy will achieve similar LNG concentrations compared to women receiving standard-dose LNG EC on DTG-based ART.

2.1.2 Secondary Hypotheses:

1) Among women receiving EFV-based ART, double-dose LNG EC will achieve significantly higher LNG concentrations than standard-dose LNG EC.

2) Women receiving standard-dose LNG EC with EFV-based ART will achieve significantly lower LNG concentrations than women receiving standard-dose LNG EC on DTG-based ART.

3) Double-dose and standard-dose LNG EC will have similar safety profiles.

2.2 Study Objectives

This Primary SAP addresses the following primary and secondary objectives listed in the study protocol. Other study objectives in the protocol will be addressed in subsequent analysis plans.

Inference framework varies by objective/hypothesis above, and some comparisons rely on interpretation of confidence intervals rather than hypothesis testing. Because there is not a single framework across the analysis, these details will be provided by outcome below.

Objectives *(copied from protocol v2)*:

2.2.1 Primary Objectives

1) To determine if doubling the dose of the LNG EC effectively overcomes the known drug-drug interaction (DDI) with EFV-based ART.

2) To determine if doubling the dose of the LNG EC effectively overcomes the expected DDI with RIF-containing TB therapy.

2.2.2 Secondary Objectives

1) To estimate the difference in LNG pharmacokinetic (PK) exposure with double-dose LNG EC compared to standard-dose LNG EC in women receiving EFV-based ART.

2) To estimate the difference in LNG PK exposure with standard-dose LNG EC in women receiving EFV-based ART compared to women receiving DTG-based ART.

3) To verify the absence of significant DDI between LNG EC and DTG-based ART.

4) To compare the safety of double-dose LNG EC compared to standard-dose LNG EC.

5) To evaluate the relationship between baseline measures of body weight (body fat percentage, total weight, and body mass index [BMI]) and LNG PK exposure.

2.2.3 Exploratory Objectives

1) To characterize the relationship between short- and long-term adherence to ART or TB therapy and LNG exposure using objective pharmacologic measures. [Note: only short-term adherence will be assessed in the primary analysis, via measured concentrations of targeted ART or TB medications.]

2.3 Overview of Sample Size Considerations

Given that a therapeutic target for minimum exposure required or average exposure expected for single dose use of LNG as emergency contraception (EC) is unknown, this study is estimating whether adjusted dosing of LNG under a known DDI achieves similar exposure to LNG single dose as measured by the geometric mean ratio (GMR) of the AUC of LNG concentrations over the 8 hours post dose.

Assuming 30 women per comparison group, coefficient of variation of AUG(LNG0-8hr)= 0.45 {and standard deviation on 0.429 of AUC(LNG) as calculated from CV using the formula square root of [ln(CV^2+1)] }, and significance level 10% (corresponding to inverting 2 one-sided tests, each at 5% significance), then under true GMR=100%, there is 88% statistical power for declaring similarity in LNG exposure between groups using No-Effect Bounds of (70%,143%). Under similar assumptions, a 90% 2-sided confidence interval (calculated as median LCB and UCB from simulations), about a true GMR=100% ranges over (83%, 120%). Final sample sizes for accrual goals were inflated by 10% to protect against losses to follow-up.

The protocol document has further details on sample size justification.

Note that information above has been copied from the protocol. For analysis and reporting purposes, it has been decided to report GMR on the ratio scale (where 1=equivalence rather than 100%), and so the No-Effect Bounds in the analysis sections below use adjusted scaling to match the GMR scale for analysis and reporting.

2.4 Overview of Formal Interim Monitoring

2.4.1 Timing of reviews

This study will be formally monitored at least annually by an ACTG network-appointed SMC. The first interim review will occur no more than one year after the enrollment of the first participant or approximately 3 months after 25 women have completed the study, whichever occurs earlier. An additional SMC review may be triggered if the accrual at one year is less than 50% of total expected accrual. The protocol provides further details on an interim review triggered by slow accrual. An unplanned interim review will be triggered if, at any time, any participant experiences an SAE that is attributed to LNG (by adjudication by the core team and DAIDS clinical

representative), or if more than five women need to be replaced in the PK analysis set (see protocol section 9.2).

Note: Eligibility and enrollment issues that cause participant replacement will not be included in the above limit of 5 women.

2.4.2 Scope of reviews

There are no plans to initiate PK testing prior to initiation of the primary and/or final analysis, and thus there are no planned early looks or interim analysis of the primary efficacy outcome, or related outcomes calculated from PK concentrations. Therefore, the scope of interim reviews will be study conduct and safety.

3 Outcome Measures

Note: Outcome Measure information in italics inside boxes reflects the clinicaltrials.gov record specifications. Even though some secondary outcomes below are evaluated after the PCD, because study duration is only one month, we anticipate that all primary and secondary outcomes will be reported with the initial clinicaltrials.gov results submission.

3.1 Primary Outcome Measures

Title: *LNG PK Parameter Area under the concentration-time curve (AUC0-8h) calculated based on intensive LNG PK samples obtained from individual participants*

Description*: AUC for each participant will be calculated from LNG concentrations measured over 8 hours using the linear up/log down version of the trapezoidal rule (i.e., noncompartmental technique) using the software package Phoenix WinNonLin (Certara®). This version of the trapezoidal rule uses linear interpolation between untransformed data up to C_{max}, and between log-transformed data from C_{max} through $C_{last.}$ Assay lower limit of quantification for LNG was 0.025 ng/mL; values < LLOQ were imputed as 0 (if pre-dose) or as 0.125 (if post-dose)*

Time Frame*: Intensive LNG PK samples within 30 minutes pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose*

Analysis Population*: Participants with PK concentrations over 8 hours post LNG dose and who took both assigned dose of LNG study treatment and expected doses of ART or TB therapy*

Reporting Groups*: A-D*

Associated Study Objective: Primary Objectives 1 and 2, Secondary Objectives 1 and 2 (see table below for more details)

Summary Statistics per group (those in italics included in clinicaltrials.gov results record):

- **Original scale (ng*h/mL, mcg*h/mL as reported by testing lab): n, mean, sd, CV, *median*, IQR *(Q1, Q3*), Range (min, max)**
- **Natural log scaled: geometric mean, 95% CI on GM**

Descriptive analysis will include the following:

a) LNG concentration-time plots will be provided to inform the derivation of the primary AUC outcome and other PK parameters (secondary outcomes)

Statistical Analysis Summary:

DTG is not expected to alter LNG PKs. Because DTG is not expected to have DDIs with LNG, Group C (DTG) acts as a control arm for certain comparisons stated in the table below.

Note 1: GMR presented on ratio scale where equivalence is 1 (and not 100%).

Note 2: The Exact reference groups require additional specification of the key other med (ARV/TB med). Group codes are given for redundancy.

Statistical Analysis	Comparison Group selection	Type of Statistical Test	Estimation Parameter	Confidence Interval	Comments
1 – primary objective #1	LNG 3.0 mg (among those on EFV) versus LNG 1.5 mg (among those on DTG); Or Group B versus Group C	**None** (non-inferiority framework uses CI rather than hypothesis testing)	Geometric Mean ratio (GMR) of AUC(LNG0-8hr) between comparison groups	2-sided, 90% interval	CI on GMR compared to reference No-Effect Bounds (0.7, 1.43) to assess similarity between groups
2 – primary objective #2	LNG 3.0 mg (among those on RIF) versus LNG 1.5 (among those on DTG); Or Group D versus Group C	**None** (non-inferiority framework uses CI rather than hypothesis testing)	Geometric Mean ratio (GMR) of AUC(LNG0-8hr) between comparison groups	2-sided, 90% interval	CI on GMR compared to reference No-Effect Bounds (0.7,1.43) to assess similarity between groups
3 – secondary objective #1	Among those on EFV, LNG 3.0 mg versus LNG 1.5 mg ; Or Group B versus Group A	Exact Wilcoxon Rank Sum test for superiority hypothesis testing framework	Geometric Mean ratio (GMR) of AUC(LNG0-8hr) between comparison groups	2-sided, 90% interval	Secondary: Evaluation if CI for GMR fully above 1
4 – secondary objective #2	LNG 1.5 mg (among those on EFV) versus LNG 3.0 (among those on DTG); Or Group A versus Group C	Exact Wilcoxon Rank Sum test for superiority hypothesis testing framework	Geometric Mean ratio (GMR) of AUC(LNG0-8hr) between comparison groups	2-sided, 90% interval	Secondary: Evaluation if CI for GMR fully below 1

3.2 Secondary Outcome Measures

3.2.1 Safety

***Title**: Percentage of participants with occurrence of any serious or targeted adverse event (AE) potentially or definitely related to one-time Levonorgestrel administration.*

***Description**: Adverse events were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017. Relationship of adverse events to study treatment was determined by the study core team and DAIDS clinical representative.*

***Time Frame**: From study entry to day 28*

***Analysis Population:** Participants who received assigned dose of Levonorgestrel*

***Reporting Groups:** A-D*

Associated Study Objective: Secondary Objective #4

Details: Occurrence of the safety outcomes (i.e., number of participants meeting a safety outcome) as defined above will be enumerated and summarized by individual study group. Safety outcomes may be summarized separately by severity grade or type (category or MedDRA grouping) of adverse event. From the protocol definition of the safety outcome, the targeted list of reportable AEs includes the following: grade 3 or higher AEs, grade 2 or higher nausea, diarrhea, menorrhagia or metrorrhagia, and ectopic pregnancies.

Inference: Comparison of the relative number (%) of participants with safety outcome who took single-dose LNG versus the relative number of participants with this outcome who took double-dose LNG, will be performed using the safety analysis comparison set as defined below. The statistical hypothesis test for this comparison will be a Fisher's exact test, using a superiority-testing framework. This comparison may also be repeated for the two following pairwise comparisons:

(1) single-dose LNG versus double-dose LNG among HIV+ women taking EFV-based ART

(2) single-dose LNG among HIV+ women taking DTG-based ART versus double-dose LNG among women living with TB taking RIF-containing TB therapy.

Since this study was not powered to compare occurrence of AEs between LNG double-dose versus single-dose, inference related to comparisons above will focus on describing the magnitude and range of plausible values of observed differences between groups, and will **not** conclude similarity based on the absence of significant differences by Fisher's exact test.

At interim review: Safety (all AE) data will be summarized by cohort and by observed LNG dose group. The only planned formal statistical hypothesis test will be for the safety outcome compared by LNG dose groups (single-dose LNG versus double-dose LNG) using the safety analysis comparison set listed below.

3.2.2 Secondary LNG PK Parameters

***Title**: LNG PK Parameters calculated based on intensive LNG PK samples obtained from individual participants*

***Descriptions**:*

Note: Unless otherwise indicated, standard noncompartmental techniques were used to determine the PK parameter using the software package Phoenix WinNonLin (Certara®).

***Cmax**: C_{max} for each participant was the maximum observed concentration.*

***Cmin**: C_{min} for each participant was the minimum observed concentration after the observed dose among post-dose concentrations. Assay lower limit of quantification for LNG was 0.025 ng/mL; values < LLOQ were imputed as 0.0125.*

***CL/F**: Apparent oral clearance (CL/F) was calculated from the observed LNG concentration from LNG PK samples at pre-dose through 48 hours post-dose. Assay lower limit of quantification for LNG was 0.025 ng/mL; values < LLOQ were imputed as 0 (if pre-dose) or as 0.0125 (if post-dose).*

***Vd:** Volume of distribution (Vd) was calculated for each participant from observed LNG concentration from LNG PK samples at pre-dose through 48 hours post-dose.*

***T1/2**: T1/2 for each participant was calculated from the observed LNG concentration from LNG PK samples at pre-dose through 48 hours post-dose. Assay lower limit of quantification for LNG was 0.025 ng/mL; values < LLOQ were imputed as 0 (if pre-dose) or as 0.0125 (if post-dose).*

***Tmin:** T_{min} for each participant was time to the minimum observed LNG concentration after the observed dose.*

***Other AUC**: AUC for each participant was from LNG concentrations calculated over 24 or 48 hours and modeled to AUCinfinity using the linear up/log down version of trapezoidal rule (i.e., noncompartmental technique). This version of the trapezoidal rule uses linear interpolation between untransformed data up to C_{max}, and between log-transformed data from C_{max} through C_{last}. Assay lower limit of quantification for LNG was 0.025 ng/mL; values < LLOQ were imputed as 0 (if pre-dose) or as 0.0125 (if post-dose).*

***Time Frame**: Intensive LNG PK samples within 30 minutes pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, and 8, 24 and 48 hours post-dose [adjusting to appropriate time frame above]*

***Analysis Population**: Participants with PK concentrations over 24 or 48 hours and who took both assigned doses of LNG study treatment and expected doses of ART or TB therapy.*

***Reporting Groups:** A-D*

Associated study objectives: **Primary Objectives 1 and 2, Secondary Objectives 1 and 2**

Descriptive Summary Statistics per group:

- **Original scale: n, mean, sd, CV, *median, Q1, Q3*, min, max**
- **Natural log scaled: geometric mean, 95% CI on GM**

Statistical Analysis Summary: Tables parallel to the Summary table for the primary outcome will be produced for subset of secondary PK parameters, which are based on LNG concentrations. The same reference interval will be used as a comparison for these additional PK parameters. PK parameters not formulated from LNG concentrations (e.g. Tmax, Terminal half-life) will only have descriptive summary statistics.

3.3 Other Outcome Measures

1) ART or RIF exposure in plasma: Targeted concentrations of ART/TB medications (Note: according to single sample testing, no PK parameters will be modeled):
   - EFV : concentration from sample drawn 12-20 hours post previous dose EFV
   - DTG: concentration from sample drawn 20-28 hours post previous dose DTG
   - RIF: concentration from sample drawn 1-16 hours post previous dose RIF

The actual time/concentration profile will be plotted for each target drug (and indicating study group for EFV). Summary statistics for the distribution of targeted drug concentrations will be provided.

For each drug/metabolite, concentrations will be categorized into 2 groups based on adequate exposure versus inadequate exposure as follows:

EFV: threshold of 650 ng/mL (reference: lower 95% prediction bound on EFV concentration 20 hours post-dose from population PK modeling as published in Csajka et.al. Clinical Pharmacology and Therapeutics, 73:1, 2003)
DTG: threshold of 398 ng/mL (based on lower 95% bound of Ctrough of 50mg dose)
RIF (and associated metabolite desacetyl RIF): LLOQ of the assay (i.e. 75 ng/mL for RIF, 37.5 ng/mL for desacetyl RIF)

Those with documented inadequate exposure to the perpetrator drug, using the thresholds above, will be flagged for exclusion from a secondary, per-protocol analysis of LNG. Note: For RIF, both RIF and desacetyl RIF metabolyte need to be LLOQ in order to be excluded in the per-protocol analysis. See below for details.

Note: References for DTG thresholds below:

1. Min, S., Sloan, L., DeJesus, E., Hawkins, T., McCurdy, L., Song, I., ... & Lalezari, J. (2011). Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. *Aids*, *25*(14), 1737-174

2. Song, I., Chen, S., Lou, Y., Borland, J., Fujiwara, T., Piscitelli, S., & Min, S. (2009, July). Pharmacokinetic and pharmacodynamic relationship of S/GSK1349572, a next generation integrase inhibitor in HIV-1 infected patients. In *International AIDS Society Conference*.

4 Statistical Principles

4.1 General Considerations

4.1.1 Analysis sets

Full analysis set:
Participants who take LNG study treatment will be included in descriptive analyses of baseline, study conduct and descriptive summaries of AEs and other safety data (see below for separate analysis set for safety outcome measures).

Primary PK analysis set (primary outcome/objective):
Participants must meet all the following:

- Took assigned dose of LNG study medication
- Reported taking scheduled doses of other Rx (ART or TB Rx) over the 72 hours prior to PK sampling and over the 8-hour PK sampling period, as applicable
- Have a AUC(0-8hr) PK parameter estimated

Note: Baseline tables may be repeated for the PK analysis set if this analysis set differs from the Full analysis set.

Per-protocol PK analysis set:
Excluding participants whose perpetrator drug (i.e. EFV, DTG, or RIF) measured concentration was below the pre-specified threshold defined above in section 3.3 above.

Safety analysis set for comparisons of safety outcome measures between single-dose and double-dose LNG:
Participants who receive a dose of LNG that does not match their assigned dose will be excluded from comparisons of single versus double-dose LNG.

4.1.2 Other general considerations

- Because comparisons are not between groups assigned by randomization (except A and B below), there will be exploration of imbalances at baseline between pairs of relevant comparison groups not based upon randomization.

  Pairwise comparisons include groups:
  - B vs C (related to comparison in primary objective #1)
  - D vs C (related to comparison in primary objective #2)
  - B vs A (related to comparison in secondary objective #1; randomized)
  - A vs C (related to comparison in secondary objective #2)

  The baseline characteristics examined will be limited to the following: age (in years), BMI (CDC categories), body fat percentage (categories or continuous), country, race/ethnicity;

and among the HIV study groups: CD4 cell count, detectable plasma HIV-1 RNA, NRTI backbone containing tenofovir. Statistical tests used will be Fisher's exact test (or extension) for dichotomous (other categorical) characteristics, and exact Wilcoxon Rank Sum test for continuous characteristics. Due to the modest sample size, any adjusted analyses may need to adjust one covariate at a time.

Note: other baseline characteristics (e.g. OB/GYN characteristics) may be summarized overall and within study group.

- There will not be any adjustments for multiple testing of safety outcomes due to interim reviews. There will not be significance level adjustment affecting confidence interval calculation for the primary outcome GMRs, as each of the primary pairwise comparisons expressed as a GMR is addressing a separate study objective.

4.2 Analysis Approaches

4.2.1 Calculating Geometric Means, GMRs and associated confidence intervals

The natural (base e) log of concentration based PK parameters will be calculated, and confidence intervals computed based on normality assumptions of the log-transformed data. The respective geometric means and CIs will be calculated by taking the antilog of (exponentiating) both the estimated means and confidence interval bounds. Differences between parallel comparison groups will be calculated as the difference of the log-transformed PK parameters (equivalent to the log of the ratio).

Variance of the difference will assume equal group variances (and thus used pooled variance). Sensitivity analyses will check this assumption by repeating CI estimation using Satterthwaite version of standard error, which does not assume equal variance between groups.

The final GMR and respective CI presented will be the exponentiated point estimate of both the difference, and the confidence bounds on the confidence interval calculated using normality assumptions.

Further details provided in the Analysis Implementation Plan.

4.2.2 Primary PK analysis

In addition to the primary PK analyses described above (calculation of GMR and associated 90% CI on LNG PK parameters), the following supplementary analyses will be conducted to test the robustness of results from this primary analysis (based on the primary PK analysis set):

1) Parallel analysis of the per-protocol PK set which excludes participants whose measured perpetrator drug concentration was below the pre-defined threshold.

2) Estimation of GMR between non-randomized groups, adjusted for prognostic factors, which may be imbalanced between groups. (Note: adjustment will be performed via normal linear regression modeling on log-transformed PK parameters). (Adjusted

GMRs may also be given for the randomized group comparison so that results presented are parallel and this may be interpreted as adjustment for chance imbalance within a small sample size despite randomization.)

Secondary Objective #3: The outcome to address this objective is AUC0-24hr, and the external comparison groups are the LNG groups as published in Pariditpan Contraception, 2017 (Pharmacokinetics of levonorgestrel and ulipristal acetate emergency contraception in women with normal and obese body mass index), and as results available via clinicaltrials.gov NCT:02689804. Within subgroups defined by normal BMI and obese BMI, the GMR and associated 90% CI for AUC0-24hrs for LNG will be estimated between A5375 Group C (DTG) and this external historical control group. (This analysis will use Satterthwaite calculation of standard error.)

Secondary Objective #5: The outcomes to address this objective including the primary outcome (LNG AUC0-8 hours), as well as the following: Cmax, and AUC48, C48 (or AUC24 and C24, if too many participants are missing PK parameters at 48 hour). The independent variables include the baseline measurements of body weight including body fat percentage, total weight in kg, and BMI in kg/m^2. To evaluate the association between these baseline independent variables and the outcome of log-transformed LNG PK parameters, generalized linear regression models will be fit, with additional explanatory variable of LNG dose and perpetrator drug. Geographic region and age will be included for in these models to provide calculation of adjusted GMRs where possible.

5 Report Contents

1. *CONSORT Diagram*
    a. *Screening and screen failures*
    b. *Enrollment and eligibility violations*
    c. *Randomization and Assignment to study groups*
    d. *Analysis sets and analysis exclusions*
2. *Baseline characteristics*
    a. *Baseline Characteristics for Full Analysis set*
    b. *Baseline Characteristics for Primary PK Analysis set*
3. *Targeted medications*
    a. *Women living with HIV: background ARV regimens*
    b. *Women with TB: TB medications*
4. *Contraceptive use*
    a. *Recent contraceptive medications and methods*
5. *Targeted Historical Medical Diagnoses*
6. *LNG Treatment dose received*
7. *Adverse events*
8. *Tolerability of LNG – targeted symptoms before and after LNG receipt*
9. *Analysis of primary outcome measures*
10. *Analysis of secondary outcome measures*
11. *Correlation of baseline body measurements with LNG exposure as measured by AUC0-8hr*