Official Title: Desogestrel-containing COCP Pharmacokinetic Validation Study

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I. Hypotheses and Specific Aims:

Specific Aim:

- To validate prior pharmacokinetic research with combined oral contraceptive pill users that supports utilizing a 24-hour trough concentration as an accurate proxy for the intensive pharmacokinetic parameter of area under the curve (gold standard pharmacokinetics).

Hypotheses:

- We hypothesize that 24-hour trough concentration measurements of etonogestrel will have high correlation ($r \geq 0.9$) with the area under the curve measurements of etonogestrel among combined oral contraceptive pill users at steady state (day 21).
- We hypothesis that 24-hour trough concentration measurements of ethinyl estradiol will have high correlation ($r \geq 0.9$) with area under the curve measurements of ethinyl estradiol among combined oral contraceptive pill users at steady state (day 21)

II. Background and Significance:

Women taking the exact same formulation of combined oral contraceptive pill (COCP) will have wide variability in their pharmacokinetic (PK) measurements of both the estrogen and progestin components[1]. Traditionally, these PK measurements for COCP users consist of an area under the curve (AUC), maximum concentration (C_{max}), time to C_{max}, elimination half-life, and 24-hour concentration (C_{24})[1-3]. These intensive PK measurements may require up to 15 serial blood samples over the course of 24-36 hours, often necessitating an overnight stay in a clinical research center. Westhoff et al. found that the C_{24} measurement alone at steady-state (21 days of COCP use) was very highly correlated with AUC values for both ethinyl estradiol ($r=0.92$, $p<0.0001$) and levonorgestrel (LNG) ($r=0.95$, $p<0.0001$) among COCP users[2,3]. They also tested the correlation between single-dose C_{24} measurements and standard AUC values and found significant yet not as robust correlation for both ethinyl estradiol ($r=0.72$, $p=0.003$) and LNG ($r=0.7$, $p=0.004$)[2,3].

Ultimately, the C_{24} measurement at steady-state represents an ideal proxy for intensive COCP PK measurements that could alleviate much of the time demand placed on participants and reduce PK study costs without compromising data integrity. However, these PK analyses have all been conducted with the same COCP formulation containing ethinyl estradiol and LNG[2]. LNG, a second generation progestin, has distinct disadvantages compared to newer progestins due to its greater androgenicity[4,5]. Desogestrel (DSG), a third generation progestin, has similar progestin receptor binding affinity as LNG, but less androgen receptor binding affinity[4,5]. Formulations of COCPs with DSG often lead to improvements in androgen-related conditions, such as acne, due to their anti-androgenic properties[6]. For this reason, we have largely moved away from prescribing LNG-containing COCPs in our actual clinical practice. Thus, validation of this prior PK work with a DSG-containing COCP would produce more generalizable and pragmatic findings for COCP users in the US.

Furthermore, DSG is a pro-drug of etonogestrel (ENG)[4], which is the progestin of focus for our ongoing pharmacogenomic research with hormonal contraception through ENG contraceptive implant users[7,8]. As we begin to consider bridging this work to COCP users, we need to validate the prior findings of Westhoff and Basaraba et al.[2,3] with a DSG-containing COCP to directly inform and support the pharmacokinetic methodology for a planned pharmacogenomic study of COCP users. This study will directly address this need through testing whether the C24 measurement maintains high correlation for the AUC measurements of ENG and ethinyl estradiol among COCP users at steady state.

III. Preliminary Studies/Progress Report: No direct preliminary studies have been conducted at our institution. See prior published pertinent literature discussed above.

IV. Research Methods

A. Outcome Measure(s):

Primary Outcome Measures:

- 24-hour AUC measurement for serum etonogestrel
- 24-hour AUC measurement for serum ethinyl estradiol
- C_{24} measurement for serum etonogestrel
- C_{24} measurement for serum ethinyl estradiol

Secondary Outcome Measures:

- C_{max} for serum etonogestrel and ethinyl estradiol
- Time to C_{max} for serum etonogestrel and ethinyl estradiol
- Elimination half-life for serum etonogestrel and ethinyl estradiol

B. Description of Population to be Enrolled:

We aim to enroll up to 20 reproductive age (18-45 years) females in this study based on the following criteria:

Inclusion Criteria

- Healthy females aged 18-45 years
- Body-mass index ≥18.5kg/m2
    - No upper body-mass index
- Willing to abstain from medications and supplements known to induce/inhibit CYP3A4 during the study[9]
- Normal blood pressure measurement at screening (systolic <140mmHg, diastolic <90mmHg)
- Negative urine pregnancy test at screening

Exclusion Criteria

- Currently taking any known CYP3A4 inducers/inhibitors[9]
- Medical conditions that affect liver function (e.g. hepatitis, cirrhosis; assessed via participant self-report)
- Any contraindications to estrogen-containing contraception (based on any category 3 or 4 recommendations from the CDC MEC guidelines[10])
- Use of an injectable contraceptive method within the last 6 months or current use of an ENG contraceptive implant
- Childbirth within the last 6 months
- Known allergy or insensitivity to combined oral contraceptive pills
- Currently taking a combined oral contraceptive pill formulation and not willing to undergo a 7-day washout period and switch to the study specific COCP formulation for the duration of the study. The prior COCP formulation (e.g. 21/7, 24/4, and continuous) and the type of progestin are not exclusion criteria for this study given the washout period.

C. Study Design and Research Methods

We propose a prospective, pharmacokinetic validation study to conduct intensive pharmacokinetic measurements on females using a COCP containing desogestrel (DSG) and ethinyl estradiol (EE). We will enroll healthy, reproductive-age females (18-45 years) for this PK validation study. We will exclude women with contraindications to the use of estrogen-containing contraception based on the CDC Medical Eligibility Criteria (MEC) guidelines for any conditions with a category 3 or 4 recommendation[10]. We will also exclude women who have used an injectable contraceptive method (e.g. depot medroxyprogesterone acetate) within the last 6 months or currently using an ENG contraceptive implant. Our remaining inclusions and exclusions criteria are listed in the section above. For body-mass index (BMI), we will utilize a lower-limit cut-off of 18.5kg/m^2 to exclude potentially underweight participants who may have altered baseline metabolism. As participants will serve as their own comparator for this study's analyses, we will not have an upper BMI cut-off. For medical conditions that affect liver function, we will assess for these

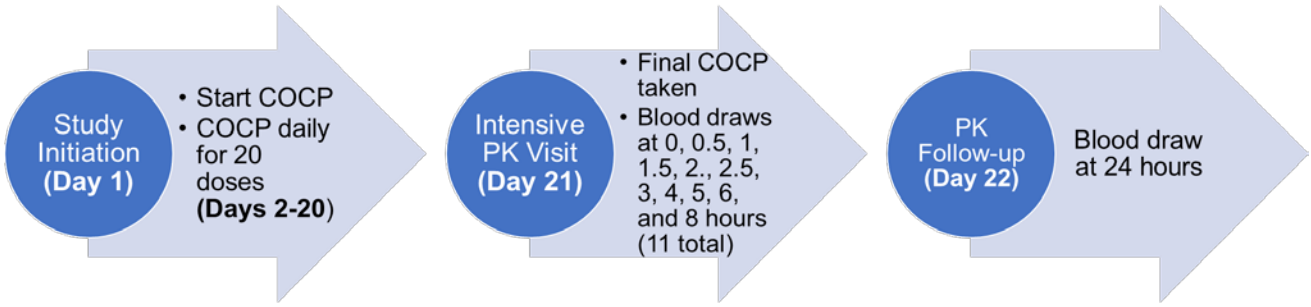
medical conditions during the screening process and confirm the lack of this exclusion criteria via self-report from interested participants. Females currently using a COCP will qualify for enrollment into the study after completing a 7-day washout from their current COCP formulation. If a female is currently on a different formulation of COCP (e.g. 24/4, continuous), then they will still qualify for enrollment into this study after completing a 7-day washout period from their current COCP formulation. Interested females will come to our CU Medicine Family Planning clinic (Comprehensive Women's Health Center [CWHC]) for a screening visit where will we confirm study eligibility including measuring height, weight, blood pressure, and a urine pregnancy test.

Eligible participants will then start a COCP formulation containing 30mcg of EE and 0.15mg of DSG. We will instruct participants to take their COCP first thing in the morning to prepare for their PK visit. After taking 20 days of the COCP, participants will return to CWHC for their steady-state PK study visit. Participants will present to CWHC fasting, take a urine pregnancy test, and then have an intravenous (IV) catheter inserted. We will then provide participants with a standard breakfast consisting of no more than 34% fat, during which they will be given their day 21 COCP to be taken with their food. Participants will then remain in our clinic for at least 8 hours, during which we will serially draw blood from the IV catheter at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 hours from the administration of the COCP. Participants will be provided a standard lunch consisting of 600-700 calories and no more than 34% fat content during their PK study visit. After the 8-hour blood draw, the IV catheter will be removed and the participants will return to CWHC again at 24 hours from COCP administration for one additional blood draw. Each participant will undergo a total of 12 blood samplings for intensive PK analyses (summarized in Figure 1).

For sample processing, we will allow samples to clot at room temperature for at least 10 minutes and then centrifuge all blood samples on site to obtain serum aliquots, which we will then store in our -80° freezer until analyzed. Oral DSG undergoes rapid and complete first-pass metabolism into ENG, and so we will only measure serum ENG as the systemic progestin component of this COCP[4].

At the conclusion of enrollment, all stored serum samples will be de-identified and shipped to an outside laboratory that contains validated assays for measurement of EE and ENG. We will measure EE and ENG serum concentrations using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays through the Biomarkers Core Laboratory at Columbia University Irving Institute[3,11]. Samples will be batched for analysis to reduce inter-assay variability.

Figure 1: Timeframe of study procedures



F. Data Analysis Plan:

We will use noncompartmental analysis procedures with the trapezoidal rule to calculate the 24-hour AUC for both serum EE and ENG. We will also determine the C_{24}, C_{max}, time to C_{max}, and elimination half-life for EE and ENG for each participant. For our primary analysis, we will calculate the Pearson correlation coefficients (r values) between the C_{24} serum measurements and the steady-state 24-hour AUC measurements for both EE and ENG. This will also include calculating 95% confidence intervals and p-values for these correlation coefficients. We have determined that duplicating a correlation coefficient of at least 0.9 will provide reassurance that C_{24} remains a valid proxy PK measurement for a DSG-containing COCP. To validate previous findings of at least an r=0.9[2,3], we would need only 7 participants with a power of 0.8 and significance cut-

off of 0.05. With 20 participants, we will have only a $5.0x10^{-7}$ chance of a type II error with duplicating an r≥0.9.

H. References:

References

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