University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Participants
Biomedical Form – Screening and Enrollment

IRB Study # 18-3402
Consent Form Version Date: Version 1.0 January 31, 2019

Title of Study: A5375 - 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

Short Title For The Study: Optimize LNG EC
Protocol Final version 1.0 2018-11-20

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This is a research study to test if a higher dose of Levonorgestrel (LNG) emergency contraception needs to be used to prevent pregnancy in girls and women who are taking some types of anti-HIV or anti-TB medications that are known to decrease the effectiveness of this form of birth control.

If you take efavirenz, you will be randomized to take either the standard LNG dose or a double LNG dose. If you take dolutegravir, you will take the standard LNG dose. If you take rifampin you will take a double LNG dose. At entry, you will have blood drawn 9 times over about 9 hours. You will return to the clinic for a blood draw at 24 and 48 hours after you took the LNG dose. You will have a small sample of hair cut from your head to measure levels of the HIV or TB drugs. You will be contacted by site staff to complete a phone survey at weeks 1, 2, and 4.

There are risks to this study drug that are described in this document. Some risks include: nausea, stomach pain, tiredness, headache, dizziness, breast pain, vomiting. Information learned from this study may help other women who have HIV or TB.

If you are interested in learning more about this study, please continue reading below.

What are some general things you should know about research studies?
You are being invited to take part in a research study. To join the study is voluntary.
You may refuse to join, or you may withdraw your consent to be in the study, for any reason.

Research studies are designed to obtain new knowledge that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign or make your mark on this consent form. You will get a copy to keep. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of the study?
Emergency contraception is birth control that prevents pregnancy. Girls and women use it after having unprotected sex. Levonorgestrel (LNG) emergency contraception is commonly known as Plan B® One-Step, or the Morning After Pill. This study will test if a higher dose of LNG needs to be used to prevent pregnancy in girls and women who are taking some types of anti-HIV or anti-TB medications. This study will also test if a higher dose of LNG is safe.
The United States Food and Drug Administration (US FDA) has approved LNG for prevention of pregnancy.

LNG works mainly by stopping the release of an egg from the ovary. It may also work by preventing fertilization of an egg, or by preventing attachment to the uterus. Girls and women can use emergency contraception to prevent pregnancy if regular birth control was used incorrectly or fails, or no birth control was used. LNG will not disrupt an existing pregnancy and using LNG does not affect your ability to have a baby in the future. After you take LNG as part of this study, you may attempt to get pregnant again as soon as your next menstrual cycle (after your next period), if you want to.

Efavirenz (EFV) is a medication commonly used to treat HIV. Rifampicin (RIF) is a medication commonly used to treat tuberculosis. Both of these medications lower the amount of LNG in your blood by about half. This may make LNG not work as well as it normally would. It is unknown if the current dose of LNG emergency contraception, in combination with EFV or RIF, is enough to prevent a pregnancy. To learn if a higher dose is needed to prevent pregnancy, you will take either a regular dose or a double dose of LNG emergency contraception.

Dolutegravir (DTG) is an anti-HIV medication that does not lower the amount of LNG in your blood. It is being used as a comparison to the other groups.

In this study, you will not be taking LNG for contraception (to prevent pregnancy), you will be volunteering to take it so that we can evaluate the impact of your other medications on the amount of LNG in your blood. You will take a dose of LNG emergency contraception by mouth. After you take the dose of LNG, the amount of LNG that is in your blood will be measured. This study will also take a hair sample that will tell researchers how often you have taken EFV, INH, and DTG over the past few weeks.

You are being asked to take part in this research study because you are a woman at least 18 years of age and:

1. You are living with human immunodeficiency virus (HIV-1) and you have been taking a combination of antiretroviral drugs (ARV) that includes either efavirenz (EFV) or dolutegravir (DTG)

   OR

2. You are living with tuberculosis (TB) infection, and you have completed the intensive phase of TB therapy and are now completing the continuation phase of TB treatment that requires taking isoniazid (INH) and rifampicin (RIF) daily.

The researcher in charge of this study at this site is Dr. David Wohl. Before you decide if you want to be a part of this study, we want you to know about the study.

Are there any reasons you should not be in this study?
You cannot be in this study if you:

- Have known allergy/sensitivity or any hypersensitivity to LNG.
- Have had Bilateral oophorectomy, hysterectomy, or postmenopausal.
- Are currently pregnant, within 6 weeks of delivery, or currently breastfeeding an infant under 6 months of age.
- Received LNG within 30 days prior to study entry.
- Received hormonal contraceptives within 30 days prior to study entry.
- Have used any drugs other than RIF and EFV known to: 1) induce CYP3A4 system within 30 days prior to study entry, and 2) inhibit the CYP3A4 system within 7 days prior to study entry.
- Have active drug or alcohol use or dependence
- Have acute or serious illness requiring systemic treatment and/or hospitalization within 14 days prior to study entry.
- Have other medical, psychiatric, or psychological condition that, in the opinion of the site investigator, would interfere with completion of study procedures and or adherence to study drug.
- You are living with HIV and are currently receiving medications for TB infection.
- You are living with HIV and missed one or more of the prescribed doses of HIV medications within 3 days prior to study entry.

- You are HIV-negative and being treated for TB and missed one or more of the prescribed doses of TB medication within 3 days prior to study entry.

How many people will take part in this study?
About 116 women will take part in this study at many sites; including about 5 women from this site.

How long will your part in this study last?
You will be in this study for about 4 weeks.

What will happen if you take part in the study?
If you decide to take part in this research study, you will be asked to sign this consent form. A screening visit will be done to make sure you are eligible to join the study. If you are found eligible, you will have one entry visit that will last 9-10 hours, a 1 hour visit 24 hours after entry, and a 1 hour visit 48 hours after entry. You will be asked to take a questionnaire over the phone 1 week, 2 weeks, and 4 weeks after entry.

If you enter the study
- At the study entry visit, you will be assigned to a study group. There are four study groups. Two will receive a standard dose of LNG, and two will receive twice the standard dose of LNG. You will not be able to choose your study group, but you will know what study group you are in.
- If you are taking EFV for HIV treatment, you will be randomly assigned (like a coin flip) to one of two possible doses of LNG. Some women will take a standard dose of LNG, other women will take twice the standard dose of LNG. More women will be assigned to take twice the standard dose, so it is more likely that you will be in this group.
- If you are taking DTG for HIV treatment, you will be assigned to receive a standard dose of LNG.
- If you are taking RIF for TB treatment, you will be assigned to receive twice the standard dose of LNG.

You will have blood samples taken during the study to measure the amount of LNG in your blood.

You will have a small sample of hair cut from your head so that we can measure levels of the anti-TB or anti-HIV drugs in this small hair sample. You may decline this procedure.

You will be asked questions about how well you take your anti-HIV or anti-TB medications and if you have any concerns about taking LNG.

You will be asked to use a reliable form of non-hormonal birth control every time you have sex that could lead to pregnancy until the study is completed. You may not enter the study if you have had sex that could lead to pregnancy within 14 days prior to starting the study.

Other
Some of your blood that is left over after all required study testing is done may be stored (with usual protectors of identity) and used for ACTG-approved HIV-related research.

Samples collected from you will be stored in the US. These samples may be stored for an indefinite

period of time. Results of testing performed on these samples will not be given to you. You may withdraw your consent for research on stored specimens at any time and the specimens will be thrown away. No matter what you decide, it will not affect your participation in this study. ***If you agree, you will be asked to sign a separate informed consent.***

A5375 Study Visits

The study staff can answer any questions you have about individual study visits, and how long they will last, or about the tests that will occur. The table below can be used as a quick reference for you, along with the explanations that follow.

Table 1: Study Schedule

Evaluation or Procedure	Screening	Entry Visit	Study Visits		Follow-Up Calls			Clinically Indicated Visit	Early Study Discontinuation
		Day 0	Day 1	Day 2	Day 7	Day 14	Day 28		
	1 hour	9-10 hours	1 hour	1 hour	30 minutes	30 minutes	30 minutes	1 hour	30 minutes
Documentation of HIV Status	√								
Medical/ Medication History	√	√							
Questions About Your Menstrual Cycle	√	√			√	√	√		√
Diagnoses Questions		√	√	√	√	√	√	√	√
Medication Questions		√	√	√			√	√	√
Acceptability and Practicality Questionnaire		√		√		√	√		√
Adherence Assessment	√	√	√	√					
Physical Exam	√	√						√	
Blood Collection	√	√							
Pregnancy Testing	√	√						√	
Hair Collection		√							
LNG EC Administration		√							
Pharmacokinetic Sampling (blood collection)		√	√	√					

Screening

If you would like to be in this study, after you have read and signed this informed consent form, you will come to the clinic for a screening visit to make sure you meet the requirements for joining the study. This visit will take about 1 hour. Up to 18 mL (1.4 tablespoons) of blood will be drawn at this visit.

- Your HIV infection status will be confirmed. If there is no record available, another HIV test will be done. You may have to sign a separate consent form before this is done.
- You will be asked questions about your medical and medication history and any medications you are currently taking. You will be asked about your menstrual period.
- You will be asked about adherence to your anti-HIV or anti-TB medications (how correctly you are taking your medications).
- You will have a physical exam.
- You will have blood drawn for routine lab tests for safety. You will be told the results of these tests when they become available.
- You will give a urine sample or have blood drawn to see if you are pregnant. This test must show that you are not pregnant for you to enroll in the study. You will be told the result of the test when it becomes available.

Entry Visit (Day 0)

If you are eligible for the study and you choose to enroll, you will come back to the clinic for an entry visit. This visit will last about 9 or 10 hours. Up to 75 mL (5.8 tablespoons) of blood will be drawn at this visit.

- You will be asked about: your medical history and any medications you are taking, your menstrual period and if there has been a change in your menstrual period since the screening visit, and adherence to your anti-HIV or anti-TB medications.
- You will have a physical exam, including measuring your neck, waist, and hips.
- If you are HIV positive, you will have blood drawn to test how much HIV is in your blood, and to test how many CD4 cells (infection-fighting cells) are in your blood. You will be told the results of these tests when they become available.
- You will have blood drawn and stored for a genetic test (a test of your DNA [genes] to better understand how fast your body removes the study drugs from your blood). Genetic testing looks at differences in people's genes. Your body, like all living things, is made up of cells, and cells contain deoxyribonucleic acid, also known as "DNA." DNA is like a string of information put together in a certain order. Parts of the string make up "genes." Genes contain instructions on how to make your body work and fight disease. The testing in this study will only look at certain genes that are known to have an effect on how your body uses hormones. The tests will not look at any other genes. You will not receive the results of these tests.
- You will give a urine sample or have blood drawn to see if you are pregnant. This test must show that you are not pregnant for you to remain in the study. You will be told the result of the test when it becomes available.
    - You will have a small sample of hair (about 50 strands) cut from your head to measure levels of the HIV or TB drugs in this hair sample. Humans lose about 100 hairs from their head every day naturally, so this amount of hair removal should not be noticeable. If you decide not to provide a hair sample, you can still be in the study. Results of this testing will not be available to you since hair levels are still a research tool.

- You will take a dose of LNG emergency contraception by mouth.
- You will be asked to remain at the clinic all day for an intensive pharmacokinetic (PK) blood sampling. For this intensive PK sampling, you will have blood drawn over 8 hours to measure the amount of LNG in your blood. To avoid many needle sticks, a small tube (intravenous device) will be placed into a vein in your arm and left in place during your stay. You will be able to move around and should not have any significant pain or discomfort once the tube is in place. Blood will be taken before you take the LNG emergency contraception dose, and then at 30 minutes, 1, 1.5, 2, 3, 4, 6, and 8 hours after you take the LNG emergency contraception dose.
- You will be asked if you have any problems or concerns after taking the LNG emergency contraception dose.

Study Visits (Days 1 and 2)
After the entry visit, you will come back to the clinic for two more study visits. The first will be 1 day after your entry visit, and the second will be 2 days after your entry visit. These study visits will last about 1 hour. Up to 6 mL (0.4 tablespoons) of blood will be drawn at this visit.

- You will have about blood drawn for PK blood sampling.
- You will be asked about: your adherence to medications, changes in your medications and diagnoses, the acceptability and practicality of emergency contraception, and any problems or concerns you have after taking the LNG emergency contraception dose.

Follow-up
A member of the study staff will call you 7 days after study entry to ask you about your menstrual period. You will also be asked about changes in your diagnoses.

A member of the study staff will call you 14 and 28 days after study entry to ask you about: changes in your diagnoses and (on day 28 only) your medications, your menstrual period, the acceptability and practicality of emergency contraception, and any problems or concerns you have after taking the LNG emergency contraception dose.

Clinically Indicated Visit
If you become pregnant or have an adverse event, you may be asked to return to the clinic for a physical exam and pregnancy test, and to discuss any changes in your medications or diagnoses.

Early Study Discontinuation (Leaving the Study Early)
If you leave the study early, you will be asked questions about your menstrual period, changes in your medications or diagnoses, questions to determine the acceptability and practicality of emergency contraception, and questions about any problems or concerns you have after taking the LNG emergency contraception dose.

What are the possible benefits from being in this study?
Research is designed to benefit society by gaining new knowledge. You will receive no benefit from being in this study. Information learned from this study may help other women who have HIV or TB.

What are the possible risks or discomforts involved with being in this study?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Risks of Levonorgestrel (LNG, Plan B® One-Step)
The following side effects have been associated with the use of LNG:

- Nausea
- Lower stomach (abdominal) pain
- Tiredness
- Headache
- Dizziness
- Breast pain
- Vomiting
- Diarrhea

Some women will have menstrual changes such as spotting or bleeding before their next period. Some women may have a heavier or lighter next period, or a period that is early or late.

- If your period is more than a week late, you should get a pregnancy test

Since the dose of LNG used in two study groups is not FDA approved (known as "off label" use), these risks could be worse in severity, and there may be additional risks that are not yet known.

Risks of Drawing Blood
Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection.

Risks of Hair Collection
There is a small risk of cutting or nicking the scalp during the hair collection, although this is extremely rare.

Risks of Social Harm
It is possible that participating in this study will make it difficult for you to keep your HIV or TB status, or information about your sexual activity, secret from people close to you.. This may lead to unwelcome discussions about or reactions to your HIV or TB status. Please talk with the study staff if you have any concerns about this.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if the drug or drug combinations in this study harm unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant until you complete the study. You may not enter the study if you have had sex that could lead to pregnancy within 14 days prior to starting the study.

You and your partner must use reliable birth control that you discuss with the study staff. You must continue to use birth control while in the study. You may choose one of the birth control methods below:

- Male condom with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Non-hormonal IUD
- Bilateral tubal ligation
- Male partner vasectomy

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices. A pregnancy test may not detect a very early pregnancy, which is why the study team asks that you not enter the study if you have had sex that could lead to pregnancy within 14 days of study entry.

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in women taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

Breastfeeding

Breastfeeding women will be included only after their infants are at least 6 months old. Birth control like LNG is allowed during breastfeeding. During long-term use of drugs like LNG, called progestins, the amount of progestin in infant blood is only 1-6% of the amount in maternal blood. No side effects of progestins have been found on breastfeeding (quality or quantity of milk), or on the health or development of the infant due to this low progestin exposure.

What if we learn about new findings or information during the study?

You will be told any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the medication may be causing bad effects, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

How will your privacy be protected?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from

the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties, University of North Carolina at Chapel Hill Institutional Review Board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If you are injured as a result of your being in this study, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.

What if you want to stop before your part in the study is complete?

You are free to leave the study at any time and for any reason.

Why Would The Study Doctor Take You Off This Study Early?

The study doctor may need to take you off the study early without your permission if:

- The study is stopped or cancelled
- You are not able to attend the study visits as required by the study
- You have a positive pregnancy test before you take the LNG dose for the study
- Your primary care doctor requests that you be taken off the study

After the study:

After you have completed your study participation, the study will not be able to continue to provide you with the LNG you received on the study. If similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

If you choose not to be in the study, what other options do you have?
Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

If you do not enroll into the study
If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, pregnancy test) information is being collected from you so that AIDS Clinical Trials Group (ACTG) researchers may help determine whether there are patterns or common reasons why people do not join a study

Will you receive anything for being in this study?

If you participate in this study, you will receive $25 at the end of each completed visit at Screening, 24 hour PK, 48 hour PK, and telephone contact interview at weeks 1, 2, & 4. You will receive $150 at the end of the entry visit which includes the 8 hour PK.
If you complete all procedures for the entire study, you will receive a total of $300.

If you travel more than 50 miles to get to the clinic for your study visit, assistance with family care and/or additional travel assistance will be made available by the site with the amount determined on a case by case basis. Parking vouchers will be provided at all visits.

Will it cost you anything to be in this study?
There will be no cost to you for LNG, study-related visits, physical examinations, laboratory tests, or other study procedures. Anti-HIV and anti-TB medicines will not be provided by the study.

You or your insurance company, or your health care system will be responsible for the costs of your regular medical care as well as for the costs of drugs not given by the study. In some cases it is possible that your insurance company will not pay for these costs.

Who is sponsoring this study?
This research is funded by NIH National Institute of Allergy and Infectious Diseases (NIAID) (the Sponsor). This means that the research team is being paid by the sponsor for doing the study. In addition, Dr. David Wohl, the principal investigator on this study, received income from Bristol-Myers Squibb Company an entity that manufactures a drug used in this study. These activities are not part of this study and may include consulting, service on advisory boards, giving speeches, or writing reports.

If you would like more information, please ask the researchers listed in the first page of this form.

What if you have questions about this study?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

If you ever have any questions about the study, or if you have a research-related injury, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research participant?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research participant, or if you would like to obtain information or offer input, you may contact the UNC Institutional Review Board at [redacted] or by email to [redacted]

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SIGNATURE PAGE

IRB Study # 18-3402

Title of Study: A5375 - 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 Final version 1.0 2018-11-20

Principal Investigator: David Wohl, MD

SCREENING AND ENROLLMENT CONSENT

Participant's Agreement:
If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____	_____
Participant's Name (print)	Participant's Signature	Date
_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature	Date