

1) Protocol Title

Title: Nexplanon Use in Women Primarily Choosing a Combined Oral Contraceptive: a Proof of Concept Trial

Protocol Version Date: August 12, 2016

2) Objectives

2.1.1 Primary objective:

Evaluate the tolerability (side effects) and acceptability (continuation of the implant throughout the study) of concomitant etonogestrel (ENG) implant use in women choosing a combined oral contraceptive (COC) for contraception.

2.1.2 Secondary objectives:

Evaluate the following outcomes:

- Demonstrate that women desiring a COC are willing to use ENG implant concomitantly as a continuous “back-up” contraceptive
- Bleeding patterns while using a COC concomitantly with ENG implant
- Continuation rate of COC over 6 months of evaluation
- Plan to continue the COC and/or implant after the study

2.1.3 Hypotheses.

1. Women who desire a COC for contraception will be willing to use ENG implant concomitantly as a continuous back-up method.
2. Women using a COC concomitantly with ENG implant will primarily experience regular bleeding patterns, especially after the third cycle of COC use.
3. Tolerability will be good and acceptability high in women who use a COC concomitantly with ENG implant
4. A high percentage of women in the study will still be using the ENG implant after 6 months.

3) Background

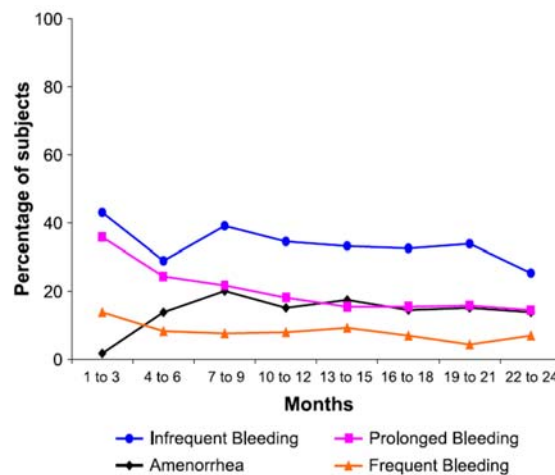
The ENG implant is a very highly effective method of contraception. The implant is designed to provide contraceptive efficacy for 3 years with a relatively quick return of fertility upon its removal. The implant and the intrauterine device comprise the types of long-acting reversible contraceptive (LARC) methods available throughout the world. Use of these methods is associated with lower rates of unintended pregnancy as compared to shorter acting methods or barrier methods of contraception (Winner 2012).

In the United States, 45% of all pregnancies are unintended (Finer 2016). This latest rate, from 2011, is a drop from a peak of 51.0% in 2008 and lower than the rates of 48.0% in 2001 and 49.2% in 1994 (Henshaw 1998, Finer 2014). This decline is potentially related to increased use of contraception, especially LARC methods

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including the intrauterine device and the ENG implant (Kavanaugh 2015). COCs still make up a much greater proportion of contraceptive use by U.S. women as compared to LARC methods, despite the comparatively lower efficacy of COCs. Approximately 26% of contracepting women in the U.S. use an oral contraceptive and a smaller percentage use a ring or patch (Daniels 2015). COCs offer women more regular bleeding patterns. However, the requirement for daily use, ability to forget to use the product, and the current status in most parts of the U.S. for women to pick up a new prescription monthly at the pharmacy significantly influences the chance for user error. As a result, real-life use of COCs results in higher unintended pregnancy rates than LARC methods.

Currently, among U.S. contraceptors, 10.3% use IUDs and 1.3% use implants for a combined LARC use rate of 11.6% (Kavanaugh 2015). The ENG implant, although it is much easier for a variety of healthcare providers to place than an IUD (since no pelvic examination is required), is underutilized as compared to IUDs. The primary reason appears to be related to menstrual irregularities, which also is associated with discontinuation or removal. The largest US trial of the ENG implant showed relatively high rates of frequent or prolonged bleeding (see figure). Accordingly, 13% of subjects discontinued for bleeding irregularities within 2 years amongst US women (Funk). A systematic review of multiple trials found discontinuation rates for bleeding irregularities or amenorrhea in the US and Europe of 13.1% and 13.6%, respectively (Mansour 2008), A recent retrospective chart review reported a discontinuation rate of 14.8% due to bleeding irregularities in women had a higher BMI (mean 28.5). Discontinuation rates due to bleeding irregularities have been reported to be as high as 23% in a study from the UK (Agrawal).



Few studies have attempted to evaluate effective treatments for bleeding irregularities in women using the ENG implant. A recently published study randomized 32 women with 7 or more days of “bothersome” bleeding to 14 days of a COC containing EE 30 mcg and levonorgestrel 150 mcg, or placebo (Guiahi 2015). Although the COC quickly decreased the bleeding, the bleeding returned within days of treatment cessation. A recently completed study by this investigator (Creinin), supported by Merck, showed that women who use COCs together with

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the implant for 28-84 days are more likely to report significant improvement in bothersome bleeding complaints as compared to placebo. These studies demonstrate the potential for using COCs to treat bothersome bleeding that can occur with implant use. For the purposes of the proposed trial, the important message from both of these studies is that women who use COCs with an implant don't have the bothersome bleeding that can occur with implant use alone.

For our society to further decrease unintended pregnancy, a continued shift of use toward LARC methods is needed. A gradual shift over time has occurred but there still remains a high proportional use of COCs. Circulating progestin levels with the ENG implant are significantly lower than with COCs and women using COCs with an ENG implant do not complain of increased adverse events based on our recent Merck supported trial. Accordingly, one could hypothesize that most women using a COC plus the ENG implant will feel simply like they are using the COC. Thus, if women wanting to use a COC will use the ENG implant concordantly, they will be using the COC they want to use while getting the significantly higher level of contraceptive protection afforded by the implant. The ENG implant acts as a continuous back-up for when the woman forgets her pill, can't get to the pharmacy, or is sick and vomiting her pill. This model of "allowing" women to use the COC they want to use while giving them a LARC method as back-up at the same time has the potential to have a huge public health impact on lowering unintended pregnancy rates.

References:

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4) Inclusion and Exclusion Criteria

Inclusion Criteria:

- Women 16 years and older being seen in a UC Davis medical office or who contact our research office
- Women currently using COCs or intending to initiate COCs at the time of the office visit for contraception
- Women who are able to consent or, if under the age of 18, be able to give assent and have a parent who is able to give parental consent. If the minors are emancipated or otherwise do not want to involve their parents, the minors must consent themselves and no parent consent is required.

Exclusion Criteria:

- Women who have contraindications to using a COC or a contraceptive implant (Category 3 or 4 in the CDC Medical Eligibility Criteria [MEC])
 - Because the CDC MEC are continuously revised, we will refer to the most updated criteria at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5904a3.htm>
- Women who are currently participating in a clinical trial or have participated within the past 30 days.

We will not be including any of the following vulnerable populations:

- Adults unable to consent
- Children 15 years and younger
- Pregnant women
- Prisoners

5) Study Timelines

Each subject will participate for up to 6 months.

We anticipate it will take up to 4 months to enroll 20 subjects for this study.

Based on the timeline below, we expect to complete all analyses by September 2017.

STUDY EVENT	MONTHS
Enrollment and 6 month follow-up of subjects	10
Close data set	2
Preparation of final study report and manuscript	3
TOTAL time	15

6) Study Endpoints

As a proof of concept study, the primary outcome is the tolerability (side effects) and acceptability (continuation of ENG implant through 6 months) of concomitant ENG implant use in women choosing a combined oral contraceptive (COC) for contraception. Continuation will be important to assess as some women may choose to discontinue the COC and rely on the ENG implant.

Secondary outcomes will include willingness to accept concomitant ENG implant use with a planned COC, COC continuation rate over 6 months, bleeding patterns and plan to continue ENG implant after 6 months.

All products being used in the study are FDA-approved for contraception. Safety data will be collected in relation to severe adverse outcomes (as defined by the FDA).

7) Procedures Involved

We will recruit women being seen in a UC Davis medical office or who contact our research office. Potential participants must be women currently using COCs or intending to initiate COCs at the time of the office visit.

- “New starters”: subjects who have the implant placed four or less weeks after the initiation of a COC or who are prescribed the COC on the day of the implant initiation.
- “Current pill users” subjects who have been using a COC for more than four weeks prior to implant placement.

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We intend to enroll approximately 10 subjects in each of the groups. We expect that most women will be recruited while in the office who decide to initiate COCs or are continuing COC use—these women will be offered the ability to talk to research staff about the study.

Visit 1 (Screening/Enrollment):

Informed consent will be obtained. As part of informed consent, subjects will be educated that there is little data available on the adverse effects of combined COC and ENG implant use. The consent form will include a standardized description of the side effects and bleeding profile of COCs and the implant. As per standard of care, subjects will also need to review the package label information for Nexplanon and sign the FDA-required Nexplanon consent. After obtaining informed consent, subjects will be screened for entry criteria. Medical history will be obtained. Eligible subjects will receive a prescription for the desired COC (if needed) and have a Nexplanon contraceptive implant placed. A urine pregnancy test will be performed prior to Nexplanon placement. The Nexplanon will be placed as indicated by the standard guidelines. A diary will be dispensed for the subject to document daily bleeding, COC use and adverse events. Subjects will be instructed to either start or continue their COCs, as indicated.

If subjects would like to complete the screening visit separate from enrollment, an additional visit will be made for implant placement. Subjects will be compensated at the time of the implant placement for screening/enrollment.

Follow-up

A follow-up visit will occur at 1 month (+1 week) and 3 and 6 months (+2 weeks) after Nexplanon placement. The diary will be reviewed and a copy made to keep with the source documentation. At the 1- and 3-month visits, additional diaries will be dispensed as needed. Adverse events will be determined by inquiry and diary review. The subject will inform the study staff if she is using her COC and if she wants to continue use of her COC and ENG implant. The ENG implant will be removed upon request at any time during the study. All subjects will be followed for the full six months regardless of whether they discontinue the implant or COC.

A phone call will occur approximately 1 week prior to the 3 and 6 month visits to check status and remind subject of the scheduled visit. Study participation will be complete after the 6 month follow-up visit.

If a subject misses a visit, efforts will be made to have her return to the research office as close to the study window as possible. She will be contacted three times and then sent a letter and certified letter to contact the research study office.

No surveys will be used that the subject fills out herself. A daily diary will be used.

No blood draws will occur during this study.

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Data to be collected by study staff include demographics, past medical and gynecologic history, prior and current contraceptive use, and reason for using COC (contraception, medical or both).

Because we are enrolling women who are already currently using COCs or who plan to start COCs, the COC is not a study drug. The study intervention (study drug) is the contraceptive implant. The systemic hormone exposure with a contraceptive implant is minimal relative to a COC. We would not expect any increase in side effects by adding a contraceptive implant to COC users. Of note, the primary risk with COC use is related to the estrogen which can increase the risk of venous thromboembolic disease. The implant has no estrogen. All products being used in the study are FDA-approved for contraception.

8) Data and/or Specimen Management and Confidentiality

All data will be presented descriptively.

The sample is a convenience sample for proof of concept. A total of 20 women will be enrolled to evaluate if women who desire a COC method are willing to accept having a ENG implant placed to use along with their planned COC.

Data that is collected will be kept in a secure and confidential manner in the Department of Obstetrics and Gynecology. Only study staff will have access to both electronic and paper study documents. All study staff will have completed IRB required CITI training and University of California Davis privacy and security trainings, as well as study specific training.

Subjects will be assigned a unique study specific subject number. All data will be associated with that number. No personal identifying information will be used in the data analysis. Study personnel who are delegated by the Principal Investigator will be responsible for the transmission, receipt and management of the data.

At University of California, Davis, the information collected for this study will be recorded on paper source documents. The source documents will be kept in a locked file cabinet in a room with limited access. Only study personnel will have access to both the room with the file cabinet and the file cabinet. This room is locked at all times when study personnel are not occupying the room. Data will be stored at least two years after publication.

All data that is kept electronically will be stored on a University of California Davis Health System server. Access to the servers, specific folders, and files will be password protected. The use of removable media (USB drives, CD/DVD, etc.) will be kept to a minimum and will only have password protected files.

The identifying information will be collected for study-contact and reimbursement related purposes include: name, phone number(s), email address, date of birth,

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address, social security number and an emergency contact. This information is collected at screening and updated at each contact with the subject. Subject contact information will be maintained confidentially as part of the subject's source documents. No identifying information will be entered into the study data base or used as part of the data analysis.

No data will be transported to an outside entity.

9) Data and/or Specimen Banking

No data or specimen will be banked for future research.

10) Provisions to Monitor the Data to Ensure the Safety of Subjects

Research staff and study investigators will monitor for side effects. The research staff and study investigators are in the research office daily. The research study staff and investigators have regularly scheduled research meetings during which enrollment, participant status and adherence, unexpected adverse events and study issues are discussed. The study investigators will review all necessary information and at shorter intervals when indicated.

Adverse events will be reported to the study PI as they occur. Any adverse events that are required to be reported to the University of California, Davis IRB will be reported according to the IRB reporting guidelines.

Safety information will be collected through subject diaries and during study visits. Subjects will record any adverse events on daily diaries, and they will be encouraged to call the research office with any questions or concerns regarding side effects. Study visits will occur at 1, 3 and 6 months.

We will use descriptive statistics to analyze the safety data.

11) Withdrawal of Subjects

Subjects may be discontinued prematurely if:

- If the subject withdraws consent
- The FDA withdraws the implant from the market

Subjects may withdraw their consent to participate in the study at any time. Subjects who choose to discontinue will be asked to return to the research office for a discontinuation visit. At this visit, final study visit procedures will be completed, including collection and review of study diaries, assessment of

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adverse events, and subject's final plans for the ENG implant. If a subject refuses to return to the site for a discontinuation visit, the staff will request that the subject return her diaries using a traceable shipping method. Subjects will be considered lost to follow-up at the end of the study.

The goal of the study is to follow all subjects for six months whether or not they continue one or both contraceptive methods (implant and COC). Subjects can discontinue one or both methods during the study, but we would want to follow their outcomes through six months.

12) Risks to Subjects

The subjects will be using COCs as part of their standard of care. Subjects who are under the age of 18 are at no greater risk during study participation than those 18 and older.

- The side effects while using an implant with the COC may be increased, specifically irregular menstrual bleeding and those associated with the progestin component of the combined oral contraceptive pill, which include mood changes, weight gain, acne, and growth of hair in areas of the face, back or chest.
- The risks specific to the contraceptive implant placement include pain, bleeding, bruising, infection, scar and swelling at placement site, expulsion of the implant, migration of the implant within the arm or rarely to other locations in the body including the lungs, injury to nerves or blood vessels in the arm, breaking of the implant making removal difficult, difficulty with removal requiring surgery to remove the implant
- Other common side effects may include: headache, vaginitis (inflammation of the vagina), breast pain, viral infections, such as sore throats or flu-like symptoms, stomach pain, painful periods, nervousness, depressed mood, back pain, nausea, dizziness or pain.
- Rare, but serious side effects may include ovarian cysts, a blood clot in your legs or lungs, stroke, high blood pressure, gallbladder problems, or liver tumors (noncancerous or cancerous).
- Should you become pregnant, the risk of ectopic pregnancy is slightly increased when pregnancy occurs when a contraceptive implant is in place. An ectopic pregnancy is a pregnancy that grows outside of the uterus. However, the likelihood of having an ectopic pregnancy is significantly decreased because the chance of becoming pregnant is very low with the implant. None of the hormones being used are known to increase the risk of abnormalities for a developing pregnancy.

13) Potential Benefits to Subjects

Participants will have a higher likelihood of preventing pregnancy because the implant is significantly more effective than a COC.

14) Multi-Site Research

N/A

15) Community-Based Participatory Research

N/A

16) Sharing of Results with Subjects

Results will not be shared with subjects.

17) Prior Approvals

This study was approved as an investigator-initiated grant by Merck & Co.

18) Provisions to Protect the Privacy Interests of Subjects

Participants will only interact with study personnel who are trained on the protocol and have completed training regarding Good Clinical Practice (GCP) codes and patient confidentiality. All questions that the participant has regarding confidentiality concerns will be addressed. Participants will be assured that their privacy will be vigilantly protected in accordance to local guidelines and HIPAA policies. Any information that is accessible to the research team will be either self-reported by the subject, or only accessed by the research team with explicit written permission from the subject.

19) Compensation for Research-Related Injury

We will use the language required by UC Davis IRB as presented in Form HRP 502- Consent:

It is important that you promptly tell the person in charge of the research if you believe that you have been injured because of taking part in this study. If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to your

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insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about compensation, you may call the IRB Administration at (916) 703-9151 or email at IRBAdmin@ucdmc.ucdavis.edu.

If the sponsor pays any of your medical expenses, we may be required to give the sponsor your name, date of birth, and Medicare ID or social security number.

20) Economic Burden to Subjects

Subjects will not be charged anything for participating in the study.

21) Drugs or Devices

Due to the nature of the study and because the study drug (Nexplanon) is FDA-approved, we will work with University of California Davis Investigational Drug Services (IDS) to store the implants in our study office as we have done for other studies. We expect most women will be recruited from our office and will be approached at the time they are receiving a COC prescription. Because the packaging is small we can store all 20 implant boxes and have regular visits from IDS to ensure compliance (as we have done with other studies).

- I confirm that all investigational drugs will be received by the Investigational Drug Service (IDS). The IDS will store, handle, and administer those drugs so that they will be used only on subjects and be used only by authorized investigators.
- I confirm that all investigational devices will be labelled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.