Title: **An Open-Label Study of Serum Testosterone and Nestorone in Females After Secondary Exposure to Nestorone ® (NES) + Testosterone (T) Combined Gel Applied to Shoulders and Upper Arms in Males: Effect of Washing or Clothing Barrier to the Application**

Protocol Number: CCN005B

IND Number: 105,079

Clinical Phase: Ib

Sponsors: National Institutes of Health
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Contraceptive Clinical Trial Network (Male)
6710B Rockledge Drive
Bethesda, MD 20814 USA

Population Council, Center for Biomedical Research
1230 York Avenue
New York, NY 10065 USA

Program Director: Diana Blithe, PhD, NICHD

Medical Monitor: Mark Payson, MD

Safety Officer: Mohcine Alami, MD, Population Council

Director: Régine Sitruk-Ware, MD, Population Council

Original Protocol: Version 1.0 (16-NOV-2016)

Investigators and Institutions:
Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center
Principal Investigator: Christina Wang, MD
Co-Investigators: Ronald S. Swerdloff, MD
Peter Liu, MBBS FRACP PhD

University of Washington
Principal Investigator: Stephanie Page, MD, PhD
Co-Investigators: William J. Bremner, MD, PhD
Bradley Anawalt, MD

Statistical & Clinical Coordinating Center:
Clint Dart, MS
Health Decisions
2510 Meridian Parkway, Suite 100
Durham, NC 27713, USA
Telephone: (919) 967-1111
Fax: (919) 967-1145
www.healthdec.com

PROTOCOL SIGNATURE PAGE

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Diana Blithe Nov 16, 2016
Diana Blithe, PhD Date
Program Director, NICHD

16 Nov 16
Mark Payson, MD Date
CCTN Contract Medical Monitor

11/16/2016
Regine Sitruk-Ware, MD Date
Distinguished Scientist, Population Council, Director

I, the undersigned, will conduct the clinical study as described in the Protocol and will adhere to the *Code of Federal Regulations*, Title 21 and Title 45, Part 46, Good Clinical Practices (GCP), International Conference on Harmonisation (ICH), and the Declaration of Helsinki. I have read and understood the contents of the Protocol and Investigator Brochure.

The signature of the investigator below indicates acceptance of the protocol and a complete understanding of the investigator obligations as outlined in Investigator Obligations.

_____
Principal Investigator Signature

Printed Name: _____ **Date:** _____

Institution and Address: _____

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALPH	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Celsius
CAP	College of American Pathologists
CBC	Complete Blood Count
CCTN	Contraceptive Clinical Trial Network
CDC	U.S. Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CMC	Chemistry and Manufacturing Controls
CRB	Contraceptive Research Branch
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
CV	Curriculum Vitae
DBP	Diastolic Blood Pressure
DHHS	Department of Health and Human Services
DHT	Dihydrotestosterone
DMPA	Depo-medroxyprogesterone acetate
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EudraCT	European DataBase for Clinical Trials
F	Fahrenheit
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practice
hCG	Human Chorionic Gonadotropin
HCO_3	Bicarbonate
HD	Health Decisions
HDL	High-Density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
hMG	Human Menopausal Gonadotropin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IEC	Institutional Ethics Committee
IM	Intramuscular
IMP	Investigational Medicinal Product

IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IP	Investigational Product
IPSS	International Prostate Score System
IRB	Institutional Review Board
IRP	Intramural Research Program
IUD	Intrauterine Device
IUS	Intrauterine System
K+	Potassium
LA	Los Angeles
LDL	Low-Density Lipoprotein
LH	Luteinizing Hormone
LTFU	Lost To Follow-Up
MedDRA®	Medical Dictionary for Regulatory Activities
Na+	Sodium
NDA	New Drug Application
NES	Nestorone®
NICHD	National Institute of Child Health and Human Development (NICHD)
NIH	National Institutes of Health
PC	Population Council
PHQ-9	Patient Health Questionnaire – 9 (Depression Module)
PI	Principal Investigator
PK	Pharmacokinetics
PSA	Prostate-Specific Antigen
PSI	Particle Science Inc
Q	Quarter
RBC	Red Blood Cells
SBP	Systolic Blood Pressure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SCCC	Statistical and Clinical Coordinating Center
SD	Standard Deviation
SHBG	Sex Hormone-Binding Globulin
SOP	Standard Operating Procedure
STI	Sexually Transmitted Infection
T	Testosterone
TEAE	Treatment-Emergent Adverse Event
UCLA	University of California Los Angeles
WBC	White Blood Cells
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title:	**An Open-Label Study of Serum Testosterone and Nestorone in Females After Secondary Exposure to Nestorone® (NES) + Testosterone (T) Combination Gel Applied to Shoulders and Upper Arms in Males: Effect of Washing or Clothing Barrier to the Application**
Protocol Number:	CCN005B
Clinical Phase:	Phase Ib
Sponsors:	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Contraception Research Branch Population Council
IND Number:	105,079
IND Holder:	Population Council
Primary Objective:	The primary objective of the study is to determine the pharmacokinetics of testosterone (T) and Nestorone (NES) concentrations in female participants after a single exposure of skin contact with a male participant dosed with a gel containing T and NES applied to the shoulders and upper arms. The skin contact with non-dosed female participants occurs 2 hours after male gel application, and has 3 variations: • With a 100% cotton T-shirt clothing barrier; • After the application site is washed with soap and water in a shower then dried; • Without washing or clothing barrier to the skin to skin contact.
Secondary Objectives:	The secondary objectives are: 1. To determine the effects of showering on the pharmacokinetics of testosterone and Nestorone concentrations in male participants after application of testosterone and Nestorone combined gel on shoulders and upper arms in men. 2. To determine the amount of testosterone and Nestorone that remained on the skin after application in men. 3. To assess the safety and tolerability of the combined gel in men. 4. To assess the safety in women possibly exposed to the gel after skin contact at the site of application of the gel in men.
Primary Endpoints:	The primary objective will be evaluated in female participants by assessing changes from baseline up to 48 hours for serum testosterone levels in Cavg, Cmax, and Cmin after secondary exposure to Nestorone + Testosterone Combination Gel (NES/T gel). Also, the Nestorone levels will be summarized after secondary exposure to NES/T gel by presenting Cavg, Cmax, and Cmin. These endpoints will be summarized for each of the 3 types of skin contact between the man and woman.
Secondary Endpoints:	The secondary objectives will be evaluated using the following endpoint measures: 1. The pharmacokinetic parameters of testosterone and Nestorone in males after wearing a T shirt and after washing will be compared to serum testosterone and Nestorone pharmacokinetics after application of the combined gel without washing. 2. Serum testosterone pharmacokinetics in males after applying NES/T gel with or without T shirt and with washing will be compared to baseline pharmacokinetic parameters. 3. Average testosterone and Nestorone levels 90 and 150 minutes after application in men as measured by adhesive D-square strips with and without showering.

	4. Incidence of adverse events and serious adverse events for both partners. 5. Changes from baseline in safety labs in both partners. 6. Percentage of females with increased (relative to baseline) acne and hirsutism at each visit. These endpoints will be summarized for each of the 3 types of skin contact between the man and woman.
Investigators and Institutions:	Investigators and sites listed below will participate in this study. Detailed information (addresses, statement of qualifications, names of sub-investigators, and name and address of each reviewing Institutional Review Board) will be maintained in a separate file. Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center Principal Investigator: Christina Wang, MD Co-Investigators: Ronald S. Swerdloff, MD Peter Liu, MBBS FRACP PhD University of Washington Principal Investigator: Stephanie Page, MD, PhD Co-Investigators: William J. Bremner, MD, PhD Bradley Anawalt, MD
Rationale, Background, Risks and Benefits:	A number of sporadic reports have shown the transfer of applied testosterone from the skin of men to women (Merhi & Santoro, 2007) and children (Brachet*, et al.*, 2005; Kunz*, et al.*, 2004) that may result in hirsutism, acne and virilization in the women and children. Previous studies have confirmed that testosterone may be transferred from men who applied transdermal testosterone gel to women upon close contact (Miller*, et al.*, 2012; Rolf*, et al.*, 2002; Stahlman*, et al.*, 2012; Stahlman*, et al.*, 2012). The transfer of testosterone to women is related to the dose of testosterone applied to men. In studies for testosterone transference, secondary exposure to women occurred after direct skin contact 2 hours after gel application. The studies showed that 2.5 g (40.5 mg) and 5 g (81 mg) of testosterone gel resulted in elevation of serum T in females with changes of all testosterone pharmacokinetics parameters as compared to baseline by 24-27% and 52 to 70% respectively. Transference of testosterone from the site where testosterone gel is applied in men to the female after close skin contact was prevented by men wearing a 100% cotton T-shirt covering the application area or by showering approximately 2 hours after application of gel (Stahlman*, et al.*, 2012; Stahlman*, et al.*, 2012). Washing the skin 2 to 6 hours after applying 81 mg of Androgel 1.62 % on the skin of men resulted in 10-14 % decrease in the average concentration of serum testosterone. Skin washing decreased the mean amount of testosterone remaining on the skin by at least 81% (Stahlman*, et al.*, 2012). Showering within 30 minutes after application of testosterone gel may lower serum testosterone in men to levels below the adult reference range and is not recommended (de Ronde*, et al.*, 2011). Possible transfer of transdermal Nestorone from men to women upon close skin contact has not been studied. In our proposed study “Clinical Evaluation of Nestorone® (NES) and Testosterone (T) Combination Gel for Male Contraception (CCN017)”, adult men will apply a combined testosterone and Nestorone gel on their arms and shoulders for approximately 68 weeks. Their female partner may be exposed to transfer of testosterone and Nestorone inadvertently though close skin contact despite the male participant being asked to wear a 100% cotton T-shirt covering the area of gel application or washing with soap and water before close skin contact with his female partner or children. This proposed study will be

	conducted to assess maximum testosterone and Nestorone transfer from the skin of the healthy male volunteers to non-dosed female participants after application of the combined testosterone and Nestorone gel over the shoulders and upper arms of the male participant. The study will assess the absorption and pharmacokinetics of testosterone and Nestorone in female healthy volunteers after single exposure of skin contact (her hands and arms) to the area where the male participant had applied the gel (his shoulders and upper arms) approximately 2 hours earlier. The study will assess the absorption and pharmacokinetics under three conditions: 1) indirect contact with the male participant wearing a 100% cotton T-shirt covering the area of application; 2) direct skin contact with male participant's skin where the gel was applied after the male has washed the application area with soap and water then dried it; and 3) direct skin contact where the gel was applied without a T-shirt barrier or shower for the male participant. The effect of showering on the pharmacokinetics of Nestorone will also be assessed in the male and compared to that obtained when there is no shower.
Study Design:	This is a two-center, open-label study conducted in healthy male and female volunteers at two academic research centers. The study will consist of three single applications of the Nestorone (NES) + testosterone (T) combined gel on the shoulders/upper arms of male participants followed 2 hours later by supervised skin contact by the non-dosed female participants on the application site on days 1, 8, and 15. On day 1, the male participant will wear a 100% cotton T-shirt over the application area before skin contact with the female. On day 8, the male participant will shower approximately 1 hour and 45 minutes after gel application and engage in skin contact with the female participant (2 hours after gel application) after washing the area with soap and water then drying it. A measurement of residual Nestorone and testosterone will be taken from the male's skin on a single location of the application site using adhesive D-square strips 90 minutes after application (30 minutes before shower/90 minutes after gel application) and 30 minutes after the shower and rubbing (150 minutes after application). On day 15, there will be no shower or clothing barrier for the male participant before skin contact with the female participant. A measurement of residual Nestorone and testosterone will be taken from a single location of the application using adhesive D-square strips site 90 minutes and 150 minutes after the application. An end of study/exit visit will occur for both male and female participants two weeks after treatment completion.
Compliance:	As gel application and skin contact will occur under direct study staff supervision, no issues with compliance are anticipated. All aspects of this study will be performed according to CFR Title 21, CRF Title 45, Part 46, Good Clinical Practices (GCP) and *International Conference on Harmonisation* (ICH) under an IND application. All principles of the *Declaration of Helsinki* will be followed.
Number of Subjects:	The protocol is expected to enroll a total of 12 healthy male subjects and their partners (i.e.12 female subjects), 6 male and 6 female subjects per site.
Study Duration:	The subjects will be evaluated for a period of about 2 months (screening up to 4 weeks, treatment phase of 17 days, and post-treatment for 2 weeks).

Investigational Product:	The investigation product is a combination gel with Nestorone® (NES) and Testosterone (T) applied transdermally.
Dosage and Regimen:	This will be a Phase Ib, open-label study with three single applications of the NES + T combined gel. The volume of gel to be applied will be approximately 5 mL. This gel volume will contain 62.5 mg of T that will deliver approximately 6 mg T to the body per day and will also contain 8.3 mg of NES that will deliver about 0.8 mg NES to the body per day (NES 8 mg/d + T 60 mg/d (NES8/T60) gel) in 5 ml of combined gel.
Inclusion Criteria:	**Male participant – Inclusion Criteria** Men who meet all the following criteria will be eligible for enrollment in the trial: 1. Good health as confirmed by medical history, physical examination, and clinical laboratory tests of blood and urine at the time of screening; 2. 18 to 50 years of age; 3. BMI ≥ 18 and < 35 kg/m2; 4. No history of androgen use prior to the first screening visit as follows: a. 1 month prior for oral or transdermal androgen, b. 3 months prior for Testosterone cypionate or enanthate injection, c. 6 months prior for Testosterone undecanoate injection; 5. Agreement to use a recognized effective method of short acting contraception with his partner (i.e. at a minimum use double-barrier method such as a condom with spermicide) during the entire study; 6. In the opinion of the investigator, male subject is willing and able to comply with the protocol; 7. Provision of valid, written and informed consent. **Female participant – Inclusion Criteria** Women who meet all the following criteria will be eligible for enrollment in the trial: 1. Good general health (BMI ≥18 and <30 kg/m^2)with no chronic medical conditions that result in periodic exacerbations which require significant medical care; 2. Aged between 18 and 40 years, at the enrollment visit; 3. Not pregnant and not breastfeeding. 4. Agreement to use a recognized effective method of contraception throughout the study 5. Willingness and ability to provide valid, written and informed consent and to comply with the protocol; 6. No desire for pregnancy within the next 6 months.
Exclusion Criteria:	**Male participant – Exclusion Criteria** Men who meet any of the following criteria are not eligible for enrollment in the trial: 1. Men participating in another clinical trial involving an investigational drug within the last 30 days prior to the first screening visit. 2. Men not living in the catchment area of the study site or within a reasonable travel time from the site. 3. Any clinically significant abnormal findings at screening per the Investigator's medical judgement. 4. Elevated PSA (e.g. levels ≥ 4 ng/mL), according to study site's local laboratory reference normal values for adult men. 5. Abnormal serum chemistry values that may indicate clinically significant liver or kidney dysfunction. Other abnormal laboratory values may also be exclusionary, if so considered by the investigator to be clinically significant.

6. Use of androgens or other anabolic steroids that may affect testosterone measurements
7. Diastolic blood pressure (DBP) ≥ 85 and Systolic blood pressure (SBP) ≥ 135 mm Hg; (BP will be taken three times at approximately 5 minute intervals and the mean of the 3 measurements will be considered).
8. History of hypertension (well-controlled treated hypertension (< 135/85) is allowed).
9. Known history of primary testicular disease or disorders of the hypothalamic-pituitary axis.
10. Known hypersensitivity to progestins or testosterone.
11. History of prostate or breast carcinoma
12. Significant lower urinary obstructive symptoms (IPSS > 19).
13. Known history of significant cardiac, renal, hepatic or prostatic disease.
14. History of thromboembolic disease.
15. A serious systemic disease such as diabetes mellitus (including diabetes controlled with treatment), HIV, or morbid obesity.
16. Current active or ongoing Hepatitis infection
17. Known or suspected current alcohol dependence syndrome, chronic marijuana use, or any illicit drug use that may affect metabolism/transformation of steroid hormones and study treatment compliance.
18. Known active or chronic dermatitis or other severe skin disorder.
19. Desiring fertility within 6 months of study participation.
20. History of severe depression or other serious mental health disorder.
21. Men participating in competitive sports where drug screening for prohibited substances (including anabolic steroids) is routine will be advised of the relative and temporary hazards that participating in this study may have for their sporting status.

Female participant – Exclusion Criteria

Women who meet any of the following criteria are not eligible for enrollment in the trial:

1. Desire to become pregnant during the study.
2. Breastfeeding
3. Known or suspected current alcoholism or drug abuse.
4. History of thrombosis
5. Serum testosterone outside normal reference ranges by local laboratory standards or evidence of hirsutism (modified Ferriman-Galwey score > 8)
6. Participation in another clinical trial involving an investigational drug within the last 30 days prior to the first screening visit.
7. Current pregnancy.
8. Known hypersensitivity to progestins or testosterone.
9. Any clinically significant abnormal findings at screening per the Investigator's medical judgement.
10. Use of androgens or other anabolic steroids that may affect testosterone measurements.
11. Known active or chronic dermatitis or other severe skin disorder.
12. Known or suspected current alcohol dependence syndrome, chronic marijuana use, or any illicit drug use that may affect metabolism/transformation of steroid hormones and study treatment compliance.

	13. Not living in the catchment area of the study site or within a reasonable travel time from the site.
Safety Parameters:	Safety parameters include enumeration of all AEs and clinically significant safety labs abnormalities. Safety laboratory tests will be performed at each clinical site. Serum testosterone and Nestorone will be measured by liquid chromatography tandem mass spectrometry at the Endocrine and Metabolic Research Laboratory at Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center.
Other Assessments:	Demographic characteristics, including age, ethnicity and race will be collected.
Statistical Analysis:	An estimated sample size of 12 couples is based on the studies conducted assessing testosterone transference. Based on the published data, a sample size of 12 female participants will give an 80% power to detect a change from baseline in serum testosterone of non-dosed females for a mean difference of 9 ng/dL with a standard deviation of 10 ng/dL (Stahlman*, et al.*, 2012) (Stahlman*, et al.*, 2012). The safety sample will be all subjects who had been exposed to one dose of the medication. The pharmacokinetic sample will consist of all subjects in the safety sample who had sufficient bioanalytical assessments to calculate a complete set of pharmacokinetic parameters. These are AUC 0-24, Cavg, Cmax, Cmin, Tmax, Tmin, Fluctuation (Cmax-Cmin/Cavg) for both serum testosterone and Nestorone.

Title: **An Open-Label Study of Serum Testosterone and Nestorone in Females After Secondary Exposure to Nestorone ® (NES) + Testosterone (T) Combined Gel Applied to Shoulders and Upper Arms in Males: Effect of Washing or Clothing Barrier to the Application**

1. Introduction and Background

Contraception options for men are limited to condoms and vasectomy, yet international surveys have shown that a large number of men would use a new contraceptive method if one were available (Heinemann *et al*., 2005; Dorman and Bishai, 2012; Martin *et al*., 2000). The goal is to develop a hormonal contraceptive method for men that proves to be effective, safe, reversible, self-delivered, user-friendly and affordable. Gonadotropins and testosterone (T) play a pivotal role in the maintenance of normal spermatogenesis, with suppression of gonadotropins by exogenous administration of androgens resulting in azoospermia/oligozoospermia in 50 – 70% of normal men (WHO Task Force, 1990; Cummings and Bremner, 1994). Azoospermia may not be achieved until both gonadotropins and T are suppressed (Nieschlag, Zitzmann, and Kamischke, 2003). Therefore, in addition to the suppression of gonadotropins, intratesticular depletion of T is also required to achieve oligozoospermia. In order to maintain androgenicity (including libido, bone structure, mental effects, hematopoiesis), T should be substituted by an androgen preparation.

The treatment with androgen alone has been shown to be highly effective in Asian men but less effective in non-Asian men enrolled in clinical trials (World Health Organization Task Force on Methods for the Regulation of Male Fertility, 1990). In order to increase the contraceptive efficacy of androgen treatment in Caucasian men, several other combinations of testosterone preparations with different progestins or gonadotropin releasing hormone antagonists have been tested in clinical trials. Depo-medroxyprogesterone acetate (DMPA) in combination with T has been shown to result in suppression of gonadotropins and spermatogenesis (Knuth, Yeung, and Nieschlag, 1989; Handelsman *et al*., 1996). Adding a single intramuscular (IM) injection of DMPA 300mg in men receiving T pellets at 800mg increased suppression of spermatogenesis from 40% in men receiving T alone, to 90% in men receiving both T and DMPA. This combination of T implants and DMPA by IM injection resulted in no significant changes in body weight or lipids (total, LDL- or HDL-cholesterol levels).

Efficacy data using this combination of T pellets (800 mg/4 months) plus DMPA injections (300 mg/3 months) was effective in preventing pregnancies in 55 couples with 36.4 person years of exposure (Turner *et al*., 2003). Similar to DMPA, both levonorgestrel and norethistrone enanthate have been shown to suppress gonadotropins and sperm counts when added to T administration (Bebb *et al*., 1996; Kamischke *et al*., 2000; Kamischke *et al*., 2002). However, all of these regimens have also been shown to decrease HDL cholesterol, possibly due to the inherent androgenic activity of 19-nortestosterone progestins (Anawalt *et al*., 1999; Wu FC *et al*., 1999; Wallace and Wu, 1990).

Nestorone® (NES) is a synthetic, 19-nor-progesterone derived progestin, with selective pharmacological profile, with no binding to androgen receptors (Kumar *et al*., 2000). NES is inactive when taken orally but very potent when given parenterally (Sitruk-Ware *et al*., 2003) and has shown no androgenic effects in animals, unlike 19-nortestosterone derived progestins such as norethisterone and levonorgestrel. The Population Council (PC) has been working on NES for use in female contraception. NES has proven to be effective as a female contraceptive when administered via vaginal rings (Laurikka-Routti, Haukkamaa, and Heikinheimo, 1990), implants (Haukkamaa *et al*., 1992; Diaz *et al*., 1995; Brache *et al*., 2000) and transdermal systems (Fraser et al., 2007; Stiruk-Ware, 1989; Sitruk-Ware, 1995).

We have previously shown the safety and efficacy of using separate NES and T gels as a strong suppressor of gonadotropins and spermatogenesis (CCN005 and CCN007) (Illani *et al*., 2012; Mahabadi

et al., 2009). Gonadotropin suppression is marked after 3 to 4 weeks of gel application. Severe oligozoospermia is observed in over 89 percent of men at 20 to 24 weeks after daily application of 8 mg NES gel and 100 mg T gel (Ilani *et al*., 2012). Results of a recent study (CCN005A) showed the combined NES/T gel, in a small volume of 5mL per dose, applied to the arms and shoulders resulted in effective suppression of gonadotropins to below 1 IU/L and levels of serum NES were comparable to those observed in the previous studies (CCN005 and CCN007) (Roth *et al*., (unpublished)).

In another proposed study "Clinical Evaluation of Nestorone® (NES) and Testosterone (T) Combination Gel for Male Contraception (CCN017)", adult men will apply a combined testosterone and Nestorone gel on their arms and shoulders for approximately 68 weeks. Possible transfer of transdermal Nestorone from men to women upon close skin contact has not been studied. Their female participant may be exposed to transfer of testosterone and Nestorone inadvertently through close skin contact despite the male participant being asked to wear a 100% cotton T-shirt covering the area of gel application or washing with soap and water before close skin contact with his female participant or children.

This proposed study will be conducted to assess maximum testosterone and Nestorone transfer from the skin of the healthy male volunteers to non-dosed female participants after application of the combined testosterone and Nestorone gel over the shoulders and upper arms of the male participant.

2. Objectives

2.1 Primary objective

The primary objective of the study is to determine the pharmacokinetics of testosterone (T) and Nestorone (NES) concentrations in female participants after a single exposure of skin contact with a male participant dosed with a gel containing T and NES applied to the shoulders and upper arms. The skin contact with non-dosed female participants occurs 2 hours after male gel application, and has 3 variations:

- With a 100% cotton T-shirt clothing barrier;
- After the application site is washed with soap and water in a shower and dried;
- Without washing or clothing barrier to the skin to skin contact.

This will be evaluated by assessing differences between average serum testosterone and Nestorone levels at baseline compared to Cavg, Cmax, Cmin after secondary exposure to Nestorone + Testosterone Combination Gel (NES/T gel).

2.2 Primary Endpoint

The primary objective will be evaluated in female participants by assessing changes from baseline up to 48 hours for serum testosterone levels in Cavg, Cmax, and Cmin after secondary exposure to Nestorone + Testosterone Combination Gel (NES/T gel). Also, the Nestorone levels will be summarized after secondary exposure to NES/T gel by presenting Cavg, Cmax, and Cmin. These endpoints will be summarized for each of the 3 types of skin contact between the man and woman.

2.3 Secondary objectives

The secondary objectives are:

1. To determine the effects of showering on the pharmacokinetics of testosterone and Nestorone concentrations in male participants after application of testosterone and Nestorone combined gel on shoulders and upper arms in men.
2. To determine the amount of testosterone and Nestorone that remained on the skin after application in men.

3. To assess the safety and tolerability of the combined gel in men.
4. To assess the safety in women possibly exposed to the gel after skin contact at the site of application of the gel in men.

2.4 Secondary Endpoints

The secondary objectives will be evaluated using the following endpoint measures:

1. The pharmacokinetic parameters of testosterone and Nestorone in males after wearing a T shirt and after washing will be compared to serum testosterone and Nestorone pharmacokinetics after application of the combined gel without washing.
2. Serum testosterone pharmacokinetics in males after applying NES/T gel with or without T shirt and with washing will be compared to baseline pharmacokinetic parameters.
3. Average testosterone and Nestorone levels 90 and 150 minutes after application in men as measured by adhesive D-square strips with and without showering.
4. Incidence of adverse events and serious adverse events for both partners.
5. Changes from baseline in safety labs in both partners.
6. Percentage of females with increased (relative to baseline) acne and hirsutism at each visit.

These endpoints will be summarized for each of the 3 types of skin contact between the man and the woman.

3. Rationale, Benefits and Risks

3.1 Rationale

A number of sporadic reports have shown the transfer of applied testosterone from the skin of men to women (Merhi & Santoro, 2007) and children (Brachet, et al., 2005; Kunz, et al., 2004) that may result in hirsutism, acne and virilization in the women and children. Previous studies have confirmed that testosterone may be transferred from men who applied transdermal testosterone gel to women upon close contact (Miller, et al., 2012; Rolf, et al., 2002; Stahlman, et al., 2012; Stahlman, et al., 2012).The transfer of testosterone to women is related to the dose of testosterone applied to men. In studies for testosterone transference, secondary exposure to women occurred after direct skin contact 2 hours after gel application. The studies showed that 2.5 g (40.5 mg) and 5 g (81 mg) of testosterone gel resulted in elevation of serum T in females with changes of all testosterone pharmacokinetics parameters as compared to baseline by 24-27% and 52 to 70% respectively. Transference of testosterone from the site where testosterone gel is applied in men to the female after close skin contact was prevented by men wearing a 100% cotton T-shirt covering the application area or by showering approximately 2 hours after application of gel (Stahlman, et al., 2012; Stahlman, et al., 2012). Washing the skin 2 to 6 hours after applying 81 mg of Androgel 1.62 % on the skin of men resulted in 10-14 % decrease in the average concentration of serum testosterone. Skin washing decreased the mean amount of testosterone remaining on the skin by at least 81% (Stahlman, et al., 2012). Showering within 30 minutes after application of testosterone gel may lower serum testosterone in men to levels below the adult reference range and is not recommended ((de Ronde, et al., 2011).

Possible transfer of transdermal Nestorone from men to women upon close skin contact has not been studied. In another proposed study “Clinical Evaluation of Nestorone® (NES) and Testosterone (T) Combination Gel for Male Contraception (CCN017)”, adult men will apply a combined testosterone and Nestorone gel on their arms and shoulders for approximately 68 weeks. Their female partner may be exposed to transfer of testosterone and Nestorone inadvertently through close skin contact despite the male participant being asked to wear a 100% cotton T-shirt covering the area of gel application or washing with soap and water before close skin contact with his female partner or children. This proposed study will be conducted to assess maximum testosterone and Nestorone transfer from the skin of the healthy male volunteers to non-dosed female participants after application of the combined testosterone and Nestorone gel over the shoulders and upper arms of the male participant. The study will assess the

absorption and pharmacokinetics of testosterone and Nestorone in female healthy volunteers after single exposure of skin contact (her hands and arms) to the area where the male participant had applied the gel (his shoulders and upper arms) approximately 2 hours earlier. The study will assess the absorption and pharmacokinetics under three conditions: 1) indirect contact with the male participant wearing a 100% cotton T-shirt covering the area of application; 2) direct skin contact with male participant's skin where the gel was applied after the male has washed the application area with soap and water; and 3) direct skin contact where the gel was applied without a T-shirt barrier or shower for the male participant. The effect of showering on the pharmacokinetics of Nestorone will also be assessed in the male and compared to that obtained when there is no shower.

3.2 Risks and Benefits

There is no immediate benefit to the participating couples. The benefits would be in the future development of a reversible and effective male contraceptive.

Previous experience with study preparations of NES and T gel suggests that serious adverse events are unlikely. The risks of participation in this study are expected to be minimal. T gel has been FDA approved for clinical use in hypogonadal men, produces minimal skin irritation, and has long-term safety data. In the United States, transdermal testosterone preparations are the popular and well accepted form of testosterone replacement therapy. Testosterone in men may produce reversible androgen related side effects such as: mild breast enlargement, acne, oiliness of skin, slight weight gain, mild increases in hematocrit, decrease in HDL cholesterol, and slight increase in the size of the prostate. In a prior study for men of NES and T gel for 24 weeks, no serious adverse events were reported. Common minor side effects included skin symptoms, including acne and dry skin, weight gain, and some mood changes including depressed mood, changes in libido, mood swings, fatigue or irritability. Transfer of applied testosterone from the skin of men to women may result in hirsutism, acne and virilization in women.

3.3 Dose Rationale

In a prior 6-month study of NES and T gel applied separately on two sites of the body daily, two doses of NES gel were evaluated, 8mg and 12 mg (Ilani *et al*., 2012). There was no significant difference in the number of men who achieved a sperm concentration <1 million/mL; therefore, the 8 mg dose was selected for a future study. In addition, previous studies tested lower than 8mg doses which showed lower doses were not effective in suppressing gonadotropins (Mahabadi*, et al.*, 2009).

Based upon long-term use of T gel for treatment of male hypogonadism and the prior studies of NES and testosterone gels (CCN005 and CCN007), the dose of 62.5 mg T was selected to deliver the appropriate amount of T (approximately 60 mg) within the combination gel in a volume of about 5 mL in order to maximize the number of treated men with a serum T in the mid-normal range, without supraphysiologic levels of T.

Based on results of a 4 week study (CCN005A) applying a combined NES + T gel delivering approximately 62.5 mg T and 8.3 mg NES per day in 5 mL volume, a larger efficacy trial of the combined gel (CCN017) is proposed. This study will test the transference effects of the combined product proposed for the larger efficacy study.

4. Study Design

This is a two-center, open-label study conducted in healthy male and female volunteers at two academic research centers. The study will consist of three single applications of the Nestorone (NES) + testosterone (T) combined gel on the shoulders/upper arms of male participants followed 2 hours later by

supervised skin contact by the non-dosed female participants on the application site on days 1, 8, and 15.

The protocol is expected to enroll a total of 12 healthy male subjects and their partners (i.e.12 female subjects), 6 male and 6 female subjects per site. The couple will be instructed to use another highly effective method of contraception for the duration of the study (i.e. at a minimum use double barrier method such as a condom with spermicide).

Screening will take approximately 2 to 4 weeks to ensure the participants meet inclusion criteria. Couples who meet the eligibility requirements will begin the treatment phase, which includes three overnight visits on days 1, 8, and 15. Within two weeks after the completion of the day 15 treatment application, a telephone call will be made to the male participants as their end of study/exit visit. At the same time, the female participants will return to the clinic for a blood draw and AE assessment for their end of study/exit visit.

A study design table outlining the schedule of assessments is provided in **Appendix 1**.

Participating clinical sites will transmit male and female subject data to the statistical and clinical coordinating center (SCCC) on a weekly basis.

5. Subject Compliance

As gel application and skin contact will occur under direct study staff supervision, no issues with compliance are anticipated.

All aspects of this study will be performed according to CFR Title 21, CRF Title 45, Part 46, Good Clinical Practices (GCP) and International Conference on Harmonisation (ICH) under an IND application. All principles of the Declaration of Helsinki will be followed.

6. Principal Investigators and Research Centers

Two investigational research centers will conduct the study. A complete list of investigators, sub-investigators and coordinators will be maintained with trial documentation.

Listed here are the investigational research centers conducting this study:

- Christina Wang, MD, PI: Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute
- Stephanie Page, MD, PhD PI: University of Washington

7. Subject Recruitment

This study will be conducted by the National Institute of Child Health and Human Development (NICHD) in its Contraceptive Clinical Trials Network (CCTN) (Male Group) at two sites in the US (Los Angeles and Seattle). This study will be listed on the website ClinicalTrials.gov and the websites of the respective institutions. Study couples will be recruited from the general population and reproductive health services affiliated with each site. Referrals from previous participants in male contraceptive clinical trials are accepted. Sites will obtain IRB approval for all recruitment materials used as part of the study. Subjects will be asked to contact one of the study sites by telephone or email. The coordinator will screen potential male subjects over the phone or email by inquiring about their age and medical history. Potential male subjects who qualify by initial screen will be scheduled with their partner for an appointment to consult with the investigator about further eligibility requirements for the study. Both the male and female subjects will sign an informed consent prior to initiation of any study screening

procedures. Couples will be selected for the study according to the selection criteria detailed in **Section 10**.

8. Study Duration

The total duration of the study for each couple is expected to be approximately 2 months. Both members of the couple will be enrolled in the study throughout this period. The study will be divided into 3 phases:

- a screening phase of 2 to 4 weeks
- a treatment phase of 17 days
- and a post-treatment phase of 2 weeks

This protocol will involve a start-up period including the time to initiate the study and begin recruitment of couples. The recruitment period for sites to enroll subjects, including the site start-up period will be about 2 months with the treatment phase for some subjects starting during this period. After Informed Consent is obtained, the couple should use a reliable method of contraception until the study exit visit occurs.

Subject recruitment is expected to begin and complete during Q1 2017. If this enrollment timeline is met, all male subjects should finish treatment by approximately the end of Q1 2017 and the study should end by approximately Q2 2017. Therefore, the total duration of the study will be approximately 6 months for each study site including pre- and post- study activities. The end of the study will occur when the last couple to be enrolled has completed their end of study/exit visits.

Results of the study are expected to be available Q3 2017.

9. Number of Subjects

The protocol is expected to enroll a total of 12 healthy male subjects and their partners (i.e.12 female subjects), 6 male and 6 female subjects per site.

Couples who do not complete the study will be replaced. Couples who discontinue will not be re-enrolled into this study.

10. Selection of Subjects

Healthy men ages 18 – 50 years with an 18 –40 year old female will be enrolled in the study according to the inclusion and exclusion criteria. Couples will be informed about the nature, aims and objectives of the study and both male and female subjects will be required to give their written consent prior to participation in the study.

Couples will be enrolled after providing informed consent and completing screening examinations, which include, but are not limited to, clinical evaluation of general and reproductive history, a detailed physical examination and analyses of blood. Screening results should be within reference ranges or assessed by the Investigator to be not clinically significant if out of normal ranges prior to couple enrollment.

The couple will be instructed to use a highly effective method of contraception for the duration of the study (i.e. at a minimum use double barrier method such as a condom with spermicide).

10.1 Inclusion criteria:

10.1.1 Male Partner Inclusion Criteria:

Men who meet all the following criteria will be eligible for enrollment in the trial:

1. Good health as confirmed by medical history, physical examination, and clinical laboratory tests of blood and urine at the time of screening;
2. 18 to 50 years of age;
3. BMI ≥18 and < 35 kg/m2;
4. No history of androgen use prior to the first screening visit as follows
    a. 1 month prior for oral or transdermal androgen,
    b. 3 months prior for Testosterone cypionate or enanthate injection,
    c. 6 months prior for Testosterone undecanoate injection;
5. Agreement to use a recognized effective method of short acting contraception with his partner (i.e. at a minimum use double barrier method such as a condom with spermicide) during the entire study;
6. ;
7. In the opinion of the investigator, male subject is willing and able to comply with the protocol;
8. Provision of valid, written and informed consent.

10.1.2 Female Partner Inclusion Criteria:

Women who meet all the following criteria will be eligible for enrollment in the trial:

1. Good general health (BMI ≥18 and <30 kg/m^2) with no chronic medical conditions that result in periodic exacerbations which require significant medical care;
2. Aged between 18 and 40 years, at the enrollment visit;
3. Not pregnant and not breastfeeding.
4. Agreement to use a recognized effective method of contraception throughout the study.
5. Willingness and ability to provide valid, written and informed consent and to comply with the protocol;
6. No desire for pregnancy within the next 6 months.

10.2 Exclusion criteria:

10.2.1 Male Partner Exclusion Criteria:

Men who meet any of the following criteria are <u>not</u> eligible for enrollment in the trial:

1. Men participating in another clinical trial involving an investigational drug within the last 30 days prior to the first screening visit.
2. Men not living in the catchment's area of the study site or within a reasonable travel time from the site.
3. Any clinically significant abnormal findings at screening per the Investigator's medical judgement.
4. Elevated PSA (e.g. levels ≥ 4 ng/mL), according to study site's local laboratory reference normal values for adult men.
5. Abnormal serum chemistry values that may indicate clinically significant liver or kidney dysfunction. Other abnormal laboratory values may also be exclusionary, if so considered by the investigator to be clinically significant.
6. Use of androgens or other anabolic steroids that may affect testosterone measurements
7. Diastolic blood pressure (DBP) ≥ 85 and Systolic blood pressure (SBP) ≥ 135 mm Hg; (BP will be taken three times at approximately 5 minute intervals and the mean of the 3 measurements will be considered).
8. History of hypertension (well –controlled treated hypertension (< 135/85) is allowed).
9. Known history of primary testicular disease or disorders of the hypothalamic-pituitary axis.
10. Known hypersensitivity to progestins or testosterone.
11. History of prostate or breast carcinoma
12. Significant lower urinary obstructive symptoms (IPSS > 19).
13. Known history of significant cardiac, renal, hepatic or prostatic disease.

14. History of thromboembolic disease.
15. A serious systemic disease such as diabetes mellitus (including diabetes controlled with treatment), HIV, or morbid obesity.
16. Current active or ongoing Hepatitis infection
17. Known or suspected current alcohol dependence syndrome, chronic marijuana use, or any illicit drug use that may affect metabolism/transformation of steroid hormones and study treatment compliance.
18. Known active or chronic dermatitis or other severe skin disorder.
19. Desiring fertility within 6 months of study participation.
20. History of severe depression or other serious mental health disorder.
21. Men participating in competitive sports where drug screening for prohibited substances (including anabolic steroids) is routine will be advised of the relative and temporary hazards that participating in this study may have for their sporting status.

10.2.2 Female Partner Exclusion Criteria:

Women who meet any of the following criteria are not eligible for enrollment in the trial:

1. Desire to become pregnant during the study.
2. Breastfeeding
3. Known or suspected current alcoholism or drug abuse.
4. History of thrombosis
5. Serum testosterone outside normal reference range by local laboratory standards or evidence hirsutism (modified Ferriman-Galwey score > 8)
6. Participation in another clinical trial involving an investigational drug within the last 30 days prior to the first screening visit.
7. Current pregnancy.
8. Known hypersensitivity to progestins or testosterone.
9. Any clinically significant abnormal findings at screening per the Investigator's medical judgement.
10. Use of androgens or other anabolic steroids that may affect testosterone measurements.
11. Known active or chronic dermatitis or other severe skin disorder.
12. Known or suspected current alcohol dependence syndrome, chronic marijuana use, or any illicit drug use that may affect metabolism/transformation of steroid hormones and study treatment compliance.
13. Not living in the catchment area of the study site or within a reasonable travel time from the site.

11. Concomitant Treatment

Any other investigational medication should be stopped 30 days before the first screening visit. Concomitant and over the counter medications are discouraged except as prescribed for the treatment of concurrent medical conditions that are not exclusionary. All prior medications taken within 30 days of screening and concomitant treatments while participating on the study for both male and female subjects will be recorded on the subject's case report form (eCRF), including the name of the drug (preferably the generic drug name), start and stop dates, dose, and reason for use from the time of informed consent signing through the end of study/exit visit.

Male and female subjects will be instructed to limit alcohol consumption while on the study to a total of 14 and 7 drinks respectively per week with no more than 2 drinks per night. Asking about concomitant medications at each visit will include asking about alcohol and recreational drug use.

11.1 Exclusionary Medications

Concomitant medications that are exclusionary for the couple include:

- Use of sex hormones/steroids
- Use of androgens or other anabolic compounds for medical purposes or for body building including hCG, FSH, clomiphene, anastrazole/letrozole, finasteride and dutasteride,
- Anticoagulants
- Antihypertensives
- Use of medications that will interfere or interact with Nestorone or Testosterone
- Use of oily cosmetic skin gels/products that would prevent absorption of steroids

Refer to **Appendix 2** for a detailed list of exclusionary medications.

Subjects who begin taking an exclusionary medication after study enrollment will require a waiver from the Medical Monitor to continue in the study. Waiver will be assessed on dose and amount of time medication will be taken against the potential effects the medication may have on the subjects.

12. Study Materials

12.1 Study Medication

The combined gel jars will be manufactured by Particle Science International supplied through the NICHD under the supervision of the Population Council. The combined gel is a transdermal treatment that will be applied as three single applications to a male subject's arms and shoulders on three different treatment days. The formulation will be a hydro alcoholic gel containing about 1.43% T (14.3 mg T/g gel). About 9 to 14% of the steroid (T or NES) in the gel applied is available to the body. The amount of gel to be applied each application will be approximately 5 mL in volume. The gel application volume will contain 62.5 mg of T that will deliver approximately 6 mg T to the body per day (Swerdloff *et al*., 2000; Wang *et al*., 2000). This gel volume will also contain 8.3 mg of NES that will deliver about 0.8 mg of NES to the body per day (NES 8 mg/d + T 60 mg/d (NES8/T60) gel). The dose of T that is delivered to the body per day is at the middle range of what is produced by the body per day in a healthy man (Ilani *et al*., 2012).

The progestin Nestorone (NES) has been tested in men as a transdermal gel with T gel in three prior studies and has an excellent safety profile (Mahabadi *et al*., 2009; Illani *et al*., 2012; Roth *et al*., (unpublished). Nestorone® (NES) is a synthetic, 19-nor-progesterone derived progestin, with selective binding to the progesterone receptors and with no binding to androgen receptors (Kumar *et al*., 2000). NES is inactive when taken orally but very potent when given parenterally (Sitruk-Ware *et al*., 2003) and has shown no androgenic effects in animals, unlike 19-nortestosterone derived progestins such as norethisterone and levonorgestrel. The Population Council has an IND for the use of NES8/T60 gel and this study will be conducted under this IND.

The current formulation tested in CCN005A will be provided for this study and was produced by Particle Science (PSI) (Bethlehem, PA), a Good Manufacturing Practice (GMP) contract manufacturing organization under the supervision of Population Council and sponsored by NICHD. NES is obtained from Population Council (New York, NY). The CMC documentation is included in the IND submission. The preparation of the investigation product to be delivered to the study subjects by the investigational pharmacists at each site is described in Appendix 6.

The summary of findings from preclinical studies and previous clinical trials is presented in the separate Investigator's Brochure.

12.1.1 Target Population

Healthy men ages 18 – 50 years, involved in a relationship with an 18 – 40 year old female partner will be enrolled in the study according to the inclusion and exclusion criteria. Approximately 12 couples will participate in the study.

12.1.2 Packaging

All packaging and labeling of the study medication will be prepared in accordance with 21CFR Section 210 and 211. The combination NES8/T60 gel study treatment will be prepared by site pharmacists in a single syringe which is placed in a bag and delivered to the clinic for each day of application (1, 8 or 15) that a couple is in clinic for transference assessment. The NES8/T60 combined gel has been formulated to deliver a total of 5 mL of the combined gel containing 8.3 mg NES and 62.5 mg T per daily dose, the formulation tested in the current CCN005A study.

Each bag will be labeled with a 2-part label which will be applied by the pharmacist. The part of the label remaining on the bag will have NICHD/PC, product identification, number of syringes of IP within the bag, subject ID, date dispensed and the FDA caution statement for an investigational new drug required by law. The detachable part of the label contains a place to enter the subject ID and date dispensed. The pharmacist will place a 1-part label on the individual syringes with the FDA caution statement, product identification and subject number. Prior to dispensing, the site pharmacist will label the bags, removing the detachable section of the label and paste it into their pharmacy dispensing log. The 1-part labels on the individual syringes will also be applied prior to dispensing.

As bags and syringes are used, they should be retained by the site for later monitor accountability.

12.1.3 Dosage and Administration

The investigational product will be provided to the male subjects as a transdermal gel in single application syringes. All male subjects will apply NES 8 mg/d + T 60 mg/d (NES8/T60) combined gel to the right and left shoulders and area of the upper arms to the top of the bicep muscle (i.e., to shoulder and arm skin area that would typically be covered by a short sleeve T-shirt) on the three treatment days. Male subject instructions regarding gel application is located in **Appendix 3**. Male subjects will push the plunger of the syringe to deliver the gel onto the palm of their hand and then gently rub gel on the skin of the upper arms and shoulders. The gel dries within a few minutes. The dose of the gel application will be done at the study visit under the direct observation of the study staff. The day and time of the treatment applications will be recorded in the source.

12.1.4 Duration of Subject Participation

Male and female subjects will be evaluated for a period of approximately 2 months and both members of the couples will be enrolled in the study throughout this period. The study will be divided into a screening phase of 2 to 4 weeks, a 17-day treatment phase, and then a 2 week post-treatment phase (see **Appendix 1**).

12.1.5 Investigational Product Accountability

Each study site is required to maintain records of administration of the test product, including dates and quantities, by subject ID number and initials of the research center personnel distributing study product. Study gel accountability logs will be provided for this purpose.

Investigational product will be shipped to each research center after the receipt and acceptance of all necessary regulatory documents. Upon receipt of investigational product, an inventory of the investigational product must be completed by the Investigator or Investigator's designee. All

investigational product administered must be recorded for each male subject. All dosing records must be consistent with the master dispensing and return records.

The site will be responsible for maintaining adequate inventory of investigational product supply at the research center(s). In order to receive additional shipments of investigational product, a request from the research centers must be emailed or faxed to their study monitor or the designated contact.

12.1.6 Storage

NES8/T60 combined gel jars will be stored at room temperature (20 °C/68 °F – 25°C/77 °F) in a dry place under controlled and secured conditions (i.e. locked storage area away from sunlight) at the study site. The investigational product will be accessible only to study personnel designated to handle the product by the Principal Investigator. While at the study site, the gel must be stored within the appropriate temperature range and secured in a limited-access area. A temperature log for the investigational product storage area must be maintained for the duration of the study.

12.1.7 Disposal/Return

Empty used syringes will be retained at the site with their dispensing bags in ziplock biohazard bags. All empty syringes will be destroyed at each study site following site and local regulatory specific drug destruction standard operating procedures once final drug accountability has been performed by the study monitor and they have authorized drug destruction. If necessary, destruction will also be performed during the study in accordance with site and local regulatory specific drug destruction standard operating procedures after accountability has been completed by the monitor and they have authorized destruction. Procedures for remaining unused study product return or disposal will be provided by the Sponsors at the end of the study.

13. Study Procedures

13.1 Clinical Assessments

13.1.1 Skin Exam

Skin Exams will be performed on female subjects at Screening and various points throughout the study using the Ferriman-Gallwey scale to assess changes in acne and hirsutism in female subjects exposed to the combination Nes/T gel. A score between 1 and 4 is assessed for nine different areas of the female body then a total score tallied. A total score of 0 on the scale indicates the absence of terminal hair. If the total score is less than 8 it is considered normal. If the total score is between 8 and 15 it is considered mild hirsutism. If the score is greater than 15 it is considered moderate or severe hirsutism.

13.2 Laboratory Tests and Evaluations

Blood samples for laboratory analyses will be collected at visits throughout each phase of the study for processing at both the central and local labs as outlined below. Venipuncture for blood sampling should be in the antecubital fossa or lower on the arm for male participants. Venipuncture for blood sampling for female participants should be in the antecubital fossa to prevent issues of her rubbing her hands and arms.

For any labs processed by the study site's local lab, the investigator must review and sign all laboratory reports and file a copy with each subject's chart. All out-of-range laboratory results must be assessed by the investigator for clinical significance. Any reports required from the screening assessment must be reviewed, signed and dated on or before the date/time of enrollment in order to properly document the determination of eligibility.

13.2.1 CBC, Clinical Chemistries, and PSA

Blood samples for laboratory analyses will be collected for analysis at the local certified laboratories at each center for the following:

- Complete Blood Counts (CBC): RBC, WBC, Hemoglobin, Hematocrit, Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Platelet Count
- Clinical chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium.
- Liver function tests: total bilirubin, alkaline phosphatase (ALPH), alanine aminotransferase (ALT), aspartate transaminase (AST), BUN, and albumin
- Prostate Specific Antigen (PSA) (male subjects only)

All local laboratory values will be recorded on case report forms (CRFs).

13.2.2 Hormone Testing

13.2.2.1 Screening Hormones

At screening, a urinary beta HCG level will be tested in females, processed by the study site's local lab and reported in the electronic Case Report Forms to confirm that the subject is not pregnant. Additionally, if at any time a urine pregnancy test on the study comes back positive after screening, then a confirmatory serum quantitative beta HCG test will be performed.

Screening serum total testosterone measurements will be done locally at both sites for male and female subjects to assess for total testosterone outside normal reference ranges by local laboratory standards. Results will be reported in the EDC system. If abnormal, the sample will be repeated with free testosterone, sex-hormone binding globulin, luteinizing hormone and follicle-stimulating hormone measurements at Visit 2 with results assessed prior to the couple being enrolled.

13.2.2.2 Treatment Hormone Measurements

All serum hormone measurements except for screening testosterone will be measured centrally at the Endocrine and Metabolic Research Laboratory at Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (LA BioMed/Harbor-UCLA). All sites will ship samples in batches throughout the study to the Endocrine and Metabolic Research Laboratory at LA BioMed/Harbor-UCLA Medical Center. This laboratory is licensed both by CLIA and the state of California and participates in CAP external quality control program and the CDC steroid assay harmonization program. The laboratory has extensive experience serving as a central laboratory for international multicenter studies and has served as the central hormone laboratory for the past five studies of the male CCTN (see **Sections 13.2.2.2 and 13.2.2.3** below).

Blood samples for hormone are collected in red top plain tubes, allowed to clot and then centrifuged within an hour before serum samples are stored. Samples that will be tested by the central lab will be frozen and stored at the local site at -20°C for later transport to the central laboratory, which will perform subject-batched analysis. A detailed description of the procedures to follow when processing, handling, and transporting hormone samples to the Endocrine and Metabolic Research Laboratory at LA BioMed will be distributed to each site prior to first subject enrollment (CCN005B Laboratory Manual). A freezer temperature log should be maintained for stored frozen samples.

When processing samples that will be measured by the central lab, 1 aliquot for central lab processing and 1 aliquot for back-up will be processed from collected samples. After shipment of aliquot 1 to the lab for processing, aliquot 2 will remain at the site as a backup in case of sample issues during transportation or testing at the lab. Further information related to back-up samples will be outlined in the Lab Manual mentioned above. Subjects will be asked to consent for any lab samples remaining at the end of the study to be stored long term for possible future studies. Otherwise, the extra samples will be destroyed once all lab testing and analysis has been completed for this study.

13.2.2.3 Testosterone Assays

Serum T samples from all sites will be measured centrally by validated methods using Liquid Chromatography Tandem Mass Spectrometry developed at the LA Biomed at Harbor – UCLA and Endocrine Research Laboratory (Shiraishi *et al*., 2008; Wang *et al*., 2008). The lower limit of quantification is 2 ng/dL. These methods have been established in the Harbor – UCLA Medical Center Endocrine Research Laboratory and is specific and sensitive, allowing for measurements of levels below the normal male range.

13.2.2.4 Nestorone Assays

The serum samples for NES measurements will be measured centrally by =methods validated following FDA/EMEA guidelines for a bioanalytical laboratory using Liquid Chromatography Tandem Mass Spectrometry developed at the Endocrine and Metabolic Laboratory at LA Biomed/ at Harbor – UCLA. The specifications of this method and the sample requirement will be detailed in the CCN005B Laboratory Manual.

13.2.3 Urine tests

Urine will be obtained from both the male and female subject as a clean-catch specimen for routine urinalysis and toxicology at the screening visit. Testing for drug screening, dipstick urinalysis will be performed locally by the research centers under usual procedures for such tests. For male subjects with abnormal results, clinical significance and need for treatment prior to approval for enrollment will be determined. All routine urinalysis and toxicology results done locally will be recorded on study case report forms (CRFs).

Urine pregnancy testing will be done for female subjects at each treatment visit before rubbing occurs and whenever there is any question about whether a woman might be pregnant at any time during the study. The urine pregnancy test kits will be supplied centrally by NICHD through a single source.

13.2.4 Safety Procedures

Efforts to reduce safety events from occurring will be completed through the following methods:

- The side effects of venipuncture and blood sampling will be minimized by having blood drawn by an experienced nurse or physician with the subject in a recumbent position.
- The effects of NES8/T60 gel in the male subjects will be minimized by applying the strict inclusion and exclusion criteria and carefully monitoring the indices of possible side effects such as hematocrit, and PSA.
- The side effects of gynecomastia, acne and oiliness of skin in the male should be minimal with the dose of testosterone used.
- The effects of NES8/T60 gel in the female subjects will be minimized by close observation of the transference amounts for careful monitoring of possible side effects such as hirsutism, acne and virilization.

14. Evaluations By Study Visit

The study will include three phases:

- a screening phase of 2 to 4 weeks
- a treatment phase of 17 days
- and a post-treatment phase of 2 weeks

Male and female subjects will be screened for study eligibility and interest in participating in this study (Screening Visit 1). All subjects will have the study explained to them and sign the informed consent prior to beginning any study procedures. Both male and female subjects must meet the inclusion criteria and have no exclusions in order for a couple to participate. Screening evaluations will continue for subjects for at least 1 additional visit in order to complete all screening assessments and to perform a testosterone assessment over 24 hours before the start of treatment. The definition of a couple for this study is a male and female subject that will participate in the entire study together. There are no obligatory relationship requirements of the two participants other than the same male and female subjects should participate for the duration of the study.

The treatment phase will be initiated once eligibility is confirmed. At least 6 visits are anticipated for both male and female subjects during the treatment phase (Visits 3-8).

The post-treatment phase will begin after the 48 hour female blood draw following the last treatment application on day 15. Two weeks after the completion of the final application a telephone call will be made to the male participants as their end of study/exit visit (Visit 9). At the same time, the female participants will return to the clinic for a blood draw and AE assessment for their end of study/exit visit (Visit 9).

Throughout the study, both male and female subjects will be encouraged to contact their study site and report by phone or visit any unusual event(s) including medical problems. Extra visits will be arranged if indicated. If necessary, the investigator or study site staff member will contact the subject more frequently in order to retain subjects. (E-mail, phone or text message communication may be used based on subject preference and study site assessment regarding this mode of communication with individual subjects).

All subject data will be recorded on electronic case report forms (eCRFs). Subject names will not be recorded on the eCRFs; instead, unique subject identifiers will be assigned to the couples per directions provided by Health Decisions.

A summary of study procedures are located in the Study Schedule of Assessments (see **Appendix 1**). Missed visits or assessments should be completed as soon as possible prior to the next scheduled visit and then the subjects will continue with their regular visit schedule. The schedule should not be updated based on a change in visit days due to the missed visit or assessment. If a missed visit or assessment cannot occur prior to the next regularly scheduled visit, the visit or assessment will just be a completely missed visit or assessment without pushing the regularly scheduled visits.

14.1 Screening Phase

The Screening Phase is expected to take 2 to 4 weeks to complete across multiple visits and occurs prior to treatment with study product. If for any reason, more than 28 days elapse between screening visit 1 and treatment day 1, repeat safety labs (CBC with differential and clinical chemistries) will be performed and results reviewed prior to treatment.

The purpose of the pre-treatment screening evaluations is to obtain baseline history, physical exam characteristics, and laboratory evaluations to determine if the couple meets eligibility criteria.

Prior to screening, potential participants will receive information about the study including potential risks and a written informed consent form. Subjects will sign the informed consent form and a copy will be given to the subject. Couples will be entered into the EDC system at time of consent.

14.1.1 Screening Visit 1 (Visit 1)

14.1.1.1 Both Partners

Both male and female partners will attend the screening visit. The following screening procedures will be performed at Screening Visit 1 for both male and female subjects:

- Undergo the informed consent process and sign the informed consent form prior to any study-specific procedures. The original signed informed consent form will be kept on file with the subject's records and a copy will be given to each subject.
- A unique subject identification number will be assigned by the site after the couple signs the informed consent form and prior to the initiation of screening assessments. Dr. Wang's UCLA site will start with subject number 31XX. Dr. Page's UW site will start with subject number 41XX. Subsequent subject numbers will be assigned in sequential order. The subject numbers will not be reused (i.e. used more than once) regardless of whether the subject is enrolled or becomes a screen failure. To differentiate the male and female participant when labeling lab samples, they will be numbered as 31XXM versus 31XXF and so on for lab samples only and by the single 31XX number for the entire couple when completing eCRF data within the EDC system.
- Determine eligibility.
- Collect demographic information including age, gender, and ethnicity/race.
- Obtain medical, reproductive and contraceptive histories.
- Vital signs will be taken including height, weight, pulse, blood pressure and respiratory rate. Blood pressure will be taken three times at approximately 5 minute intervals with a rest period in between and the three values averaged. BMI will be calculated in kg/m ² using the formula weight (kg)/height(m)^2 for determining eligibility but will be automatically calculated by the EDC system upon data entry.
- Blood samples will be obtained for the following measurements:
    - Complete blood count (CBC): hemoglobin, red blood cell count (RBC), red cell distribution width (RDW), packed cell volume (PCV), mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), hematocrit, platelets, white cell count, neutrophils, lymphocytes, monocytes, eosinophils and basophils
    - Clinical chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium.
    - Liver function tests: total bilirubin, alkaline phosphatase (ALPH), alanine aminotransferase (ALT), aspartate transaminase (AST), BUN, and albumin
    - Full lipid panel: total cholesterol, HDL, LDL, and triglycerides
    - Hormone assessments: Total testosterone concentration. Should this be abnormal, then this will be repeated at screening visit 2.
    - Serum pregnancy test for females only.
- Participants will be questioned regarding prior and concomitant medications. Concomitant medications taken from time of consent will be reported, in addition to indications for the medications and reasons for discontinuing. Asking about concomitant medications will include asking about alcohol and recreational drug use.

14.1.1.2 Male Partner Only

The following screening procedures will be performed for the male subject at Screening Visit 1:

- Obtain andrological history.

- Complete physical exam, including detailed andrological examination.
- PSA will be drawn.
- Urinalysis will be done to evaluate the subject's health and screen for illicit or illegal drugs.

14.1.1.3 Female Partner Only

The following screening procedures will be performed for the female subject at Screening Visit 1:

- Obtain gynecological and menstrual history.
- The female partner will undergo a serum pregnancy test and serum T (screening serum T in the female should be within the referenc range of the local laboratory).
- Assess any kind of body acne or hirsutism (using Ferriman-Gallwey score).

REMINDER: To assure that Good Clinical Practices (GCP) guidelines for documenting subject study data are followed, physicians and site staff will record subject histories and study specific examinations in the subject's medical record. Physicians and site staff will review source documents prior to study enrollment to ensure that all subject histories and examinations are appropriately captured in the subject's medical record. Original medical records will be made accessible to the study auditor during any audit visit that occurs. This includes allowing review of Electronic Medical Records [EMR] when it is the original medical record entry for a given assessment related to the study.

Once lab results are obtained and considered normal or not clinically significant (if out of normal ranges) by the investigator as per the inclusion/ exclusion criteria for enrollment, the participants will be informed of the lab results. If conformance to the inclusion/exclusion is confirmed, the couple will be scheduled to return to the study site for the second screening visit (Visit 2).

Subjects will be advised to refrain from taking medications and excessive amounts of grapefruit juice, recreational drugs and alcoholic beverages during the study.

Subjects and their partners will also be required to use a reliable method of contraception throughout the study as this is not a contraceptive efficacy study.

If any results are abnormal, according to local laboratory standards, and are clinically significant in the clinical judgment of the investigator, the subject will be informed and excluded from the study and referred to their primary health care provider. At the discretion of the investigator, abnormal laboratory assessments may be repeated before a final determination of exclusion is made.

Subjects will be entered into the EDC system at time of consent.

If for any reason, more than 28 days elapse between screening visit 1 and treatment day 1, repeat safety labs (CBC with differential and clinical chemistries) will be performed and results reviewed prior to treatment.

14.1.2 Screening Visit 2 (Visit 2)

Once couples have passed all screening assessments and eligibility is confirmed, both partners will return to the clinic for a 24-hour in-patient clinic stay to obtain baseline 24 hour T PK samples. The couple should report to the clinic by 7 am on the day the draws are to begin. Samples will be collected at 1, 2, 4, 8, 12, 16, 20 and 24 hours. Concomitant medications and adverse events will be assessed. Asking about concomitant medications will include asking about alcohol and recreational drug use.

Visit 3 can occur as quickly as completion of Visit 2 (i.e. couple would come for their baseline 24 hour PK draws (Visit 2) and then continue directly into starting Visit 3, thus staying for 48 hours in the clinical research unit).

14.2 Treatment Phase (Visits 3-8)

If both partners qualify for the study and have completed the baseline 24-hour PK draws, they will return to the study clinic and the male partner begins treatment using the NES8/T60 combination gel (Visit 3). This will be the start of the couple's treatment phase of the study. Only the female subject is required to come in for Visit 4 (Day 3), Visit 6 (Day 10), and Visit 8 (Day 17).

The Treatment Phase is expected to take 17 days. In this phase, the study gel will be applied as three single applications to a male subject's shoulders and area of the upper arm to the top of the biceps muscle (i.e., to shoulder and arm skin that would be covered by a short sleeve T-shirt) on three different treatment days (1, 8, and 15). Approximately two hours following the gel application, the male subject will have supervised skin contact with the female subject. Venipuncture for blood sampling should be in the antecubital fossa or lower on the arm for male participants. Venipuncture for blood sampling for female participants should be in the antecubital fossa to prevent issues of her rubbing her hands and arms.

14.2.1 Treatment Phase Visit 3 (Day 1), Visit 5 (Day 8), and Visit 7 (Day 15) (+7 day window)

14.2.1.1 Pre- Gel Application

14.2.1.1.1 Both Partners

The following procedures will be performed for both male and female subjects prior to the study gel administration:

- Both subjects will arrive at the clinic by 7 am for the 24-hour in-patient clinic stay
- Vital signs will be taken including weight, pulse, blood pressure and respiratory rate. Blood pressure will be taken three times at approximately 5 minute intervals with a rest period in between and the three values averaged. BMI will be calculated in kg/m ².
- Concomitant medications and adverse events will be assessed. Asking about concomitant medications will include asking about alcohol and recreational drug use.

14.2.1.1.2 Male Partner Only

- Serial blood draws for Nestorone and testosterone measurements will be collected from the male partner only at -15 and -5 minutes before gel application.

14.2.1.1.3 Female Partner Only

The following procedures will be performed for female subjects:

- The female subject will wear a sleeveless top to the clinic visit.
- The current contraception method and last menstrual bleeding date will be recorded.
- Urine pregnancy test will be administered prior to the male's NES/T gel application to reconfirm a negative test. If urine comes back positive, a confirmatory serum beta hcg test should be performed. If serum test is positive, the couple will be discontinued form the study.

14.2.1.2 Gel Application

14.2.1.2.1 Male Partner Only

- At about 8 am (± 30 min), the male participant will apply 2.5 mL of the testosterone/Nestorone gel over a wide area over one shoulder and upper arm above the elbow and then 2.5 mL gel to the other shoulder and upper arm again on a large surface area (see Appendix 3) under supervision. The gel should dry in less than 5 minutes and the male participant will wash his hands with soap and water.

14.2.1.3 Post- Gel Application

14.2.1.3.1 Male Partner Only

- Serial blood draws for Nestorone and testosterone measurements will be collected from the male partner only at 1, 2, 4, 8, 12, 16, 20 and 24 hours (± 15 min) after gel application.

14.2.1.3.2 Both Partners

- After the blood draw at 2 hours post treatment (+15 min), the female participant will engage in close skin contact with the male participant's area of NES8/T60 gel application. Under direct observation, the female participant, using her hands, wrists, and arms, will rub up and down the arms and shoulders of the male partner during a contact period of 15 minutes. After 2 minutes of rubbing, the female participant may take a rest period of 1 minute before continuing rubbing, repeating the 2 minute rubbing to 1 minute break process until the 15 minute time period is reached. Study staff will witness the entire rubbing process.

14.2.1.3.3 Female Partner Only

- The female participant will wash her hands with soap and water after skin contact is complete. The female participant will not shower for 24 hours after the contact period. The antecubital area of the female's arm where the intravenous catheter has been placed will be covered during the contact period to prevent potential blood sample contamination.
- Blood samples will be collected for measurement of testosterone and Nestorone at 2, 3, 4, 5, 6, 8, 10, 14, 18, 22 and 26 hours (±15 minutes) post male participant's gel application.

14.2.1.3.4 For Visit 3 (Day 1) Only – Post Application:

- After the gel is dry, the **male** subject will don a 100% cotton T-shirt (provided by the investigators) immediately after the applied gel has been allowed to dry. The male subject will continue to wear the T-shirt until female participant rubs the area of the T-shirt covering the gel application site at approximately 2 hours (±15 minutes) post male participant gel application.

14.2.1.3.5 For Visit 5 (Day 8) Only – Post Application:

- The **male** subject will don a 100% cotton T-shirt (provided by the investigators) immediately after the applied gel has been allowed to dry. The male subject will continue to wear the T-shirt until he showers (and washes the gel application site with soap and water) one hour 45 minutes after the gel application. The female participant will rub the gel application site 2 hours (±15 minutes) after gel application and just after male subject has showered and dried skin.
- At 90 minutes/1.5 hours (±15 minutes) after application and again at 30 minutes after shower and rubbing (150minutes/2.5 hours (±15 minutes) after application), using adhesive D-square strips (Cuderm Corporation, Dallas TX) a single location on the application site will be stripped on the **male** participant a total of ten times and the strips will then be analyzed for testosterone and Nestorone.

14.2.1.3.6 For Visit 7 (Day 15) Only – Post Application:

- The **male** subject will don a 100% cotton T-shirt (provided by the investigators) immediately after the applied gel has been allowed to dry. The male participant will remove the T-shirt immediately prior to the female subject rubbing the gel application site 2 hours (±15 minutes) after gel application.
- At 90 and 150 minutes (1.5 and 2.5 hours) (±15 minutes) after application, using adhesive D-square strips (Cuderm Corporation, Dallas TX) a single location on the application site will be stripped on the **male** participant a total of ten times and the strips will then be analyzed for testosterone and Nestorone.
- Blood samples will be obtained for the following measurements on day 16 for **both male and female** subjects prior to leaving the in-patient clinic:

- Complete blood count (CBC): hemoglobin, red blood cell count (RBC), red cell distribution width (RDW), packed cell volume (PCV), mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), hematocrit, platelets, white cell count, neutrophils, lymphocytes, monocytes, eosinophils and basophils
- Clinical chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium.
- Liver function tests: total bilirubin, alkaline phosphatase (ALPH), alanine aminotransferase (ALT), aspartate transaminase (AST), BUN, and albumin

14.2.2 Treatment Visit 4 (Day 3), Visit 6 (Day 10), and Visit 8 (Day 17) (no window)

Only the female partner is required to come to the clinic for these visits. These visits will occur the next day after the female subject has finished each in-patient treatment clinic visit. No day visit window is allowed for these visits to be pushed out from the day of treatment as these visits are required for timed PK draws. As a result, treatment day visits should be planned accordingly within their window to ensure the female subject is able to return for blood sampling after exiting the in-patient visit.

14.2.2.1 Female Partner

The following procedures will be performed for female subjects:

- The female participants will return at around 10 am (± 2 hour) on the day after finishing the in-patient clinic visit.
- Vital signs will be taken including weight, pulse, blood pressure and respiratory rate. Blood pressure will be taken three times at approximately 5 minute intervals with a rest period in between and the three values averaged. BMI will be calculated in kg/m ².
- Concomitant medications and adverse events will be assessed. Asking about concomitant medications will include asking about alcohol and recreational drug use.
- Blood samples will be collected for measurement of testosterone and Nestorone at 50 hours post male participant's gel application (or hour 48 post female exposure) at visits 3, 5, and 7.

Assess any kind of body acne or hirsutism (using Ferriman-Gallwey score)

14.3 End of Study/Exit Visit – Visit 9 (Day 31) (-12/+14 days)

The End of Study/Exit Visit will occur two weeks after the completion of the final gel application. This visit will be conducted via telephone call for the male participants. At the same time, the female participants will return to the clinic for their end of study/exit visit (Visit 9).

14.3.1 Both Partners

During this visit, the following procedures will be performed for both male and female subjects:

- Concomitant medications and adverse events will be assessed. Asking about concomitant medications will include asking about alcohol and recreational drug use.

14.3.2 Male Partner

There are no other assessments specific to the male subject only at this visit.

14.3.3 Female Partner

During this visit, the following procedures will be performed for the female subject:

- Vital signs will be taken including weight, pulse, blood pressure and respiratory rate. Blood pressure will be taken three times at approximately 5 minute intervals with a rest period in between and the three values averaged. BMI will be calculated in kg/m ².

- Blood samples will be collected once for measurement of testosterone and Nestorone to assess residual levels.
- Assess any kind of body acne or hirsutism (using Ferriman-Gallwey score) The current contraception method and last menstrual bleeding date will be recorded.

14.4 Contacts Between Visits

Subjects may, at the discretion of the Principal Investigator or Designee, be contacted between study visits to ensure subject retention and compliance with study requirements. This contact may be via text, phone or email. If the subject does not respond when text or email contacts are attempted, the study clinic staff should contact the subject by phone.

In addition, the female subject may also be contacted at the discretion of the Principal Investigator or Designee to evaluate for pregnancy as indicated by clinical symptoms.

All such contacts and attempts should be documented in the subject's source file. It is suggested that testing of any cell phone number provided by both male and female subjects prior to enrollment be completed to ensure number correctly connects to the subject.

14.5 Early Discontinuation Visit

At any time a subject decides to discontinue his/her participation in the study (or is discontinued from the study for any other reason), the **female** will be advised to return to the clinic to complete the end of study/exit visit Visit 9). This visit will be conducted via telephone call for the male participants.

Every effort must be made to follow-up with subjects who discontinue with adverse experiences, in order to determine the final outcome of adverse events.

14.6 Unscheduled Visits (UNS)

Unscheduled visits can occur any time that an Investigator feels additional assessment is warranted. During unscheduled visits, the investigator will perform vital signs, physical exams, appropriate laboratory tests and provide appropriate treatment, as necessary. Male subjects should be discouraged from any self-medication; rather they should visit the research center for assessment and treatment. Similarly, male subjects should be discouraged, but not prohibited, from seeking treatment at facilities other than the research center for a non-serious event. For serious events, subjects should always obtain appropriate immediate medical care and the site should request release of medical records by the subject upon notification of the event.

Based on the results of the unscheduled visit assessments, if the investigator determines that the subject should be discontinued, the Early Discontinuation Visit procedures (as detailed in **Section 14.5**) will be performed and the subject will be discontinued from the trial.

15. Adverse Events: Recording and Reporting

15.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

Any adverse change from the study subject's baseline condition that occurs following the signing of the Informed Consent is an adverse event for both male and female participants. This includes the occurrence of a new adverse event or the worsening of a baseline condition, whether or not considered related to the study product.

Adverse events include but are not limited to: adverse changes in the general condition of the study subject; signs and symptoms noted by the study subject or his/her care giver; concomitant disease with onset or increased severity after the signing of the Informed Consent and clinically meaningful adverse changes in laboratory safety parameters occurring after the signing of the Informed Consent. Day-to-day fluctuations in pre-existing conditions that represent a clinically significant change in the subject's status should be reported as adverse events.

15.2 Study Reporting Period for Adverse Events

Adverse events (AEs) will be reported on this study. All AEs will be carefully monitored and categorized by severity and causality and time. AEs will be documented in an AE form that is included as part of the study eCRFs. All events including illnesses with onset during the study, or exacerbation of pre-existing illnesses should be reported as AEs. The reporting period for adverse events is the period immediately after informed consent has been obtained and lasts through the end of study/exit visit. AEs will not need to be submitted for screen failed subjects unless the subject experiences a SAE. Those events that occur between the screening and the enrollment visits will be analyzed as pre-treatment signs and symptoms and not as treatment-emergent adverse events.

At every visit/contact study staff will ask each subject how they felt since their last visit/contact and indirectly ask if they have experienced any adverse events.

For all AEs, the Investigator must pursue and obtain information adequate to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event. Resolution of an AE is defined as the return to baseline status or stabilization of the condition with the expectation that it may remain chronic. Follow-up of the AE, even after the date of IP discontinuation, is required if the AE persists. For the purpose of study analysis, if a non-serious AE has not resolved at the end of the study-reporting period, it will be documented as still ongoing on the AE eCRF. However, the Investigator must make every effort to follow events to stabilization or resolution and report the findings/outcome to HD as soon as possible. A minimum of three follow-up attempts with different methods of communication (i.e. telephone, certified mail, email) should be documented. Male participants who exhibit persistent or severe AEs or concomitant illnesses will be removed from the study based on the Investigator's medical judgment and will no longer use the study product nor will the study product be re-applied. The monitor will be notified if such an event occurs.

Please refer to **Sections 15.6.2 and 15.6.3** regarding the reporting of SAEs for this study.

15.3 Recording of Adverse Events

Adverse events will be reported on the AE eCRF using a recognized medical term or diagnosis that accurately reflects the event. Information recorded on the Adverse Event Case Report Form must be substantiated in the source documents. All adverse events must be recorded in the subject's CRF and must include the following information (when applicable):

- Specific condition or event
- Possible etiologies and whether the event meets criteria as a serious adverse event and therefore requires immediate notification to the sponsor. See guidelines below for assessment of severity and relationship, respectively, and for the definition of Serious Adverse Events

- Indication of whether the condition was preexisting prior to study entry or not and if yes, whether it has worsened in severity or frequency in which case it is reported as an AE. Conditions present prior to study entry that do not worsen in severity are not considered AEs. Conditions identified and treated at screening, i.e. laboratory abnormalities are included in medical history and are not reported as AEs.
- Date of occurrence
- Date of resolution. If the event has not resolved at the end of the study-reporting period, it will be documented as still present on the case report form. However, every effort should be made to obtain outcome.
- Severity. AEs that change in intensity are recorded at the intensity level that is the most severe reported by the subject over consecutive days. If the intensity category changes over a non-consecutive period of time, then these changes should be recorded separately (with distinct onset dates).
- Relationship to study drug as evaluated by the investigator (causality assessment)
- Action taken with the study drug per the investigator medical judgment (study drug continued, interrupted or discontinued)
- AE outcome (recovered, ongoing, etc.)
- Seriousness according to the approved regulatory classification {i.e. any event that is fatal, life-threatening, disabling, incapacitating, results in or prolongs hospitalization, or is a medically significant event, e.g., an intervention to prevent one of the above outcomes, or any other serious criteria (cancer, congenital anomaly, overdose, other significant criteria) is considered serious.

The severity of the AE will be characterized as mild, moderate, or severe using the following criteria:

- **Mild**: Participant was aware of the event, but was still able to do all activities.
- **Moderate**: Participant had to discontinue some activities due to the event.
- **Severe**: Participant was incapacitated by the event and unable to perform normal activities.

15.4 Relationship to Study Product

The site investigator is responsible for assessing the relationship between the AE and the study product. Site investigator must determine whether there is a reasonable possibility that the study product caused or contributed to an AE. The relationship assessment, based on clinical judgment, often relies on the following:

- A temporal relationship between the event and administration of study product,
- A plausible biological mechanism for the study product to cause the AE,
- Another possible etiology of the AE,
- Previous report of similar AEs associated with the study product or other agents in the same class.

The terms used to assess the relationship of an event to the study product are:

Causality Assessment	**Criteria for Assessment (note that re-challenge will not be done in this study)**
Highly Probable	The experience occurs immediately following trial drug administration, related pharmacologically (not related to underlying condition/concurrent disease or other drugs or chemicals) and follows a known response pattern to the study drug.
Probably Related	The experience follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the suspected trial drug and cannot be reasonably explained by other

	factors such as the participant's clinical state, therapeutic intervention or concomitant therapy.
Possibly Related	The experience follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the trial drug but could have been produced by other factors such as the participant's clinical state, therapeutic intervention or concomitant therapy.
Unlikely Related	Improbable temporal relationship. The experience was most probably produced by other factors such as the participant's clinical state, therapeutic intervention or concomitant therapy and does not follow a known response pattern to the study drug.
Not Related	There is not a reasonable possibility that the AE is related to the study product; when an AE is assessed as not related to the study product, an alternative etiology, diagnosis or explanation for the AE should be documented. If new information becomes available, the relationship of any AE should be reviewed again and updated, as required.
Insufficient data to assess	Selection of this rating should usually not occur in a clinical trial because the Investigators have an obligation to obtain and provide this information. In exceptional instances, this rating may be used in order to avoid delay in initial reporting of fatal or life-threatening SAEs from clinical trials. Such cases should include documentation in the source with rationale for why an assessment could not be made.

15.5 Adverse Event Follow-Up

Investigator must make every effort to follow events to stabilization or resolution. Exceptions to this are cases where the subject is lost to follow-up or the adverse event is otherwise explained. Unresolved SAEs at the conclusion of the study will be assessed by the investigator with a follow-up plan documented and approved by the Medical Monitor on a case-by case basis.

15.6 Serious Adverse Events (SAEs)

15.6.1 Definition of a SAE

An AE is considered "serious" if, in the view of either the investigator or Sponsor, it:

- Results in death;
- Is life-threatening;
    - This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization;
    - In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs or SAEs as defined above. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity; or
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor

medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect.

Medical or scientific judgment should be exercised in deciding whether (expedited) reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should also be considered serious. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that result in hospitalizations; or development of drug dependency or drug abuse. In addition, cancer and drug overdose are included in the classification of an SAE for this study.

15.6.2 Study Reporting Period for SAEs

The reporting period for SAEs is the period immediately after Informed Consent has been obtained and lasts through the end of study/exit visit. Individual SAEs must be followed until resolution, even if this extends beyond the study-reporting period. Resolution of a serious adverse event is defined as the return to baseline status or stabilization of the condition with the expectation that it may remain chronic.

Serious adverse events (SAEs) as defined by ICH and Code of Federal regulations will be reported within the 24 hours that the site is informed of the SAE as outlined in this section and **Section 15.6.3**

15.6.3 Notification to Sponsor of SAEs and Sponsor Reporting of SAEs

All Serious Adverse Events (SAEs) will be reported promptly in accordance with the FDA regulations and recorded on the appropriate forms. As the Sponsor of this IND, the Population Council is responsible for complying with the reporting requirements of SAEs to the FDA in accordance with 21 CFR 312.50. Health Decisions will serve as the third party monitoring body of SAEs and will notify the NICHD Medical Monitor and the Safety Desk of Population Council upon occurrence. If warranted, the NICHD Medical Monitor will recommend to the NIH Project Officer and discuss with the Safety Desk of the Population Council, if action is required to convene the DSMB or if the trial should be stopped prematurely, undergo modification, or be placed on hold. Both PC and Health Decisions may also recommend to the NICHD Medical Monitor if any of these actions are warranted based on the SAE reports. The Population Council will be responsible for the appropriate recording, review and compliance with regulatory reporting requirements to the FDA of the SAE.

WHEN ANY SAE, REGARDLESS OF RELATIONSHIP TO THE STUDY PRODUCT, IS ENCOUNTERED DURING THIS CLINICAL TRIAL AT AN INVESTIGATOR'S SITE, THE INVESTIGATOR, IN ACCORDANCE WITH 21 CFR 312.64(b), MUST NOTIFY BOTH PC AND HEALTH DECISIONS WITHIN 24 HOURS OF IDENTIFICATION/AWARENESS OF THE SAE BY REPORTING THE EVENT VIA THE ELECTRONIC DATA CAPTURE SYSTEM. **SAE SUBMISSION SHOULD BE COMPLETED FOR ANY SAE THAT IS EXPERIENCED AFTER THE SUBJECT HAS SIGNED THE INFORMED CONSENT FORM, EVEN IF INVESTIGATIONAL PRODUCT HAS NOT YET BE ADMINISTERED.**

The investigator should complete the SAE eCRF within the EDC system which will send the appropriate notifications to the Medical Monitor as well as the appropriate HD, NICHD, PC staff and PC Safety Desk. In the event of a system outage or other complication, notification may be made to the Population Council's Safety Desk at: +1-212-237-9410 (telephone). Immediately following phone communication, the clinical investigator is to follow up with an SAE Report submission by email to both PC at

safety@popcouncil.org (email) and by fax or email to Health Decisions at +1-919-967-1145 (fax)/nichd@healthdec.com (email). HD will then notify the NICHD Medical Monitor by facsimile or email.

In the event that serious adverse events occur in the course of the study, participants will be referred to a specialist. Treatment or laboratory tests will be conducted at the discretion of the Investigator. If the event causality assessment is probably or highly probably related with the investigational product, the Investigator must discontinue the couple from the study immediately.

Additional supporting documentation for SAEs (i.e. hospital discharge summary, lab report, etc.) which should be provided whenever possible (with participant name redacted) to verify the medical diagnosis includes hospital discharge summaries and death certificates/autopsy reports (where applicable), surgical procedure summaries, histology reports, and imaging reports should be uploaded to the study document repository or Health Decisions EDC page as outlined in the Study Procedures Manual within 3 days of receipt at the site. HD will ensure appropriate copies of supporting document are provided to the Medical Monitor and Population Council.

NOTE: Investigators should not wait to collect the additional information needed to fully document the event before submission of an SAE. An SAE report should be completed for any SAE that is experienced after the subject has signed the Informed Consent Form, even if investigational product has not yet been administered.

For system outages, or other complication, which prevents reporting of the SAE information through the HD electronic systems, when sending follow up information after phone notification, please email the following documents to the Population Council Safety Desk (Email: Safety@popcouncil.org) if available at time of report.

- Serious Adverse Event Report Form
- Medical History Case Report Form
- Concomitant Medication Case Report Form or a list of concomitant medications
- Relevant laboratory/diagnostic test results and medical record progress notes

Under 21 CFR 312.32 and 312.33, Pop Council, in consultation with the Medical Monitor, is responsible for notifying the FDA and all participating investigators of: (1) any unexpected fatal or life-threatening adverse experience associated with the use of the study drug by telephone or fax as soon as possible, but no later than 7 calendar days after the sponsor's initial receipt of the information about the event, and (2) any adverse experience associated with use of the drug that is both serious and unexpected. Notification should occur in writing no later than 15 calendar days after the sponsor's initial receipt of the information. Pop Council, as the IND holder, is also responsible for submitting annual study progress reports to the FDA.

15.6.4 Notification of IRB or Independent Ethics Committee of SAEs

All IND Safety reports (expedited SAEs) that occur at each site must be directly reported to the local IRB or Ethics Committee and to the local health/regulatory authorities (other than the FDA) by the Investigator or designee after case adjudication by the Population Council Safety Desk staff and the Medical Monitor. The Population Council as IND holder will report SAEs to the FDA if appropriate according to expectedness and causality assessment. The site should report non-expedited SAEs for their own site per their IRBs reporting guidelines.

The investigator must comply with the applicable regulatory requirements related to the reporting of SAEs to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB or IEC must be informed in a timely manner by the investigator of SAEs occurring during the study. Investigators

must also submit applicable safety information provided by Population Council to their IRB or IEC. The final adjudication of an SAE will be conducted by the Population Council Safety Desk and the final CIOMS form will be sent to all sites for submission to their respective IRBs/IECs for applicable events.

15.6.5 Pregnancy Determination and Follow-up

The couple should agree to use an effective contraceptive method during the study. However, if despite this, a pregnancy would occur, information on pregnancy will be recorded on all couples becoming pregnant during the treatment phase of the study through study exit.

If a female subject becomes pregnant during the trial, the Investigator must inform Health Decisions, NICHD and the Population Council of the pregnancy within 24 hours of determination.
If a female subject is found to be pregnant during the study, the treatment of the male partner will be stopped. Study participation will be terminated for the couple and all procedures scheduled for the Early Discontinuation Visit as detailed in **Section 14.5** should be performed. The site will submit a Pregnancy Notification eCRF to Health Decisions with 24 hours of determination, who will notify the Medical Monitor, NICHD, and PC immediately. Additional pregnancy data will be submitted as it becomes available.

The estimated date of conception will be made by the Investigator based upon results of the following pregnancy determination criteria, listed in ascending order of accuracy:

- Transvaginal ultrasound.
- Estimate based on pelvic and/or abdominal examination or pregnancy outcome.
- Coital diary information (e.g. last menstrual period and sexual activity).
- Quantitative β-hCG determination.
- Investigator estimation in the absence of the above criteria.

Female subjects who become pregnant during the study will be informed of pregnancy options and referred for appropriate care. All pregnancies will be monitored until outcome (i.e., 9 months follow-up or until outcome information is obtained). Information will also be collected on any maternal or fetal complications. A pregnancy will not be considered an adverse event for this study. Congenital anomalies or birth defects will be classified as serious adverse events (SAEs). Pregnancy outcome data will be collected for analysis. Reports of pregnancy outcome and examinations during the pregnancy will be requested from the attending physician/outside clinic, if applicable. Every attempt should be made to obtain outcome data, including hospital and/or physician records. Pregnancy outcome data will include the rates of spontaneous abortion, stillbirth and live preterm and full-term births. If a female subject has a spontaneous abortion or ectopic pregnancy this will not be considered as a SAE unless it meets one of the SAE criteria indicated **Section 15.6.1** or per the Investigator's medical judgment it should be recorded as an SAE. In addition, congenital malformations and anomalies will be recorded and summarized. If a female subject continues with her pregnancy through childbirth, every effort will be made to maintain contact with her so that her health and the health of the baby can be evaluated at 6 months and 12 months following birth. A clinical summary of the prenatal and postnatal events will be reported in a narrative format as part of or separate from the Clinical Study Report (CSR) at the end of the study. Any outstanding data at the end of the study that is collected will be submitted to the FDA as a Safety Update to the NDA submission. A clinical summary of the prenatal and postnatal events will be reported separately from the case report form in narrative format in the clinical study report.

16. Medical Monitor

Mark Payson, MD, is the Medical Monitor for the protocol. Dr. Payson has experience with NIH research. He is board certified in obstetrics & gynecology and reproductive endocrinology & infertility. Dr. Payson will be responsible for evaluating requests for waivers, reviewing protocol safety information and providing the NIH Project Director with a final recommendation based on the input from the Data and Safety Monitoring Board (DSMB) should one occur.

Medical Monitor Contact Information:
Mark Payson, MD
Telephone: 240-463-9115
Email: markpayson@gmail.com

17. Safety Desk

Population Council will maintain a Safety Desk. Mohcine Alami, MD, at PC, is the Safety Expert manning the Safety Desk for the study. Contact information for the Safety Desk is as follows:

Mohcine Alami, MD
Director, Global Medical Safety & Medical Affairs
Population Council
4301 Connecticut Avenue, NW Suite 280
Washington, D.C. 20008
Direct: +1 202-237-9410
Switchboard: +1 202-237-9400
Toll Free: +1 877-237-9400
Facsimile: +1 202-237-8410

18. Safety and Efficacy Monitoring (DSMB)

All SAEs will be reported within 24 hours to the NICHD Project Director and Medical Monitor (see **Section 15.6.3**). An independent, autonomous Data Safety and Monitoring Board (DSMB) has been established by the NICHD. The Medical Monitor will be tasked to review the adverse events and safety considerations at routine intervals during the study. The CCTN DSMB will be charted by NICHD to review the adverse events and safety considerations on an ad hoc basis if required by an unexpected serious adverse event that could be attributable to the treatment regimen. If more than one unexpected serious adverse event occurs with causality assessment of probably or highly probably related the study will be stopped. Recommendations from the DSMB will be forwarded by the NICHD Project Officer to the Central IRB and the CCTN Principal Investigators in this Protocol. If the DSMB reviews the trial, they will make recommendations if the trial should be stopped prematurely, undergo modification, or continue.

19. Study Conduct

19.1 Deviation from the Protocol

The Investigator should not deviate from the protocol without prior approval issued in a protocol waiver sent from HD and approved by the NICHD Medical Monitor, with the exception of minor visit window deviations, unless it is necessary to protect the subject's immediate safety and welfare. In the event that the investigator or the subject deviates from the protocol without a protocol waiver, notification should be provided to HD as soon as possible detailing the circumstances who will assess the deviation for expedited reporting criteria to the NICHD. Certain protocol violations may require the couple to be terminated early from the study. It is the responsibility of the research centers to report all protocol waivers and protocol violations to their IRB/IEC according to IRB/IEC policy.

19.2 Amendments to the Protocol

Any change of the clinical trial must be written and filed as an amendment to this protocol. Such amendments will be made jointly by the NICHD and the investigator(s) upon NICHD final approval. The investigator(s) must submit the protocol amendment for review by their IRB/IEC and shall obtain the approval of their IRB/IEC before it is implemented.

In cases of emergency, when the protocol change or deviation is to eliminate or reduce an immediate hazard or risk to human subjects, the amendment may be implemented before review or approval by their IRB. In such cases, the investigator shall notify their IRB/IEC of the change or deviation in writing within 10 working days after implementation. Any protocol-related issues that pose an immediate or significant hazard to subjects must be reported to NICHD and HD immediately. If the protocol amendment is an administrative change, it will be sent to their IRB/IEC for information (updating of file).

All modifications of the clinical trial will be written and filed with FDA by PC as an amendment to this protocol, maintaining original section identification. Such modifications will be made jointly by the NICHD, HD, PC, and all the investigators with the approval of all the IRBs/IECs.

19.3 Subject Confidentiality

Information on individual subjects arising from this study will be considered confidential and transmitted to the sponsor and Clinical Research Organization (CRO) in a form that will not permit identification of individuals. Subject confidentiality will be maintained by the use of coded subject ID numbers. All study records will be kept in a secure storage area with limited access. Coded subject numbers will identify all laboratory specimens and evaluation forms in order to maintain subject confidentiality. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring by the FDA, NICHD, the Population Council, Health Decisions, local Clinical Research Organizations (CROs) contracted to monitor the study, or local regulatory authorities.

19.4 Discontinuing Subjects

Subjects will be considered to have completed the clinical trial after they have completed 2 weeks of using the study product followed by an end of study/exit visit plus the final set of data has been collected and entered on the appropriate CRF pages.

Discontinuation of one participant (male or female) automatically results in discontinuation of their partner. The Principal Investigator can discontinue a given participant if, in her/his opinion, either member of the couple no longer meets the inclusion/exclusion criteria or the clinical observations during the study suggest that it might be unsafe for the participant/couple to continue.

A subject (male or female) **may be** discontinued prematurely for any of the following reasons:

- Emergence of adverse or serious adverse event that, in the judgment of the investigator, continuation in the trial would negatively impact the health of the subject.
- Emergence of adverse effects such as symptoms (e.g. severe skin irritation, changes in libido or weight, acne, or non-specific symptoms) or biochemical changes (new or persistent abnormalities in clinical chemistry or hematological tests) that are considered medically hazardous by the supervising physician
- Inter-current illness that, in the judgment of the investigator, should result in premature discontinuation.
- Poor compliance or co-operation of the participant as judged by the Investigator.
- Use of prohibited medications/products, including any outlined in the Inclusion/Exclusion criteria (see **Section 11.1**).

- Pathologically changed laboratory values.
- Suspected drug interaction.
- Knowledge of new risks necessitating new benefit/risk evaluation.
- Other non-study related reasons: change of address that makes participation unfeasible, termination of participant-partner relationship; no need of contraception.
- Not using another method of contraception.
- Major protocol violation.
- Subject lost to follow-up.
- Trial closed-out.

A subject (male or female) **must be** discontinued for any of the following reasons:

- Failure to attend more than one study visit.
- Emergence of a serious adverse event that is probably or highly probable related to study product.
- Pregnancy of the female subject (see above section on pregnancies).
- Either participant (male or female) withdraws his/her consent to the study (e.g. due to personal reasons).

All subjects/couples who terminate early from the trial will undergo an Early Discontinuation Visit/Exit Visit as outlined in **Section 14.5** regardless of the reason for discontinuation with the exception of those couples who have lost contact with the research center. The necessary clinical and laboratory examinations planned at the last visit should be performed whenever it occurs. The Investigators will document the discontinuations in detail within the source files for the subject. The reasons for premature discontinuation will be recorded on the End of Trial eCRF. If discontinuation from the study is due to an adverse event, this information will also be recorded on the Adverse Event form. It is required that, throughout the study, the CCTN site study coordinators be informed with respect to enrolment and withdrawals from the study for their site's subjects. If the sponsor determines that the study must be stopped, all subjects will be required to end participation at that time.

A couple cannot be considered lost to follow-up (LTFU) until the research center performs and documents at least three (3) attempts to contact him/her. Documentation must include a letter sent with a return receipt requested to the subject/couple instructing him/her/them to call the research center. Every effort must be made to follow-up with subjects who terminate with adverse experiences, in order to determine the final outcome of adverse events.

Subjects (male or female) may withdraw from the study at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject may be discontinued by the investigator or the sponsor if he/she violated the protocol (i.e. he is non-compliant) or for other safety reasons.

Couples discontinuing from the study will be replaced, regardless of the reason for discontinuation, such that 6 couples at each site complete the study.

19.5 Withdrawals from Study

Any study participant (male or female) has the right to withdraw from the study at any stage and for any reason without giving reasons. Withdrawal of one participant automatically results in withdrawal of their partner.

All efforts should be made to contact the study participant when they decide to withdraw so that appropriate discontinuation safety and efficacy data can be obtained from both the male and female

participants. Such contact will never be used to dissuade any subject (male or female) who wishes to terminate the study.

19.6 Medication Errors

As gel application will occur under direct study staff supervision, no issues with compliance are anticipated. However, if one occurs the site should inform Health Decisions immediately upon determination.

20. Study Monitoring and Documentation

20.1 Clinical Monitoring, Quality Control, and Quality Assurance

The Principal Investigator and sub-investigators will allow representatives from HD, PC and NICHD direct access to all eCRFs, source documents, and corresponding portions of the medical records for each participant at mutually convenient times for periodic review during the study and after the study has been completed. The monitoring visits provide HD with the opportunity to:

- Initiate the research center.
- Evaluate the progress of the study.
- Verify the accuracy and completeness of the eCRFs.
- Ensure that all protocol requirements, applicable FDA and other health authority regulations, and investigators' obligations are being fulfilled.
- Resolve any inconsistencies in the study records.
- Close out the trial at the research center.

In addition to routine monitoring, NICHD or its designee may, at its discretion, perform site audits. The purpose of such audits will be to evaluate site trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements. If an audit is performed, a site must provide the auditors with direct access to all relevant records and documentation related to the study.

20.2 Administrative and Record Management

All investigative site records will be kept in a secure and hazard free storage area with limited access. Access will be restricted to personnel authorized to handle research documents. These records are to be retained for at least 2 years after approval of the marketing application or at least 2 years have elapsed since formal discontinuation of clinical development for this investigational product. NICHD should be notified before destruction of any site records.

20.3 Study Documentation

Sites will maintain source documentation of all study visits assessments completed for each subject. Source documentation data will be transcribed into the eCRFs.

Health Decisions is responsible for assuring that the essential documents maintained in the trial master file at the research center are accurate and complete. Essential documents in the trial master files at Health Decisions will be maintained according to written SOPs.

20.4 Electronic Data Capture System/Data Transmission

Electronic Data Capture will be used to transmit data electronically from the site to the Data Coordinating Center (HD). All requested information should be entered in the Electronic Data Capture (EDC) system. Prior to the start of the clinical trial, the investigator will complete an authorized signature sheet showing the signatures and handwritten initials of all individuals who are authorized to maintain study records and submit data using the EDC system. More detailed instructions regarding the EDC system will be provided by Health Decisions in training and the instructions documents. The data in the database including any updates as a result of data cleaning will be compared to the source documents at subsequent monitoring visits.

20.5 Data Handling and Processing

Health Decisions' Electronic Data Capture (EDC) will be used to create, modify, maintain, archive, retrieve and transmit study data generated for the clinical trial. The research centers will record clinical trial data (except for the central hormone laboratory data) on an electronic web-based CRF (eCRF). Laboratory data from the central laboratory will be sent electronically to HD and imported into a SAS® database maintained by the HD Biometrics Department. HD Data Management will follow written standard operating procedures for processing EDC data. Archiving of the EDC data will be done by the EDC vendor.

20.6 Confidentiality and Reporting of Results

The information on individual subjects arising from this study is to be considered confidential and transmitted to the sponsor only in a form that will not permit identification of the individual. Regulatory and sponsoring agencies may request access to the study records and related medical records of each participating subject, and if requested, the subject's identity will remain confidential to the extent permitted by the applicable laws and regulations. All records will be kept in a secure storage area with limited access.

The information obtained from the subjects that can be identified with the subject will remain confidential within the research team. Subject names will not be entered into the EDC system; instead, unique subject identifiers will be assigned to the couple. The results of the research will be released to public agencies including regulatory agencies, clinical investigators, and research organizations without reference to items identifiable to a particular subject. Medical records will be kept at the research center and will be available to study staff and the NICHD, Health Decisions, PC, or the FDA only while at the study site. The results will be published such that the identity of the subjects will not be disclosed and cannot be ascertained. All data will only be used for the purpose for which it has been approved. Data collected during this study and any analyses of that data will not be used in any way other than those ways already approved without further approval from the NICHD and/or PC.

20.7 Retention of Data

The Investigator will maintain adequate records of the study including subjects' CRFs, medical records, laboratory reports, consent form, drug disposition records, safety reports, information regarding participants who discontinued, and other pertinent data. All records are to be retained by the Investigator for a period of at least 2 years after the last approval of a marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (per FDA CFR 312.62, "2 years after the investigation is discontinued and FDA is notified."). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The Investigator will contact NICHD, the Population Council and Health Decisions for authorization prior to destruction of any such records or in the event of accidental loss or destruction of any study records.

20.8 Publication Policy

Data on the use of the study medication and results of all clinical and laboratory studies are considered private and confidential. NICHD will encourage publication of the results of the study. Any publications or presentations that result from this study will maintain participant confidentiality. The IND and proprietary information about the investigational drug, Nestorone, are under the supervision of the Population Council. Institutions and/or the Principal Investigators agree to submit all proposed publications, papers, abstracts, manuscripts, posters or other written materials which include data relating to the Study or the use of the Product supplied under this Agreement, and all outlines of any proposed oral presentations with respect thereto, to NICHD and PC at least thirty (30) days prior to either (a) submission of such written materials for publication or (b) any proposed oral disclosure to a third party outside of the NICHD CCTN. NICHD and PC shall have the right to comment on such written material or outline within (30) days of receipt, and such comments shall be considered in good faith by the Principal Investigators in determining the final form of disclosure. PC shall also have the right to eliminate any reference to confidential or proprietary information provided to Institutions and/or the Principal Investigators or the Staff pursuant to this Agreement. Institutions and the Principal Investigators agree to acknowledge the NICHD and PC's contribution to Institution's and/or the Principal Investigator's work in any publication or public disclosure unless requested by the Council not to do so.

20.9 Financing and Insurance

Financing and insurance are addressed in separate documentation.

21. Evaluations

This is a single dose, open label study designed to assess the secondary exposure in females after male application of NES + T combination gel to shoulders and upper arms. The effect of washing or clothing barrier to application will also be assessed.

21.1 PK Evaluations

The pharmacokinetics (PK) evaluations will be evaluated by assessing differences between average serum testosterone and Nestorone levels at baseline comparted to Cavg, Cmax, and Cmin after secondary exposure to NES/T gel. PK differences in exposure will be assessed with a 100% T-shirt clothing barrier, after washing the application site with soap and water and without washing or a T-shirt barrier to skin to skin contact.

PK evaluations relative to the level of testosterone and Nestorone remaining on the skin 2 hours after application with and without washing will also be completed.

21.2 Safety Evaluations

Each subject's health status will be monitored carefully throughout the trial. Safety evaluations completed during the study will include:

- Adverse event reports
- Vital signs
- Safety lab tests including CBC, blood chemistries, and liver panel
- Monitoring of pregnancies that occur during study participation
- Facial acne and hirsutism assessment (in females)

21.2.1 Safety Parameter Methods

Each subject's health status will be monitored carefully throughout the trial. Baseline data collected at the screening visit will consist of the medical history and vitals. Baseline data obtained from clinical chemistries and a complete blood count (CBC) will be used to monitor liver and renal function and hematologic status.

Adverse event reports will be collected and assessed at each visit. The results of the CBC and blood chemistries, will be reviewed by the investigators when results are available. If there is any clinically significant abnormal finding, the test will be repeated and the results reviewed and discussed with the medical monitor. If the subject has persistent abnormal parameters, the subject will be discontinued from the study and reassessed in a month. If the parameter does not return to normal after drug withdrawal at the end of the study/exit visit, the subject will be referred for appropriate assessment and treatment, if necessary. The outcome will be followed in 3 months by contacting the subjects.

Subjects who withdraw from the study will have all safety assessments repeated with the exception of medical history and STI screening. Interviews with subjects will include a review of any AE recorded on the log or otherwise reported in order to obtain as much information as possible. The AEs will be recorded at each visit on the CRF and on the appropriate forms. The principal investigator (or designated medical designee) will review each study event, assess severity, causality, seriousness, and report it in accordance with established procedures. There will be strict adherence to SAE reporting (see **Sections 15.6.2 and 15.6.3**). The site IRB/IEC will be notified of any serious, unexpected adverse events in compliance with IRB/IEC research requirements. PC, as the sponsor of the IND for Nestorone, will make the final adjudication and submit IND safety reports as required to FDA.

Safety evaluations will be based primarily on the incidence of AEs, including study product reactions, study discontinuation information, changes from screening to the last assessment in vital signs and clinical laboratory tests, including hematology and blood chemistry.

22. Statistical and Analytical Methods

A detailed statistical analysis plan will be developed prior to performing the statistical analysis for this trial. Further details of the statistical methodology in addition to the below will be described in the statistical analysis plan (SAP). Statistical methods in the statistical analysis plan that are different than the methods presented in the protocol will be discussed in the analysis plan. The final study report will discuss any deviations from the final statistical analysis plan.

22.1 Sample Size

An estimated sample size of 12 couples is based on the studies conducted assessing testosterone transference. Based on the published data, a sample size of 12 female participants will give an 80% power to detect a change from baseline in serum testosterone of non-dosed females for a mean difference of 9 ng/dL with a standard deviation of 10 ng/dL (Stahlman*, et al.*, 2012).

22.2 Analysis populations

The following analysis populations will be created:

1. **All Enrolled:** All couples that are enrolled into the study.
2. **All Treated**: All enrolled couples where the man applied at least one dose of study drug.

Overview of analyses to be performed for each analysis population:

Analysis Population	Demographics and Subject Characteristics	Exposure	AEs	PK/Hormones
All Enrolled	✓			
All Treated (Safety)	✓	✓	✓	✓

22.2.1 Primary Analysis

The primary analysis will be evaluated in female participants by assessing changes from baseline up to 48 hours for serum testosterone levels in Cavg, Cmax and Cmin after secondary exposure to Nestorone + Testosterone Combination Gel (NES/T gel). Also, the Nestorone levels will be analyzed after secondary exposure to NES/T gel by presenting Cavg, Cmax, and Cmin. These endpoints will be summarized for each of the 3 types of skin contact between the man and woman.

22.2.2 Secondary Analysis

Secondary analysis will include:

- Pharmacokinetic parameters of testosterone and Nestorone in men will be compared with and without wearing a T shirt and washing.
- Serum T pharmacokinetics parameters in males with and without T shirt and washing will also be compared with baseline pharmacokinetic parameters.
- Average Testosterone and Nestorone levels on male skin 90 and 150 minutes after application as measured by adhesive D-square strips.
- .
- Change from baseline in safety lab parameters for all who received or were exposed to study drug.
- Incidence of adverse events and serious adverse events for both partners.
- Percentage of females with increased (relative to baseline) acne and hirsutism at each visit.

These endpoints will be summarized for each of the 3 types of skin contact between the man and woman.

22.3 CBC and Clinical Chemistry Parameters

CBC and Chemistry mean changes from baseline to final evaluation will be summarized in both partners. The summary will present data for the screening visit and the mean change from screening to final evaluation. The sample size, mean, SD, median, minimum, and maximum values will be presented for each parameter at each time measured. A summary of shifts from screening to final evaluation will be given for each parameter. The normal range for each parameter will be used to create categories of low, normal, or high. Any result that is higher (lower) than the upper (lower) limit of normal will be categorized as high (low) and any result within the lower and upper limits of normal will be categorized as normal. The number of subjects in each shift category from screening to final evaluation will be shown for each parameter.

22.4 Hormones

Percentage changes from baseline for Testosterone will be summarized for the All Treated population. Nestorone levels at each time point after dosing will also be summarized.

22.5 Adverse Events (AEs)

Treatment-Emergent Adverse Events (TEAEs) are defined as AEs that began on or after first use of the investigational gel and up to 14 days after final investigational gel use, and pre-existing conditions that worsened during the same timeframe.

The number (percentage) of subjects with at least one treatment-emergent AE will be presented in a frequency table by MedDRA® system-organ class and per MedDRA® "preferred" term. A similar summary will be created for SAEs and AEs leading to discontinuation. Summaries will also be presented by relationship to investigational product ("drug related" is defined as possibly, probably, or highly probable related to investigational product) and intensity of AE. Adverse event summaries will be done for the All Treated population in order to look at AE rates in all subjects combined as well as looking at the subset of subjects that did not enter the efficacy phase and the subset of subjects that did enter the efficacy phase.

22.6 Deaths

Subjects who died during the clinical trial will be listed and the following variables will be included: main reason(s) for death (as reported by the investigator), diagnosis of the SAE contributing to the death, date of death relative to the first day and last day of product use, and relationship to investigational product according to the investigator and NICHD. Subject SAE narratives, including information regarding the death (Certificate of death, autopsy report, etc.), will be part of the final clinical study report.

22.7 Other Safety Analyses

Changes from baseline in other safety parameters (e.g., vital signs, physical exam, etc.) will be summarized.

22.8 Disposition of Subjects

The number of subjects, who are enrolled, treated, attended the various assessments and who complete the clinical trial will be tabulated.

22.9 Demographic and Other Subject Characteristics

Baseline demographics and characteristics will be summarized.

23. Ethical Considerations

23.1 Statement of Compliance

All aspects of this study will be performed according to CFR Title 21, CFR Title 45, Part 46, Good Clinical Practices (GCP) and International Conference on Harmonisation (ICH) under an active U.S. IND Application of the Population Council and equivalent health authority permission in other countries. All principles of the Declaration of Helsinki will be followed. Conduct of the trial will be monitored by NICHD's designated CCTN Statistical and Clinical Coordinating Center (SCCC). The trial will be registered at ClinicalTrials.gov. Investigators from all sites have been trained in human research subject protection and the privacy of protected health information.

23.2 Interactions with Ethics Committees

The protocol will be reviewed by the FDA and the Central IRB designated by NICHD and the Statistical and Clinical Coordinating Center (SCCC). This protocol and any protocol amendments, together with the required documents will be submitted by the study site to the responsible ethics committees according to

the applicable requirements at the site. The study will commence at each participating site only after their relevant ethics committees (IRB/IEC) has granted full approval. Investigators/institutions will permit trial related monitoring, audits, IRB/IEC review and regulatory inspection(s) providing direct access to source data/documents.

23.3 Informed Consent

The principles of informed consent will be implemented according to the 1996 revision of the Declaration of Helsinki, ICH Consolidated Good Clinical Practice (E6), and current FDA regulations.

Principal investigators must provide the NICHD and the Population Council with a copy of the Informed Consent approved for both male and female subjects by their local Institutional Review Board (IRB). It is the investigator's responsibility to assure that each subject is provided an explanation of the details contained in the informed consent statement and other locally required documents prior to the individual signing the informed consent form certifying voluntary participation in the trial and prior to study participation. If required by the IRB/IEC or local regulations, a witness (impartial observer to the informed consent process) must also sign the informed consent form. The subject is to receive a copy of this consent form after signatures of the investigator or his/her designees are obtained. Under this consent, the subject shall understand that he/she is authorizing access to medical records as required for monitors, auditors, IRBs and regulatory authorities. To expedite collection of supporting documentation in the event of a serious adverse event, the subject should also be asked to provide a release of medical records authorization at the enrollment/treatment day 1 visit.

Subjects, male and female, that agree to participate in the study must sign the informed consent form (ICF) prior to study-specific procedures. The principles of informed consent will be implemented according to the 1996 revision of the Declaration of Helsinki and current NIH, DHHS, and FDA regulations. The informed consent form will be HIPAA compliant.

The subjects will be informed of their right to privacy and the fact that personal information will be treated as strictly confidential and will not be publicly available in accordance with HIPAA regulations. They will also be informed that the NICHD and the FDA have the right to inspect and possibly photocopy their medical records to verify the accuracy and completeness of the clinical trial results. The subject is to receive a copy of this consent form.

Prior to study participation, all study candidates will:

- Be informed of the nature and purpose of the study.
- Be given an explanation of the procedures to be followed in the study.
- Be given a description of any attendant discomforts and risks reasonably to be expected from the study, as well as from the study product.
- Be given an opportunity to ask any questions concerning the study.
- Be instructed that consent to participate in the study may be withdrawn at any time; and that the participant may discontinue participation in the study without prejudice.
- Be given a copy of an informed consent form.
- Be given the opportunity to decide to consent or not to consent to the study without coercion.
- Be informed of alternative contraceptive methods available.
- Be given information for whom to contact if there are questions about the research, participant rights, or to report research-related injury.

23.4 Conflicts of Interest

Investigators will be affiliated with their study sites. They will receive support for this clinical trial from the NICHD/NIH, which is a sponsor of this study, but will not profit from results, either positive or negative,

with regard to the product being evaluated. Population Council, a sponsor for this study and the IND holder, which is a not for profit organization, could profit from the successful development of this product.

23.5 Confidentiality

The information on individual subjects arising from this study is to be considered confidential and transmitted to the sponsor only in a form that will not permit identification of the individual. The information obtained from the subjects that can be identified with the subject will remain confidential within the research team. Regulatory and sponsoring agencies may request access to the study records and related medical records of each participating subject; the subject's identity will remain confidential to the extent permitted by the applicable laws and regulations. The results of the research will be released to public agencies including regulatory agencies, clinical investigators, and research organizations without reference to items identifiable to a particular subject. The results will be published such that the identity of the subjects will not be disclosed and cannot be ascertained. National and international agencies and sponsoring agencies may request access to the medical records of each participating subject, and if requested, the subject's identity will remain confidential. All records will be kept in a secure storage area with limited access.

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INVESTIGATOR OBLIGATIONS

Clinical research studies are subject to the regulations of the FDA. Prior to beginning the study, the investigator will be asked to demonstrate compliance with ICH E6, 8.2 and 21 CFR 312 by providing the signed essential documents required for the clinical trial. The responsibilities imposed upon investigators by the FDA are summarized in the "Statement of Investigator Form" (Form FDA-1572) which documents that he or she will follow the FDA regulations with respect to this study.

The investigator agrees to assume the responsibilities stated on the Form FDA-1572, and signifies his or her agreement by signing the Form FDA-1572, these responsibilities include:

- To conduct the study in accordance with the Study Protocol, Investigator Brochure, GCPs, ICH, and Declaration of Helsinki.
- To secure prior approval of the study by an appropriate Institutional Review Board (IRB). This board should be constituted in conformity with FDA regulations.
- To report on the progress of the study to the IRB and to submit a final report within three (3) months of the conclusion of data collection.
- To maintain current records of the receipt, dispensing, and disposition of study product and to return (or destroy as recommended when appropriate) all unused product to the sponsor or the sponsor's designated agent.
- To obtain a valid, fully informed, freely given written consent from each subject who participates in the study.
- To maintain adequate study documentation including web-based electronic case report forms (eCRFs), hospital records, and lab results, and to store these case histories for a minimum of two years following notification by the sponsor that all investigations have been discontinued or that the FDA has approved the drug application.
- To identify all sub-investigators who will also supervise drug administration.
- To report all Adverse Events to the sponsor or designated agent promptly.
- To notify the Population Council Safety Desk and HD within 24 hours of identifying a serious adverse event, regardless of the presumed relationship to the study product.
- To allow inspection or copying by the FDA, sponsor, or sponsor's designated agent of case histories and records of drug distribution.

Investigator Documentation required:

Prior to beginning the study, the investigator will be asked to comply with ICH E6, 8.2 and 21 CFR 312 by providing the following essential documents, including but not limited to:

(a) An original signed Investigator Agreement page of the protocol.
(b) An original signed acknowledgement of receipt of the Investigator's Brochure.
(c) An IRB/IEC-approved Informed Consent (as described in **Section 23.3**) in the local language.
(d) Local IRB/IEC approval of protocol and informed consent.
(e) Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
(f) Current Curriculum Vitae (CV) for the investigator and each sub investigator listed on Form FDA 1572.
(g) Financial disclosure information to attest to the absence of financial interests and arrangements, including any equity interests in the sponsor or proprietary interest in the tested product, which could introduce bias in the study conduct.

Appendix 1: Schedule of Assessments

Assessment	Screening Phase			Treatment Phase[a]							End of Study[a]	UNS
Visit Number	1	2[j]		3	4	5	6	7	8		9	
Study Day^	-28 to 0			1	3	8	10	15	17		31	
Both Partners												
Informed Consent	X											
Assign Subject Number	X											
Determine/Confirm Eligibility	X											
Demographics	X											
Medical, Reproductive, and Contraceptive History	X											
Questions on Contraceptive and Pregnancy Planning	X											
Vital Signs[d]	X			X	X[l]	X	X[l]	X	X[l]		X[l]	X
CBC and Clinical Chemistry[b]	X							X				X
Urinalysis	X											X
Hormone assessment (total testosterone only)[c]	X											
24-hour T PK sampling[k]		X										
Overnight Stay		X		X		X		X				X
Supervised Skin Contact				X		X		X				X
Adverse Events		X		X	X[l]	X	X[l]	X	X[l]		X	X
Concomitant Medications	X	X		X	X[l]	X	X[l]	X	X[l]		X	X
Male Partner												
Andrological History	X											
Complete Physical Exam[e]	X											X
PSA	X											X
Gel Application				X		X		X				X
Wear 100% Cotton T-shirt				X								X
Shower						X						X
NES and T sampling[f]				X		X		X				X
Residual Nestorone and testosterone Measurements[g]						X		X				X
Phone Contact											X	X
Female Partner												
Gynecological and Menstrual History	X											
Serum pregnancy Test	X											

Assessment	Screening Phase			Treatment Phase[a]							End of Study[a]	UNS
Visit Number	1	2[j]		3	4	5	6	7	8		9	
Study Day^	-28 to 0			1	3	8	10	15	17		31	
Urine Pregnancy Test				X		X		X				X
Skin exam for Acne and Hirsutism Assessment [i] (Ferriman-Gallwey)	X				X		X		X		X	X
Contraception and Menstrual Bleeding Questions				X		X		X			X	X
Post Skin Contact Washing				X		X		X				X
NES and T sampling[h]				X	X	X	X	X	X		X	X

Footnotes:
^ A 28 day window is allowed for the screening period before safety labs must be repeated. Treatment Visits 3, 5 and 7 have a +7 day window. Treatment Visits 4, 6 and 8 must occur the day after the female subject has finished each in-patient treatment visit (Visits 3, 5, and 7) (i.e. no day visit window is allowed for these visits). End of Study Visit should occur on day 31 (-12 days/+14 days).
[a] Only the female partner is required to come in for visits on days 3, 10, 17 and 30.
[b] CBC (complete blood counts) and Clinical Chemistry panel (glucose, liver and renal function tests including urea, creatinine, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin) will be done for both men and women at screening and then again on day 16 prior to leaving the in-patient clinic. If a couple discontinues early, a CBC and Clinical Chemistry draw will occur for the female subjects only at the early discontinuation visit.
[c] If total testosterone is abnormal, this will be repeated with free testosterone, sex-hormone binding globulin, luteinizing hormone and follicle-stimulating hormone measurements at the Visit 2 with results assessed prior to the couple being enrolled.
[d] Vitals includes weight, pulse, blood pressure and respiratory rate. Height will also be collected at screening in order to calculate BMI. Three blood pressure measurements will be taken with 5-minute rest period in between readings and the mean of the three measurements will be documented.
[e] Complete physical exam should include a detailed andrological exam
[f] For the male partner, serial blood draws for Nestorone and testosterone measurements will be collected at -15 and -5 minutes before gel application and at 1, 2, 4, 8, 12, 16, 20 and 24 hours after gel application.
[g] Using adhesive D-square strips a single location on the application site will be stripped on the male partner a total of ten times and the strips will then be analyzed for testosterone and Nestorone.
[h] For the female partner, serial blood draws for Nestorone and testosterone measurements will be collected at 2, 3, 4, 5, 6, 8, 10, 14, 18, 22, 26 and 50 hours after male participant gel application. She will also return at around 10 am on days 3, 10 and 17 for a single 50 hour post male participant gel application blood draw. A single blood draw at Visit 9 (Day 31) will occur to assess residual levels of testosterone and Nestorone.
[l] For the female partner, an examination should be done to assess any kind of facial acne or hirsutism. [j] Screening Visit 2 can occur one day prior to Visit 3/Day 1 (i.e. couple would come for their baseline 24 hour PK draws (Visit 2) and then continue directly into Visit 3/Day 1, thus staying for 48 hours straight.
[k] 24-hour Testosterone PK assessment before the first dose.
[l] Vitals signs will only be collected for female subjects.

Appendix 2: List of Exclusionary Medications

The following list includes some of the common drugs that contraindicate study participation. Please note that this list is NOT exhaustive; drugs not on the list should be researched by the study center staff and approval granted from the Medical Monitor if a site is uncertain about contraindication.

Subjects who begin taking an exclusionary medication (i.e. antibiotic) after study enrollment will require a waiver to continue in the study.

Certain antibiotics can interfere with metabolism of hormone contraceptives. **Please request an approval from Medical Monitor for specific antibiotics you are unsure of**	
Accutane	Isotretinoin
Azathioprine	Lithium
Cytotec	Misoprostol
Diethylstilbestrol (DES)	Phenylbutazone
High dose Vitamin A	Prednisone
human growth hormone	Ritonavir
Immuoprin	somatotropin
Imuran	Thalidomide
Sex Hormones/Steroids	
Androgens/Anabolic Compounds	
anastrazole/letrozole	finasteride
clomiphene	FSH
dutasteride	hCG
All Androgens, Estrogens and Progestins not specified	
Androgen Receptor Blocker	
flutamide	
Anticoagulants	
Anticonvulsant	
alprazolam	Klonopin
benzodiazepines	Neurontin
clonazepam	Restoril
clorazepate	temazepam
Depakote	Tranxene
diazepam	triazolam
divalproex sodium	Valium
gabapentin	Xanax
Halcion	
Antihypertensives	
Interfere/Interact with Nestorone or Testosterone	
anisindione	Kynamro
Arava	leflumomide

Aubagio	lomitapide
Coumadin	mipomersen
dicumarol	Miradon
Jantoven	teriflunomide
Juxtapid	warfarin
Interfere with the metabolism of hormone contraceptives:	
barbiturates	Oxcarbazepine
Griseofulvin	Primidone
Isoretinoin	Topiramate
Modafinil	
Liver enzyme inducers:	
carbamazepine	Phenytoin
Carbatrol	Rifampin
Dilantin	Rifabutin
Lansoprazole	St. John's Wort
phenobarbital	Tegretol
FDA List of CYP3A4 Inhibitors	
STRONG:	
Boceprevir	(12) nefazodone
Biaxin	nelfinavir
clarithromycin	posaconazole
conivaptan	ritonavir
(11) indinavir	saquinavir
itraconazole	telaprevir
ketoconazole	telithromycin
lopinavir/ritonavir	voriconazole
mibefradil	
MODERATE:	
Amprenavir	erythromycin
aprepitant	fluconazole
atazanavir	fosamprenavir
ciprofloxacin	(11) imatinib
darunavir/ritonavir	verapamil
diltiazem	
Lipid-lowering Statin Drugs	
Atorvastatin	Pravastatin
Lipitor	Provachol
lovastatin	simvastatin
Mevacor	Zocar
spironolactone	
Aceon	Mavik
Accupril	Moexipril

Altace	Monopril
benazepril	Perindopril
Capoten	Prinivil
captopril	Quinapril
Enalapril	Ramipril
Fosinopril	Trandolapril
Lisinopril	Univasc
Lotensin	Zestril
Chemotherapeutic agents	
Vaccinations within 3 months of study treatment	
Measles	Rubella
Mumps	Varicella
Oily Cosmetic Skin Gels/Products that would prevent absorption of steroids	

Appendix 3: Instructions for Gel Application – Male Contraceptive

- Gel should be applied to clean dry skin at approximately 8am under study staff supervision.
- The syringe cap should not be removed until the male participant is ready to use the gel.
- The male participant should wash his hands and then push the plunger of the syringe to deliver the gel to his hand.
- Using his palms, the male participant will apply the prescribed daily dose of the gel to the right and left shoulders and area of the upper arms to the top of the bicep muscle (i.e., to shoulder and arm skin that would be covered by a short sleeve T-shirt)as shown in the shaded areas in Figure 1 below.

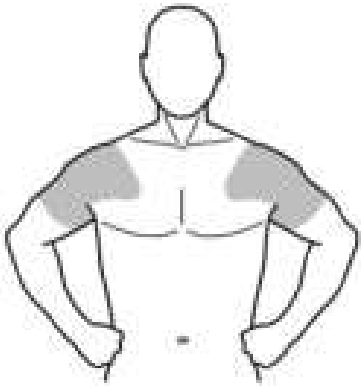


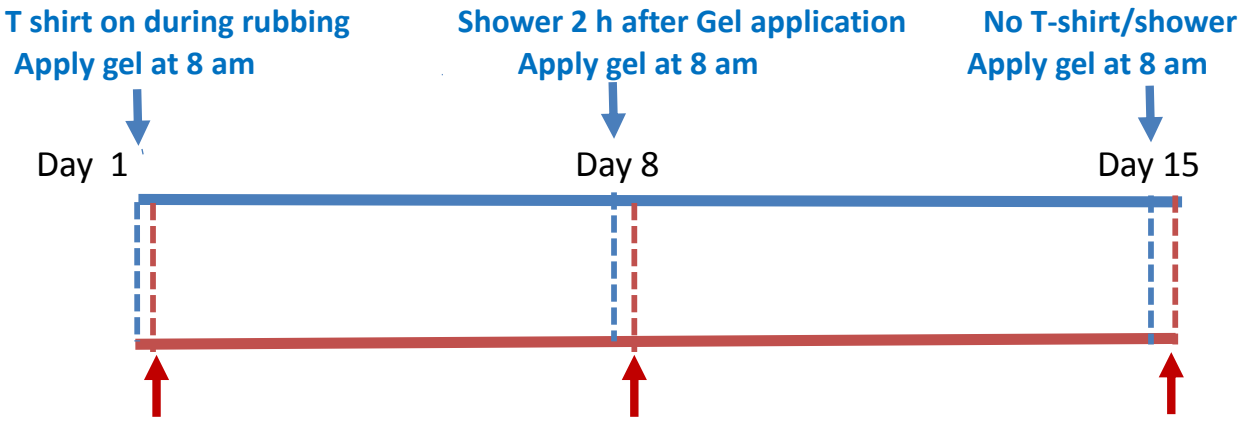
Figure 1: Application sites for the study gel

- Once the application site is dry, the site should be covered with clothing until time of rubbing with female participant, at which time specific visit rubbing non/coverage requirements will be followed. Treatment and contact variations are as followed for each specific treatment day:
    - Day 1/Visit 3 - “Shirt” PK day: Apply gel and don shirt (provided by the investigators) immediately after applied gel has been allowed to dry. Continue to wear the T-shirt until female participant rubs the area of the T-shirt covering the gel application site at approximately 2 hours (±15 minutes) post gel application;
    - Day 8/Visit 5 - “Shower” PK day: Apply gel and don shirt (provided by the investigators) immediately after applied gel has been allowed to dry. Continue to wear the T-shirt until showering occurs (washing the gel application site with soap and water) one hour 45 minutes after the gel application. The female participant will rub the gel application site 2 hours (±15 minutes) after gel application and just after showing once skin has been dried.;
    - Day 15/Visit 7 - “Bare, unshowered” PK day: Apply gel and don shirt (provided by the investigators) immediately after applied gel has been allowed to dry. Remove the T-shirt immediately prior to the female subject rubbing the gel application site 2 hours (±15 minutes) after gel application.
- Wash hands thoroughly with soap and water after gel application. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including the study gel, are flammable.
- Clothing should be worn over the gel application area or a shower should be taken prior to close skin contact with women or children outside of supervised study procedures outlined within the study protocol.

Appendix 4: Study Procedures for Male and Female Subjects

Male

- **Blood draws for NES at -15, -5 minutes and at 1, 2, 4, 8, 12, 16, 20,and 24 h after gel application each treatment day (days 1, 8 and 15).**



Female

- **Supervised close skin contact by rubbing male gel application site 2h after male gel application on day 1, 8, 15**
- **Blood draws for T and NES 2, 3, 4, 5, 6, 8, 10, 14, 18, 22, 26 and 50 h after male participant gel application**

Appendix 5: Outline of Timed NES and T sampling

Hour for draw time	-15 min	-5 min	0/gel applied	1	2	3	4	5	6	8	10	12	14	16	18	20	22	24	26	50
Men	X	X		X	X		X			X		X		X		X		X		
Women					X	X	X	X	X	X	X		X		X		X		X	X

Appendix 6: Preparation of Nestorone/Testosterone (NES/T) Combined Gel Investigational Product by the Investigational pharmacists at each site

• The combined NES/T gel will be shipped in glass jars from Particle Science to the Investigational Pharmacy of each site. Each jar will be used only for one participant.
• In advance of a day that the male participant will be coming to administer the gel (day 1, 8, and 15), the pharmacist will aspirate the gel from the glass jar using 6 mL plastic syringes. Precaution should be taken to avoid excess periods that would allow for evaporation of gel.
• Air bubbles and excess gel will be displaced from the syringe using the plunger until 5 mL of the combined gel is in the syringe. A syringe cap will then be placed on the tip of the syringe
• The pharmacist will place a label on the individual syringes to identify the study product. Refer to Section 12.1.2 regarding label information.
• The pharmacist will prepare a single syringe for each subject visit and store them at room temperature and then place the syringe into a bag, sealed, and delivered to the clinic for the participant. The opaque bag will have a two part label that will be applied by the pharmacist. Refer to Section 12.1.2 regarding label information.

Appendix 7: Ferriman-Gallwey Scale for Skin Exam