Title: A randomized, placebo-controlled trial of 13-*cis* retinoic acid for the treatment of men with oligoasthenoteratozoospermia

IND #: application pending

Clinical Phase: II

Sponsor(s): University of Washington
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List of abbreviations

BMI	Body mass index
BP	Blood pressure
CRF	Case record form
CBC	Complete blood count
CI	Confidence interval
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug Application
IRB	Institutional Review Board
LC/MS	Liquid chromatography/mass spectroscopy
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
NICHD	National Institute of Child Health and Human Development
OAT	Oligoasthenoteratozoospermia
SAE	Serious adverse event
T	Testosterone

Synopsis

Study Title	A randomized, placebo-controlled trial of 13-*cis* retinoic acid for the treatment of men with oligoasthenoteratozoospermia
Study Phase	II
Sponsor	National Institute of Child Health and Human Development
Study Drug	13-*cis* retinoic acid
Objective	**Primary Objective**: To determine the effect of 13-*cis* retinoic acid administration on total motile sperm count in men with oligoasthenoteratozoospermia **Approach:** Sixty men with infertility due to oligoasthenoteratozoospermia (total, motile sperm count of <10 million), but not known genetic abnormalities, will be enrolled in a prospective six-month, randomized, double-blinded, placebo-controlled 3-arm pilot trial of daily oral therapy with placebo, 20 or 40 mg daily of 13-*cis* retinoic acid. The impact of treatment on spermatogenesis will be determined by monthly semen analysis. **Secondary Objectives**: • To determine the chance of pregnancy during treatment with 13-cis retinoic acid • To determine the concentration of 13-cis retinoic acid in the seminal plasma of treated men • To determine the side effects associated with treatment with 13-cis retinoic acid
Principal Investigator	Dr. John K. Amory MD, MPH
Rationale	Men with infertility and normal gonadotropins have few options for treatment. Recent research has demonstrated the lower intratesticular concentrations of 13-cis retinoic acid are associated with abnormal sperm parameters. Older studies of 13-cis retinoic acid administration to normal men demonstrated increases in sperm concentrations, but the effect of 13-cis retinoic acid on sperm concentrations in men with infertility has never been studied. If 13-cis retinoic acid increased sperm concentrations in infertile men, it could help infertile men father pregnancies without the need for IVF and/or ICSI.

Study Design	This is a prospective, randomized, double-blinded, trial to evaluate 13-cis retinoic acid for the treatment of oligoasthenoteratozoospermia We will conduct a prospective, three-arm, randomized, double-blinded, placebo-controlled interventional trial to determine the impact of therapy with 13-*cis* retinoic acid on sperm indices in infertile men. Sixty (n=20/group) infertile men with abnormal sperm analyses will be enrolled in a 24-week study of 20mg or 40 mg of 13-*cis* retinoic acid or matching placebo daily. The subjects will be closely followed for side effects related to treatment. The impact of treatment on indices of spermatogenesis will be determined by monthly seminal fluid analyses. All aspects of this study will be performed in compliance with Good Clinical Practice (GCP) regulations, ICH guidelines, the Declaration of Helsinki, and under an FDA Investigational New Drug (IND) application.
Number of Subjects	Sixty men.
Duration of Trial	Enrolment should be completed in about 12 months, resulting in total study duration of about 24 months including screening, treatment phase, end of study visit procedures, close out and data analysis.
Duration of Treatment	The active treatment phase will be 24 weeks
Dosage and Regimen	13-cis retinoic acid at 20 or 40 mg daily or matching placebo
Inclusion Criteria	Subjects will be infertile men (no pregnancy with partner with normal cycles and normal hysterosalpingogram despite >1 year of unprotected intercourse) and abnormal sperm analyses with a total, motile sperm count of less than 10 million sperm as assessed by semen analysis on two occasions separated by one week
Exclusion Criteria	Exclusion criteria include: known genetic infertility (e.g. Klinefelter syndrome or Y-chromosome microdeletions), hypogonadotropic hypogonadism (that might respond to gonadotropin injections), the use of anabolic steroids, illicit drugs, or the consumption of more than 4 alcoholic beverages daily, severe mental health problems, or current therapy with retinoic acid (e.g. Accutane) or vitamin A.

Efficacy Parameters	In this study, count of total, motile sperm after 24 weeks of treatment.
Safety Parameters	• CBC, clinical chemistry panel (glucose, liver and renal function tests including urea, creatinine, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin), full lipid panel including Total cholesterol, HDL, LDL, triglycerides at screening and at the end of treatment. Additional measures will be conducted if any abnormal values are found until the end of study visit. • Adverse event and concomitant medications throughout the study. Other safety parameters include vital signs; and changes in pre- and post-treatment physical examination results and score on the PHQ9 depression questionnaire.
Evaluations	The following determinations will be made in all subjects: • Serum samples will be collected for the measurement of concentrations of vitamin A, all-trans and 13-cis retinoic acid, testosterone, FSH and LH will be collected before the beginning of the treatment, and monthly during treatment.
Other Assessments	Demographic characteristics, including age and race, will be collected
Statistical Analysis	The primary endpoint is the effect of treatment on the count of total, motile sperm between treatment groups after 24 weeks. This analysis will be conducted using a Kruskal-Wallis ANOVA is the primary endpoint.

1.0 Introduction and Background

Infertility affects 10-15% of all couples, with 1.5 million couples seeking medical assistance for infertility yearly (1). Infertility attributable to the male partner accounts for 30-40% of all cases of infertility. The most common form of male infertility involves some type of impairment in spermatogenesis (2). Unfortunately, over 80% of men with infertility from impaired spermatogenesis do not have a medically treatable cause, such as a gonadotropin deficiency (3). In men with idiopathic infertility, surgical sperm extraction from the testis coupled with *in vitro* fertilization or intra-cytoplasmic sperm injection offers some hope of fertility; however, these procedures are invasive, expensive, unsuccessful in 30-40% of cases, and don't address the underlying cause of infertility (4). Therefore, new approaches to the treatment of male infertility are sorely needed.

The essential role of vitamin A (retinol) in spermatogenesis has been long appreciated. Vitamin A deficient male mice are sterile due to impaired spermatogenesis and supplementation of deficient mice with vitamin A restores fertility (5, 6). Vitamin A is required for spermatogenesis as it is converted to retinoic acid in the seminiferous tubules via the activity of testes-specific retinol and retinal dehydrogenases. Retinoic acid is known to mediate most of the effects of vitamin A in tissues. In the testes, two retinoic acid receptors, α and γ, are present in both Sertoli cells and developing germ cells (7-10), and targeted deletion of these receptors in mice results in male infertility (11-13). From this work, it is clear that retinoic acid plays several essential roles in spermatogenesis, including necessary functions in spermatogonial differentiation, spermatid adhesion to Sertoli cells and spermiation (14). Given the crucial role of retinoic acid in spermatogenesis, it seems quite possible that some men with "idiopathic" infertility have intratesticular concentrations of retinoic acid below those necessary to initiate and/or maintain optimal spermatogenesis, but whether relative deficiencies of intratesticular retinoic acid contribute to male infertility in

humans is unknown. In theory, poor dietary intake of vitamin A could lead to infertility; however, a nutritional cause of infertility seems improbable in the US. More likely, low intratesticular concentrations of retinoic acid could occur in infertile men either due to impaired retinoic acid biosynthesis from vitamin A or increased metabolism of retinoic acid to inactive metabolites within the testes.

Despite the known importance of retinoic acid for spermatogenesis in animals, there has been relatively little work examining the role of retinoic acid on spermatogenesis in humans. In this proposal, we will perform a clinical trial of retinoic acid administration to infertility patients to determine whether retinoic acid therapy improves sperm quality in infertile men. Intriguingly, there is a suggestion that the administration of retinoic acid to men may improve sperm production. During the development of 13-*cis* retinoic acid (Accutane) for acne, three human studies examining the effect of oral administration of 13-*cis*-retinoic acid on sperm production in men were performed to determine if 13-*cis* retinoic acid was harmful to male fertility. Interestingly, men in these studies had increased sperm concentrations during treatment (see below), suggesting that 13-*cis* retinoic acid administration enhanced spermatogenesis in these normal men with acne (15-17).

If the administration of retinoic acid were shown to improve spermatogenesis in some *infertile* men, it would have tremendous significance for our current approach to the treatment of male infertility**.** Because of its widespread use in humans for over 25 years, 13-*cis* retinoic acid is widely available in a generic formulation and could be quickly incorporated into male infertility treatment algorithms. Ideally, retinoic acid therapy would increase an infertile man's chances of successfully fathering a pregnancy without the need for assisted reproductive technologies such as intra-cytoplasmic sperm injection and/or surgical methods of sperm extraction that are invasive for both the man and the woman, expensive and fail in many of cases.

Our group has completed the first ever study in humans to examine intratesticular retinoic acid concentrations. With IRB approval, we enrolled 24 men having scrotal surgery in an observational study to examine the association between intratesticular

retinoids and spermatogenesis. Interestingly, we observed that intratesticular 13-*cis* retinoic acid is significantly lower in men with sub-normal sperm quality as compared to men with normal sperm quality as defined by the WHO criteria (18) (Figure 1).

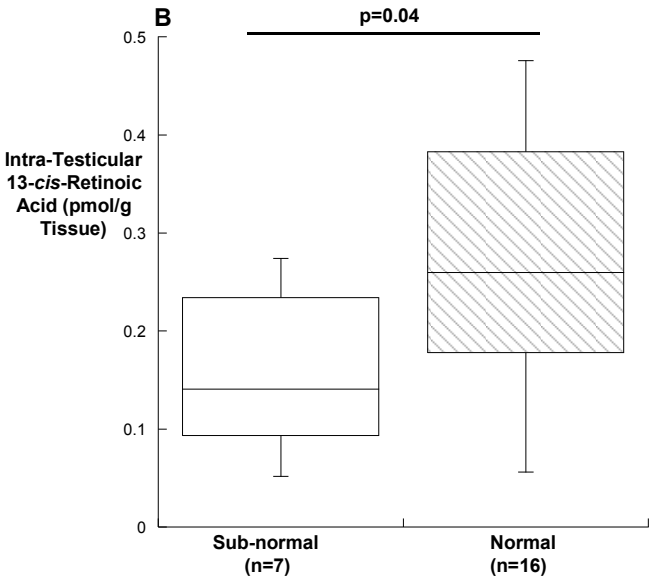

Figure 1. Intratesticular 13-*cis* retinoic acid in 24 men expressed as median and interquartile ranges. 13-*cis*-retinoic acid is significantly lower in men with sub-normal sperm quality as compared to men with normal sperm analyses (p=0.04) (41).

This data suggests that lower intratesticular retinoic acid is associated with impaired spermatogenesis; however, it is unclear from this cross-sectional data if the low retinoic acid is a result of the infertility or a cause of it. Only an interventional trial of retinoic acid in infertile men will answer the question of the ability of retinoic acid to improve spermatogenesis in this population.

Objectives

2.1 Primary Objective:

To determine the effect of 13-*cis* retinoic acid administration on total motile sperm count in men with oligoasthenoteratozoospermia

2.2 Secondary Objectives:

- To determine the chance of pregnancy during treatment with 13-cis retinoic acid
- To determine the concentration of 13-cis retinoic acid in the seminal plasma of treated men
- To determine the side effects and tolerability of treatment with 13-cis retinoic acid

3. Rationale, Benefits and Risks

Male infertility is common and difficult to treat unless men have an easily identified gonadotropin deficiency. Many men have idiopathic infertility. Retinoids are necessary for spermatogenesis, but no controlled studies of retinoic acid administration to men with infertility have been conducted. We have shown that men with abnormal spermatogenesis have lower than normal levels of intratesticular retinoic acid, suggesting that intratesticular retinoic acid deficiency is associated with infertility. In this study, we aim to determine if retinoic acid therapy can improve sperm counts in men with low sperm counts. The medication, 13-cis retinoic acid is widely available and prescribed for the treatment of acne, suggesting that serious adverse events, especially at the low doses to be tested are unlikely.

4. Compliance

All aspects of this study will be performed according to GCP and ICH guidelines, under an active IND.

5. Study Design

We will conduct a prospective, three-arm, randomized, double-blinded, placebo-controlled interventional trial to determine the impact of therapy with 13-*cis* retinoic acid on sperm indices in infertile men. Sixty (n=20/group) infertile men with abnormal sperm analyses will be enrolled in a 24-week study of 20mg or 40 mg of 13-*cis* retinoic acid or matching placebo daily. The subjects will be closely followed for side effects related to treatment. The impact of treatment on indices of spermatogenesis will be determined by monthly seminal fluid analyses. All aspects of this study will be performed in compliance with Good Clinical Practice (GCP) regulations, ICH guidelines, the Declaration of Helsinki, and under an FDA Investigational New Drug (IND) application.

6. Duration of the Study

Subjects: Subjects will undergo a screening phase of up to 60 days. After fulfilling all entry criteria, the first 60 subjects will be randomly assigned to one of the three groups. The treatment phase will last for 24 weeks and subjects will have two post-treatment visits, about 4 and 12 weeks after the end of treatment.

Enrolment should be completed in approximately 12 months, resulting in total study duration of about 24 months including screening, treatment phase, end of study visit procedures, close out and data analysis.

7. Number of Subjects

60 men will participate in the study (n=20/arm)

8. Dosage and Administration

13-cis retinoic acid at 20 or 40 mg daily (purchased commercially) or matching placebo

9. Selection of Subjects

9.1.1 Inclusion Criteria

1. Subjects will be infertile men (no pregnancy with partner with normal cycles and normal hysterosalpingogram despite >1 year of unprotected intercourse).
2. Abnormal sperm analyses with a total, motile sperm count of less than 10 million sperm as assessed by semen analysis on two occasions separated by one week.
3. In the opinion of the investigator, is able to comply with the protocol, understand and sign an informed consent and HIPAA form.

9.2 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
2. Men not living in the catchment area of the clinic
3. Clinically significant abnormal findings at screening
4. Known genetic infertility (e.g. Klinefelter syndrome or Y-chromosome microdeletions),
5. Hypogonadotropic hypogonadism (that might respond to gonadotropin injections),
6. The use of anabolic steroids, illicit drugs, or the consumption of more than 4 alcoholic beverages daily
7. Severe mental health problems requiring medications
8. Current therapy with retinoic acid (e.g. Accutane) or vitamin A.
9. Abnormal serum chemistry values according to local laboratory normal values, which indicate liver or kidney dysfunction. Other abnormal lab values may also be exclusionary, at the discretion of the investigator

10. Concomitant Treatment

Concomitant medications that are exclusionary include:

- Use of sex hormones for treatment
- Use of androgens or other compounds for body building
- Use of retin-A or Accutane for the treatment of acne

Concomitant medications are discouraged except as prescribed for the treatment of intercurrent medical conditions. All concomitant treatments will be recorded on the subject's case record form (CRF), including the generic name of the drug, start and stop dates, and reason for use.

11. Study Materials

11.1 Study Medication

Each subject will receive the study medication assigned per the randomization list. The first dose will be administered at the clinic under the observation of the study staff. The day and time of the start of treatment will be recorded on the CRF in the appropriate space provided. The subjects will be given enough supply of medication (for 28 days) until their next visit.

Study medication log (diary) will be provided to the subjects for recording the time of application of gel. These medication logs will be reviewed at each visit. The investigator will retain the copies of these logs.

11.2 Storage

Study medications will be stored at a temperature not to exceed 25 C in a locked storage area at the study site. Study medication will be accessible only to study personnel designated to handle study medication.

11.3 Disposal

Empty used pill bottles will be returned to the clinic and retained at the site. All unused medication will be returned to the University of Washington investigational pharmacy for destruction once final drug accountability has been performed.

12. Study Procedures

12.1 General

There will be a total of three treatment groups as described in Section 7. The study will consist of 3 periods:

1. Pre-treatment period (including screening) for up to 60 days.
2. Treatment period for 24 weeks

3. Recovery period for about 12 weeks

The treatment period will begin with Day 1 of treatment, daily for 24 weeks. The recovery period will last for about 12 weeks.

12.2 Laboratory Samples

Blood samples for laboratory analyses will be collected at the two screening visits, Day 1 and at the treatment visits every four weeks with the subject in a fasting state (no food or drink other than 4 to 6 ounces of water or non-sweetened clear liquids for a minimum of 10 hours). If the subject is in a non-fasting state, the investigator will reschedule the visit within two days. The investigator will review all laboratory reports and file a copy with each subject's chart and CRFs. The CBC and blood chemistry samples will be analysed at the local hospital laboratory at the University of Washington.

The serum samples for measurements of retinoic acid will be frozen for analysis at the end of study to prevent inadvertent breaking of the blind. Briefly, the blood samples will be collected into vacutainers (containing serum separating tube gel and clot activator) and gently mixed. After wrapping in aluminum foil to prevent light exposure that can degrade retinoic acid, samples will be allowed to clot for 1-2 hours at room temperature before centrifugation at 1000-2000g for 15 minutes. Following centrifugation, the serum samples will be frozen at –20 C.

12.3 Visits in Pre-treatment period

All visits will be scheduled between 9:00am and 5:00pm.

12.3.1 Screening Visit

The following screening procedures will be performed at the screening visit:

- Each participant must sign an IRB-approved informed consent form before any of the study-related procedures can be performed. The original signed informed consent form will be kept on file by the investigator with the subject's record and a signed copy will be given to the subject.
- A screening number will be assigned.
- A general medical history will be taken and will include information on current and previous diseases and treatment.
- Vital signs (pulse, blood pressure and respiratory rate) will be taken and recorded.
- Complete physical exam including measurement of testicular volume will be performed.
- Fasting blood samples will be obtained for the following measurements: Complete blood count (CBC), clinical chemistry including glucose, liver and renal function tests (urea, creatinine, albumin, alanine aminotransferase, aspartate aminotransferase, gamma glutamine transferase, alkaline phosphatase, bilirubin, albumin, full lipid panel including total cholesterol, HDL, and LDL, triglycerides, hematology (hematocrit, hemoglobin), and hormones (LH, FSH, T)
- Semen analysis will be done to measure sperm concentration, motility and morphology
- Height and weight will be collected
- Participants will be questioned regarding concomitant medications and adverse events.
- Once lab results are obtained and considered consistent with idiopathic infertility by the investigator as per the inclusion/ exclusion criteria for enrollment, the participant is informed by telephone of his lab results. If conformance to the inclusion/exclusion is confirmed, he is scheduled to return to the clinic for the 2nd sperm collection. If this 2nd sperm collection also meets enrollment criteria, the subject is schedule to begin on treatment
- Successful volunteers will be assigned subject numbers in sequence as they meet the study requirements.
- If any results are abnormal, according to local laboratory standards and in the clinical judgment of the investigator, the subject will be informed and excluded from the study and referred to his primary physician.

12.4 Visits in treatment period

Seven visits will occur in the treatment period: week 0, week 4, week 8, week 12, week 16, week 20 and week 24. All visits are ± 4 days.

12.4.1 Visit 1 (week 0)

This is the day 1 of treatment. The following will be done at this visit:

- Vital signs (pulse, blood pressure, respiratory rate) and weight will be taken and recorded.
- Subjects will be questioned regarding concomitant medications and adverse events. If the subject is taking a medication that is listed as disallowed the subject should not be enrolled in the study.
- The subject will complete the PHQ9 questionnaire (see appendix xx)
- A blood samples will be drawn, and the time of day of the blood draw will be noted in the CRF.
- A semen sample will be obtained for the measurement of sperm count, concentration, motility and morphology.
- Subjects will be given enough supply of study medication for 30 days (plus a supply for 2 additional days in the event of scheduling issues) as per their assigned group.
- A study medication log will be dispensed to record the date and time of administration of the study medication. Subjects will be instructed to take the medication in the morning, except on the day of the visit. Subjects will be scheduled to return to the clinic after 28 $\pm$ 4 days.

12.4.2 Visits 2-7

These visits are for weeks 4,8,16, 20 and 24. The following procedures will be done at each of these visits:

- Vital signs (pulse, blood pressure, respiratory rate) and weight will be taken and recorded.
- The subject will complete the PHQ9 questionnaire
- Complete physical exam including testicular examination and volume measurement will be performed.
- Subjects will be questioned regarding concomitant medications and adverse events.
- Any unused study medication will be collected at this visit.
- Study medication log will be reviewed to check the date and time of drug administration. These logs will be collected at this visit.

- A blood sample will be drawn. The time of day of the blood draws will be recorded in the source.
- A semen sample will be obtained for the measurement of sperm count, concentration, motility and morphology
- Fasting blood samples will be obtained for the following measurements: CBC, clinical chemistry including glucose, liver and renal function tests (urea, creatinine, albumin, alanine aminotransferase, aspartate aminotransferase, gamma glutamine transferase, alkaline phosphatase, bilirubin, and albumin), full lipid panel including total cholesterol, HDL and LDL, triglycerides, hematology (hematocrit, hemoglobin), and testosterone, FSH and LH. In addition, two serum samples will be frozen for the future analysis of serum retinoid levels.
- Subjects will be given the next month's supply of medication.
- Subjects will be scheduled to return to the clinic after additional 4 weeks visit.

12.4.3 Visit 8 and 9 (Follow-up Visits)

The following will be done at this visit:

- Vital signs (pulse, blood pressure and respiratory rate) will be taken and recorded.
- The subject will complete the behaviour questionnaire
- Subjects will be questioned regarding concomitant medications and adverse events.
- A blood sample will be drawn for the measurement of serum FSH, LH, T, and retinoids.
- A semen sample will be obtained for the measurement of sperm count, concentration, motility and morphology

13. Study Withdrawals

Subjects withdrawing from the study can be replaced only if the withdrawal occurs before the start of the treatment. Subjects who have had medication will not be replaced, regardless of the reason for discontinuation. All efforts should be made to contact any subject who decides to discontinue study participation for the end of study safety procedures (Visit 9). The necessary clinical and laboratory examinations planned at the last visit should be performed at the end of the study whenever it occurs. The reasons for discontinuation will be documented.

Post-Admission Withdrawal Criteria

Subjects may be discontinued prematurely for any of the following reasons:

- Emergence of a severe condition(s) such that, in the judgment of the investigator, continuation in the trial would negatively impact the health of the subject.
- Personal reasons (*e.g.* withdrawn consent).
- Subject lost to follow-up

All subjects in a treatment arm may be discontinued prematurely if greater than 25% of the subjects in an arm are discontinued for the emergence of the same severe condition that requires individual subjects to be discontinued.

14. Statistical Considerations

Data analysis and Interpretation of Results: The primary endpoint is the count of total motile spermatozoa in the ejaculate at week 24 of treatment compared with baseline. Secondary endpoints include other changes in sperm quality, and any pregnancies occurring during treatment as well as the incidence of side effects. The number of total motile sperm after six months of treatment will be compared between the three groups using a Kruskal-Wallis ANOVA with a Wilcoxon rank-sum post-hoc test. The change in the total motile sperm count from baseline (a secondary endpoint) will be performed with a Wilcoxon sign-rank test. Linear regression will be performed to determine if significant relationships between baseline (or delta) retinoic concentrations and changes in sperm quality are present using STATA Version 10.0 (College Park, TX, USA). For all comparisons, an alpha of 0.05 will be considered significant.

14.1 Sample size consideration

Inclusion of 20 men per group will allow for an 80% power to detect a greater than a 20% difference for total motile sperm count at week 24 compared with placebo with a variance of 25% and allowing for a drop-out rate of 10% at an alpha of 0.05.

14.2 Efficacy

Primary: The primary efficacy outcome is increase in the count of total, motile sperm after twenty-four weeks of study treatment.

Secondary: The magnitude and changes between baseline and week 24 in terms of total, motile sperm count will be described for subjects in each treatment arm.

14.3 Safety

Laboratory data, physical examination results, vital signs and chemistry levels will be assessed and compared for each subject from screening to end of study. All adverse events will be recorded and coded using the body system coding of MedDRA.

The incidence of adverse events will be examined by dose and where appropriate for trend by subject, clinic and time, using descriptive statistics. Clinical chemistries and allied data will be examined for change over time.

15. Adverse Events

Adverse Events (AE) should be carefully monitored and an AE form is included in the CRF. Serious adverse events (SAE) as defined below will have to be reported on the SAE form included as an appendix.

All adverse experiences must be recorded in the study event record of the subject's CRF, and must include the following information (when applicable):

- Specific condition or event
- Indication of whether the condition was pre-existing or not and if yes, whether it has worsened in severity (including an increase in frequency)
- Date of occurrence
- Date of resolution
- Relationship to study medication as evaluated by the investigator (causality assessment). The investigator must enter their opinion of causality on the AE forms.
- Action taken (study medication continued or not) and outcome
- 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) is considered serious}.

When any serious adverse drug experience, regardless of causality, is encountered during this clinical trial at an investigator's site, the investigator must notify the Study Monitor by facsimile using the form provided as an appendix. This report must be submitted within 2 calendar days from the time the investigator's staff is notified of the event.

All serious adverse events that are unexpected will be reported to the FDA by the principal investigator or his designated surrogate. All serious adverse events will be followed until fully characterized. The investigator will collect and forward to the FDA via fax, all available supporting documentation (with subject name redacted) for serious events, including at a minimum hospital discharge summaries and death certificates (where applicable). Additional supporting documentation that should be collected whenever possible, to verify the medical diagnosis, includes autopsy reports (where applicable), surgical procedure summaries, histology reports, and imaging reports.

16. Ethical Considerations

16.1 Informed Consent

Principal investigators will provide the NICHD with a copy of the Informed Consent approved by their local Institutional Review Board (IRB). The appended Informed Consent (Appendix 2 and Appendix 3) will be translated and certified into the language of the respondent as needed.

Under this consent, the subject shall understand that he 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 visit.

16.2 Conflicts of Interest

The investigators will not profit from results, either positive or negative, with regard to the product being evaluated.

16.3 Subject Recruitment

The subjects will be recruited from our Infertility and Urology clinics as well as from greater Seattle Metropolitan infertility clinics, who see >300 such men annually. The study coordinator will screen potential subjects over the phone by inquiring about their age and medical history. Potential subjects who qualify by phone screen will be scheduled for an appointment to consult with the investigator about further eligibility requirements for the study.

17. 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. 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.

18. Investigative Record Management

All investigative site records will be kept in a secure storage area with limited access. NICHD should be notified before destruction of any site records.

19. Data Transmission

Not applicable

20. Publication Policy

Data on the use of the study medication and results of all clinical and laboratory studies are considered private and confidential, and NICHD will encourage publication of the results of the study.

21. Investigator Documentation

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 following essential documents, including but not limited to:

1. An original signed Investigator Agreement page of the protocol.
2. An original signed acknowledgement of receipt of the Investigator's Brochure.
3. An Institutional Review Board (IRB) -approved Informed Consent (as described in section 18.1) in the local language.
4. Local IRB approval.
5. Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
6. Current curriculum vitae (CV) for each principal investigator and each sub investigator listed on Form FDA 1572.
7. 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.

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23. List of appendices

1. Schedule of Events
2. Informed Consent Document
3. HIPPA Informed Consent Document
4. PHQ-9 Questionnaire
5. Serious Adverse Event Report Form

Appendix 1: Schedule of Events

		Screening		Treatment		Follow-up
	Visit Number	**1**	**2**	**1**	**2-7**	**3**
	Study Day	**6 0**	**-30**	**0**	**Wk 4, 8, 12, 16, 20 and 24**	**Wk 28 and 36**
Administrative	**Inform consent/HIPAA signed**	**X**				
Clinical	**Vital signs**	**X**		**X**	**X**	**X**
	Medical history	**X**				
	Physical exam	**X**		**X**	**X**	**X**
	AE & ConMed	**X**		**X**	**X**	**X**
	Semen analysis	**X**	**X**	**X**	**X**	X
	PHQ9 questionnaire	**X**	**X**	**X**	**X**	**X**
Blood Sampling	**CBC and Clinical Chemistry**	**X** [a]		X	**X** [a]	X
	FSH, LH, T, retinoids	**X**		**X** [b]	**X** [b]	**X**
Drug Administration	**Dispense study medication**			**X**		
	Dispense study medication log			**X**		
	Collect and review study medication log				**X**	
	Collect unused study medication				**X**	

a: This blood collection requires fasting.

b: Sampling of blood will be collected every 15 minutes for one hour during which a total of five samplings (0, 15, 30, 45 and 60 minutes) will be collected for this visit.

Appendix 4: PHQ9 Questionnaire

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ DATE:_____

Over the last *2 weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____

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Appendix 5: Serious Adverse Event Report Form

SERIOUS ADVERSE EVENT REPORT	CBR SERIAL NO:

I. EVENT INFORMATION

1. PATIENT INITIALS	1.a COUNTRY	2. DATE OF BIRTH Day Month Year	2.a. AGE years	3. SEX	3.a. HEIGHT cm	3.b. WEIGHT kg

7.- 13. DESCRIBE EVENT. ___EXPECTED UNEXPECTED

DIAGNOSIS:

.....

Description:

4.-6. EVENT ONSET
Day Month Year

_____

_____

8.-12. SERIOUSNESS CRITERIA
CHECK ALL APPROPRIATE TO EVENT

___DEATH (DATE)
Day Month Year

___HOSPITALIZATION

___DISABILITY OR INCAPACITY

___LIFE-THREATENING

___OTHER SERIOUS CRITERIA
(Cancer, congenital anomaly, overdose, significant)

___NOT APPLICABLE

II. SUSPECT DRUG INFORMATION

14. SUSPECTED DRUG(S) (include generic name(s))

15. DAILY DOSE (include schedule)	16. ROUTE OF ADMINISTRATION

20. DID EVENT ABATE AFTER STOPPING DRUG?
___YES
___NO
___NOT APPLICABLE

17. INDICATION(S) FOR USE		21. DID EVENT RE-APPEAR AFTER REINTRODUCTION? __YES __NO __NOT APPLICABLE
18. THERAPY DATES (from/to) Day Month Year Day Month Year	19. THERAPY DURATION UNTIL REACTION ONSET	

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diseases, allergies, pregnancy etc.)

IV.IND HOLDER INFORMATION

24.a. NAME AND ADDRESS OF IND HOLDER

Population Council
Center for Biomedical Research
1230 York Avenue
New York, NY 10021 USA
Fax:+1(212)327 86 73

BATCH NO. (when relevant)	24.b. PATIENT IDENTIFIER NO
24.c. DATE RECEIVED Day Month Year	24.d. TRIAL NUMBER
24.e. DATE OF THIS REPORT Day Month Year	25.a. REPORT TYPE __INITIAL __FOLLOW-UP

V. INVESTIGATOR'S ASSESSMENT

23.d. OUTCOME	23.e. CAUSALITY
__ Recovered __ Recovering __ Not Recovered __ Sequelae __ Fatal __ Unknown	__ Not Related __ Unlikely __ Possible __ Probable __ Highly Probable __ Insufficient Data

26. NAME AND ADDRESS OF REPORTING PHYSICIAN

Add another page if not sufficient space. If this case is from literature, please attach an original article