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Sperm suppression and contraceptive protection provided by norethisterone enantate (NET-EN) combined with testosterone undecanoate (TU) in healthy men

Submission date
22/03/2004

Recruitment status
No longer recruiting

Registration date
01/04/2004

Overall study status
Completed

Last Edited
17/02/2021

Condition category
Pregnancy and Childbirth

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
There are good reasons for developing a male contraceptive: women who have health-related difficulties with the currently available contraceptives will benefit, and secondly, a male option other than condoms addresses important issues regarding shared responsibilities in family planning. This study is designed to test whether the combination of norethisterone enantate (NET-EN) and testosterone undecanoate (TU) represents a safe, effective, reversible, and acceptable method of male contraception. The two main objectives are to assess the rate of suppression (reduction) of sperm production caused by NET-EN and TU taken every 8 weeks for up to 6 months, and the level of contraceptive protection provided by the continued use of NET-EN and TU every 8 weeks for up to 56 weeks.

Who can participate?
Healthy men and women

What does the study involve?
Male participants provide semen, blood and urine samples and undergo physical examinations including a prostate examination. Their female partners are tested for normal reproductive function and pregnancy. Male participants then receive an injection of NET-EN and TU every 8 weeks for up to 26 weeks. During this time, couples use alternative contraception and the male participants undergo regular semen tests. When two consecutive semen tests have demonstrated low enough levels of sperm, the male participants continue to receive injections of NET-EN and TU every 8 weeks for up to 56 weeks. During this phase, participants are asked to rely only on the injections for contraception. When this phase is complete, male participants no longer receive injections, but are regularly followed for up to 52 weeks until their sperm count rises again. Alternative contraception is resumed. Participants are asked to provide information on sexual activity and the acceptability of the injections at scheduled times throughout the study.

What are the possible benefits and risks of participating?
Participants benefit from using a long-acting, reversible male contraceptive option, which offers important gender issues of shared responsibilities for family planning decisions. This is particularly relevant for couples that wish to use a highly-effective method, but the female partner has health-related problems with currently available methods for women. The male participant in this study will also benefit from receiving regular, study-related healthcare for up to 2.5 years. The risks are expected to be the same as those experienced in other hormone-based studies of contraceptives for men.

Where is the study run from?
World Health Organization (Switzerland)

When is the study starting and how long is it expected to run for?
January 2008 to May 2012

Who is funding the study?
1. United Nations Development Programme (UNDP)/United Nations Population Fund (UNFPA) /World Health Organization (WHO)/World Bank - Special Programme of Research, Development and Research Training in Human Reproduction (HRP)
2. CONRAD (USA)

Who is the main contact?
1. Kirsten Vogelsong (vogelsongk@who.int)
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Type(s)
Scientific

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Clinical Trials Information System (CTIS)
2007-005315-26

Protocol serial number
WHO/HRP ID A25165

Study information

Scientific Title
Sperm suppression and contraceptive protection provided by norethisterone enantate (NET-EN) combined with testosterone undecanoate (TU) in healthy men

Study objectives
Establish the contraceptive efficacy of a combined androgen and progestogen regimen for male fertility regulation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. WHO Research Ethics Review Committee, 17/08/2007
2. Institutional IRBs have granted approval

Study design
Added 24/09/2007: Single-arm open-label trial (Phase IIb)

Primary study design
Interventional

Study type(s)
Quality of life

Health condition(s) or problem(s) studied
Male contraception

Interventions
Interventions as of 24/09/2007:
Study participants will receive the following:

Norethisterone enantate (NET-EN) 200 mg and testosterone undecanoate (TU) 1000 mg injections at eight week intervals.

When a volunteer's sperm concentration is suppressed to 1 million/mL or below, he and his partner will be asked to rely on these injections as their primary method of contraception for a period of approximately one year. Men will be followed until their sperm concentrations recover to levels generally accepted as fertile.

Previous intervention information:
Study participants will receive the following:
Norethisterone enantate (NET-EN) 200 mg and testosterone undecanoate (TU) 1000 mg injections at eight week intervals.

When a volunteer's sperm concentration is suppressed to 1 million/mL, he will be randomly assigned to one of the following groups:
1. NET-EN 200 mg and TU 1000 mg injections at eight week intervals for 48 weeks (4/5 of men), or
2. Placebo and TU 1000 mg injections at 8 week intervals for 48 weeks (1/5 of men)

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Norethisterone enantate, testosterone undecanoate

Primary outcome(s)
1. The proportion of male participants who are rendered azoospermic and/or severely oligozoospermic (sperm concentrations less than or equal to 1 million/ml) at any point in the Suppression Phase
2. 12-month contraceptive method failure rates.

Key secondary outcome(s))
1. Proportion of men who remain azoospermic and/or severely oligozoospermic (sperm concentrations less than or equal to 1 million/ml) throughout the Efficacy Phase
2. Average length of time that men remain azoospermic and/or severely oligozoospermic (sperm concentrations less than or equal to 1 million/ml) in the Efficacy Phase
3. Proportion of men who recover, as defined in the protocol, within 12 months after their last “missed” injection
4. Average length of time to recovery among all men who enter the Efficacy Phase
5. Changes in steroid and peptide hormone levels compared with baseline
6. Reports of adverse events, overall and product-related
7. Changes in key physical findings, endocrinology levels, serum chemistries, urinalysis, hematology tests and PSA levels at study end compared with baseline
8. Answers to key questions on acceptability questionnaires

Completion date
30/05/2012

Eligibility

Key inclusion criteria

Amended 13/08/2010:
Male participants:
3.1. Sperm concentration greater than or equal to 15 million sperm/ml semen or total sperm count greater than or equal to 39 million sperm per ejaculate in two semen samples, with no gross abnormalities of sperm motility and morphology, per investigator's discretion
3.2. Screening gonadotropin (LH and FSH) and testosterone levels should be within the centre's normal ranges, however gonadotropin levels may fall below the lower limit of the normal ranges assuming the overall endocrine profile and semen parameters are indicative of a normal reproductive state

Female partners:
3. Age 18 to 39 years, inclusive
All other inclusion criteria remain the same.

Current information as of 24/09/2007:
Male participants:
1. Signed written consent form
2. Male healthy volunteer
3. Normal reproductive state demonstrated by:
3.1. Sperm concentrations greater than or equal to 20 million sperm/ml semen in two semen samples with no gross abnormalities if sperm motility and morphology per investigator's discretion
3.2. Screening gonadotropin and testosterone levels within the centre's normal ranges
4. Body mass index between 20 and 32 kg/m^2
5. History and clinical examination without pathological findings relevant to the study including symptoms or signs of a sexually transmitted infection
6. Digital rectal examination of the prostate does not reveal any abnormal findings and prostate specific antigen (PSA) level is within normal range
7. Laboratory assays do not suggest the presence of any illness
8. Sexually active with female partner, with a coital frequency of twice a week, on average
9. In a stable, mutually monogamous relationship/partnership with the female partner for at least one year within first visit and intends to remain in the relationship for the course of the study
10. Willing to comply with the requirements of the protocol
11. No desire for partner pregnancy within the next two years and willing to accept a low but unknown risk of pregnancy

Female partners:
1. Signed written consent form
2. Female healthy volunteer
3. Age 18 to 35 years, inclusive
4. No tubal ligation
5. Sexually active with male volunteer, with a coital frequency of twice a week, on average
6. Normal reproductive state, demonstrated by:
6.1. Regular menstrual cycles (23 - 38 days) by volunteer history for the past three months
6.2. Medical and gynaecological history without findings suggestive of impaired fertility
6.3. No contraindication to pregnancy
6.4. No signs or symptoms of a sexually transmitted infection

7. In a stable mutually monogamous relationship/partnership with the male volunteer for at least one year and intends to remain in the relationship for the course of the study
8. Willing to comply with the requirements of the study protocol
9. Not pregnant at the time of entry into the Suppression phase
10. No desire for pregnancy within the next two years and willing to accept a low but unknown risk of pregnancy

Information at time of registration:
Male participants:
1. General good health, aged 18 to 45
2. Normal reproductive state:
2.1. Sperm concentration 20 million/mL
2.2. Sperm motility 50% [grades a + b] or 25% or more with grade a
2.3. Sperm morphology 10% normal forms
2.4. Gonadotropin and testosterone levels within the centre's normal range
3. Body mass index between 20 and 32 kg/m^2
4. Clinical examination without pathological findings relevant to the study
5. No desire for children within the next two years

Female partners:
1. Aged 18 to 35
2. Normal reproductive state:
2.1. Regular menses
2.2. Medical and gynaecologic history without findings suggestive of impaired fertility or contraindication to pregnancy)
3. History of fertility in couple

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
320

Key exclusion criteria
Amended 13/08/2010:
Male participants:
4. History of or current prostate or testicular pathology (including varicocele that is visible or palpable without Valsalva maneuver) or male infertility.
All other exclusion criteria remain the same.

Added 24/09/2007:
Male participants:
1. Participation in another clinical trial within 30 days preceding the first drug administration, or simultaneous participation in another clinical trial
2. Institutionalised or imprisoned by order of the court
3. Competition in sports which use World Anti-Doping Agency (WADA) monitoring
4. History of prostate or testicular pathology or male infertility
5. Serious organic or psychiatric disease suspected from history and.or clinical examination
6. Diseases (including tumours) that may be affected by testosterone use or that may affect the outcome of the study, for example:
6.1. Prostate disease
6.2. Past or present history, or family history, of thrombotic or embolic diseases
6.3. Hypertension requiring therapy (blood pressure [BP] greater than or equal to 140/190 mmHg)
6.4. Acute or chronic hepatic diseases
6.5. Manifest renal diseases with renal dysfunction
7. Biochemical and/or haematological laboratory values outside normal ranges, unless the investigator confirms that the deviations are of no clinical revelance
8. Any indication of chronic use of illicit drugs or alcohol abuse
9. Use of any disallowed medications or of any drug known to affect absorption, distribution, metabolism or elimination (ADME) of testosterone within the 30 days preceding the first administration of the test compounds
10. Use of oral anti-coagulatory drugs (e.g. warfarin) within the 30 days preceding the first administration of the test compounds and during the study (aspirin is allowed)
11. Implantation of a sustained-action sex hormone within 8 months of screening
12. History of allergy to any component of the study drugs

Female partners:
1. Participation in any other clinical trial that would affect fertility
2. Use of depot medroxyprogesterone acetate (DMPA) 12 months prior to screening
3. Any indication of chronic use of illicit drugs or alcohol abuse

Date of first enrolment
04/09/2008

Date of final enrolment
10/11/2010

Locations

Countries of recruitment
United Kingdom

Australia

Chile

Germany

India

Indonesia

Italy

Study participating centre
Department of Andrology
The Anzac Research Institute
Concord Hospital and University of Sydney
Concord
Australia
-

Study participating centre
Prince Henry's Institute of Medical Research
Monash Institute of Medical Research
Melbourne
Australia
-

Study participating centre
Department of Obstetrics and Gynecology
S. Orsola Hospital and University of Bologna
Bologna
Italy
-

Study participating centre
Department of Medical Biology
Faculty of Medicine
University of Indonesia
Jakarta
Indonesia
-

Study participating centre
Centre of Reproductive Medicine and Andrology
University of Munster
Münster
Germany
-

Study participating centre
Instituto Chileno de Medicina Reproductiva (ICMER)
Santiago
Chile
-

Study participating centre
Department of Reproductive Biomedicine
National Institute of Health & Family Welfare
Munirka
New Delhi
India
-

Study participating centre
Andrology Research Unit, Centre for Endocrinology and Diabetes
Institute of Human Development, Faculty of Medical and Human Sciences
University of Manchester, Central Manchester University Hospitals NHS Foundation Trust
Manchester
United Kingdom
-

Study participating centre
Centre for Reproductive Medicine and Andrology
University Hospital Halle (Saale)
Martin Luther University Halle-Wittenberg
Halle
Germany
-

Study participating centre
Centre for Reproductive Biology
Queen's Medical Research Institute
The University of Edinburgh
Edinburgh
United Kingdom
-

Sponsor information

Organisation
UNDP/UNFPA/WHO/World Bank - Special Programme of Research, Development and Research Training in Human Reproduction (HRP)

Organisation
CONRAD (USA)

Funder(s)

Funder type
Research organisation

Funder Name
United Nations Development Programme (UNDP)/United Nations Population Fund (UNFPA) /World Health Organization (WHO)/World Bank - Special Programme of Research, Development and Research Training in Human Reproduction (HRP)

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, Gates Learning Foundation, William H. Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Funder Name
United States Agency for International Development

Alternative Name(s)
U.S. Agency for International Development, Agency for International Development, USAID

Funding Body Type

Government organisation

Funding Body Subtype
National government

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
All essential study documents including analytic datasets will be stored in the HRP e-Archive system. They are not available for public access. The researchers do not own individual-level data, so when appropriate data share agreements are in place, the data manager of the e-Archive system will be able to transfer the dataset to the recipient. If the de-identified study dataset has not been migrated to the e-Archive system yet, then the statistician or study data-manger would be sharing the dataset upon receipt of necessary data share agreements.

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/12/2016	04/01/2021	Yes	No