Efficacy and Safety of an Injectable Combination Hormonal Contraceptive for Men

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Context: The development of a safe and effective reversible method of male contraception is still an unmet need.

Objective: Evaluation of suppression of spermatogenesis and contraceptive protection by coadministered im injections of progestogen and testosterone.

Design: Prospective multicentre study.

Setting: Ten study centers.

Participants: Healthy men, aged 18–45 years, and their 18- to 38-year-old female partners, both without known fertility problems.

Intervention: Intramuscular injections of 200-mg norethisterone enanthate combined with 1000-mg testosterone undecanoate, administered every 8 weeks.

Main Outcomes Measures: Suppression of spermatogenesis by ejaculate analysis, contraceptive protection by pregnancy rate.

Results: Of the 320 participants, 95.9 of 100 continuing users (95% confidence interval [CI], 92.8–97.9) suppressed to a sperm concentration less than or equal to 1 million/mL within 24 weeks (Kaplan-Meier method). During the efficacy phase of up to 56 weeks, 4 pregnancies occurred among the partners of the 266 male participants, with the rate of 1.57 per 100 continuing users (95% CI, 0.59–4.14). The cumulative reversibility of suppression of spermatogenesis after 52 weeks of recovery was 94.8 per 100 continuing users (95% CI, 91.5–97.1). The most common adverse events were acne, injection site pain, increased libido, and mood disorders. Following the recommendation of an external safety review committee the recruitment and hormone injections were terminated early.

Conclusions: The study regimen led to near-complete and reversible suppression of spermatogenesis. The contraceptive efficacy was relatively good compared with other reversible methods available for men. The frequencies of mild to moderate mood disorders were relatively high. **(*J Clin Endocrinol Metab* 101: 4779–4788, 2016)**

Highly effective family planning, a goal men and women share, first became feasible in the second half of the 20th century with the availability of reliable, reversible, steroidal contraceptive methods for women. By the 21st century, the number of methods for women had expanded, whereas options for men to control their own fertility remain limited to withdrawal, condoms, and sterilization. In the past 4 decades, studies have demonstrated

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Abbreviations: AE, adverse event; CI, confidence interval; CV, coefficient of variation; DSMC, Data Safety and Monitoring Committee; FV, final visit; NET-EN, norethisterone enanthate; RP2, Research Project Review Panel; TU testosterone undecanoate; WHO, World Health Organization; WHO/RHR, WHO Department of Reproductive Health and Research.

that reversible hormonal suppression of spermatogenesis in men can prevent pregnancies in their female partners, although commercial product development has stalled (1–3).

In previous clinical studies, testosterone administration to men demonstrated contraceptive efficacy comparable with modern female methods (4–6). However, supraphysiological doses of testosterone had to be administered, with potential long-term adverse effects in healthy men. The testosterone dose can be reduced by coadministration of a progestogen (7); however, only 2 small-scale studies evaluated the contraceptive efficacy and safety of such a combination (8, 9). The present multicenter study was designed to test the contraceptive efficacy and safety in men of a regimen of im injections of a long-acting progestogen, norethisterone enanthate (NET-EN), when administered with replacement doses of a long-acting androgen, testosterone undecanoate (TU), that appeared to be promising in smaller clinical trials for reversible sperm suppression without raising safety concerns (10–13).

Materials and Methods

Primary and secondary objectives

The primary objectives of the study were: 1) the rate of suppression of spermatogenesis below the threshold criterion for contraception of sperm concentration less than or equal to 1 million/mL induced by a regimen of NET-EN and TU administered every 8 weeks for up to 26 weeks (up to 4 injection visits) (5, 14); and 2) the level of contraceptive protection for an efficacy period of up to 56 weeks.

Secondary objectives were: 1) maintenance of suppression of spermatogenesis; 2) reversibility of the regimen as determined by the return of sperm concentrations to the lower reference limits of a fertile population (≥15 million/mL or total sperm count to ≥39 million per ejaculate), as defined by the World Health Organization (WHO) (15, 16); 3) alterations in circulating concentrations of steroid hormones and gonadotropins; 4) safety, as monitored by reports of adverse events (AEs); and 5) acceptability of the regimen, as assessed by questionnaires.

Study design

A prospective, phase II, single arm, multicenter study design was applied. The research was conducted in compliance with the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guideline, following ethics committee, institutional, and national approvals, as required, at each of the 10 study sites (2 sites in Australia, Germany, and United Kingdom and 1 site in Chile, India, Indonesia, and Italy), as well as the approval of the WHO Ethical Review Committee which functioned as the trial's central Institutional Review Board.

The study protocol included a screening phase lasting up to 8 weeks, a suppression phase of up to 26 weeks (ie, injections at 0, 8, 16, and 24 wk), during which men received the intervention, an efficacy phase of up to 56 weeks with continued injections, during which eligible couples were exposed to the risk of pregnancy, and a recovery phase (beginning 8 wk after the final injection) for up to 1 year. The planned sample size (227 couples completing the efficacy phase) was calculated, assuming a 1% true failure probability and 25% dropout during the efficacy phase, with a goal to rule out a 4% failure rate with 95% confidence intervals (CIs) (95% CI, 1 sided) and with 90% power. The trial was registered with International Standard Randomized Clinical Trial Number 07760234.

Study population

Healthy men, aged 18–45 years, and their 18- to 38-year-old female partners, in stable, monogamous relationships, were invited to participate in the study. Both partners were informed about the nature, aim, and objectives of the study and gave written informed consent before the initiation of any study procedures, including screening.

Male volunteers were required to have a normal reproductive state as demonstrated by sperm concentration more than or equal to 15 million/mL or total sperm count more than or equal to 39 million/ejaculate in 2 semen samples, with no gross abnormalities of sperm motility and morphology; normal gonadotropin and testosterone levels; history and clinical examination without pathological findings relevant to the study, including serious organic or psychiatric diseases and symptoms or signs of a sexually transmitted infection; normal digital rectal examination of the prostate and prostate-specific antigen level within normal range; laboratory test results not suggesting the presence of any illness; and body mass index 20–32 kg/m^2.

Female partners were required to be healthy with normal reproductive state, no contraindication to pregnancy, and not pregnant at the time of entry to the suppression phase.

For the couple, a stable, mutually monogamous partnership for at least 1 year was required, along with a coital frequency of twice/week on average, an intent to remain in the relationship for the course of the study, no desire for pregnancy within the next 2 years, and willingness to accept a low but unknown risk of pregnancy.

Participant follow-up

After completing screening, eligible couples entered the suppression phase. The male participants received 200-mg NET-EN (200 mg/mL) + 1000-mg TU (250 mg/mL) by 2 separate gluteal injections every 8 weeks for up to 4 injection visits. All injections

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were administered by health professionals. During this time, couples were instructed to use alternative, nonhormonal contraception, and the male partner provided semen samples after 8 and 12 weeks in suppression phase and then every 2 weeks throughout the remainder of the suppression phase until the criterion for entry into the efficacy phase was met.

Couples entered into the efficacy phase when the male partner had produced 2 consecutive semen samples within 2 weeks demonstrating sperm concentrations less than or equal to 1 million/mL. In this phase, he continued to receive the study injections every 8 weeks, for a maximum of 7 injection visits. Couples enrolled in the efficacy phase were asked to rely only on these injections for contraception. In efficacy phase, semen samples were analyzed every 8 weeks at each injection visit.

When the efficacy phase was completed or when sperm concentrations remained higher than required during suppression phase to enter efficacy, or when sperm concentrations rebounded in efficacy phase with concentrations more than 1 million/mL confirmed by a repeated semen analysis within 2 weeks, and at early termination of injections (see below), the male participants were transitioned into the recovery phase and follow-up visits including semen analysis were scheduled every 4 weeks until sperm numbers returned to the normal range (≥15 million/mL or 39 million per ejaculate) (15). Alternative contraception was resumed if required to avoid pregnancy. The final visit (FV) was scheduled within 30 days after sperm recovery as defined above but not later than 36 weeks of recovery. In case of nonrecovery of spermatogenesis, follow-up visits for semen analysis and monitoring of AEs were continued for up to 52 weeks of recovery. Urine pregnancy tests were performed at the beginning of the suppression, efficacy, and recovery phases.

The first study participant was enrolled on September 4, 2008, and the last participant completed the study on May 30, 2012.

Physical examinations and registration of AEs

Physical examinations were done at baseline and at 8-week intervals in the suppression, efficacy and up to week 16 of recovery phase. Digital rectal examination of the prostate was performed at baseline and FV. Participants were asked about AEs at each study visit from the beginning of the suppression phase.

Laboratory analysis

Semen analysis was performed according to WHO recommendations (16). Safety clinical chemistry and serum hormone analysis (screening samples only) were performed at each study center by that center's standard procedures. Further serum samples for hormone analysis in the suppression, efficacy, and recovery phase were frozen and shipped to the central laboratory at the Center of Reproductive Medicine and Andrology in Münster, Germany, for analysis after completion of the study. Serum concentrations of LH and FSH were determined using highly specific time-resolved chemiluminescent microparticle immunoassay (Architect i1000; Abbott Diagnostics). Mean intraassay coefficients of variation (CVs) were below 2% and mean interassay CVs below 5%. Concentrations of testosterone and estradiol were determined using a Shimadzu QP2010 gas chromatography-mass spectrometry system. For testosterone, the lower limit of detection was 0.034 nmol/L, the lower limit of quantitation was 0.084 nmol/L. For estradiol, the lower limit of detection was 2.61 pmol/L, the lower limit of quantitation was 7.71 pmol/L. Precision calculated as CV was 8.36% for testosterone and 13.2% for estradiol, respectively. No serum samples for central hormone analysis could be received from the Indonesian center.

Acceptability questionnaires

Acceptability questionnaires were provided to the male participants 4 times and female partners 3 times throughout the study: suppression week 8 (male only), beginning of the efficacy and recovery phases, and at the FV.

Statistical analysis

The statistical analysis was done by statisticians of the WHO Department of Reproductive Health and Research (WHO/RHR) according to an intent-to-treat analysis using SAS/STAT software (17). Survival graphics and box-and-whisker plots were generated using R software (18).

The normality assumption was not fulfilled for the repeated continuous hormonal variables, and hence median change and corresponding interquartile range for the last individual visits in suppression phase, efficacy phase, and recovery phase compared with baseline were reported. Wilcoxon signed rank test was used for comparison of ranked mean change from baseline for these hormonal outcomes. For all other continuous outcomes, the normality assumption was assumed, and mean change from baseline and corresponding 95% CI were reported. Z test *P* values were used to determine statistical significance at the 5% level, of the mean decline/increase in these continuous outcomes.

For time-to-event outcomes, cumulative hazard rate probabilities were computed using the Kaplan-Meier product-limit method (19), with 95% CI based on the complementary log-log transformation. Contraceptive failure Pearl incidence rate with 95% CI was determined using Poisson distribution, using SAS Procedure Genmod.

Early termination of injections

An independent Data Safety and Monitoring Committee (DSMC) was established by WHO/RHR and CONRAD before the start of the trial. At the scheduled meeting on January 17, 2011, the committee reviewed the interim analysis data and determined the study met all criteria for continuation. As part of WHO/RHR's continuing monitoring review of all its ongoing studies, the department's Research Project Review Panel (RP2), an external peer-review committee, met in March 2011, reviewed the same data and determined that, for safety reasons, recruitment should be stopped and enrolled participants should discontinue receiving injections and be transitioned to the recovery phase. Sperm recovery and other data collection and analyses were to continue. This decision was based on RP2's review of study AEs and conclusion that the risks to the study participants outweighed the potential benefits to the study participants and to the increased precision of the study outcome findings from having the full cohort contribute to the final analysis. The AEs of concern to the RP2 were reports of mood changes, depression, pain at the injection site, and increased libido. The study DSMC, the investigators, and the study participants were informed of this decision by the study sponsors.

Results

Disposition and characteristics of subjects

Baseline characteristics of male participants and female partners are given in Table 1. The study participant flowchart is provided in Figure 1.

Primary study objectives

Suppression of spermatogenesis

Of the 320 participants who received at least 1 injection, 274 suppressed to a sperm concentration less than or equal to 1 million/mL by the end of 24 weeks, with the rate of 95.9 per 100 continuing users (95% CI, 92.8–97.9) (Kaplan-Meier method; Figure 2A). There were no significant differences of cumulative sperm suppression rates by ethnic group at the end of suppression phase (Kaplan-Meier analysis; data not shown).

Table 1. Participants' Baseline Characteristics

Male participants (n = 320)	
Age, years (median [IQR])	32.0 (27.0–36.0)
Ethnic group, n (%)	
White	149 (46.6)
Asian	106 (33.1)
Hispanic/Latino	63 (19.7)
Other	2 (0.6)
Sperm at first baseline visit (median [IQR])	
Concentration (million/mL)	54.7 (35.5–85.0)
Count (million)	161.7 (95.3–278.7)
Sperm at second baseline visit (median [IQR])	
Concentration (million/mL)	55.7 (37.3–82.8)
Count (million)	156.8 (92.0–280.5)
BP, mm HG (median [IQR])	
Systolic BP	120.0 (114.0–130.0)
Diastolic BP	77.0 (70.0–80.0)
Body mass index, kg/m^2 (median [IQR])	24.1 (21.5–26.5)
Hormones (median [IQR])	
LH (IU/L)	3.6 (2.4–4.8)
FSH (IU/L)	3.5 (2.3–5.1)
Testosterone (nmol/L)	17.7 (13.9–21.3)
Estradiol (pmol/L)	85.0 (67.8–106.5)
Female partners (n = 320)	
Age, years (median [IQR])	28.0 (25.0–32.0)
Any previous pregnancy, n (%)	242 (75.6)
Primary method of contraception at time of screening visit, n (%)	
Withdrawal	16 (5.0)
Natural family planning	6 (1.9)
Condoms, male or female	120 (37.5)
IUD, nonmedicated	10 (3.1)
IUD, hormone releasing	3 (0.9)
Progesterone only pill	14 (4.4)
Combined oral contraceptive pill	71 (22.2)
Hormonal injection	38 (11.9)
Hormonal implant	10 (3.1)
Hormone releasing vaginal ring/patch	9 (2.8)
No contraceptive method	23 (7.2)

IQR, interquartile range

Contraceptive efficacy

During the efficacy phase, 4 pregnancies (3 delivered and 1 terminated) occurred among the partners of the 266 male participants, with the rate of 1.57 per 100 continuing users (95% CI, 0.59–4.14). All pregnancies occurred before the 16th week of the efficacy phase (Figure 2B). Three of the 4 participants had a sperm concentration less than or equal to 1 million/mL, but none was azoospermic before or after the estimated date of conception; the fourth had sperm concentration of 0.2 million/mL a few days before and 1.6 million/mL a few days after the estimated date of conception. The Pearl index was calculated as 2.18 pregnancies per 100 person-years (95% CI, 0.82–5.80).

Secondary study objectives

Maintenance of suppression and recovery of spermatogenesis

Six men exhibited sperm rebound during the 56-week efficacy phase. Three men had a sperm rebound with repeated sperm concentrations more than 1 million/mL at the first injection visit in efficacy phase (E1), 2 men at the second injection visit in efficacy phase (E2), and 1 men at the third injection visit in efficacy phase (E3). Sperm concentrations at injection visits with sperm rebound ranged from 2.0 up to 16.6 million/mL.

The cumulative rate of recovery of spermatogenesis in recovery phase to a sperm concentration of more than or equal to 15 million/mL or total sperm count of more than or equal to 39 million per ejaculate for the 266 participants transitioned to the efficacy phase was 94.8 per 100 continuing users (95% CI, 91.5–97.1) by 52 weeks of recovery phase (Kaplan-Meier method) (Figure 2C).

Eight participants had not recovered to meet the criteria of return to fertility after 52 weeks in recovery phase, the last visit according to the study protocol. These participants were followed on a case by case basis until they regained normal sperm counts (n = 5, up to 74 wk of recovery) or declined further follow-up (n = 2). One volunteer did not recover within 4 years since his last injections.

Combined method failure rate

The combined method failure rate (Kaplan-Meier method) was defined by nonsuppression by the end of suppression phase, or sperm rebound during efficacy phase, or pregnancy during efficacy phase. Applying this definition, the combined method failure rate was 7.5%.

Reproductive hormones

Serum concentrations of LH and FSH were significantly suppressed compared with preinjection baseline at the last visits of suppression and efficacy phase, respectively (Supplemental Table 1 and Figure 3). Testosterone

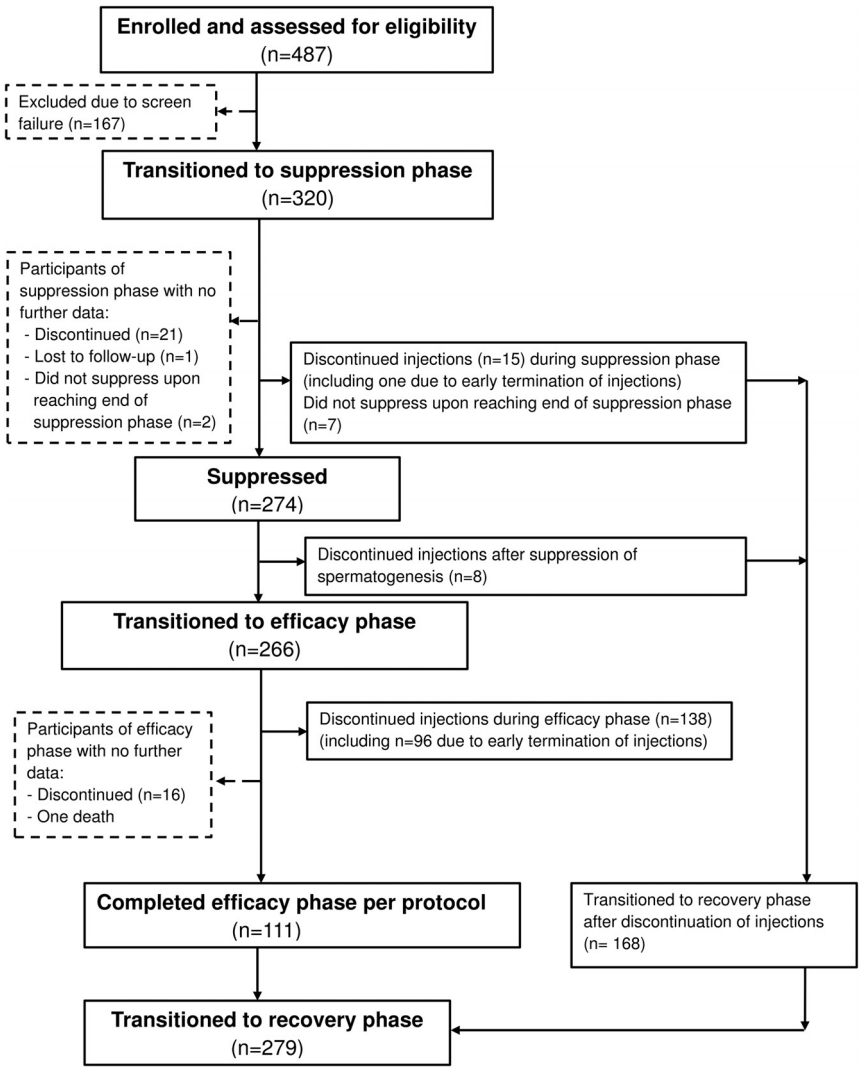

Figure 1. Study participant flowchart. For the transition between the main study phases (suppression, efficacy, and recovery phase), participants who discontinued in the study followed 1 of 2 patterns. Those groups of participants who discontinued in that particular study phase but transitioned to recovery phase (n = 168) are on the right side. Those groups of participants who discontinued study participation (n = 24 during the suppression phase, and n = 17 during the efficacy phase) and did not transition to recovery phase (ie, with no follow-up data) are indicated by interrupted lines on the left side of the flowchart.

and estradiol levels were significantly lower compared with baseline at the last visits of suppression phase. At the last visits of efficacy phase, testosterone was slightly, albeit significantly, elevated and estradiol unchanged compared with baseline. Although LH and testosterone were still significantly decreased at the last measurements in recovery phase, estradiol and FSH levels were statistically indistinguishable from baseline levels.

Physical findings, prostate-specific antigen, serum chemistries, and hematology tests

There were a number of parameters that changed significantly from baseline throughout the study. One participant was discontinued due to an increase in blood pressure (BP). No other changes were considered clinically significant requiring medical follow-up. Detailed analysis is provided in the Supplemental Tables 2 and 3.

AEs and discontinuation of injections

During the course of the trial, 1491 AEs were reported by the male participants; 38.8% of these were assessed as being not related to use of the study products. Table 2 summarizes the AEs that were assessed as being possibly, probably, or definitely related to use of the study products and that were reported at least 5 times, the number of participants reporting these events, the relation to study products as judged by the investigators, and the severity. Thirty-one percent of the AEs listed were considered "possibly related," 40% "probably related," and 29% "definitely related"; 91% of all these AEs were classified as mild and 99% were considered mild or moderate.

The AEs determined as "product related" were not unexpected, had been previously reported after progestogen and/or testosterone administration, and were noted on the study consent form as possible side effects. Sixty-two of the 65 reported emotional disorders were reported at 1 center (Indonesia), with all of these AEs at this center rated "mild" (see also Table 2). Similarly, reports of increases in injection site pain and myalgia were primarily reported by men of the Indonesian center (69 of 103 for injection site pain and 65 of 71 for myalgia). Increased libido reports were also high at the Indonesian center (63 of 124) and the Chilean center (34 of 124), with 100% (Indonesia) and 73.5% (Chile) classified as mild. The number of reports of acne was high (147), but these were distributed among the centers. The Indian center reported very few AEs.

There was 1 death by suicide in the efficacy phase that was assessed as not related to the study regimen. The participant received 3 injections and committed suicide 1 month after the last injection. The family indicated that he could not cope with his academic pressure. Other nonfatal serious AEs were 1 case of depression (assessed as probably related) and 1 case of intentional paracetamol over-

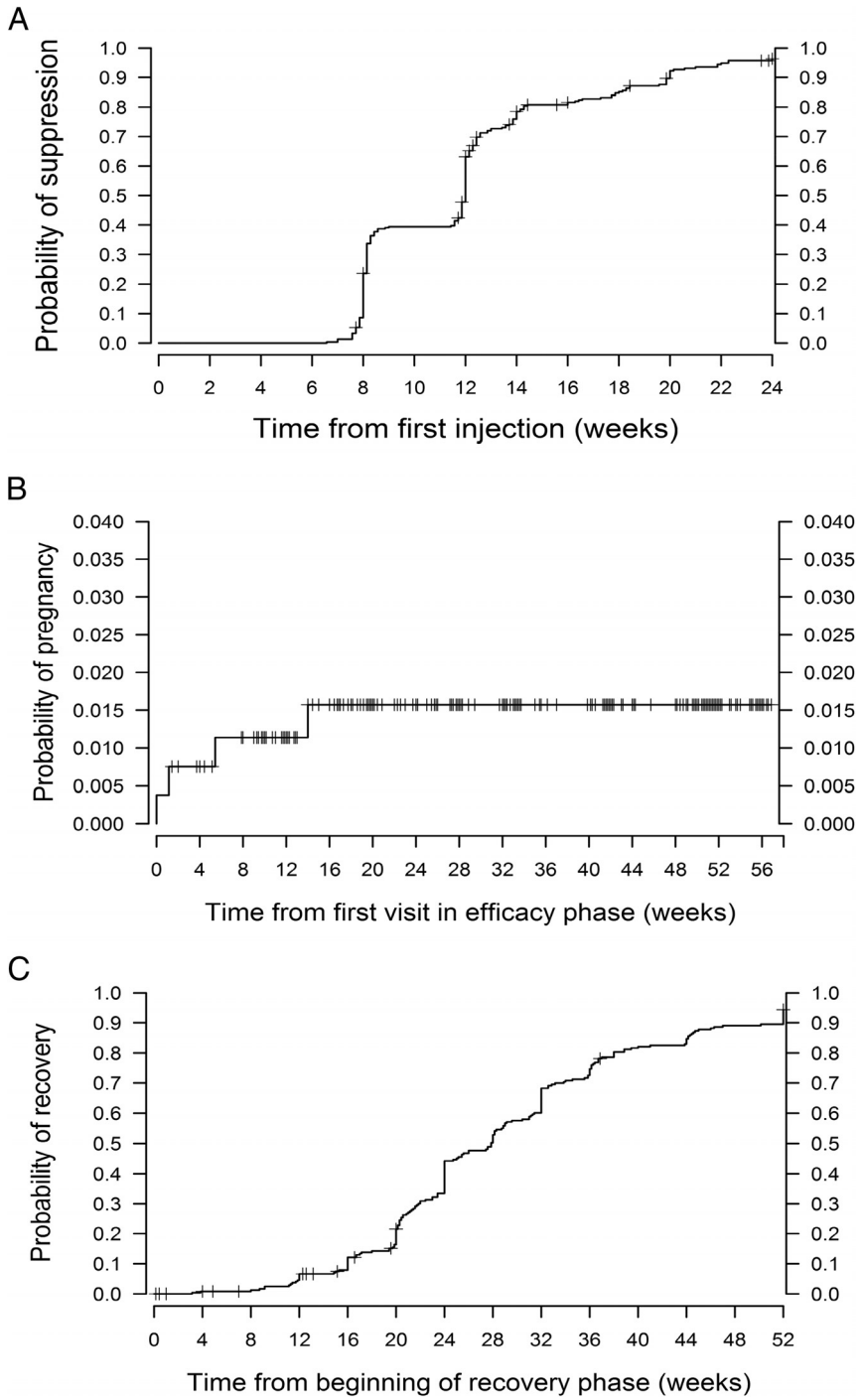

Figure 2. A, Cumulative rate of suppression of spermatogenesis (Kaplan-Meier method) up to 24 weeks after first injection (sperm concentration, ≤1 million/mL, twice on consecutive examinations; n = 274, see also Figure 1). B, Cumulative rate of pregnancy (Kaplan-Meier method) among those men transitioned to efficacy phase (n = 266, see also Figure 1). C, Reversibility of suppression of spermatogenesis (Kaplan-Meier method) among those men who had entered efficacy and also recovery phase (cumulative rate of recovery to at least 15 million/mL or total sperm count of at least 39.0 million per ejaculate; n = 247; 2 participants were excluded from this analysis because of missing semen analysis, see also Figure 1).

dose (assessed as possibly related) during the suppression phase, as well as 1 case of tachycardia with paroxysmal atrial fibrillation (assessed as possibly related) during the recovery phase. Ten other serious AEs were assessed as not being related to the study regimen. Twenty men discontinued the study due to product-related side effects. Of these 20, 6 men discontinued only for changes in mood, and 6 men discontinued for the following single reasons: acne, pain or panic at first injection, palpitations, hypertension, and erectile dysfunction. Eight men discontinued for more than 1 side effect, including multiple reasons related to changes in mood.

Acceptability questionnaires

Responses to key acceptability questions by male participants and female partners demonstrated high rates of satisfaction with the method of contraception applied in this study (Table 3). Most of the couples would use a method of contraception like this with highest positive response rates of 87.9% for male participants and 87.5% for female partners at the beginning of efficacy phase of this trial (Table 3).

Discussion

The present multicenter study demonstrates that repeat injections of the progestogen NET-EN when administered along with injections of the androgen TU at 8-week intervals lead to a near-complete suppression of spermatogenesis and effective maintenance of suppression of sperm concentrations less than or equal to 1 million/mL. The rate of recovery of spermatogenesis at 1 year after ceasing hormone injections is comparable with the rate when using other androgen or androgen-progestogen combinations for suppression of spermatogenesis (20). The number of couples completing the efficacy phase was lower than planned because of the early termination of injections. Nevertheless, the contraceptive efficacy is high, especially when compared with other reversible methods available for men, and is comparable with the efficacy of female oral contraceptive methods, as typically used (21, 22).

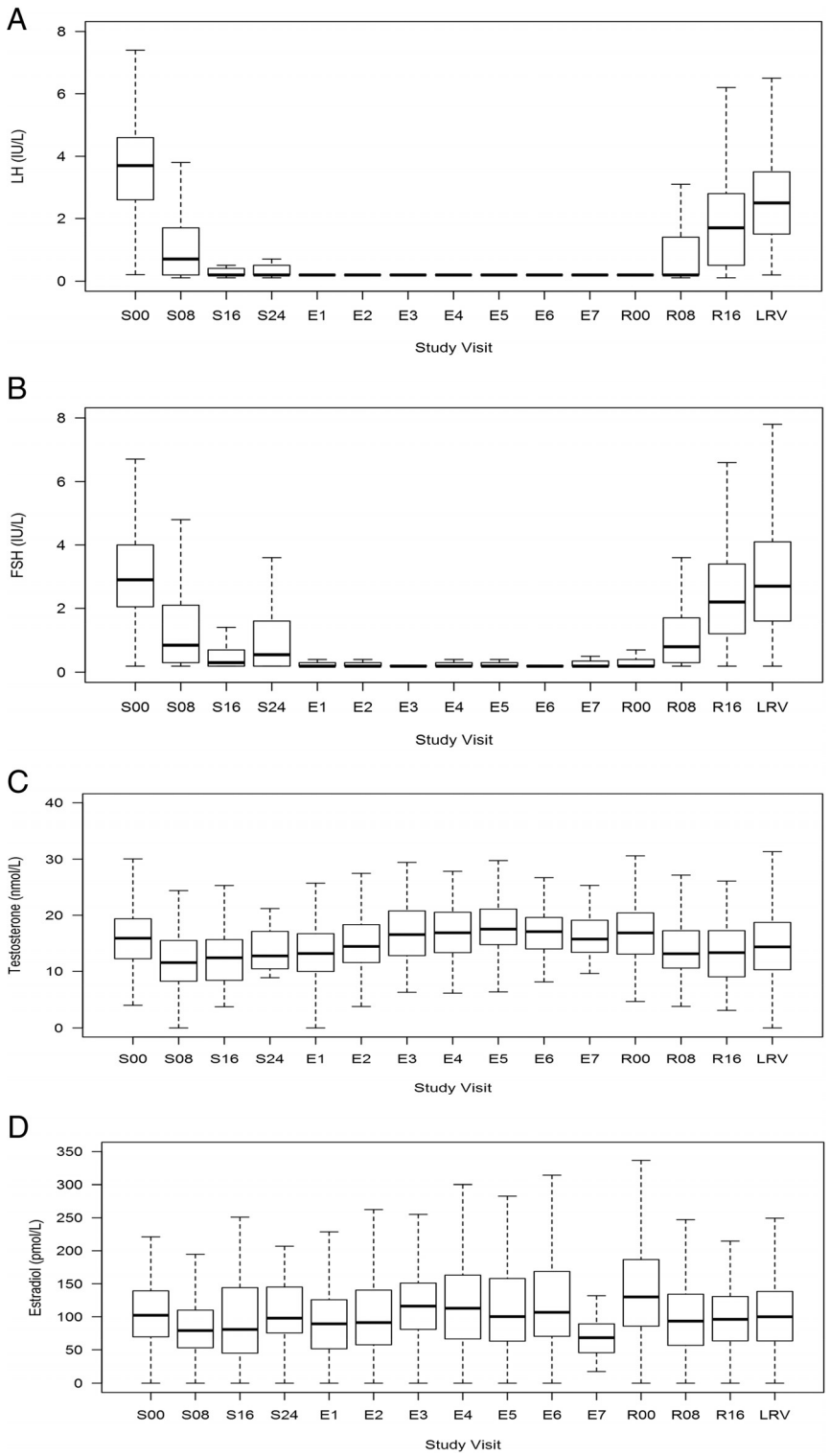

Figure 3. Box-and-whiskers plot of serum concentrations of LH (A), FSH (B), testosterone (C), and estradiol (D) during the study course. S00, first study visit in suppression phase; S08–S24, study visits after 8–24 weeks in suppression phase; E1–E7, study visits for hormone injections in efficacy phase every 8 weeks; R00, beginning of recovery phase; R8–R16, study visits after 8 and 16 weeks, respectively, in recovery phase; LRV, last recovery phase visit.

Clinical examinations and laboratory analyses did not reveal any unexpected untoward findings in this study. However, the frequency of reported moderate and severe mood disorders including depression heightens awareness of the potential behavioral effects that this combination regimen may have on some individuals. It is well known from other trials of hormonal regimens in men (which tested suppression of spermatogenesis but not contraceptive efficacy) that AEs are reported frequently in these long-term studies, even in a placebo group (23). That being said, 2 independent safety committees, the DSMC established by the sponsors and the WHO/RHR RP2, came to different conclusions on the safety of the regimen, which resulted in early termination of the study injections. Contraceptive efficacy studies cannot involve placebo groups for obvious ethical reasons. Therefore, a definitive answer as to whether the potential risks of this hormonal combination for male contraception outweigh the potential benefits cannot be made based on the present results.

As noted, there appeared to be study site differences in the number of AE reports, including those AEs related to changes in mood, sexual interest, and injection site pain. Although these AEs were not unexpected, particularly injection site pain with a multiple injection dosing regimen, the frequency of the mood disorders at the Indonesian center, for example, was unusually high, as compared with reports of similar AEs from earlier studies (10–12). These are considered real differences, given the uniformity of study instruments (AE forms) and training of all investigators.

It cannot be excluded that some of the AE reported on mood could be due to levels of serum testosterone below the reference range for some participants at least at the end of the injection intervals after the first TU plus NET-EN injections (see Figure 3C and Supplemental Table 1). However, the lack of a placebo-treated control group and the different time points in the suppression phase for assessment of AE and serum hormones, respectively, does not

Table 2. AEs in Men Assessed as Being Possibly, Probably, or Definitely Related to the Study Products and Reported at Least 5 Times

AE Preferred Term	Number of Participants Reporting AEs (% of 320 Participants)	Number of AE (≥5) out of 913 Total Reported AEs	Relation to Study Products			Severity		
			Yes Possible	Yes Probable	Yes Definite	Mild	Moderate	Severe
Acne	147 (45.9)	197	84	104	9	178	18	1
Injection site pain	74 (23.1)	103	3	20	80	98	4	1
Sexual disturbances								
Libido increased	122 (38.1)	124	11	50	63	109	12	3
Libido decreased	13 (4.1)	13	11	2	0	11	2	0
Mood disorders								
Emotional disorder	54 (16.9)	65	8	41	16	63	2	0
Mood altered/mood swings	15 (4.7)	19	12	7	0	16	3	0
Hostility	12 (3.8)	12	4	7	1	12	0	0
Depressed mood/depression	9 (2.8)	9	6	3	0	2	5	2
Aggression	6 (1.9)	8	6	2	0	6	2	0
Affective disorder	5 (1.6)	5	4	1	0	4	1	0
Musculoskeletal disorders								
Myalgia	52 (16.3)	71	5	39	27	71	0	0
Musculoskeletal pain	14 (4.4)	14	0	0	14	14	0	0
Gynaecomastia	18 (5.6)	21	10	7	4	20	1	0
Headache	17 (5.3)	20	19	1	0	18	2	0
Hyperhidrosis	17 (5.3)	17	11	6	0	13	4	0
Increased appetite	16 (5.0)	16	11	4	1	16	0	0
Weight increased	12 (3.8)	12	7	4	1	11	1	0
Night sweats	9 (2.8)	9	6	2	1	6	3	0
Irritability	9 (2.8)	9	5	4	0	6	2	1
Pruritus	6 (1.9)	6	3	3	0	6	0	0
Testicular pain/discomfort	6 (1.9)	6	6	0	0	4	2	0
Procedural complication	5 (1.6)	5	1	3	1	4	1	0
Contusion	5 (1.6)	5	2	1	2	5	0	0
Fatigue	5 (1.6)	5	4	1	0	5	0	0
Totals	N/A	771	239	312	220	698	65	8

allow for the appropriate statistical analysis in this study. The still low levels of LH and testosterone at the end of the recovery phase might be due to the prolonged terminal elimination half-life of the progestogen preparation used in this study. Due to the complexity of pharmacokinetics of testosterone and progestogen levels and their interaction it might be that a modified injection schedule for TU and NET-EN administration could lead to fewer AE, especially on mood, in future studies on hormonal male contraception (24).

Table 3. Responses to Key Acceptability Questions by Male Participants and Partners

	S08	E00	R00	FV
In general, how satisfied are you with this method?				
Male participant				
Number of responses	299	265	273	271
Satisfied/very satisfied (%)	73.9	91.9	83.5	80.1
Neither satisfied nor dissatisfied (%)	24.4	16.6	12.5	14.8
Unsatisfied/very unsatisfied (%)	1.3	1.5	3.7	5.2
Female partner				
Number of responses		265	269	250
Satisfied/very satisfied (%)		79.6	81.8	78.0
Neither satisfied nor dissatisfied (%)		19.6	13.4	16.4
Unsatisfied/very unsatisfied (%)		0.8	4.5	5.6
Would you use a method of contraception like this?				
Male participant				
Number of responses	299	265	273	271
Yes (%)	84.6	87.9	81.7	82.3
No (%)	1.3	1.1	5.1	5.2
Not sure/undecided (%)	14.0	10.9	13.2	12.5
Female partner				
Number of responses		265	269	250
Yes (%)		87.5	80.3	76.0
No (%)		0.8	5.6	6.4
Not sure/undecided (%)		11.7	14.1	17.2

S08, at 8 weeks of suppression phase; E00, beginning of efficacy phase; R00, beginning of recovery phase. Only the 2 key acceptability questions are reported here.

Despite the various AEs and clinically intensive study regimen, male participants and their partners found this combination to be highly acceptable at the end of the trial, even after being made aware of the early termination of the study intervention. More than 75% reported being at least satisfied with the method and willing to use this method if available, which supports further development of this approach (25).

This multicenter clinical study, the first large-scale, multicountry trial of a combination regimen of testosterone and progestogen to investigate contraceptive efficacy in men, provides an important reference for future efficacy and safety trials of male contraception. Such trials are urgently required to enable full assessment of the potential of this approach to new contraceptive product development (26, 27).

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