Daily Oral Administration of the Novel Androgen 11β-MNTDC Markedly Suppresses Serum Gonadotropins in Healthy Men

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Background: 11β-methyl-19-nortestosterone (11β-MNT) is a modified testosterone (T) with androgenic and progestational activity. A single oral dose of the prodrug, 11β-MNT dodecylcarbonate (11β-MNTDC), was well tolerated in healthy men.

Methods: We conducted a randomized, double-blind study at 2 academic medical centers. 42 healthy men (18–50 years) were randomized to receive oral placebo or 11β-MNTDC, 200 or 400 mg daily, for 28 consecutive days. Primary outcome (safety and tolerability) measures were assessed twice per week. Subjects underwent serial blood sampling over 24 hours on days 1 and 28 to assess secondary outcomes: pharmacokinetics (serum drug concentrations); pharmacodynamics of 11β-MNTDC (serum sex steroids and gonadotropins); and mood and sexual function (via validated questionnaires).

Results: There were no serious adverse events. No participants discontinued because of an adverse event or laboratory test abnormality. 11β-MNTDC resulted in a dose-related increase in serum 11β-MNTDC and 11β-MNT concentrations sustained over 24 hours. Administration of 11β-MNTDC resulted in a marked suppression of serum gonadotropins, T, calculated free T, estradiol, and SHBG over the treatment period ($P < 0.01$). Adverse effects that may be related to 11β-MNTDC included weight gain, acne, headaches, fatigue, and mild mood changes, with 5 men reporting decreased libido and 3 decreased erectile/ejaculatory function. Serum low-density lipoprotein cholesterol, weight (~2 kg), hematocrit, and hemoglobin increased and serum high-density lipoprotein cholesterol decreased in both 11β-MNTDC groups.

Conclusion: Daily oral 11β-MNTDC for 28 days in healthy men markedly suppressed serum gonadotropin and T concentrations without serious adverse effects. These results warrant further evaluation of 11β-MNTDC as a potential male oral contraceptive. **(*J Clin Endocrinol Metab* 105: e835–e847, 2020)**

Key Words: androgen, progestin, gonadotropins, testosterone suppression, male hormonal contraception

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

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Received 28 October 2019. Accepted 23 January 2020.
First Published Online 24 January 2020.
Corrected and Typeset: 29 February 2020

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Presented in part at the 101st Annual Meeting of the Endocrine Society, ENDO2019, New Orleans, LA.

Abbreviations: 11β-MNT, 11β-methyl-19-nortestosterone; 11β-MNTDC, 11β-methyl-19-nortestosterone dodecylcarbonate; AUC, area under the curve; Cavg, average concentration over 24 hours; CI, confidence interval; Cmax, maximum concentration; DMA, dimethyl-19-nortestosterone; E2, estradiol; T, testosterone; t1/2, half-life; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLOQ, lower limits of quantification; PHQ-9, Patient Health Questionnaire-9

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It is estimated that 44% of pregnancies worldwide were unintended from 2010 to 2014 (1). The overall rate of unplanned pregnancy remains high (1). Unintended pregnancies remain a major public health concern and source of health care costs (2). Clearly, there are unmet contraceptive needs. Worldwide, nearly 25% of contraceptive use requires male cooperation (condoms 8%, withdrawal 3%, fertility awareness 3%, vasectomy 2%) (3); however, these methods are associated with high failure rates (coitally dependent methods) or lack of reversibility (vasectomy). Truly reversible and effective male hormonal contraceptive methods are in active development (4, 5).

Local testosterone production within the testes maintains testicular testosterone concentrations at levels that are higher than those in serum, with the high local testosterone concentrations supporting spermatogenesis (6). Multiple contraceptive efficacy studies have demonstrated that injectable testosterone alone or in combination with a progestin results in approximately 95% overall contraceptive efficacy. Exogenous testosterone administration with and without a progestin acts via a negative feedback on the hypothalamus and pituitary to suppress serum gonadotropins resulting in suppression of testicular testosterone production below a threshold needed to support spermatogenesis. If the inhibition is maintained by a progestin, exogenous replacement of testosterone is necessary for normal androgen-dependent functions other than sperm production (7). This progestin-testosterone combination bypasses the challenges of testosterone-only regimens that require supraphysiologic doses of testosterone for contraceptive efficacy (8, 9) and improves the rapidity and reliability of sperm suppression compared with androgens alone (7). Oral testosterone undecanoate is safe, available, and approved in many countries (including the United States), but requires ingestion 2 to 3 times daily, a regimen that is not feasible for a contraceptive either alone or in combination with an oral progestin (10–12). A study of 7 men administered oral testosterone undecanoate capsules 3 times per day was ineffective in suppressing spermatogenesis (10). Men from many countries in survey studies have indicated a preference for an oral method of contraception compared with gels/creams, injections, or implants (13, 14), but the feasibility and acceptability of an oral contraceptive pill for men have not been ascertained.

11β-methyl-19-nortestosterone dodecylcarbonate (11β-MNTDC) is a candidate male hormonal contraceptive. This novel androgen is an orally bioavailable prodrug of the active metabolite 11β-methyl-19-nortestosterone (11β-MNT). 11β-MNT is a modified testosterone that is structurally and functionally similar to dimethandrolone (7α,11β-dimethyl-19-nortestosterone [DMA]), another oral androgen with progestational effects that is under development as an oral male birth control method (15–17). 11β-MNT binds avidly to the androgen receptor, greater than 10-fold more avidly than 5α-dihydrotestosterone, and in transactivation assays for 11β-MNT androgenic activity was 30-fold more potent than 5α-dihydrotestosterone (18). Preclinical studies demonstrate that when 11β-MNTDC is administered to castrated rats, gonadotropins are suppressed, whereas prostate and seminal vesicle weights and lean body mass are maintained (19). In contrast to oral 17-alkylated testosterone derivatives such as 17α-methyltestosterone, 11β-MNTDC does not appear to be hepatotoxic (20, 21). We previously reported that single oral doses of 11β-MNTDC, up to 800 mg, were safe and well-tolerated in healthy men, and led to reversible, dose-dependent suppression of testosterone concentrations at doses of 200 mg or greater when administered with food. These results suggest that 11β-MNTDC may offer the convenience of single daily dosing (18). Based on these results and encouraging data from a parallel study of oral DMAU (18, 22, 23), we tested the hypothesis that 11β-MNTDC, administered orally with food daily for 28 days, would be safe and well tolerated and would reversibly suppress the hypothalamic-pituitary-testis axis.

Research Participants and Methods

Research participants

We recruited healthy men, 18 - 50 years old. Inclusion criteria included good general health and normal reproductive function while exclusion criteria included significant medication use or chronic medical conditions (24). The study was conducted by the National Institute of Child Health and Human Development Contraceptive Clinical Trials Network at participating clinical sites at The Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA, and the University of Washington, Seattle, WA, with statistical support, clinical coordination, and monitoring by Health Decisions (Durham, NC). The respective institutional review boards approved the study. All participants provided written informed consent before any study procedures.

Investigational drug

11β-MNTDC was manufactured by Ash Stevens, LLC (Riverview, MI) and formulated in castor oil/benzyl benzoate (70:30) as capsules containing 100 mg of active drug under Good Manufacturing Practices by SRI International (Menlo Park, CA). Placebo capsules

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in castor oil/benzyl benzoate were also manufactured by SRI International.

Study design and procedures

A total of 42 men were randomized to receive placebo or 11β-MNTDC (200 mg or 400 mg) daily for 28 days. For each dosage, 5 men received placebo and 15 men received active drug. Randomization was done using a 3:1 ratio (active: placebo) using a fixed block size and was stratified by site. Subjects were recruited in a dose-escalation manner, with a safety assessment midway through a dosage group before finishing the dose group and proceeding to the next higher dosage (24). On days 1 and 28 (with a +2-day window), participants were admitted to a clinical research unit for a 24-hour pharmacokinetic study. They underwent observed dosing with breakfast containing 25 to 30 g of fat at 0 hours. Hourly vital signs and serial blood sampling for serum 11β-MNTDC, 11β-MNT, and hormones were obtained at baseline (-0.5, 0 hours), then 1, 2, 4, 6, 8, 12, 18, and 24 hours. Electrocardiograms were performed 4 to 6 hours after dosing and before discharge from the clinical research unit the following morning. Participants were seen twice a week between days 1 and 28 for safety assessments and drug accountability. Blood draws to measure trough concentrations of serum 11β-MNTDC, LH, follicle stimulating hormone (FSH), total testosterone (T), calculated free T (25), estradiol (E2), and SHBG were obtained at each of these on-treatment visits and also at 48 (day 30) and 72 hours (day 31) after the last dose. Additional samples were drawn on a visit between days 49 and 56, and at an end of study visit, approximately 6 to 7 weeks after the last dose. Participants exited the study when all safety parameters, including vital signs, physical examination, laboratory tests, and semen analyses, were within normal reference ranges. Semen analyses, after 2 to 7 days of ejaculatory abstinence, were obtained at screening (twice) to determine baseline, at day 28, at a visit between days 49 and 56, and at study exit. At the end of study visit, if the semen analysis was not within the reference range for sperm concentration, motility, and morphology, semen was analyzed every 4 weeks until all parameters were within the normal range. Validated questionnaires, Patient Health Questionnaire-9 (PHQ-9) (26) and a 7-Day Psychosexual Daily Questionnaire (27, 28), were used to evaluate mood and sexual function, respectively, at baseline, end of treatment (day 28), and end of study.

Analytical methods

Safety laboratory tests were analyzed at the respective licensed clinical laboratory at each study site. All hormones were quantified centrally by the Endocrine and Metabolic Research Laboratory at The Lundquist Institute at Harbor-UCLA Medical Center using validated methods. Serum 11β-MNTDC, 11β-MNT, T, and E2 concentrations were measured using liquid chromatography-tandem mass spectrometry after solid or liquid phase extraction using previously described assays developed for the analysis of 11β-MNTDC, its active metabolite, and other steroids (18, 29, 30). The intra-assay and inter-assay precision were less than 13% for 11β-MNTDC, 11β-MNT, T, and E2. The accuracy ranged from 95% to 110% spanning different concentrations within the relevant concentrations for each compound. The lower limits of quantification (LLOQ) for T, E2, 11β-MNTDC, and 11β-MNT were 2 ng/dL, 2 pg/mL, 1 ng/mL, and 0.5 ng/mL, respectively (24). Serum LH, FSH, and SHBG were quantified by an immuno-chemiluminescent assay using a Roche Platform (Cobas e411). The LLOQ for serum LH and FSH were 0.1 IU/L and SHBG was 2 nmol/L. The within-run and between-run variation was <6% (18). Semen analysis was performed at the local laboratories of each study site, in accordance with the WHO Semen Manual (5th Edition, 2010) (31).

Primary and secondary outcomes

The primary endpoints for the clinical study were the safety and tolerability of oral 11β-MNTDC dosed at 200 mg or 400 mg daily for 28 days in men. This was assessed in the "all-treated population," participants who received at least 1 dose of the investigational drug. Analyses included the number of men with each adverse event and the absolute change in the numeric value of certain safety parameters from baseline to day 28. Vital signs included pulse rate, blood pressure, and weight; laboratory tests included complete blood count, electrolytes, renal function, liver function, fasting lipids, and prostate-specific antigen; electrocardiogram included QTc interval.

The secondary endpoints included 11β-MNTDC and 11β-MNT pharmacokinetics, pharmacodynamics, and quantification of mood and sexual function. The pharmacokinetics of 11β-MNTDC and 11β-MNT were assessed by 24-hour serum drug concentrations on days 1 and 28. The pharmacokinetic parameters over 24 hours were calculated as area under the curve of serum 11β-MNTDC/11β-MNT concentrations estimated by 10 timed blood samples over 24 hours for each dose of 11β-MNTDC and computed using the trapezoid method (AUC_{0-24}), average concentration over 24 hours (Cavg), minimum concentration, maximum concentration (Cmax), time to reach maximum concentration, and half-life ($t_{1/2}$). The $t_{1/2}$ was calculated assuming exponential decay when there were at least 3 measurable

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concentrations after Cmax. Trough concentrations of 11β-MNTDC were measured throughout the 28 days and 48 and 72 hours after the last dose on day 28. The pharmacodynamics of 11β-MNTDC were evaluated by monitoring the suppression of serum LH, FSH, T, calculated free T, E2, and SHBG throughout the 28 days of treatment and during follow-up. Secondary outcomes were analyzed using the "efficacy-evaluable population," defined as all treated participants who received at least 21 days of study drug and during that period used at least 90% of the investigational drug (determined by the participants diaries and the number of capsules returned).

Statistical analyses

All analyses were performed using SAS (version 9.4, Cary, NC). All participants receiving placebo across the doses were pooled into a single treatment group. With 30 men receiving active treatment, there is at least 80% power to detect grade 3 safety abnormalities occurring in approximately 5% of men; in each dosage group of n = 15 men, there is at least 80% power to detect grade 3 safety abnormalities occurring in approximately 20% of men. Grade 3 safety abnormalities (severe) are defined in the protocol as events where the participant was incapacitated by the event and unable to perform normal activities and the adverse event was medically significant but not immediately life threatening. The incidence rate of adverse events was calculated for each treatment group. The number and percentage of participants with FSH and LH ≤ 1.0 mIU/mL (both must meet the criteria at the same visit) at any time after dosing were summarized by treatment group. Safety parameters are presented as means and 95% confidence intervals (CIs) and analyzed using a repeated measures model including parameters, time (days 0 and 28), dose group (0, 200, and 400 mg), dose × time interaction, participants' baseline values, and study center. All hormone and drug concentrations are presented as medians and 95% CI in the graphs and changes from baseline analyzed by nonparametric methods (Wilcoxon signed-rank test). Generalized linear models using a binomial response were estimated using generalized estimating equations to assess the effect of dose on the proportion of individuals who suppressed both FSH and LH to predetermined thresholds (≤1.0, 0.5, and 0.1 IU/L) across multiple timepoints. Pearson Product-Moment correlations are calculated to explore the relationship between drug levels (AUC on day 28, Cavg on day 28, and average trough concentrations while on treatment from days 4 to 28, of MNTDC, and MNT) with analytes T, calculated free T, E2, FSH, LH, and SHBG concentrations.

Results

Study participant demographics

A total of 72 participants were screened, 30 were excluded; 42 received at least 1 dose of study medication (all-treated population); and 36 completed the entire study including recovery. Of the 6 who did not complete the entire study, 4 completed through the treatment period including the last pharmacokinetics study but did not complete follow-up in recovery; 1 completed 23 days of treatment and met efficacy evaluable criteria; and 1 did not meet efficacy evaluable criteria (Fig. 1). Baseline characteristics of the participants are provided in Table 1 and none of the parameters were significantly different among the participants in the 3 treatment groups.

Safety and tolerability

Overall, 11β-MNTDC was well tolerated; there were no serious adverse events and none of the participants discontinued because of an adverse event. The most common adverse events, occurring in >5% of the all-treated participants, are listed in Table 2. Overall, a greater proportion of participants in the active treatment groups reported adverse events compared to placebo, including acne, headaches, fatigue, mood changes, subjective weight gain, decreased libido, and decreased erectile/ejaculatory function (the latter only in the 200-mg group). All adverse events were categorized as mild or moderate. The other adverse events (including nausea, elevated lipids and transaminases, folliculitis, seborrhea, abnormal hair growth, and elevated diastolic blood pressure) occurred in less than 5% of all participants, more in those on drug compared with placebo. A few participants had an upper respiratory tract

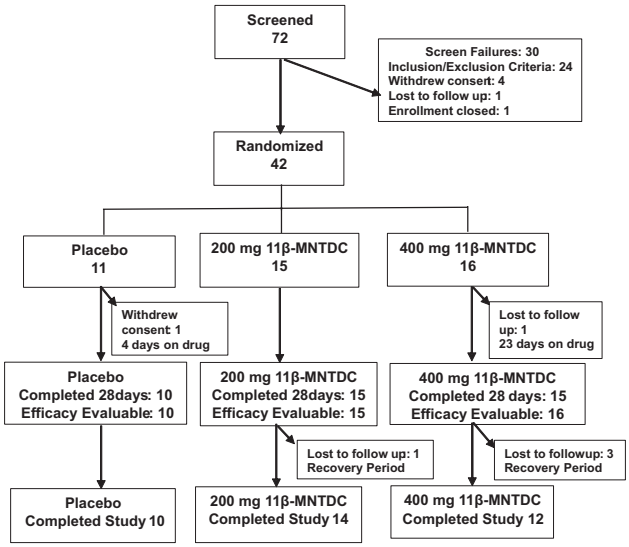

Figure 1. Disposition of participants in the trial.

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Table 1. Baseline Characteristics of All Treated Participants

	Placebo (n = 11)	200 mg (n = 15)	400 mg (n = 16)	*P* Value
Race				
Caucasian	7 (63.6)	6 (40.0)	5 (31.3)	0.716
Black	1 (9.1)	2 (13.3)	4 (25.0)	
Asian	2 (18.2)	5 (33.3)	4 (25.0)	
Other	1 (9.1)	2 (13.3)	3 (18.8)	
Ethnicity				
Hispanic	3 (27.3)	6 (40.0)	5 (31.3)	0.778
Non-Hispanic	8 (72.7)	9 (60.0)	11 (68.8)	
Age (year)	25 (21.0, 33.0)	33 (26.0, 36.0)	27 (22.0, 36.0)	0.247
Weight (kg)	74 (66.6, 87.5)	86.8 (75.8, 92.8)	77.5 (67.4, 86.6)	0.126
BMI (kg/m^2)	23.2 (21.1, 26.5)	25.6 (23.8, 29.3)	25.5 (24.2, 27.8)	0.232
Serum T (ng/dL)	445.0 (369.0, 557.0)	457.0 (395.0, 570.0)	531.5 (434.0, 599.5)	0.439
Serum FSH (IU/L)	3.3 (2.5, 5.3)	2.8 (1.7, 5.2)	4.0 (3.3, 5.9)	0.661
Serum LH (IU/L)	4.8 (3.9, 6.5)	4.9 (3.6, 6.2)	5.4 (4.9, 7.1)	0.271
Sperm concentration (million/mL)	71.4 (41.0, 133.8)	47.3 (32.9, 59.0)	50.5 (29.4, 136.1)	0.293
Total sperm count/ejaculate (million)	189 (63.0, 250.0)	143 (53.0, 177.0)	139.5 (71.0, 277.5)	0.514

Categorical variables (race, ethnicity) displayed as count (percent of treatment group total).
Continuous variables (age, weight, BMI, Total testosterone, FSH, LH, sperm concentration, and total sperm count) displayed as median (25th percentile, 75th percentile).
BMI, body mass index; T, testosterone.

Table 2. Adverse Events in >5% of All Treated Participants

		11β-MNTDC		
	Placebo (n = 11)	200 mg (n = 15)	400 mg (n = 16)	Total (n = 31)
Headache	**2 (18%)**	3 (20%)	6 (38%)	**9 (29%)**
Upper respiratory tract infection	**3 (27%)**	3 (20%)	4 (25%)	**7 (23%)**
Acne	**1 (9%)**	3 (20%)	2 (13%)	**5 (16%)**
Mood changes	**1 (9%)**	3 (20%)	1 (6%)	**4 (13%)**
Fatigue	**0 (0%)**	1 (7%)	3 (19%)	**4 (13%)**
Subjective weight increased	**0 (0%)**	1 (7%)	2 (13%)	**3 (10%)**
Libido decreased	**0 (0%)**	3 (20%)	2 (13%)	**5 (16%)**
Decreased erectile/ejaculatory function	**0 (0%)**	3 (20%)	0 (0%)	**3 (10%)**

All adverse events were considered possibly, probably, or related to study medications except upper respiratory tract infections. The columns indicating placebo and treatment groups are highlighted in bold.
11β-MNTDC, 11β-methyl-19-nortestosterone dodecylcarbonate.

infection during the study; however, there was no difference between placebo (27%) and active treatment groups (23%).

Table 3 shows the baseline and changes in safety parameters in the 11β-MNTDC treated groups compared with the placebo group. Overall, there were no clinically relevant changes in 24-hour average blood pressure, creatinine, or liver enzymes in the treatment groups compared with placebo. In the men dosed with 11β-MNTDC, the QTc interval reduced from their baseline, but not in men who received placebo (mean change: placebo 7.3 ms, 200 mg -9.9 ms, 400 mg -10.1 ms, $P < 0.05$ for both dose groups compared with placebo) (Table 3). The mean change in ALT (+3.9 IU/L) across the 400-mg dosage group was significantly higher than the 200-mg group (-2.1 U/L, $P = 0.04$) but not different from the placebo (-0.5 U/L, $P = 0.14$). Creatinine increased slightly in both treatment groups (+0.10 and + 0.08 mg/dL) compared with placebo (-0.02 mg/dL, $P < 0.001$ and $P < 0.01$, respectively).

There was a significant dose-related increase in weight from baseline in the 400-mg group (2.0 kg, $P < 0.01$ compared with placebo), whereas the participants in the 200-mg group had an increase in weight (1.2 kg) that was not statistically significant compared with placebo ($P = 0.13$). There were statistically significant increases in hematocrit and low-density lipoprotein cholesterol (LDL-C) and decreases in high-density lipoprotein cholesterol (HDL-C) in both dosage groups compared with placebo (Table 3). The changes in HDL-C and LDL-C did not correlate with increases in weight (data not shown).

Depression (PHQ-9) scores did not change with active treatment. On a scale of 0 to 7, sexual desire score was reduced in the 400-mg group only (mean change -1.1, $P = 0.01$) compared with placebo, but there were

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Table 3. Baseline and Changes from Baseline in Safety Laboratory Parameters in All Treated Participants (Mean, 95% CI)

Parameter		Placebo (n = 11)	200 mg (n = 15)	*P* Value 200 mg vs Placebo	400 mg (n = 16)	*P* Value 400 mg vs Placebo	*P* Value 200 vs 400 mg
Weight (kg)	Baseline	75.6 (68.9–82.3)	83.9 (77.9–99.0)		77.4 (71.3–83.6)		
	Mean change from baseline	0.5 (-0.4 to 1.3)	1.2 (0.8–1.6)	0.13	2.0 (1.4–2.6)	0.004[b]	0.03[a]
24-h average SBP (mm Hg)	Baseline	114.8 (108.4–121.2)	120.2 (114.6–125.8)		116.5 (111.8–121.2)		
	Mean change from baseline	-3.1 (-6.3 to 0.1)	-2.3 (-7.0 to 2.4)	0.79	0.3 (-3.1 to 3.7)	0.14	0.36
24-h average DBP (mm Hg)	Baseline	68.8 (62.8–74.8)	71.4 (66.9–75.9)		68.3 (64.7–71.9)		
	Mean change from baseline	-0.6 (-5.0 to -3.7)	0.6 (-1.9 to 3.0)	0.63	1.2 (-1.9 to 4.4)	0.50	0.74
QTc on electrocardiogram (ms)	Baseline	400.9 (383.1–418.7)	400.1 (390.9–409.4)		394.4 (382.7–406.2)		
	Mean change from baseline	7.3 (-4.7 to 19.3)	-9.9 (-19.7 to -0.2)	0.03[a]	-10.1 (-19.9 to -0.4)	0.03[a]	0.98
AST (U/L)	Baseline	20.5 (16.1–24.8)	21.1 (18.2–23.9)		20.0 (16.8–23.2)		
	Mean change from baseline	1.8 (-0.1 to 3.6)	-0.2 (-2.6 to 2.3)	0.20	3.8 (-0.4 to 8.1)	0.36	0.11
ALT (U/L)	Baseline	19.5 (12.6–26.5)	22.3 (15.9–28.6)		23.0 (13.5–32.5)		
	Mean change from baseline	-0.5 (-2.7 to 1.7)	-2.1 (-4.7 to 0.4)	0.32	3.9 (-1.3 to 9.0)	0.14	0.04[a]
Creatinine (mg/dL)	Baseline	0.92 (0.82–1.01)	0.88 (0.80–0.95)		0.93 (0.86–1.00)		
	Mean change from baseline	-0.02 (-0.07 to 0.03)	0.10 (0.07–0.14)	<0.001[c]	0.08 (0.03–0.12)	0.005[b]	0.33
HDL-C (mg/dL)	Baseline	48.4 (43.3–53.4)	50.1 (43.7–56.5)		47.1 (40.3–53.8)		
	Mean change from baseline	2.1 (-1.4 to 5.6)	-8.1 (-10.4 to -5.8)	<0.001[c]	-11.6 (-17.0 to -6.1)	<0.001[c]	0.237
LDL-C (mg/dL)	Baseline	99.2 (75.1–123.2)	89.6 (76.9–102.3)		89.4 (76.1–102.7)		
	Mean change from baseline	-4.4 (-13.9 to 5.1)	9.0 (2.9–15.0)	0.02[a]	23.2 (10.1–36.3)	<0.001[c]	0.06
Total cholesterol (mg/dL)	Baseline	164.7 (138.0–191.5)	154.5 (136.8–172.1)		153.3 (136.4–170.1)		
	Mean change from baseline	-0.2 (-9.4 to 9.0)	0.5 (-6.3 to 7.2)	0.91	11.7 (-2.6 to 26.0)	0.15	0.16
Hemoglobin (g/dL)	Baseline	14.7 (13.9–15.4)	14.0 (13.4–14.7)		14.6 (14.2–14.9)		
	Mean change from baseline	-0.2 (-0.7 to 0.2)	0.4 (0.1–0.7)	0.03[a]	0.3 (0.2–0.5)	0.03[a]	0.71
Hematocrit (%)	Baseline	43.1 (40.8–45.3)	41.6 (40.0–43.1)		43.1 (42.0–44.2)		
	Mean change from baseline	-0.5 (-1.9 to 1.0)	2.3 (1.0–3.7)	0.006[b]	1.3 (0.7–2.0)	0.03[a]	0.21
PHQ9 total score	Baseline	0.9 (0.0–1.8)	1.2 (0.3–2.1)		0.9 (0.0–1.8)		
	Mean change from baseline	0.2 (-1.3 to 1.7)	1.2 (0–2.4)	0.31	1.8 (0.6–3.0)	0.11	0.48
Overall sexual desire (Q1 PDQ)	Baseline	3.0 (2.2–3.8)	3.7 (2.7–4.6)		4.3 (3.4–5.2)		
	Mean change from baseline	0.5 (-0.4 to 1.3)	-0.2 (-1.0 to 0.5)	0.21	-1.1 (-1.8 to -0.4)	0.007[b]	0.09
Sexual activity (Q4 PDQ)	Baseline	2.4 (1.2–3.7)	2.4 (1.5–3.3)		2.4 (1.6–3.2)		
	Mean change from baseline	-0.2 (-0.9 to 0.6)	-0.4 (-1.1 to 0.2)	0.60	-0.4 (-1.0 to 0.2)	0.70	0.87

Data were analyzed by repeated measures models.
Means reported are least square means.
CI, confidence interval; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PDQ, Psychosexual Daily Questionnaire (measure of sexual function); PHQ9, Patient Health Questionnaire-9 (measure of depression); SBP, systolic blood pressure.
[a]$P < 0.05$; [b]$P < 0.01$; [c]$P < 0.001$.

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no significant changes in sexual activity. A change of ≥0.7 or in sexual desire score is considered clinically meaningful in older hypogonadal men (28, 32). Four of 5 men who complained of decreased libido had a decrease in sexual desire score of ≥0.7. The change in sexual desire in the 400-mg group did not correlate with average serum drug concentrations, serum testosterone or E2 levels, or changes in serum testosterone or E2 levels. The changes in the safety parameters did not show consistent statistical correlation with average trough serum 11β-MNTDC and 11β-MNT concentrations, Cmax, or AUC during the treatment period (data not shown).

Pharmacokinetics of 11β-MNTDC and 11β-MNT

Administration of 11β-MNTDC resulted in increases in serum 11β-MNTDC and 11β-MNT concentrations over 24 hours (Fig. 2). The pharmacokinetic data are shown in Table 4. The AUC, Cavg, and Cmax of 11β-MNTDC on day 28 were significantly higher in the 400-mg group compared with the 200-mg group suggesting a dose proportional increase in drug concentration. The median 11β-MNT AUC, Cavg, and Cmax, though higher in the 400-mg group compared with the 200-mg group, failed to reach statistical significance, likely due to the large between-participant variation. The AUC and Cavg of serum 11β-MNTDC were not significantly different on day 28 compared with day 1 (200 mg, $P = 0.599$; 400 mg, $P = 0.421$). In contrast, the AUC and Cavg of 11β-MNT were significantly higher on day 28 in the 200-mg group only ($P = 0.026$ and 0.037, respectively). Based on these data, the in vivo bioavailability (ratio of AUC of 11β-MNT to 11β-MNTDC X100) was 0.45% on day 1 and 0.72% on day 28. The mean serum level of 11β-MNTDC decreased by 83% and 92% at 48 and 72 hours, respectively, after 200 mg of 11β-MNTDC, and by 90% and 96% at 48 and 72 hours after 400 mg of 11β-MNTDC. The mean serum concentration of 11β-MNT decreased by 98% and 99% at 48 and 72 hours after 200 mg of 11β-MNTDC, and 92% and 100% after 400 mg of 11β-MNTDC. The $t_{1/2}$ of 11β-MNT was not significantly different in the 200-mg compared with the 400-mg group, nor were they significantly different on day 1 compared with day 28 (Table 4).

Pharmacodynamics: Suppression of LH, FSH, T, and E2

The increase in serum 11β-MNT was accompanied by a profound suppression of serum gonadotropins, T, calculated free T, E2, and SHBG over the treatment period (Fig. 3). Throughout the treatment period (days 4–28) and at day 28, serum LH, FSH, T, calculated free T, E2, and SHBG were significantly decreased in the treatment groups compared with placebo. There was a trend toward greater suppression of LH, FSH, T, E2, calculated free T, and SHBG concentrations in the 400-mg group compared with the 200-mg group throughout the treatment period and at day 28; however, none of the differences were significantly different between the doses (24).

In the 200-mg group, the average on-treatment trough concentrations across the treatment period (day 4 to 28) of serum T ($R^2 = -0.58$, $P = 0.02$) and calculated free T ($R^2 = -0.60$, $P = 0.02$) were significantly negatively correlated with trough serum 11β-MNT concentrations, but no correlation was seen with serum LH, FSH, or E2. In the 400-mg group, the average on-treatment trough concentrations of serum T ($R^2 = -0.74$, $P < 0.01$), calculated free T ($R^2 = -0.74$, $P < 0.01$), LH ($R^2 = -0.76$, $P < 0.01$), FSH ($R^2 = -0.59$, $P = 0.02$), and E2 ($R^2 = -0.53$, $P = 0.03$) were significantly negatively correlated with trough serum 11β-MNT concentrations (24).

Fig. 4 depicts the percentage (%) of men who had suppression of both LH and FSH to ≤ 1.0 and ≤ 0.5

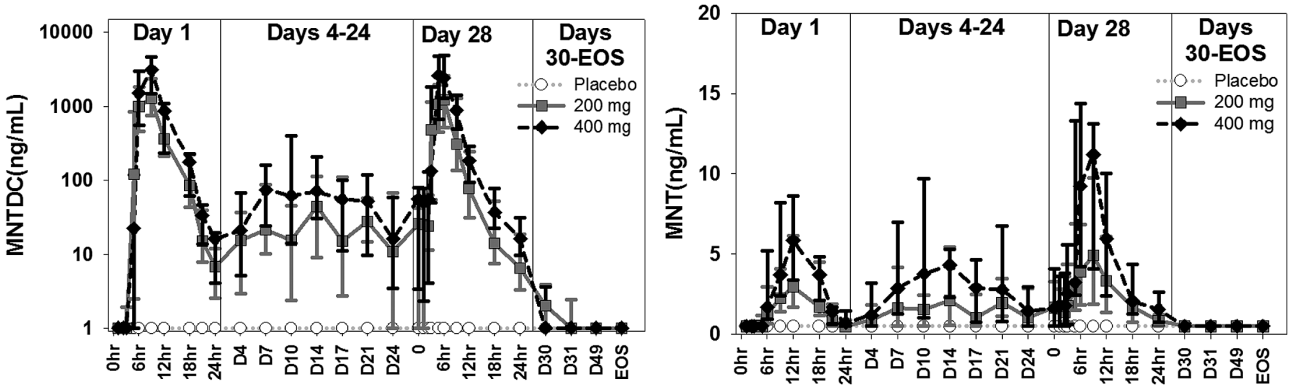

Figure 2. Serum concentrations of 11 β-MNTDC and MNT after oral administration of 0 (placebo), 200, and 400 mg 11 β-MNTDC for 28 days in healthy male volunteers. Twenty-four hour multiple blood sampling was performed on days 1 and 28 and trough concentrations were obtained in between the pharmacokinetic studies. Data are presented as medians and 95% CI. D, day; EOS, end of study

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Table 4. Twenty-Four Hour Pharmacokinetics for 11β-MNTDC and 11β-MNT on Days 1 and 28 in Efficacy Evaluable Population (Median, 95% CI)

		11β-MNTDC		
Parameter	**Day of Treatment**	**200 mg (n = 15)**	**400 mg (n = 16)**	**200 vs. 400 mg; *P* Value**
$AUC_{0–24}$	1	6914 (4839–13 417)	13171 (7748–33 160)	0.129
	28	8221 (3202–14 834)	18975 (7127–29 754)	0.033[a]
Cavg (ng/mL)	1	289 (201–559)	572 (322–1379)	0.129
	28	342 (133–618)	791 (296–1240)	0.033[a]
Cmax (ng/mL)	1	1760 (940–2590)	3160 (1480–5610)	0.122
	28	1620 (676–3320)	3790 (2610–6120)	0.015[a]
Cmin (ng/mL)	1	0 (0–1.9)	0 (0–0)	0.102
	28	5.8 (3.3–18.5)	12.9 (1.5–31.3)	0.371
Tmax (h)	1	6.0 (4.2–6)	6.0 (5.9–6.0)	0.828
	28	6.0 (4.0–6.0)	4.0 (4.0–6.0)	0.801
$t_{1/2}$ (h)	1	2.87 (2.40–3.24)	2.98 (2.57–3.21)	0.066
	28	3.04 (2.63–3.55)	2.94 (2.61–3.98)	0.454
11β-MNT				
Parameter	**Day of Treatment**	**200 mg (n = 15)**	**400 mg (n = 16)**	**200 vs. 400 mg *P* value**
$AUC_{0–24}$	1	28.8 (18.1–63.1)	63.9 (36.3–123.3)	0.151
	28	64.5 (25.1–109.9)	122.6 (48.8–199.1)	0.267
Cavg (ng/mL)	1	1.2 (0.8–2.6)	2.8 (1.5–5.1)	0.154
	28	2.7 (1.0–4.6)	5.1 (2.0–8.3)	0.262
Cmax (ng/mL)	1	2.9 (1.7–6.1)	7.3 (3.6–12.0)	0.108
	28	5.3 (1.9–9.7)	12 (4.2–14.8)	0.198
Cmin (ng/mL)	1	0 (0–0)	0 (0–0)	>0.999
	28	0.7 (0–1.2)	1.4 (0–2.2)	0.261
Tmax (h)	1	8.0 (6.0–8.0)	8 (7.9–8.0)	0.507
	28	8.0 (6.0–8.0)	6.3 (6.0–8.0)	0.829
$t_{1/2}$ (h)	1	5.08 (4.39–7.58)	4.78 (3.93–7.53)	0.191
	28	6.60 (4.72–10.22)	6.31 (5.58–7.97)	0.133

Data were analyzed using Wilcoxon signed-rank tests.
$AUC_{0–24}$, area under the curve estimated by the trapezoid method; Cavg, average serum concentrations over 24 h; Cmax, maximum concentration; Cmin, minimum concentration; Tmax, time to reach maximum concentration; t1/2, half-life.
[a] $P < 0.05$.

(preset thresholds) and ≤ 0.1 mIU/mL (LLOQ of assays). Overall (including data from all time points), none of the participants in the placebo group, 46.7% (7/15) participants in the 200-mg group and 66.7% (10/15) of the participants in the 400-mg group had gonadotropins suppressed to ≤ 1.0 IU/L at day 28 (Fig. 4). By applying the generalized estimating equations method that takes into account the dependency of data from the same subject at multiple timepoints, we found that a greater proportion of men in the higher 400-mg group suppressed both gonadotropins to prespecified thresholds compared with men in the lower 200-mg group ($P = 0.029$ for both LH and FSH suppressed to ≤ 1.0 mIU/mL, and $P = 0.017$ for both LH and FSH suppressed to ≤ 0.5 mIU/mL).

The sperm concentration was not significantly changed in any of the groups, consistent with the short duration of treatment (28 days).

Discussion

This study demonstrates that oral 11β-MNTDC taken at dosages of 200 and 400 mg for 28 days is tolerated by healthy men. There were no serious adverse events, no participant discontinued because of an adverse event or effect, and treatment-related adverse events were anticipated and generally mild. The higher dose of 11β-MNTDC resulted in a greater proportion of men suppressing gonadotropins to predetermined thresholds thought to be consistent with effective male hormonal contraception (33) and there was no clear dose-related pattern in the incidence of the most common adverse events. Importantly, there were no statistically significant changes in markers of liver injury (i.e., elevations of AST, ALT), suggesting that oral 11β-MNTDC in humans, as in preclinical studies, is very unlikely to be associated with liver toxicity, as opposed to oral alkylated androgens such as methyltestosterone (20, 21). This phase 2 study was powered to detect safety abnormalities that occur in more than 10% of healthy participants; thus, the numbers are too small to detect changes that may occur in a smaller minority of men. None of the adverse events required treatment. Inclusion of a placebo group in future studies will be important in further evaluating the side effect profile of 11β-MNT.

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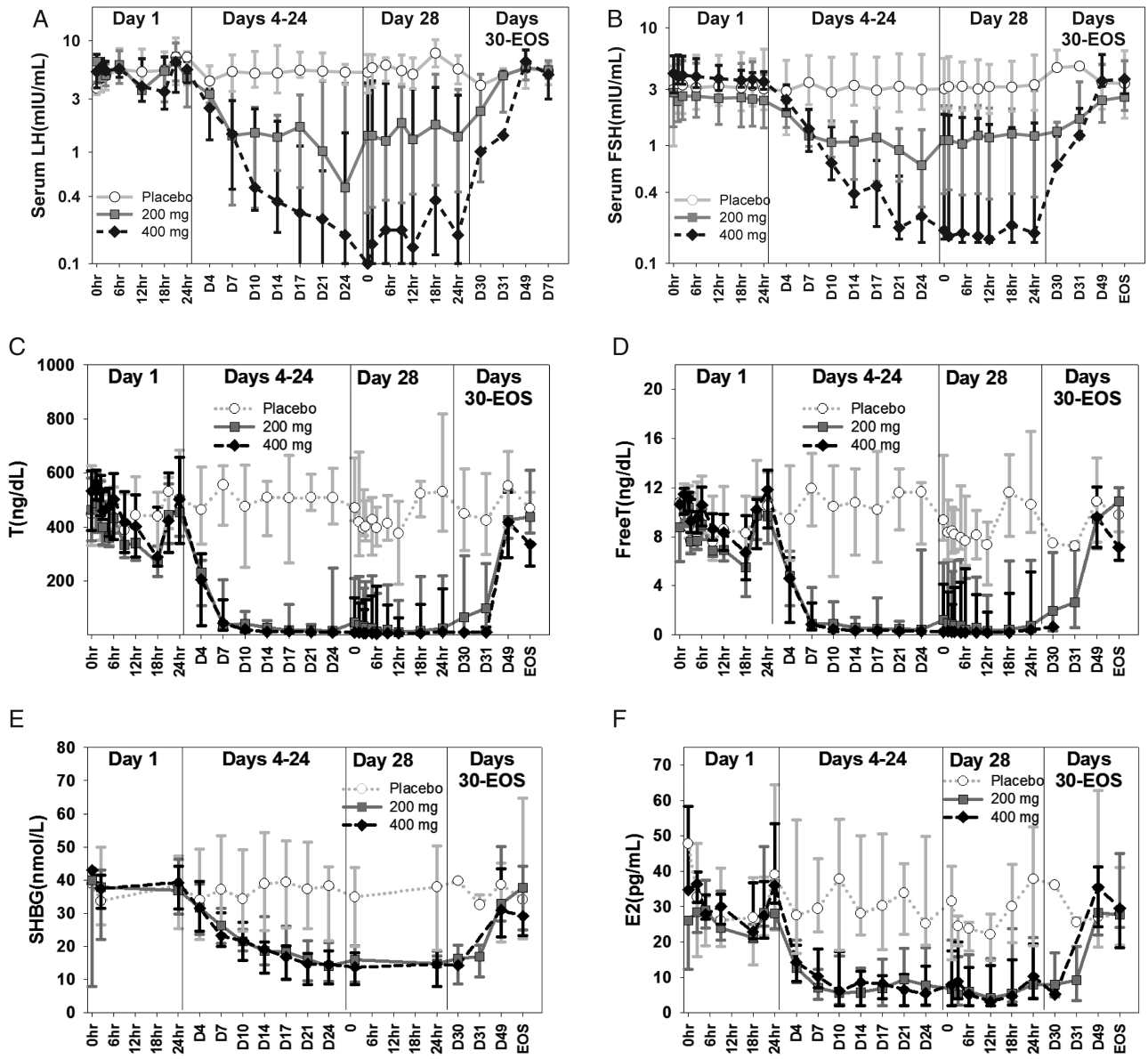

Figure 3. (A) Serum LH, (B) FSH, (C) T, (D) calculated free T, (E) SHBG, and (F) E2 were suppressed from day 4 to 28 and returned to baseline concentrations at day 49. LH and FSH are displayed on a log scale to enhance visualization of the low values. Dotted lines represent the reference ranges of these hormones. D, day; EOS, end of study

No significant changes in blood pressure or heart rate were observed. The QTc interval decreased, a known effect of androgen administration, but the observed magnitude was not considered to be clinically meaningful (34, 35). Creatinine increased slightly in both treatment groups; the 95% CI was 0.07 to 0.14 and 0.03 to 0.12 mg/dL in the 200- and 400-mg groups, respectively. Increased creatinine may be due to androgen-induced increases in muscle mass (36); however, creatinine increases are not a common effect of exogenous androgens (37). Future studies evaluating body composition in conjunction with longer term administration of 11β-MNT are planned to further explore the potential impact of 11β-MNT on renal function.

The detailed pharmacokinetics of 11β-MNTDC and 11β-MNT on day 1 were similar to those observed in our prior reported single-dose study (18). There was a trend towards higher Cavg on day 28 compared with day 1 with both 11β-MNTDC and 11β-MNT, reaching significance only for 11β-MNT at the 200-mg group. Trough concentrations of 11β-MNTDC or 11β-MNT were similar during the entire treatment period from days 4 to 28 (Fig. 2), indicating no significant drug accumulation when administered daily over 28 days. The in vivo conversion of 11β-MNTDC to 11β-MNT was 0.45% on day 1, comparable to results obtained with single doses (18), and increased to 0.72% on day 28, possibly because of upregulation of endogenous

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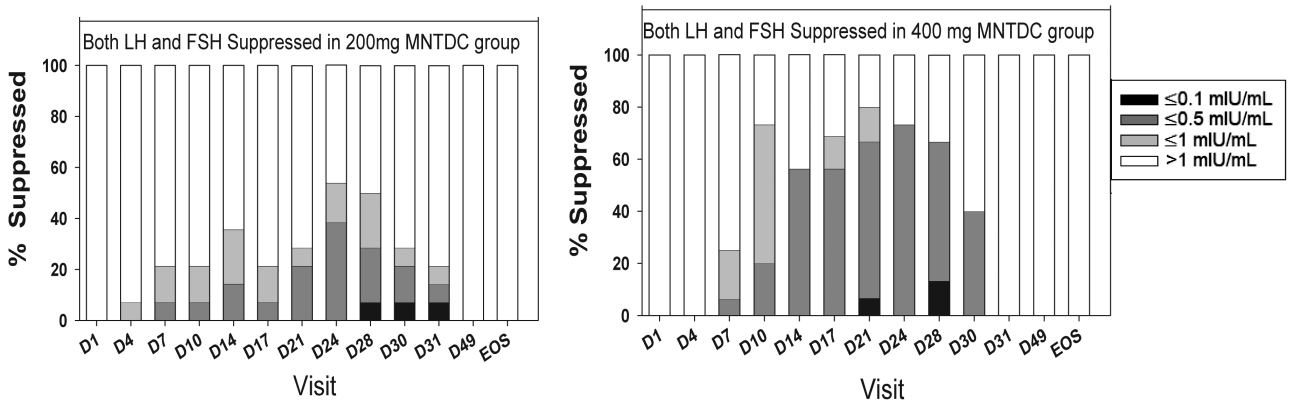

Figure 4. Percent of men that showed suppression of both serum LH and FSH from days 1 to 31. None of the participants in the placebo group had both LH and FSH suppressed to <1 IU/L (data not shown). More men had suppression of both gonadotropins in the 400-mg dose group than the 200-mg group ($P = 0.029$ using threshold ≤1 mIU/mL). The lower limit of quantification for both LH and FSH is 0.1 IU/L. D, day; EOS, end of study.

esterases required for the conversion of 11β-MNTDC to 11β-MNT with repeated dosing.

Sustained suppression of circulating FSH, LH, T, and E2 (Fig. 3 A to D) were observed in both active treatment groups, indicating suppression of the hypothalamic-pituitary-testis axis. There is a dose-dependent effect on suppression of gonadotropins; more participants in the 400-mg group had both FSH and LH ≤ 1.0 IU/L than in the 200-mg group ($P = 0.029$) (Fig. 4). We have previously shown that suppression of LH and FSH to these thresholds at day 28 is predictive of eventual suppression of spermatogenesis to levels associated with effective contraception (33). Correlations of average trough concentrations of 11β-MNT with gonadotropins also suggest that the 400-mg dose is more likely to achieve more uniform suppression of the gonadotropins and testosterone. Of note, some participants on active treatment had undetectable trough drug concentrations, which may reflect person-to-person variation in absorption, metabolism, or perhaps noncompliance with some doses. 11β-MNTDC was very effective in suppressing gonadotropins. Longer trials comparing oral DMAU and 11β-MNTDC are needed to directly compare the metabolic and contraceptive efficacy of these 2 compounds.

Human spermatogenesis takes approximately 70 to 75 days (38), and our assessment of sperm output was done before completion of 1 spermatogenesis cycle. We did not expect that many participants would demonstrate suppression of spermatogenesis to very low levels compatible with contraception within the limited study time of 28 days. In other male hormonal contraceptive clinical trials using a combination of testosterone and a progestin, a small proportion of men experience profound sperm output suppression by 28 days (39–42). 11β-MNT has relatively lower binding affinity to the progesterone receptor compared with the progestins used in these prior studies, and a shorter half-life than compounds administered via implant or injection. Future studies are necessary to determine whether a longer duration of treatment with 11β-MNTDC will result in sufficient suppression of LH and FSH to suppress spermatogenesis to levels consistent with contraceptive effectiveness.

Expected androgenic adverse effects with daily exposure to 11β-MNTDC were seen (e.g., acne, small increases in hematocrit and hemoglobin). Serum SHBG was suppressed by 11β-MNTDC, most likely because of its androgenic/progestational action (Fig 3E); despite suppression of SHBG, both free and total T as well as E2 were profoundly suppressed by day 7 of treatment in both dose groups to below castrate concentrations (< 50 ng/dL for total T) (Fig. 3C and F). Suppression of SHBG is a well-known effect of androgen administration (43). Low levels of SHBG in men have been directly associated with increased risk of metabolic syndrome and type 2 diabetes (44, 45), but this association may be due to the co-regulation of SHBG and insulin (46). Whether SHBG suppression induced by androgen administration has a direct metabolic impact is controversial (47).

The suppression of serum T to castrate levels by 11β-MNTDC was not associated with marked symptoms of acute hypogonadism such as hot flashes. Several men complained of a decrease in libido (5/31 treatment, 0 placebo), a more frequent complaint in those who received 200 (20%) versus 400 mg (10%). Conversely, the decreases in the 7-Day Psychosexual Daily Questionnaire score were only significant in the 400-mg group. Mood changes were more frequently reported by those receiving 11β-MNTDC compared with placebo (4/31 treatment, 1/11 placebo) without significant changes in the PHQ9 score. Given that other markers of androgenicity were observed, including

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increases in hemoglobin/hematocrit and decreases in SHBG, it is possible that reported sexual side effects and mood changes were either from the low serum concentrations of E2 or from the progestational activity of the compound. Of note, we found no relationship between serum testosterone and E2 concentrations or changes in serum testosterone or E2 concentrations with changes in sexual desire. Both serum testosterone and E2 was suppressed to below the lower limit of reference range (Fig 3D). It remains to be seen if this suppression of serum E2 is associated with adverse changes to body composition or bone mineral density with long-term use of 11β-MNTDC (48, 49). Bone mineral density was maintained in studies of 11β-MNTDC in castrated rats (19), but longer term studies sufficient to detect changes in bone mineral density and strength as well as serum markers of bone metabolism have not yet been performed in humans.

Mean weight gain of 1 to 2 kg in the 200- and 400-mg groups, respectively, was noted over the 28 days; however, whether this increase was due to increases in muscle mass (a well-described effect of androgens) (48, 50–52), fat mass, or sodium and water retention (53–55) requires further investigation. Body composition studies in castrated rats administered 11β-MNTDC suggest that increases in weight are from increases in lean mass and associated decreases in fat mass (19).

We noted significant decreases in HDL-C and increases in LDL-C with administration of oral 11β-MNTDC, particularly in the 400-mg group. Of note, the changes in weight and HDL-C and LDL-C concentrations were not related to the average trough concentrations of prodrug nor drug during the treatment period. Although mild decreases in HDL-C have been observed with parenteral androgen administration (56), more marked decreases occur with oral androgen administration (11, 18), likely from first-pass liver metabolism. The long-term consequences of changes in HDL-C are unclear (57). Recent data have indicated that HDL function may affect cardiovascular risk more than HDL-C concentration (57) and that hypogonadism is associated with reduced HDL-mediated cholesterol efflux (58). The observed increase in LDL-C with 11β-MNTDC administration was not anticipated. Comparable increases in LDL-C have not been observed with physiological non-oral androgen replacement therapy but have been reported with supraphysiological concentrations of intramuscular testosterone esters and oral androgens (59). In a study using low-dose transdermal testosterone with high doses of oral levonorgestrel, an androgenic progestin, LDL-C increased (60). However, in the majority of studies examining transdermal and injectable testosterone in combination with progestins, LDL-C generally does not significantly increase (56). LDL-C lowering with specific medical therapies such as statins decreases cardiovascular risk, so it will be important to explore these lipid changes more fully in longer studies of 11β-MNTDC to determine whether they are sustained, worsened, or improved.

This study has many strengths. These consist of inclusion of a placebo group; the use of highly sensitive, state-of-the-art assays to measure serum hormones and drug concentrations; detailed pharmacokinetic assessments and repeated measures of hormones to determine changes over time; use of validated questionnaires for assessment of mood and sexual function; and low attrition of subjects. However, given the small number of participants, we are limited in our ability to correlate adverse events and changes in safety assessments noted with treatment or hormone or drug concentrations. Because of the short duration of this study, we are unable to determine if daily oral 11β-MNTDC will suppress sperm production in healthy men. Longer duration studies of 11β-MNTDC will be required to assess this critical end point.

In summary, the novel oral androgen, 11β-MNTDC, appears safe in men when taken daily at doses of 200 mg and 400 mg for 28 days. We observed a dose-dependent suppression of serum gonadotropins and profound suppression of serum testosterone with administration of 11β-MNTDC with minimal adverse effects. Further testing of 11β-MNTDC in long-term studies is needed to further delineate the metabolic effects and potential spermatogenic suppression of this promising single-agent oral male contraceptive.

Acknowledgments

The authors thank Min S. Lee, PhD, in the Contraceptive Development Program, NICHD, and Toufan Parman, PhD, Jia-Hwa Fang, PhD, and Jennie Wang, PhD, at Stanford Research Institute International for manufacture of both 11β-MNTDC and placebo capsules; research coordinators Xiao-Dan Han, Elizabeth Ruiz, Isabel Payan, and Kathryn Torrez-Duncan for their assistance with the study; the staff of the Endocrine and Metabolic Research Laboratory at The Lundquist Institute and the University of Washington Center for Research in Reproduction and Contraception; and, most importantly, our research participants.

Financial Support: This study was conducted in the Contraceptive Clinical Trials Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD; HHSN27520130024I to The Lundquist Institute, (HHSN27520130025I to the University of Washington, and HHSN2752012002 to Health Decisions). The work was also supported by the Robert McMillen Professorship in Lipid Research (to S.T.P.) and the National

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Heart, Lung, and Blood Institute (NHLBI; K24HL138632 to P.Y.L.).

Clinical Trial Information: ClinicalTrials.gov registration number NCT02754687 (registered April 28, 2016).

Additional Information

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Disclosure Summary: W.B. is a member of the Data Safety and Monitoring Committee for the TRAVERSE trial supported by the Testosterone Replacement Therapy Manufacturers Consortium. R.S. and J.K.A. are consultants for Clarus Therapeutics. R.S. received research support from Clarus Therapeutics and TRT Manufacturer Consortium. C.W. receives research support from Clarus Therapeutics, Antares, and TesoRX. C.D. and H.W. are employees of Health Decisions. J.L. and D.L.B. are employees of the US government. The remaining authors have nothing to disclose.

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