Title:

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EFFICACY AND SAFETY OF A NEW TOPICAL TESTOSTERONE REPLACEMENT GEL THERAPY FOR THE TREATMENT OF MALE HYPOGONADISM

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ABSTRACT

Objective: Testosterone replacement therapy is indicated for male hypogonadism. This study aimed to evaluate the efficacy and safety of testosterone gel 2% (Tgel) over 90 days.

Methods: This phase 3, open-label, noncomparator study was conducted in adult hypogonadal men (2 consecutive fasting serum testosterone values <300 ng/dL and >86% subjects with symptoms consistent with testosterone deficiency). Subjects applied Tgel 23 mg/day (single pump-actuation using a hands-free cap applicator). The dose was uptitrated to 46 mg/day after 2 weeks if the 4-hour serum total testosterone level was <500 ng/dL. The dose could be further up- or downtitrated to 23, 46, and 69 mg on Days 21, 42, and 63. The primary endpoint included the percentage of subjects with average testosterone concentration ($C_{ave\ (0\text{-}24)}$) between 300 and 1,050 ng/dL on Day 90. Safety endpoints were adverse events (AEs), laboratory parameters, and vital signs.

Results: Of the 159 who enrolled, 139 men completed the study. Approximately three-quarters (76.1%) of subjects met C_{ave} criteria on Day 90. Most AEs were mild to moderate. There were 5 serious AEs, and 1 (myocardial infarction) was judged as possibly related to Tgel. Confirmed excessive increases in prostate-specific antigen or hematocrit levels were rare. Tgel had a favorable local skin tolerability profile.

Conclusion: Overall, 76% of subjects achieved C_{ave} between 300 and 1,050 ng/dL with Tgel. Symptoms of testosterone deficiency improved with few safety concerns. **(Endocr Pract. 2017;23:557-565)**

Abbreviations:
AE = adverse event; **$C_{ave(0\text{-}24)}$** = average testosterone concentration; **CI** = confidence interval; **C_{max}** = maximum concentration; **IIEF** = International Index of Erectile Function; **MAF** = Multidimensional Assessment of Fatigue; **PK** = pharmacokinetic; **PSA** = prostate-specific antigen; **SAE** = serious adverse event; **SF-12** = Short Form 12 Health Survey; **Tgel** = testosterone gel 2%; **T_{max}** = time to achieve maximum concentration; **TRT** = testosterone replacement therapy

INTRODUCTION

Male hypogonadism, which is associated with symptoms and serum total testosterone <300 ng/dL, has a significant health burden. It commonly affects middle- to older-aged men, though it is not rare in younger men (1). A large population-based study in the U.S. showed the prevalence of symptomatic hypogonadism to be 5.6% in men aged 30 to 79 years (2).

Testosterone replacement therapy (TRT) is the preferred treatment for hypogonadism, in men who are not interested in fertility (1). TRT in these men can improve

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symptoms affecting quality of life, particularly fatigue, mood, sexual dysfunction, increased fat mass, reduced muscle mass and strength, and decreased bone mineral density (1). Importantly, the potential benefits and risks of TRT with respect to cardiovascular diseases are controversial (3). As a result, the U.S. Food and Drug Administration has requested companies, which market TRT products to conduct large clinical trials to address this issue (4).

Of the various testosterone formulations (1), topical hydro-alcoholic gels are popular due to the ease of application, high bio-availability, and dose flexibility. Side effects including wide swings in peak/troughs in serum testosterone levels with short-acting injectable testosterone esters, extrusion and infection risk with pellets, and application site reactions with patches are uncommon with gels (5). Although skin reactions rarely occur with gels, transfer of testosterone from residual gel at the application site remains a potential risk that can lead to virilization in women and children (6).

Testosterone gel 2% (Tgel) is a homogeneous, transparent, nonstaining, topical hydro-alcoholic formulation developed by Ferring Pharmaceuticals A/S (Saint-Prex, Switzerland). It has shown good efficacy and tolerability profile when applied to the shoulder and upper arm using a newly designed hands-free cap applicator that limits gel contact with the hands, limits waste, and reduces the risk of secondary transfer (7). Furthermore, this novel highly viscous gel formulation allows the use of a small application volume in combination with the hands-free applicator. Testosterone is partially metabolized to dihydrotestosterone by 5-alpha reductase activity in skin and other tissues. Importantly, as with other transdermal products, Tgel is not subject to first-pass metabolism (6). The current study evaluated the efficacy and safety of this gel in hypogonadal men in terms of serum testosterone normalization over a 90-day period.

METHODS

Study Subjects

Men aged 18 to 75 years with fasting morning testosterone values <300 ng/dL on 2 occasions (separated by ≥3 days) were included in the study. The ADAM (Androgen Deficiency in the Aging Male) questionnaire used as a supportive tool for enrollment, showed >86% subjects with symptoms consistent with testosterone deficiency. Eighty-two percent of the subjects answered that their erections were less strong, 82.4% noted decreased libido (sex drive), 84.3% reported decreased erection strength and/or endurance, and 86.2% of subjects felt a lack of energy. Men previously treated with a testosterone gel or an injectable testosterone product within 12 weeks, topical/oral/nasal testosterone products within 2 weeks, or testosterone pellets within 4 months of the initial screening period were excluded from the study. Other key exclusion criteria were body mass index <18 or >35 kg/m^2, prostate cancer/suspected prostate malignancy, skin inflammation/disease, International Prostate Symptom Score >19, significant cardiovascular disease, untreated sleep apnea, and hemoglobin A1c >9.0%.

Ethics

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. Study protocol and all sites were approved by Institutional Review Board. All subjects provided written informed consent before entering the study.

Study Designs and Settings

This was a phase 3, open-label, noncomparator study, consisting of a 60-day screening period and a 90-day treatment period (end of efficacy evaluation), followed by a 30-day follow-up period (end of safety evaluation). The study was conducted at 23 centers in the U.S. from July 2014 to June 2015 (clinicaltrial.gov identifier NCT02149264).

Study Treatments

The dosing regimen and titration sampling times were determined based on data from previous clinical studies of Tgel (NCT01665599, NCT01703741) (8,9). The gel was administered using a metered-dose dispenser with a hands-free cap applicator. Treatment was initiated at a dose of 23 mg/day testosterone, which could remain unchanged or uptitrated to 46 mg/day (2 pump actuations) after 2 weeks and further up to 69 mg/day, based on a 4-hour postdose serum total testosterone levels on Days 14, 35, and 56. Dose adjustment occurred if the serum total testosterone levels were outside the target range (500-1,050 ng/dL).

Study Endpoints

The primary efficacy endpoint was serum total testosterone responder rate, defined as the percentage of subjects having average serum total testosterone concentration ($C_{ave(0-24)}$) within the physiologic range of 300 to 1,050 ng/dL on Day 90. Efficacy criteria were met if proportion of responders was ≥75% and lower limit of 95% confidence interval (CI) was ≥65%.

Secondary efficacy endpoints included C_{ave} on Days 14, 35, and 56. Changes from Baseline (Day 1) to Days 35 and 90 in erectile function (International Index of Erectile Function [IIEF]), fatigue (Multidimensional Assessment of Fatigue [MAF]), and general well-being (Short Form 12 Health Survey [SF-12] total and domain scores) were also evaluated. Additionally, dose titration decisions made based on the 4-hour testosterone levels versus hypothetical decisions based on 2- and 6-hour testosterone levels; dihydrotestosterone/testosterone ratio at Day 90; and the measurement of other pharmacokinetic (PK) parameters on Days 14, 35, 56, and 90, were also assessed as secondary endpoints.

Safety and tolerability were assessed throughout the study. These included evaluation of treatment-emergent adverse events (AEs), changes from Baseline in vital signs, skin reactions and application site reactions, prostate-specific antigen (PSA) levels (including percentage of subjects with PSA >4.0 ng/mL), subjects with a hematocrit ≥54% or hemoglobin concentration >18 g/dL.

Study Assessments

Average serum total testosterone levels were calculated over a 24-hour period. Blood samples were collected pre-dose, and at 2, 4, 6, 8, 10, 12, 18 and 24 hours after application of gel on Day 90. On Days 14, 35, and 56, similar time points were evaluated except at 10, 12, and 18 hours. Application of gel was witnessed by site staff. The Covance Central Laboratory Services (Indianapolis) used a liquid chromatography-mass spectrometry/mass spectrometry assay to determine the levels of serum total testosterone and dihydrotestosterone. These assays were cross-validated for ranges of 10 to 1,000 ng/dL for testosterone and 2 to 200 ng/dL for dihydrotestosterone.

Individual domain IIEF (10) scores were determined for sexual functioning for 5 domains (i.e., erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction). Fatigue was assessed using the MAF (11), which evaluated 4 dimensions (severity, distress, degree of interference in activities of daily living, and timing). Overall health was measured using the SF-12 (12). Additionally, a treatment satisfaction questionnaire was used to assess overall satisfaction with the gel and cap applicator.

The ratio of serum concentrations of dihydrotestosterone/testosterone was calculated on Day 90 at time points similar to those used in the primary efficacy analysis. The PK parameters were evaluated on Days 14, 35, 56, and 90. These included measurement of C_{ave}, maximum concentration (C_{max}), minimum concentration (C_{min}), area under concentration-time curve ($AUC_{(0-\tau)}$), and time to achieve maximum concentration (T_{max}), for serum total testosterone and dihydrotestosterone.

AEs were recorded throughout the study. Vital signs were measured during screening and on Day 90. Skin application site reactions, serum PSA, and hematocrit/hemoglobin levels were assessed at Baseline and Days 14, 35, 56, 90, and 120.

Statistical and Pharmacokinetic Analyses

All subjects who received at least 1 dose of study medication were included in safety and intention-to-treat analyses. All efficacy analyses were performed using the full analysis set (FAS), and included subjects who had sufficient PK data to determine $C_{ave(0-24)}$ for responder rates on Days 14, 35, 56, and/or 90, or discontinued prematurely due to safety reasons. Sufficient PK data was defined as a data set that included at least 4 concentrations, including a predose value and a 23- to 25-hour postdose value. A subset of subjects who had no major protocol deviations that could affect the PK data and did not have probable contamination at the venipuncture site on Day 90 were also evaluated for responder analysis (per-protocol completer analysis set). The 95% CIs of the responder rates were calculated using normal approximation to binomial distribution. The last observation carried forward approach was used if $C_{ave(0-24)}$ concentrations were not determined. If the subject did not have sufficient PK data from any visit, he was considered as a nonresponder. Subjects withdrawn for safety reasons were considered nonresponders regardless of their PK results. The IIEF (15 questions), MAF (16 questions), SF-12 (12 questions), and treatment satisfaction (8 questions) scores were summarized descriptively, and changes from Baseline values were analyzed using 1-sample t test. The potential impact of using a 2- or 6-hour testosterone level instead of a 4-hour testosterone level on the dose titration decision was assessed by cross-tabulating the hypothetical decisions and actual decisions. The PK parameters were presented descriptively using noncompartmental analysis. AEs were summarized for safety analysis set.

RESULTS

Of the 940 subjects screened, 160 were enrolled, 159 were treated and 139 (87.4%) completed all visits (Fig. 1). The demographics and baseline characteristics are presented in Table 1. Primary hypogonadism was observed in 3.8% subjects, while secondary hypogonadism was observed in 96.2% subjects at baseline. Hypertension was the most prominent comorbidity. The serum total testosterone responder rate increased from Day 14 (29.1%) to Day 56 (75%), up to Day 90. A total of 76.1% (95% CI 69.4, 82.8) of 155 subjects in FAS had serum total testosterone C_{ave} within the target range of 300 to 1,050 ng/dL at Day 90. The study thus met the predefined efficacy criteria of responder rate ≥75% and lower limit of 95% CI ≥65%. A total of 139 subjects had a full PK assessment at Day 90, and the responder rate for this group was 82%. Each individual IIEF domain score showed a significant improvement from Baseline to Days 35 and 90 (both $P<.0001$, Fig. 2). The mean Global Fatigue Index score showed a significant improvement ($P<.0001$) from Baseline (27.6) to Days 35 (19.4) and 90 (15.8). Individual MAF domain scores also showed significant improvement from Baseline at both time points ($P<.0001$, Fig. 2). The average total physical component summary (PCS) score obtained from the SF-12 showed a significant improvement from Baseline (48.2) to Days 35 (49.4) and 90 (49.9) ($P = .0343$ and .0033, respectively). Similarly, significant improvements from Baseline were observed in individual PCS domain scores at both time points ($P<.05$) and approached statistical significance ($P = .0559$) for the Bodily Pain domain score at Day 90.

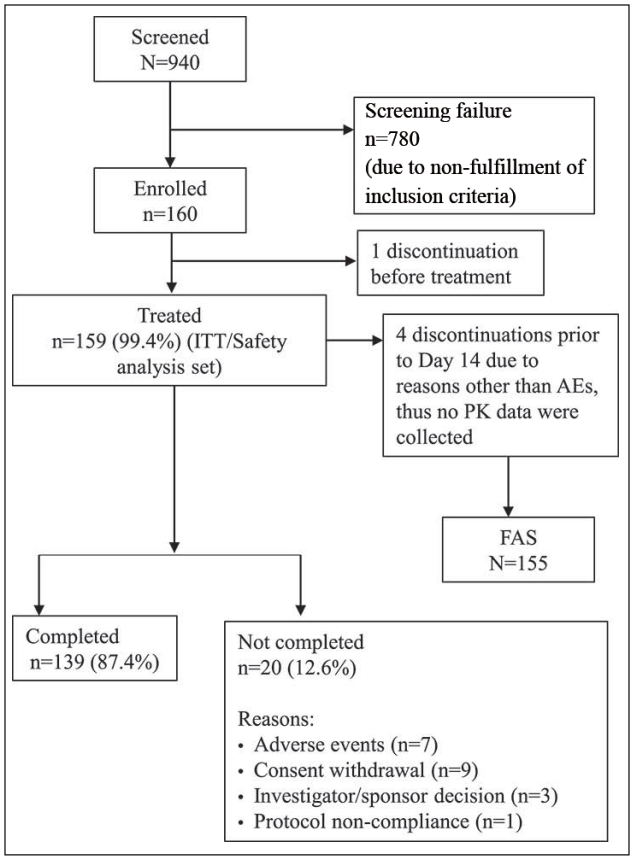


Fig. 1. Subject disposition. *AE* = adverse event; *FAS* = full analysis set; *ITT* = intention-to-treat; *PK* = pharmacokinetic.

The average total mental component summary (MCS) score significantly improved from Baseline (43.7) to Days 35 (50.4) and 90 (50.5) (both $P<.0001$), in addition to individual MCS domain scores at both time points ($P<.0001$). A treatment satisfaction questionnaire showed that 93.5% subjects were very satisfied/satisfied using the hands-free cap applicator; 87.7% felt that it was very easy to use, and 87% felt less risk of transfer of testosterone to child/partner through direct contact with application site or hands.

The hypothetical titration decisions at 2 and 6 hours showed that the testosterone levels at 2 hours tended to be somewhat higher, resulting in more men being downtitrated; whereas, the 6-hours values were somewhat lower, resulting in more men being uptitrated (Fig. 3).

The ratio of dihydrotestosterone to testosterone at Day 90, following application of Tgel showed a similar trend for all 3 doses. There was a steep decline in the ratio at 2 hours, followed by a gradual increase, thus reaching a level nearly similar to the predose level (Fig. 4).

The concentration-time curves at Day 90 for all the three Tgel doses showed steep increases in testosterone level at 2 hours after drug administration, followed by a gradual decline, thereby reaching a level similar to that at time zero. A similar trend was observed for dihydrotestosterone levels at Day 90, where the concentration increased up to 4 hours, followed by a gradual decline (Fig. 5). The average serum testosterone levels and other PK parameters at Day 90 were similar within the uptitrated 46- and 69-mg doses, but were lower with the 23-mg dose. The median testosterone T_{max} was approximately 2 hours for 46- and 69-mg doses, while it was approximately 4 hours for the 23-mg dose (Table 2). On Day 14, total testosterone C_{max} for all subjects was <1,500 ng/dL. On Day 90, total testosterone C_{max} was <1,500 ng/dL for 108 (77.7%)

Table 1
Subject Demographic and Baseline Characteristics (ITT/Safety Population)

	n = 159
Age (years), Average (SD)	54.1 (9.3)
Age Range, n (%)	
<65 years	138 (86.8)
≥65 years	21 (13.2)
Race, n (%)	
Caucasian	123 (77.4)
African American	31 (19.5)
Asian	3 (1.9)
Other	2 (1.3)
Ethnicity, n (%)	
Hispanic	22 (13.8)
Non-Hispanic	137 (86.2)
BMI (kg/m^2), Average (SD)	30.7 (3.2)
Most common medical histories, n (%)	
Hypertension	73 (45.9%)
Hypercholesterolemia	40 (25.2%)
Type 2 diabetes mellitus	32 (20.1%)
Gastroesophageal reflux disease	30 (18.9%)
Seasonal allergy	24 (15.1%)
Benign prostatic hyperplasia	23 (14.5%)
Blood pressure (mm Hg), Average (SD)	
Systolic	129.3 (12.7)
Diastolic	80.4 (7.2)
IIEF erectile function domain average score (SD)	15.1 (9.4)
IPSS average score (SD)	6.4 (5.3)
Global Fatigue Index average score (SD)	27.5 (11.1)
PCS average total score (SD)	48.4 (8.8)
MCS average total score (SD)	43.7 (11.0)
PSA <4 ng/dL, n (%)	157 (100)

Abbreviations: BMI = body mass index; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score (inclusion score ≤19); ITT = intention-to-treat; MCS = mental component summary; PCS = physical component summary; PSA = prostate-specific antigen.

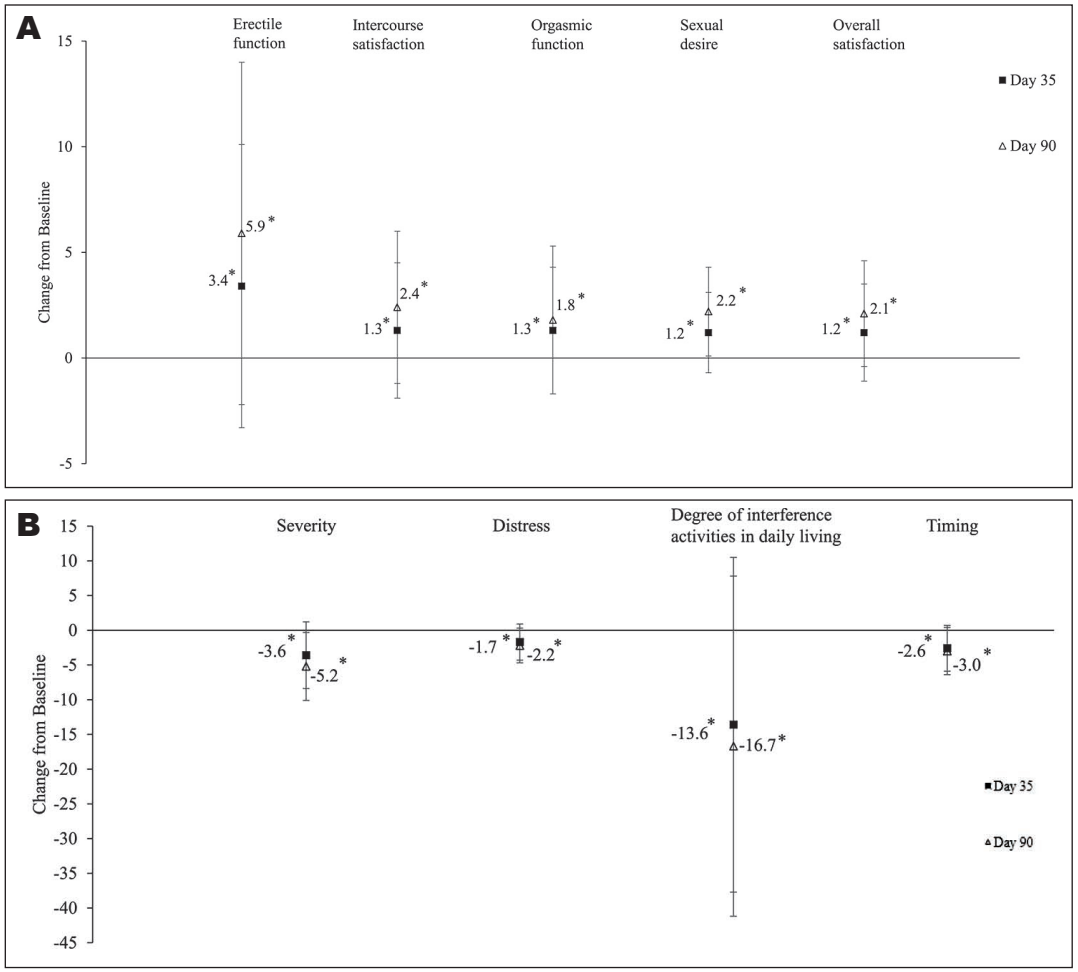


Fig. 2. Change from Baseline in (*A*) IIEF domain scores and (*B*) MAF domain scores at Day 35 and Day 90 (FAS). Values are mean ± SD; **P*<.0001. *FAS* = full analysis set; *IIEF* = International Index of Erectile Function; *MAF* = Multidimensional Assessment of Fatigue.

subjects, while 14 (10.1%) and 12 (8.6%) subjects had a single, brief, sporadic peak value between 1,500 and 1,800 ng/dL and 1,800 and 2,500 ng/dL, respectively. The 5 (3.6%) subjects who had total testosterone C_{max} values >2,500 ng/dL on Day 90 returned for a repeat evaluation, and 4 of these subjects had C_{max} <2,500 ng/dL, indicating sporadic increases. The fifth subject also had high serum testosterone at the repeat evaluation. His sex hormone-binding globulin (SHBG) was normal at screening (32.8 nmol/L [ref range: 17.3-65.8 nmol/L]) and increased to 169.6 nmol/L at Day 90. This very high SHBG accounted for the high testosterone levels. When further evaluating the isolated brief C_{max} values >1,500 ng/dL on Day 90, reasonable explanations such as sample aberrations, skin disease, or study noncompliance were found to explain the high C_{max} values in 13 cases.

Overall, 119 AEs were reported by 59 subjects, most of which were mild to moderate in severity. The most common AEs were bronchitis, upper respiratory tract infection, and cough, each in 5 (3.1%) subjects. Serious AEs (SAEs) were experienced by 5 subjects (malignant lung neoplasm, upper limb fracture, unstable angina, myocardial infarction with stent placement, and progression of degenerative osteoarthritis). Only 1 of these was judged as possibly related to study drug (myocardial infarction with stent placement). Two subjects with cardiovascular events (myocardial infarction and unstable angina) had a medical history of cardiovascular diseases and thus were at increased risk at Baseline.

There were 7 discontinuations due to AEs, of which 4 were due to SAEs (malignant lung neoplasm, upper limb fracture, unstable angina, and myocardial infarction with stent placement). Additionally, 2 subjects discontinued due to application site reactions and 1 due to erectile dysfunction, which were assessed as possibly related to treatment. No clinically significant changes in vital signs were observed. The local tolerability was generally good, and mild-to-moderate application site reactions were observed in 8 subjects. Of the 5 subjects having C_{max} for testosterone >2,500 ng/dL at Day 90, 1 subject experienced a moderate skin rash, which was not related to treatment. This subject had a history of winter rashes that were not reported at

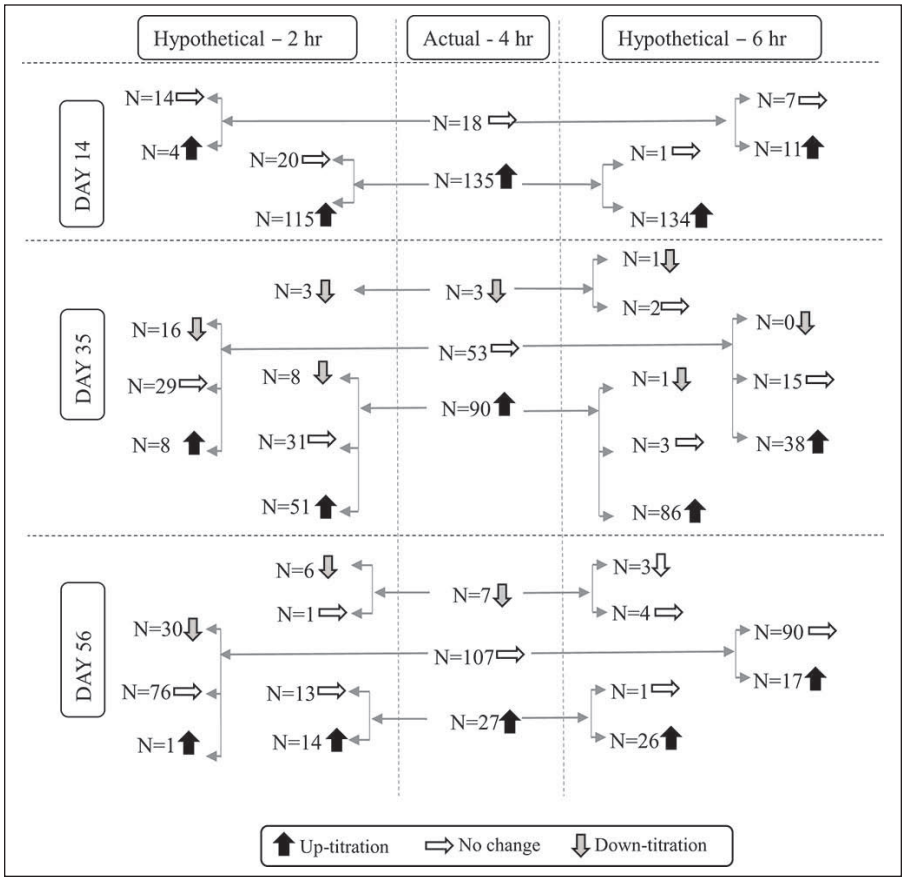
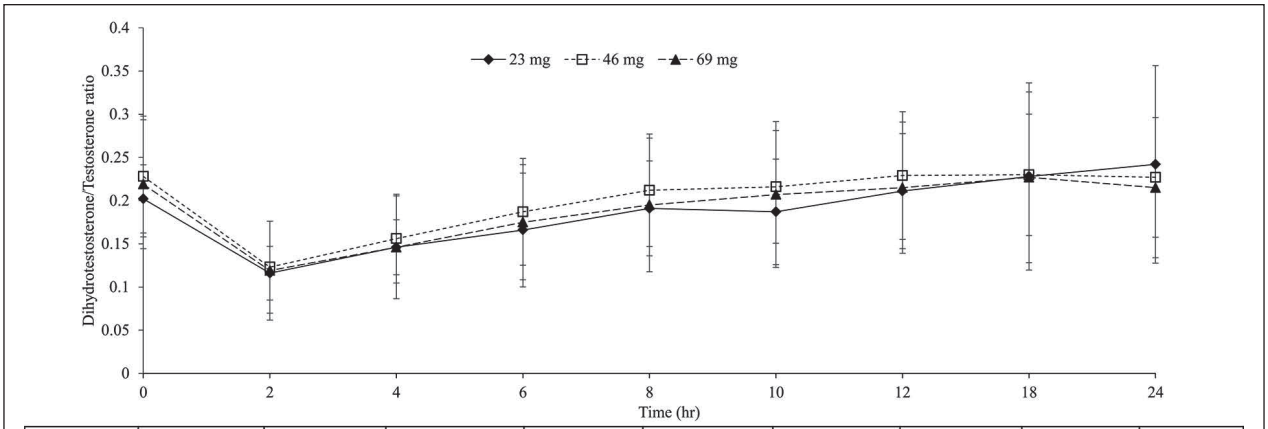


Fig. 3. Agreement of dose titration. The value at 4 h shows actual titration decision, and the values of 2 and 6 h correspond to hypothetical titration decisions.



23 mg (N=5)	0.202 (0.0395)	0.116 (0.0311)	0.146 (0.0319)	0.166 (0.0658)	0.191 (0.0549)	0.187 (0.0610)	0.211 (0.0667)	0.228 (0.1083)	0.242 (0.1143)
46 mg (N=45)	0.228 (0.0699)	0.123 (0.0532)	0.156 (0.0513)	0.187 (0.0617)	0.212 (0.0651)	0.216 (0.0652)	0.229 (0.0739)	0.230 (0.0702)	0.227 (0.0693)
69 mg (N=89)	0.219 (0.0746)	0.119 (0.0572)	0.146 (0.0595)	0.175 (0.0667)	0.195 (0.0773)	0.207 (0.0844)	0.215 (0.0759)	0.227 (0.0988)	0.215 (0.0811)

Fig. 4. Dihydrotestosterone/Testosterone ratio at Day 90 (Safety set). Values are mean ± SD.

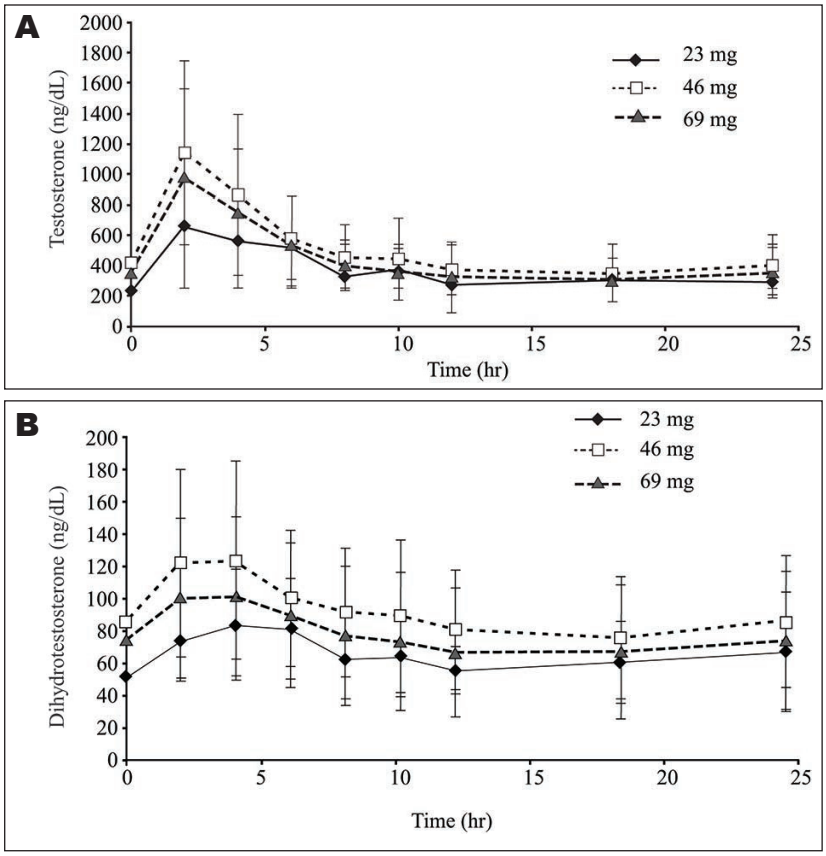


Fig. 5. Concentration-time curve at Day 90 for (*A*) testosterone and (*B*) dihydrotestosterone. Values are mean ± SD.

screening visit. No other AEs were reported in the other 4 subjects having testosterone C_{max} >2,500 ng/dL at Day 90.

Four subjects had confirmed PSA levels >4.0 ng/mL at various time points during the study; however, PSA levels were <4.0 ng/mL when retested and throughout the remainder of the study. These 4 abnormal PSAs were not reported as AEs. Also, these subjects had testosterone C_{max} <1,500 ng/dL.

Of the 5 subjects with C_{max} >2,500 ng/dL at Day 90, 2 subjects had increased hematocrit (%) from Baseline at Day 120; the highest hematocrit was at 54%. In the remaining 3 subjects, hematocrit values were <50% at the end of study. Overall, the study showed an increase in hematocrit from Baseline to Day 120 (average ± SD, 43.75 ± 2.68 to 45.68 ± 3.19, respectively). Subjects with high hematocrit and hemoglobin levels were not the individuals with high testosterone C_{max}.

DISCUSSION

Tgel restored serum testosterone levels in men with low baseline testosterone levels, and there were commensurate improvements in sexual function, fatigue, and quality of life. More than 76% subjects who initiated treatment achieved average serum testosterone levels within the normal range of 300 to 1,050 ng/dL at Day 90. Only a small proportion of subjects had brief, supraphysiologic levels of testosterone, and few had application site reactions.

The study met the prespecified efficacy success criteria of C_{ave} 300 to 1,050 ng/dL in ≥75% subjects, and the lower bound of the 95% CI was ≥65% (study value 69.4%). The responder rate in this study showed similar efficacy of Tgel compared to other approved transdermal testosterone gels (13) and topical 2% testosterone solution (14).

The efficacy of the titration regimen used in this study was substantiated by comparison of hypothetical titration at 2 or 6 hours with the actual decision at 4 hours. The hypothetical titration decisions based on testosterone levels at 2 hours tended to be somewhat higher, resulting in more men being downtitrated. On the other hand, 6-hour titration decisions were somewhat lower, resulting in more men subsequently being uptitrated. This suggests that dose titration 2 to 4 hours postapplication is a practical option for this Tgel.

The study also analyzed the ratio of dihydrotestosterone to testosterone following Tgel application. The ratio was reduced at 2 hours as compared with the baseline and later times. When ratios fall below 2-SD of the values shown in this graph and are accompanied by unusually high testosterone levels, it suggests the possibility of a high testosterone value due to skin contamination at the phlebotomy site or laboratory error.

Table 2
Pharmacokinetic Parameters

Time point	Dose (mg)	C_{max} (ng/dL)	T_{max} (h)	C_{min} (ng/dL)	$AUC_{0-\tau}$ (ng•hr/dL)	C_{ave} (ng/dL)
		Average ± SD	Median	Average ± SD	Average ± SD	Average ± SD
Testosterone						
Day 14	23 (n = 154)	435 ± 195	2.04	194 ± 64	6,431 ± 1,938[a]	268 ± 80[a]
Day 35	23 (n = 18)	642 ± 238	2.15	230 ± 74	8,552 ± 2,800	359 ± 116
	46 (n = 128)	732 ± 387	2.00	216 ± 93	8,665 ± 3,664[b]	361 ± 152[b]
Day 56	23 (n = 8)	637 ± 300	2.00	175 ± 49	6,624 ± 1,765	278 ± 73
	46 (n = 59)	890 ± 424	2.08	262 ± 115	10,320 ± 3,042	429 ± 127
	69 (n = 75)	987 ± 652	2.00	261 ± 200	11,152 ± 6,507[c]	464 ± 271[c]
Day 90	23 (n = 5)	721 ± 254	4.02	191 ± 49	8,831 ± 2,829	368 ±121
	46 (n = 45)	1,228 ± 640	2.02	277 ± 140	12,245 ± 5,010	506 ± 207
	69 (n = 89)	1,099 ± 595	2.08	229 ± 82	10,590 ± 3,979	438 ± 164

Abbreviations: $AUC_{0-\tau}$ = area under concentration-time curve; C_{ave} = average concentration; C_{max} = maximum concentration; C_{min} = minimum concentration; T_{max} = time to achieve maximum concentration.

[a] n = 151, [b] n = 127, [c] n = 73

The package inserts for testosterone gels differ in the blood sampling times for dose titration. Some use the 24-hour value (15) and some recommend sampling every 2 to 6 hours (13,16) after gel application. In the present study, 97% of subjects required titration to the 46- or 69-mg/day dose. The PK profiles, including the average serum concentrations of testosterone and dihydrotestosterone, were similar for the 46- and 69-mg doses at Day 90, validating the need for titration and suggesting an optimized titration regimen. Median testosterone T_{max} was 2 hours for the 46- and 69-mg doses, which was similar to a previous phase 3 study with Tgel (Ferring data on file), and another study with 1% gel (17).

The overall safety and tolerability profile of the drug was considered favorable. The 2 subjects experiencing cardiovascular SAEs were men >55 years with a medical history of hypertension and coronary artery disease. Although, cardiovascular risk increases with age, the relationship with testosterone treatment is controversial and of concern. Other than this, the safety results were consistent with the results from previous studies using marketed testosterone gels (13,15,18,19).

The potential strength of the Tgel in the present study was that subjects achieved physiologic serum levels of testosterone with lesser gel volume and a smaller surface area for application. The cap applicator facilitated hands-free application, thereby reducing the risk of secondary exposure. The current study was open-label and was not placebo-controlled, limiting the interpretation of the subject-reported outcomes and AEs. Also, the study duration was 3 months, which did not permit the assessment of testosterone levels and potential benefit over longer periods of time and did not show the long-term safety profile.

CONCLUSION

Tgel applied with a specifically designed hands-free cap applicator was efficacious in restoring serum testosterone levels to physiologic range in hypogonadal men. The titration scheme was considered effective in achieving and maintaining physiologic serum testosterone levels. This novel testosterone gel formulation and application system, which uses an applicator instead of the hands, provides a new option for TRT in hypogonadal men.

ACKNOWLEDGMENT

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DISCLOSURE

G.C. and G.B. have received honorarium for speaking from Ferring Pharmaceuticals. G.C. has been a consultant for several other pharma companies (AbbVie, Apricus, Besins, Clarus Therapeutics, Endo Pharma, Lilly, Pfizer, and Repros Therapeutics). L.B. has received honorarium and lecture payments from Astellas and Bayer. M.G. has received research grants from Ferring. D.C., A.N., and M.A. are the employees of Ferring Pharmaceuticals. J.M. of Target Health Inc was involved in conducting these studies.

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