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Journal:

Andrologia 2018

Accepted: 21 December 2016

DOI: 10.1111/and.12801

ORIGINAL ARTICLE

WILEY ANDROLOGIA

Efficacy and safety of testosterone replacement gel for treating hypogonadism in men: Phase III open-label studies

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Funding information
Ferring Pharmaceuticals

Summary

Efficacy and safety of testosterone gel 2% (TG) were evaluated in two phase 3, open-labelled, single-arm, multicentre studies (000023 and extension study 000077). Hypogonadal men having serum testosterone levels <300 ng/dl at two consecutive measurements were included. Study duration was 9 months (000023: 3 months; 000077: 6 months). Starting dose of TG (46 mg) was applied on upper arm/shoulder. The primary endpoint (000023) was responder rate (subjects with average 24-hour serum testosterone concentration 300-1050 ng/dl on Day 90). Study 000077 evaluated the safety of TG in patients rolling over from study 000023 over a period of 6 months. Of 180 subjects in 000023, 172 completed and 145 rolled over to 000077, with 127 completers. The responder rate was 85.5%. Fewer subjects in 000077 (12.7%) *versus* 000023 (31.8%) had maximum testosterone concentration (C_{max}) >1500 ng/dl, with no significant safety concerns. Significant improvements in sexual function and quality of life were noted in both studies. Subjects experienced few skin reactions without notable increases in prostate-specific antigen and haematocrit levels. TG was efficacious with an acceptable safety profile. C_{max} >1500 ng/dl did not exhibit distinct impact on safety parameters. However, further optimisation of titration schema to reduce C_{max} is warranted while maintaining the average steady state total testosterone concentration.

KEYWORDS
androgen deficiency, hypogonadism, prostate-specific antigen, quality of life, sexual functioning, testosterone

1 | INTRODUCTION

Hypogonadism, characterised by low levels of total serum testosterone, is diagnosed in about 4–5 million men in the USA. Although its prevalence is higher in older men (60–80 years) with a crude prevalence of up to 38.7% (Mulligan, Frick, Zuraw, Stemhagen, & McWhirter, 2006), it is not uncommon in the younger population (Huhtaniemi, 2014). Both early and late onset hypogonadism adversely affect the quality of life (QoL) largely because of compromised sexual function, depression, fatigue, and an adverse impact on bone and muscle health (Kelly & Jones, 2013; Tenover, 1992). Evidence shows that restoring testosterone to normal levels using testosterone replacement therapy (TRT) could improve sexual function and other symptoms of hypogonadism, and hence QoL (Lakshman & Basaria, 2009).

Topical testosterone preparations are increasingly being prescribed owing to ease of application, good bioavailability with favourable tolerability and reduced instances of supraphysiological testosterone levels compared to, for example injectable products (Surampudi, Wang, & Swerdloff, 2012; Ullah, Riche, & Koch, 2014). However, topical preparations are associated with an increased risk of secondary exposure that could result in, for example, virilisation in women and premature puberty in children, underlining the need to minimise such risks (Surampudi et al., 2012).

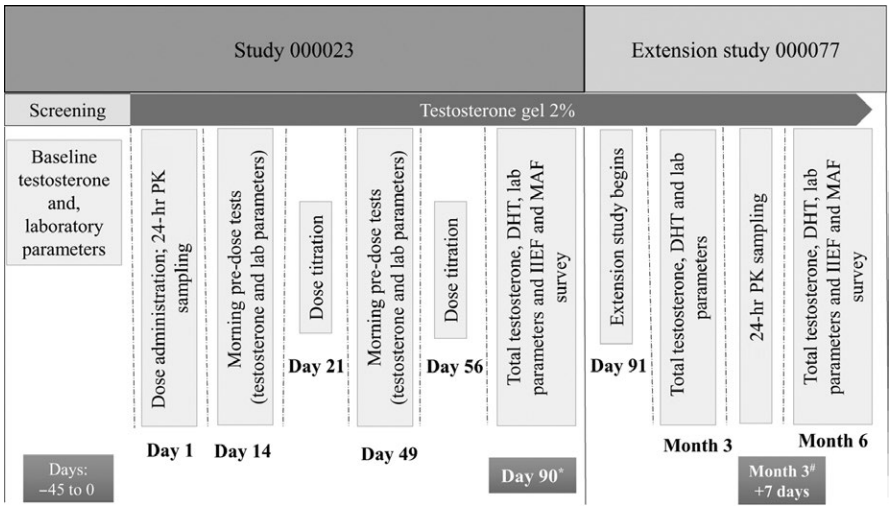

FIGURE 1 Study design. *Primary endpoint for study 000023 (responders with total testosterone levels between 300 and 1050 ng/dl); #primary endpoint for extension study (responders with total testosterone maximum concentration between/above pre-determined limits); DHT, Dihydrotestosterone; IIEF, International Index of Erectile Function; MAF, Multidimensional Assessment of Fatigue; PK, Pharmacokinetics

Testosterone gel 2%, developed by Ferring Pharmaceuticals, is a novel hydroalcoholic, homogeneous, transparent, nonstaining and highly viscous topical gel formulation with a hands-free cap applicator that allows precise dispensing and application on the shoulder or upper arm. The cap applicator helps minimise the risk of secondary testosterone exposure in children and women and has shown better compliance than hand application (Dobs et al., 2012; Efros, Carrara, & Neijber, 2015). Previous studies have shown that testosterone gel 2% is rapidly absorbed in a dose-dependent manner leading to normalisation of testosterone levels (Dean, Carnegie, Rodzvilla, & Smith, 2004).

The present phase 3 study (000023, NCT01665599) and its 6-month extension study (000077, NCT01703741) evaluated the efficacy, safety, local tolerability and pharmacokinetics (PK) of testosterone gel 2% in hypogonadal men.

2 | SUBJECTS AND METHODS

2.1 | Subjects

Men with hypogonadism (18–75 years) with two screening serum testosterone values <300 ng/dl taken at least 3 days apart within 45 days of initial treatment, and clinical symptoms of testosterone deficiency based on response to the Androgen Deficiency in the Aging Male (ADAM) questionnaire (Morley et al., 2000) were included. Key exclusion criteria were previous use of testosterone products (within 8 weeks of screening for injectables or 2 weeks of screening for other preparations), palpable prostatic mass(es), urinary tract or cardiovascular disease, abnormal liver function tests, haematocrit <35% or >51%, creatinine level >2 ng/ml, use of medications interfering with androgen metabolism, and men with pregnant or nursing partners.

2.2 | Ethics

The studies were conducted in accordance with the Declaration of Helsinki and its amendments, International Conference on Harmonization-Good Clinical Practice Guidelines and in compliance with the approved protocol and applicable regulatory requirements. All subjects provided written informed consent before enrolment.

2.3 | Study designs and settings

Both phase 3 studies were open-labelled, single-arm and multicentre studies. Subjects completing study 000023 were eligible to participate in study 000077. The treatment duration was 3 months for study 000023 and 6 months for study 000077, thereby providing the data for an extended use up to 9 months (Figure 1). Study 000023 was conducted across 19 centres in the USA and Canada from July 2012 to May 2013. All centres except one participated in the extension study from December 2012 to October 2013.

2.4 | Study treatments

Subjects applied testosterone gel 2% on clean dry skin between 6:00 a.m. and 10:00 a.m., alternatively to each upper arm/shoulder areas using a cap applicator. Each pump actuation delivered 1.15 ml gel corresponding to 23 mg testosterone. The application site was allowed to dry for about 5 min before being covered, and the subjects were instructed to wash their hands, and avoid contact of the application site with children, pregnant women and partner. Subjects were also instructed not to bathe at least 6 hr after the gel application, and to avoid direct sunlight on the application area.

In study 000023, the starting dose for all subjects was 46 mg of testosterone gel 2%. The dose could be up-titrated or down-titrated to 69 mg or 23 mg, respectively, at two time points (Day 21 and Day 56), based on morning pre-dose serum testosterone sample (titration range 300–600 ng/dl) taken on Day 14 and Day 49. In study 000077, subjects continued with the dose established on Day 56, except for those having maximum testosterone concentration (C_{max}) total testosterone level ≥1500 ng/dl on Day 90/91 of study 000023 that could not be explained as a spurious result (a high pre-dose testosterone level or levels inconsistent with a dihydrotestosterone [DHT] level). In this case, the dose was down-titrated by 1 pump actuation right at the start of study 000077.

In study 000023, titration decision was based on pre-dose serum testosterone levels, and as a result, some of the subjects in study 000023 were potentially up-titrated to higher doses, which was not required. Therefore, in study 000077, dose adjustments were made 2-hour post-dose testosterone measurement as C_{max} levels were achieved by 2-hour post-dose. Thus, for subjects who were on a stable dose for at least a month, testosterone dose could be down-titrated at Month 3 if C_{max} total testosterone levels were ≥1500 ng/dl based on a single 2-hour post-dose testosterone measurement.

2.5 | Study endpoints

The primary efficacy endpoint of study 000023 was the proportion of subjects achieving average steady state serum total testosterone concentration ($C_{ave\ (0–24)}$) between 300 and 1050 ng/dl on Day 90. The secondary efficacy variables included sexual functioning, fatigue and QoL on Day 90. The same efficacy parameters were evaluated in study 000077. PK assessments for total testosterone and DHT levels were also performed. Safety endpoints included the incidence of adverse events (AEs), proportion of subjects with total serum testosterone maximum concentrations (C_{max}) between or above pre-determined limits (1500–1799, 1800–2499 and ≥2500 ng/dl), proportion of subjects with prostate-specific antigen (PSA) >4.0 ng/ml, haematocrit levels ≥54% and a physical examination evaluating local tolerability.

2.6 | Study assessments

Blood samples were collected over a 24-hour period to determine the proportion of responders on Day 90 in study 000023, and Month 6 in study 000077. Subjects with spurious C_{max} testosterone level ≥1500 ng/dl at Day 90/91 were retested at a follow-up visit to confirm the result. In study 000077, a 24-hour PK assessment was carried out for subjects on a stable dose for at least one month at Month 3. Total testosterone and DHT levels were measured using a liquid chromatography-mass spectrometry/mass spectrometry method. Sexual function was assessed by the International Index of Erectile Function (IIEF) scale that evaluates the domains of male sexual functioning; a higher score representing a better sexual functioning (Rosen et al., 1997). Fatigue was assessed using the Multidimensional Assessment of Fatigue (MAF) scale where a lower score represents better status (MAF User's Guide). The overall health status was assessed using Short Form-12 Health Survey (SF-12) that measures the domains of health status with reference to disease (SF-12® questionnaire). IIEF, MAF, ADAM and SF-12 questionnaires were completed at baseline (Day 1 of study 000023) and Day 91, in study 000023, and at Month 6 in study 000077. Luteinizing hormone (LH), follicle stimulating hormone (FSH), oestradiol, sex hormone-binding globulin and insulin levels were evaluated at the end of study 000023 only.

2.7 | Statistical and PK analysis

The primary efficacy analysis of study 000023 was conducted for the full analysis set (FAS) population, which included all subjects who had testosterone PK data at Day 90. The efficacy was also evaluated in per protocol (PP) population to measure the robustness of the primary analysis. The PP population included all subjects with available PK data from Day 1 to Day 90, with no protocol violations. The two-sided 95% confidence interval (CI) of the responder rate was calculated using the normal approximation to binomial distribution. In study 000077, all PK assessments were conducted for the PP population. Changes from baseline in IIEF, MAF, ADAM and SF-12 scores were summarised at Day 91 of study 000023 and Month 6 of study 000077 for the intention-to-treat (ITT) population, which included all subjects who received at least one dose of the study drug. The statistical significance was assessed by one-sample *t* test at each time point independently.

3 | RESULTS

Of 180 subjects receiving study drug (safety and ITT populations), 172 subjects completed study 000023 (FAS population). Of these, 154 were included in the PP population. Of 172 subjects completing the study 000023, 145 were enrolled in study 000077 (safety and ITT populations), and 127 subjects completed the study. Overall 110 subjects completed the 9 month of treatment period (FAS population) and had 24-hour testosterone PK data. The baseline characteristics of subjects are presented in Table 1.

In study 000023, five subjects were down-titrated to 23 mg, 155 subjects were up-titrated to 69 mg and 12 subjects remained on the 46 mg dose. The initial dose for the 106 subjects (PP population) rolling over to study 000077 was fixed, based on the Day 56 titrations. However, 52 subjects with C_{max} total testosterone level ≥1500 ng/dl

TABLE 1 Demographics—ITT/Safety population

	Testosterone gel 2%	
	Study 000023 (*N* = 180)	**Extension study 000077 (*N* = 145)**
Race (*n*)*		
American Indian Or Alaska Native	1	1
Asian	2	2
African American	19	14
Caucasian	157	127
Age (years), Mean (*SD*)	56.8 (9.4)	57.1 (9.7)
Age group, *n* (%)		
≤65 years	145 (80.6)	116 (80.0)
>65 years	35 (19.4)	29 (20.0)
BMI (kg/m^2), Mean (*SD*)	30 (3.4)	-
BMI group, *n* (%)		
≤30 kg/m^2	84 (46.7)	>30 kg/m^2
>30 kg/m^2	96 (53.3)	-

*One subject refused to identify his race; BMI, Body Mass Index; *SD*, Standard Deviation; ITT, Intention-to-Treat.

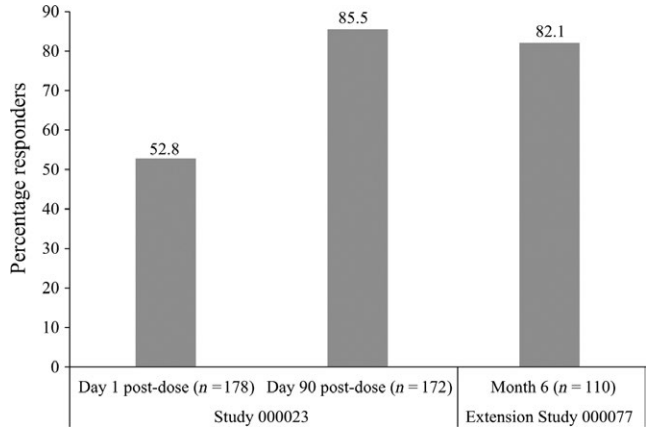

FIGURE 2 Responder rate—study 000023 and extension study 000077

on Day 90/91 of study 000023 were down-titrated by 1 pump actuation. These subjects remained on the same dose till the end of study 000077 with no further dose titrations (10 were on 23 mg; 40 were on 46 mg and 56 were on 69 mg dose).

The responder rate at Day 90 in study 000023 was 85.5% (95% CI: 80.2–90.7, Figure 2). More than half of the subjects (52.8%) achieved a responder status as early as Day 1 of treatment. With continued treatment in study 000077, the responder rate reached 82.1% (95% CI: 74.3–89.3) at the end of Month 6 (Figure 2). Overall, the responder rate for 110 subjects who completed a total of 9 months treatment in studies 000023 and 000077 was fairly consistent (84.5% and 82.7% subjects respectively).

The IIEF mean total score demonstrated a significant improvement from baseline to Month 3 (mean improvement of 13.8 ± 17.1, $p < .0001$) in study 000023. This benefit was sustained in study 000077 (mean improvement of 17.5 ± 17.1, $p < .0001$; Figure 3). There was a significant improvement in fatigue as shown by MAF scores for all the four domains and global fatigue index (GFI) in study 000023 (Figure 3), and this benefit was sustained up to Month 9 ($p < .0001$, Figure 3). In study 000023, a statistically significant improvement in the QoL for all four domains, physical and mental component summaries and the mean total score was observed ($p < .0001$, Figure 4), which sustained up to Month 9 ($p < .0001$, Figure 4). About 44% subjects showed significant improvement in severity and symptoms of low testosterone from baseline as shown by ADAM questionnaire scores.

Of the 52 (30.2%) subjects with testosterone C_{max} >1500 ng/dl on Day 90 (Table 2), 14 subjects receiving 69 mg dose, had C_{max} ≥2500 ng/dl. With adjustment in titration decision time point in study 000077, fewer (12 [11.3%]) subjects had C_{max} levels >1500 ng/dl (Table 2). Of these 12 subjects, only three subjects had C_{max} ≥2500 ng/dl (two subjects receiving 46 mg and one subject receiving 69 mg dose). In study 000077, two subjects in FAS had C_{max} values of 4900 ng/dl and 1810 ng/dl, respectively, suspected due to possible contamination or duplicate administration of study drug. Further details for total testosterone and DHT have been presented as supplemental data (Tables S1,S2).

In study 000023, a total of 62 subjects experienced 95 AEs, of which 22 AEs were considered as treatment-related (Table S3). Three subjects had clinically significant abnormal physical examination results at Day 91 (acne on face and upper arms, small testicles [were also found at screening], and mild scaling and erythema on both arms). There was a significant increase from baseline to Day 91 in free testosterone, oestradiol and insulin levels, and statistically significant decrease in sex hormone-binding globulin (SHBG), FSH and LH levels ($p < .0001$ for all). There were three serious adverse events (SAEs; myocardial infarction leading to death, compression fracture lumbar spine and tachyarrhythmia). None of these SAEs were considered related to study drug.

In study 000077, a total of 28 subjects experienced 49 AEs, of which 14 AEs were considered treatment-related (Table S3). All AEs were mild-to-moderate in intensity except two events which were severe (periodontal disease and increased libido). There was a reasonable possibility that the AE of increased libido was related to study drug; hence, the dose was reduced for this subject. Two subjects discontinued from the study due to an AE (haematocrit >54%). Seven subjects had PSA value >4.0 ng/ml; however, none of those were reported as AEs. One subject experienced three SAEs (dehydration, worsening of diverticulitis and exacerbation of diverticulitis after 1 week). However, none of these events were considered possibly

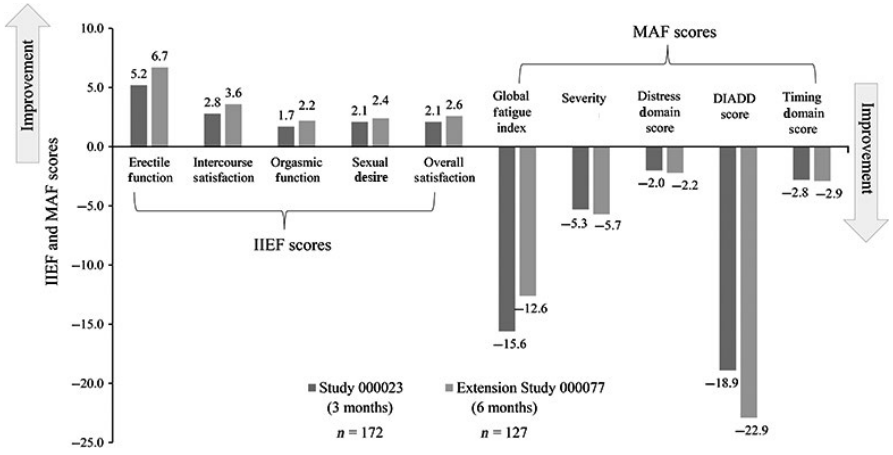

FIGURE 3 Change from baseline in IIEF and MAF scale scores. $p < .0001$ for all domains of IIEF and MAF; DIADD, Degree of Interference in Activities of Daily Living Domain; IIEF, International Index of Erectile Function; MAF, Multidimensional Assessment of Fatigue

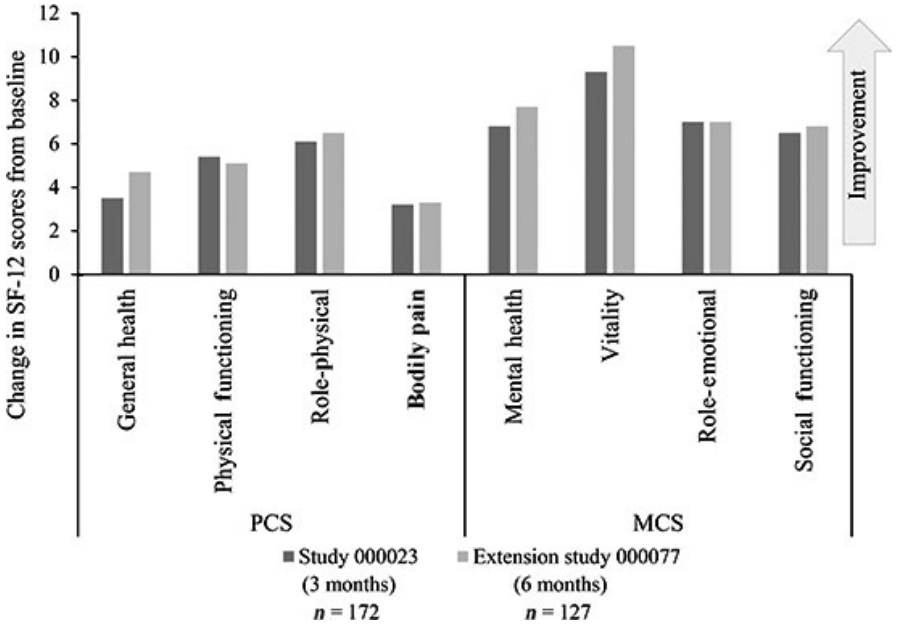

FIGURE 4 SF-12: QoL survey. MCS, Mental Component Summary; PCS, Physical Component Summary; QoL, Quality of Life; SF, Short Form

TABLE 2 Subjects with total testosterone C_{max} (000023 and extension study 000077)

C_{max} (ng/dl)	Study 000023, *N* (%)	Extension study 000077, *N* (%)
≥1500 and ≤1799	20 (11.6)	6 (5.7)
≥1800 and ≤2499	18 (10.5)	3 (2.8)
≥2500	14 (8.1)	3 (2.8)
Total >1500	52 (30.2)	12 (11.3)

C_{max}, Serum testosterone maximum concentration observed.

related to study drug. The majority of events were resolved by the end of study.

4 | DISCUSSION

The present study demonstrated that treatment with testosterone gel 2% was efficacious in normalising the serum testosterone levels and had an acceptable tolerability profile. The responder rate was greater than 82% for both studies and was considered comparable to other testosterone gels although with a much lesser dose. This can be attributed to its novel hydroalcoholic transdermal gel formulation with high bioavailability facilitating quick absorption through the skin with cap applicator providing the ease of hands-free administration. The formulation and the hands-free application may also minimise the risk of secondary exposure of testosterone.

More than half of the subjects achieved normal testosterone levels as early as with the first dose of testosterone gel 2%. By Month 3 (000023) and Month 9 (000077), more than 85.5% and 82.1% subjects, respectively, had normal testosterone levels. These results are comparable to a phase 2 study, where 81.2% subjects achieved normal testosterone levels with testosterone gel 1%, although only after 6 month treatment with higher doses (50, 75 or 100 mg testosterone) (Pexman-Fieth, Behre, Morales, Kan-Dobrosky, & Miller, 2014). Similar results were observed in another study, where >81% subjects achieved testosterone levels between 300 and 1000 ng/dl in approximately 3.7 months, again with a higher dose of topical testosterone gel 1.62% (1.25 g, 2.5 g, 3.75 g and 5.0 g equivalent to 20, 25, 60 and 81 mg of testosterone) (Kaufman et al., 2011). In an open-label study with another testosterone gel 2% (Fortesta™) where treatment was initiated with a 40 mg dose of testosterone (1 g/ml) that could go up to 70 mg, 77.5% subjects achieved serum testosterone levels between 300 and 1140 ng/dl after 3 months of treatment. The responder rate in this study was lower as compared with the present study, although the doses were comparable (Dobs et al., 2012).

Notably, significant improvements in sexual functioning, fatigue and overall QoL were observed from baseline to end of study 000023, which sustained till the end of study 000077. This has a high clinical significance, suggesting that an increase in testosterone levels could provide relief from some of the most concerning clinical symptoms of hypogonadism, such as sexual functioning, and fatigue which severely impact the QoL.

Testosterone levels reached the maximum values between 2 and 4 hr at Month 3 and Month 9, indicating a rapid absorption at the site of application, with testosterone peak levels similar to normal physiological levels. The 24-hour average testosterone levels at Month 3 were well above the lower limit of the normal values, that

is 515 ± 132 ng/dl, 407 ± 160 ng/dl and 495 ± 184 ng/dl for 23 mg, 46 mg and 69 mg dose respectively. In TRiUS study, the average total testosterone levels were 485 ± 284 ng/dl at Month 3 (Miner, Bhattacharya, Blick, Kushner, & Khera, 2013), which increased to 500.6 ± 248.2 ng/dl following 12 months treatment (Khera et al., 2011); however, the doses used in this study were twice as high as used in present study. This suggests that lower doses of testosterone gel 2% used in the present study were efficacious in restoring serum testosterone levels, coupled with a significant improvement in sexual functioning, fatigue and QoL.

The data demonstrated that frequent titration to the highest dose of 69 mg could have potentially been reduced, while maintaining testosterone C_{ave} within normal range along with reduced incidence of C_{max}>1500 ng/dl. This suggests that although titration using testosterone pre-dose levels achieved the high efficacy response rate, it might have resulted in some subjects being titrated to a higher dose than needed. Titration at other time points (close to the C_{max}) may reduce the number of subjects with supraphysiological testosterone levels. However, the possibility of inadvertent application of the gel by the subjects before going to the clinic or contamination of the serum samples from the application site could not be ruled out. Based on these findings, titration decision was adjusted and was taken using 2-hour post-dose C_{max} levels in study 000077 as compared to pre-dose in study 000023. Furthermore, taking clue from studies 000023 and 000077, the titration decision was optimised in a subsequent study (NCT02149264) by basing the decision on 4-hour post-dose serum testosterone levels, consistent with time to maximum testosterone concentration, rather than pre-dose serum testosterone levels. These results will be subject to a follow-up publication.

Most of the AEs observed were mild-to-moderate. The safety results analysed for subjects with total testosterone C_{max} outside the normal range and within pre-determined safety limits did not exhibit distinct evidence that the C_{max} had any impact on incidence of AEs, free testosterone, SHBG or PSA levels. There were no major skin reactions in the present study, suggesting an acceptable local tolerability profile of testosterone gel 2% as noted in a previous study where skin reactions were the most common AEs experienced by the subjects (Dobs et al., 2012).

In conclusion, testosterone gel 2% application was found to be efficacious with an acceptable safety profile in hypogonadal men. This study also gave an important insight for titration decision time point. The incidence of the testosterone C_{max} >1500 ng/dl was greater than expected and for these subjects the C_{max} could have been reduced, while maintaining C_{ave} within normal range. An improved titration schema, both with respect to dosing and titration decision time point, which could reduce the incidence of supraphysiological levels of serum testosterone levels, is also to be considered.

ACKNOWLEDGEMENTS

The studies reported in this analysis were sponsored by Ferring Pharmaceuticals. Medical writing support (funded by Ferring) was provided by Dr Payal Bhardwaj and Mohit Joshi of Tata Consultancy Services.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Belkoff L, Brock G, Carrara D, Neijber A, Ando M, Mitchel J. Efficacy and safety of testosterone replacement gel for treating hypogonadism in men: Phase III open-label studies. *Andrologia*. 2018;50:e12801. https://doi.org/10.1111/and.12801