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New testosterone 2% gel using Ferring Advanced Skin Technology (FAST), for the treatment of testosterone deficiency in men, with a novel applicator

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Abstract

Introduction: Testosterone deficiency (TD) is an increasing problem that can affect a man's physical and psychological health, and quality of life. Testosterone replacement therapy (TRT), combined with weight reduction, lifestyle advice and the treatment of co-morbidities, is the treatment of choice in men who are not concerned about fertility. However, there remains an unmet need in this therapeutic area, relating to factors such as inconvenient or painful administration, fluctuations in testosterone levels, supra-physiologic testosterone levels, poor tolerability and secondary safety issues, which may be associated with the current TRT options. Advances in transdermal delivery systems has resulted in the development of a new 2% transdermal testosterone gel, that may offer some additional features over the other currently available TRTs.

Areas covered: We performed a comprehensive review of the published and grey literature to identify randomised studies and non-randomised studies (NRS) involving adult men receiving treatment for low testosterone levels.

Expert opinion: Topical gels are often the most convenient first line treatment for testosterone deficiency, but options are important as patient preference is more important than virtually any other clinical area of medicine. The chosen therapy must be convenient to use and reach reliable therapeutic levels to effectively and consistently relieve symptoms. Testavan a new 2% testosterone gel, goes some way to achieving these goals.

Keywords: Testosterone, testosterone deficiency, testosterone replacement therapy, transdermal delivery systems, testosterone gel, testavan.

Article highlights

- TD and ED are now recognised as independent risk factors for CVD
- TD is not a simple consequence of male ageing but is associated with important co-morbidities. 80% of men maintain adequate testosterone levels throughout life
- Screening for TD is now recommended by several international expert guidelines in all men with type 2 diabetes, metabolic syndrome, ED and type 2 diabetes.
- TRT for men with low testosterone levels, who fail with generic PDE5 inhibitors, may be more acceptable and cost effective than proceeding to second line ED therapies
- Patients with TD present with bothersome clinical symptoms and expect these to be treated.
- Multiple therapy options are required to address patient expectations.
- There are several unmet needs with currently available therapies.
- New therapies and combination strategies are required to meet patient unmet needs
- Testavan is a new 2% transdermal testosterone gel
- In phase III trials, Testavan treatment restored serum testosterone levels in men with TD and was associated with commensurate improvements in fatigue, sexual function and quality of life^{25,26}
- Testavan was well tolerated in phase II and III trials, with the most common adverse events being application site reactions, affecting 4% of subjects²⁸
- With greater and more rapid absorption than Testogel, and testosterone peaks clearly above the steady-state level, Testavan may provide a treatment effect that more closely mimics that of the natural diurnal variation in testosterone¹⁹
- Testavan's optimal absorption and bioavailability, smaller treatment volumes and applicator application may reduce the risk of secondary transference of testosterone¹⁵ and therefore improve compliance in men who are concerned about this

1. Introduction

Testosterone is the main androgen in men. It plays a crucial role in the development and maintenance of secondary male characteristics, and influences body composition, sexual and cognitive function, erythropoiesis, and bone and muscle health¹.

When testosterone levels fall, men can suffer a variety of physical, sexual and psychological effects, and a subsequent reduction in quality of life². TD has been shown, in multiple longitudinal studies, to be linked to earlier all-cause and cardiovascular disease (CVD)-related mortality, and incident type 2 diabetes³.

The clinical burden of TD has increased notably over the last few years⁴, paralleling the increasing rates of obesity, metabolic syndrome, type 2 diabetes and opiate use⁵. In the European Male Ageing study (EMAS), the prevalence of TD was 2.1% overall in men aged 40-79 years and rates increased with age, from 0.1% in men in their 40's, to 0.6% in those in their 50's, to 3.2 % in those in their 60's, to 5.1% in those in their 70's⁶. Projected estimates suggest that TD will affect as many as 6.5 million American men aged between 30-79 years by 2025; a 38% increase from 2000⁷.

While testosterone levels decrease naturally with advancing age⁸, the EMAS study found that three-quarters of men maintained normal testosterone levels into old age, which suggests that TD is not solely a consequence of ageing⁹. Furthermore, only a small percentage of older men with suppressed testosterone levels develop the genuine syndrome of TD, associated with diffuse physical (e.g. frailty and loss of vigour), sexual (e.g. erectile dysfunction) and psychological (e.g depression) symptoms⁸.

The global prevalence of testosterone deficiency (TD) ranges from 10–40%. The actual diagnosis of TD is controversial, as Internationally, a wide range of total testosterone (TT) thresholds are used for diagnosis 200–400 ng/dL, (7-14nmol/L), and physicians differ in their emphasis placed on clinical symptoms. There are also significant global differences in the prescription patterns of testosterone replacement therapy (TRT). In the United States, for

example, prescription of TRT is significantly higher than the rest of the world, increasing 3-fold over the last 10 years and more so in eugonadal men which is concerning¹⁰.

TD occurs as a result of testicular abnormalities (primary TD), defects in the pituitary or hypothalamus (secondary TD), or a combination of both (combined/mixed TD)¹¹. TD is more likely to affect men of advanced age and those with obesity, metabolic syndrome (MetS) and poor general health³.

TD signs and symptoms vary depending on age at onset, duration and severity^{1,12,13}. Physical signs and symptoms include decreased body hair, gynaecomastia, reduced muscle mass and strength, poor sleep, hot flushes/sweats, fatigue and osteoporosis. Cardio-metabolic signs and symptoms include increased Body Mass Index (BMI), visceral obesity, Metabolic Syndrome (MetS), insulin resistance and type 2 diabetes mellitus. Sexual signs and symptoms include small testicles, delayed puberty, infertility, decreased sexual desire/activity, reduced frequency of sexual thoughts, absent or fewer morning/night-time erections, ED, delayed ejaculation and decreased volume of ejaculate. Psychological signs and symptoms include mood changes, impaired cognitive function and decreased well-being or poor self-rated health^{1,2,11-14}.

A diagnosis of genuine TD requires both clinical and biochemical evidence of suppressed testosterone levels^{12,14}. In this regard, testosterone replacement therapy should only be prescribed when blood levels are unequivocally low, in the presence of clinical signs & symptoms & in the absence of any other potentially treatable causes.

2. Overview of the market

When TD is a consequence of insufficient endogenous testosterone secretion, treatment with exogenous testosterone can restore levels to within the normal range¹⁵. Normalisation of serum testosterone levels leads to subsequent improvements in the clinical signs and symptoms of TD¹, and health-related quality of life².

There are numerous testosterone formulations available, with different routes of administration, pharmacokinetic, pharmacodynamic and tolerability profiles. These include oral and buccal formulations, injectable and implantable products, topical gels and patches.

Testosterone injections and testosterone gels are the most commonly used formulations currently.

While a benefit of the injections is that they don't have to be administered as frequently (usually between 3 and 14 weeks), some preparations may result in high testosterone concentrations shortly after administration, followed by a slow and predictable decline to hypo-gonadal levels. These high peak levels and subsequent troughs may cause significant fluctuations in mood and libido with short acting injections. Other disadvantages include pain at the injection site, polycythaemia in around 6% of men, coughing after administration with the long acting formulation, and they are contraindicated in men with bleeding disorders¹⁶. A long duration of action may be a negative factor in the advent of adverse events.

Testosterone gels are favoured over other transdermal preparations due to their ease of application and dose titration, favourable efficacy and tolerability profiles, and variety of available formulations^{4,15,17}. Gel treatment can be easily customised according to the treatment response⁴ and has a reduced occurrence of supra-physiologic testosterone levels compared to the injections¹⁸. However, a downside of the testosterone gel formulations has been low bioavailability and the need for a large volume to be applied, which some patients may find inconvenient¹⁹. Larger treatment volumes, combined with the fact that the gel formulations are usually applied by hand, also increases the potential for secondary transfer of testosterone to other individuals, which could lead to premature puberty in children and virilisation in women^{4,15,18}.

TD signs and symptoms resolve at different time frames with testosterone treatment, ranging from 3 weeks to more than 12 months²⁰. While the optimal duration of TRT will vary between individuals, based on the cause of their symptoms and the degree of improvement, long-term continuous therapy may be necessary to derive the maximal benefit²¹. However, research suggests that adherence to TRT is often poor²².

A study including 15,435 hypogonadal men, who received an initial topical testosterone prescription in 2009, found that only 34.7% of patients had continued on medication by 6 months and just 15.4% by 12 months. Adherence rates were numerically similar in subjects using AndroGel or Testim gels and did not differ between the age groups. Approximately

50% of the subjects who discontinued their treatment, did resume it though, using the same medication and dose²².

A more recently published study investigated adherence to TRT in 3,184 hypogonadal men who initiated treatment with topical gels (91%), transdermal patches (8.6%), or creams or ointments (<1%) between 2007-2014. Over 1 year of follow-up, 81% of men discontinued their treatment. The mean number of days of persistent use was 98 and a substantial proportion of subjects discontinued their treatment within 30 days of the index date²¹.

Trying to find a TRT that is effective and well-tolerated, which patients will adhere to long-term, can be challenging. New and improved formulations and delivery systems are thus still required, together with patient and physician education about the importance of regular and continued dosing, with careful follow-up.

The approach should be to involve the patient in treatment decisions, explain the aetiology and pathophysiology of TD, and detail the increased cardiovascular risk of untreated TD. Patient education is required to check understanding, and explore any misconceptions and barriers to adherence. It is important to provide an action plan and written information, and to explain the need to continue therapy and the importance of follow up. Lifestyle changes should, wherever possible, involve the spouse or partner. The use of tools such as mobile phone alarms & electronic reminders can be helpful.

3. Testavan®

Advances in transdermal testosterone delivery systems has resulted in the development of Testavan, a new 2% testosterone gel¹⁵. Testavan provides enhanced absorption and higher bioavailability, meaning smaller doses, and therefore smaller volumes, can be used^{15,19}.

Enhanced absorption results from Ferring's Advanced Skin Technology (FAST), which uniquely combines volatile and non-volatile solvents with permeation enhancers to temporarily increase skin permeability, reducing both the volume of gel required and the residual volume. Testavan is also applied with an applicator, instead of the hand, which further reduces the risk of secondary exposure⁴.

4. Pharmacokinetics, clinical efficacy and adverse events

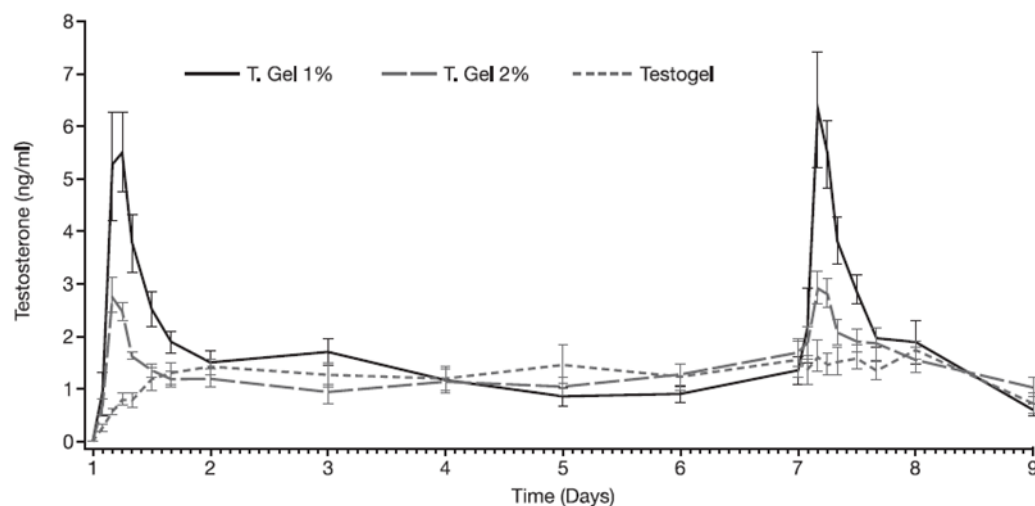
4.1 Phase 1 studies

A randomized, open-label, multiple-dose, three-way cross-over study compared the pharmacokinetics and bioavailability of transdermal testosterone gels 1% and 2% (Testavan) with Testogel® 1%, in 10 healthy men aged between 23-45 years, who underwent pharmacological suppression of endogenous testosterone with triptorelin¹⁹.

Following a 21-day run-in and down-regulation period, subjects received one of 6 treatment sequences. Each sequence involved daily administration over 7 consecutive days, of either 5g testosterone gel 1%, 2.5g of testosterone gel 2%, or 5g Testogel 1% (each dose being equivalent to 50mg testosterone), with a 6-9 day washout period between the different treatment periods¹⁹.

On day 1, the testosterone 1% and 2% gels displayed greater relative bioavailability than Testogel (2.6- and 1.6-fold respectively; $p \leq 0.001$), which persisted, to a lesser extent, on day 7 ($p \leq 0.05$). Initial absorption was fastest and highest with the testosterone 1% and 2% gels¹⁹.

Figure 1. Mean (SE) testosterone concentrations for testosterone gel 1% and 2% formulations, and Testogel from days 1 to 9. Reprinted with permission from [19]



The mean times to maximum levels (T_{max}) of serum testosterone were around 5-6 hours after application with testosterone gel 1% and 2% on days 1 and 7, and around 20 hours following application with Testogel on day 1, with no marked T_{max} after administration on day 7¹⁹.

Maximum serum concentrations (C_{max}) on day 1 were 6.25 and 2.97 ng/mL for Testosterone gel 1% and 2% respectively, occurring around 5-6 hours post-application, versus 1.71 ng/mL after around 24 hours with Testogel. These differences were similar on day 7. All of the treatments appeared to reach a similar steady-state level with the first 24 hours¹⁹.

While the terminal half-life (T_{1/2}) was similar for testosterone gel 1% and 2% on day 1 (around 15 hours), it was more than twice as long for testosterone gel 2% on day 7 (around 21 hours vs around 9 hours for testosterone gel 1%). The T_{1/2} was considerably longer with Testogel than testosterone gel 1% or 2% on days 1 and 7 (around 53 and 72 hours respectively), as a result of its slower absorption. However, please note that we are advised to treat these results with caution, in light of the shallow slopes in the terminal parts of the curve¹⁹.

Serum DHT concentrations closely followed the serum testosterone time course, though with smaller amplitudes, reflecting metabolic conversion by 5- α reductase activity in the skin. The area under the concentration–time curve from the first and last doses on days 1 and 7 (AUC) and C_{max} were significantly higher with testosterone gel 1% than with Testogel on days 1 (p<0.0001 and p=0.0003 respectively) and 7 (p=0.0376 and p=0.0013 respectively). While the AUC was significantly higher with testosterone gel 2% than Testogel on day 1 (p=0.0415), there was no statistically significant difference between these treatments in AUC on day 7 and C_{max} on days 1 and 7. No application-site reactions were observed with any of the formulations. In conclusion, this study confirmed that Testavan has higher bioavailability than Testogel, and can deliver more testosterone in a smaller volume¹⁹.

Table 1. Intra-individual comparison of serum testosterone and dihydrotestosterone geometric mean and mean ratios for AUC and C_{max} for the testosterone 1% and 2% formulations versus Testogel for days 1 and 7. Reproduced with permission from [19]

Parameter	Day	Testosterone gel 1% (n=11) Geometric mean	Testosterone gel 2% (n=10) Geometric mean	Testogel (n=11) Geometric mean	Mean ratio	90% CI	P-Value
Testosterone AUC (ng/mL h)	1	57.1	-	21.7	2.63	2.18; 3.17	<0.001
	7	66.7	-	33.4	2.00	1.53; 2.60	0.001
	1	-	35.0	21.7	1.61	1.33; 1.96	0.001
	7	-	46.6	33.4	1.39	1.06; 1.83	0.050

C _{max} (ng/mL)	1	5.49	-	1.59	3.45	2.66; 4.49	<0.0001
	7	5.74	-	2.07	2.78	2.07; 3.73	<0.0001
	1	-	2.88	1.59	1.18	1.38; 2.38	0.0015
	7	-	3.18	2.07	1.54	1.14; 2.08	0.0238
Dihydrotestosterone AUC (ng/mL h)	1	15.7	-	8.8	1.79	1.48; 1.16	<0.0001
	7	16.2	-	11.5	1.42	1.08; 1.86	0.0376
	1	-	11.3	8.8	1.29	1.06; 1.58	0.0415
	7	-	13.5	11.5	1.18	0.89; 1.57	0.3266
C _{max} (ng/mL)	1	1.0	-	0.6	1.71	1.39; 2.11	0.0003
	7	1.1	-	0.7	1.63	1.31; 2.02	0.0013
	1	-	0.7	0.6	1.22	0.98; 1.54	0.1375
	7	-	0.8	0.7	1.16	0.92; 1.46	0.2750

AUC – area under the concentration-time curve from the last dose (Day 7) and 24 hours post dose. C_{max} – maximum serum concentrations. Endpoints are ln-transformed before analysis, and results are transformed back and presented as ratios. The model is a mixed linear model and includes treatment and period as fixed effects, and subjects as random effect. The mean is the geometric least square means estimated from the model. The P-Value is based on a two-sided test of the difference. 90% confidence intervals (CI) are given.

Readers should be aware though, that levels of testosterone do not always correlate with clinical effects or outcomes due to androgen receptor issues mentioned later in the document.

The diurnal rhythm of serum testosterone means that values are highest in the early morning¹¹, and although this variation may be substantially blunted in older men¹⁴, it may still exist, even in the elderly²³. With its greater and more rapid absorption versus Testogel, and testosterone peaks clearly above that of the steady-state level, Testavan may also provide a treatment effect that more closely mimics that of the natural diurnal variation in testosterone¹⁹.

4.2 Phase II studies

The efficacy, bioavailability and safety of Testavan 2% testosterone gel was evaluated in two small, phase II sequential, dose escalation studies. Each study included 20 hypogonadal men, aged between 18-75 years, with serum testosterone levels <300ng/dl and one or more symptoms of TD (fatigue, decreased libido, or decreased sexual functioning)²⁴.

Study 1 evaluated the bioavailability of 3 Testavan volumes/testosterone doses, 1.25 ml/23 mg, 2.50 ml/46mg and 3.75 ml/70 mg, applied once daily by hand, to the shoulder/upper arm over 10 days. It also evaluated the bioavailability of a single Testavan 2.50 ml dose,

applied to three different sites, the upper arm/shoulder, thigh and abdomen. Study 2 evaluated the bioavailability of Testavan 1.25, 2.50 and 3.75 ml applied by applicator, versus Testavan 2.5 ml applied by hand, once daily, to the shoulder/upper arm over 7 days²⁴.

The primary endpoint in both studies was the responder rate, defined as the percentage of subjects with minimum observed testosterone levels in the normal range (C_{\min}) or average steady-state serum testosterone concentrations (C_{ave}) between 298-1050 ng/dl). The secondary pharmacokinetic endpoints were the serum-concentration time profiles of total testosterone, free testosterone (study 1 only) and dihydrotestosterone (DHT) following all single- and multiple-dose applications²⁴.

The key efficacy measures in study 1 were change from baseline in Multidimensional Assessment of Fatigue (MAF) scores (including severity, distress, degree of interference in activities of daily living, and timing), and International Index of Erectile function (IIEF) scores (including erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction). In study 2, the key efficacy measure was subject satisfaction with using the applicator²⁴.

In study 1, after 10 days treatment with Testavan applied by hand, 73.7, 77.7 and 75% of subjects were C_{ave} responders, and 20, 40 and 55% of subjects were C_{\min} responders, in the 1.25, 2.50 and 3.75 ml dose groups respectively. Absorption and bioavailability of Testavan was higher with application to the upper arm/shoulder than to the thigh and abdomen. Multiple-dose application to the shoulder/upper arm was also associated with a dose-proportional increase in absorption, reflected by total and free testosterone levels, and metabolism of testosterone to its biologically active form, DHT²⁴.

In study 2, after 7 days of treatment with Testavan applied by applicator, increasing response rates paralleled increasing doses, with 16.7, 50 and 77.8% of subjects responding to the 1.25, 2.50 and 3.75 ml doses respectively. The response rate with Testavan 2.5 ml was similar for hand- and applicator-application. There was no difference in mean total testosterone concentrations with hand- or applicator-application of Testavan 2.5 ml. C_{\max} , C_{\min} and C_{ave} were also comparable for both total testosterone and DHT with hand- and applicator-application. No subjects had average testosterone levels above normal levels (C_{ave}

>1050 ng/dl). Six subjects had maximum testosterone levels above normal levels (C_{\max} >1050 ng/dl)²⁴.

More than 80% of subjects preferred applicator-application to hand-application, more than 70% found the applicator easy to use and more than 65% found the applicator more convenient²⁴.

There were significant improvements in IIEF scores, for all domains, except erectile function, which showed a numerical improvement. All four domains of the MAF improved significantly²⁴.

In study 1, after single-application of Testavan 2.5ml, there was 1 mild adverse event (AE; mild erythema on the inner thigh). After multiple dosing, there were 5 mild AEs (elevated transaminase level, gastrointestinal distress, nipple pain and two incidences of increased PSA), 4 of which were considered possibly related to the study drug. In study 2, only one individual experienced an AE (mild erythema)²⁴.

The study authors concluded that Testavan was efficacious and well tolerated over the evaluated doses, and absorption and bioavailability were greatest from the shoulder/upper arm area. The pump-applicator allowed precise dosing and was associated with better acceptance and compliance than hand-application²⁴.

In this study however, the dose-dependent increase in responder rate where applicator-application was used, was not apparent where hand-application was used. This might have been due to the difference in the number of men with a BMI $\geq 30\text{kg/m}^2$ (25% in the applicator-application study versus 40% in the hand-application study), as BMI may affect the absorption of testosterone. When translated to clinical practice, men with an increased BMI may thus require higher doses of exogenous testosterone to achieve normal testosterone levels²⁴.

4.3 Phase III studies

The efficacy and safety of Testavan was evaluated in a pivotal phase III study with a 90 day treatment period. This study included hypogonadal men aged between 18-75 years with fasting morning testosterone levels <300 ng/dl measured on 2 occasions, at least 3 days

apart. More than 86% of subjects had symptoms of TD based on the ADAM questionnaire, 82% said their erections were less strong, 82% reported decreased libido, and 86% noted a lack of energy²⁵.

The primary efficacy endpoint was the responder rate (defined as the number of subjects achieving a steady-state serum total testosterone concentration (C_{ave}) between 300-1050 ng/dl on day 90). Secondary efficacy endpoints included C_{ave} on days 14, 35 and 56, changes from baseline to days 45 and 90 in IIEF, MAF and, Short-Form-12 Health survey (SF-12), and DHT/testosterone ratio at day 90. Safety and tolerability were assessed throughout²⁵.

Of the 159 subjects treated, 139 completed all visits. Primary TD affected 3.8% of subjects and secondary TD affected 96.2%. The responder rate increased from 29.1% on day 14, to 75% on day 56, with 76.1% of the 155 patients in the full analysis set being C_{ave} responders at day 90²⁵.

At day 90, the testosterone:DHT ratio showed a similar trend for all 3 doses, and the pharmacokinetic profiles of testosterone and DHT were similar for the 46 and 69 mg doses. Only a small number of subjects experienced brief supraphysiological levels of testosterone and there were few application site reactions. The overall safety and tolerability of Testavan were considered favourable²⁵.

There were significant improvements in each individual IIEF domain score from baseline to days 35 and 90 (each $p < 0.0001$). See Table 1. Global Fatigue Index and MAF scores also improved significantly from baseline to days 35 and 90 (both $p < 0.0001$) See Table 2. There was also significant improvement from baseline to days 35 and 90 in the total physical component summary, derived from the SF-12, ($p = 0.0343$ and 0.0033 respectively) and the average total mental component summary ($p < 0.0001$ for both days)²⁵.

Based on a treatment satisfaction questionnaire, 93.5% of subjects were satisfied or very satisfied with using the applicator, 87.7% considered it easy to use and 87% thought it posed a lower risk of transference of testosterone to a partner or child than direct contact with application site or hands²⁵.

Belkoff *et al*²⁶, evaluated the efficacy, safety, local tolerability and pharmacokinetics of Testavan in two supportive, open labelled, single-arm, multicentre phase III studies. The

studies included men with TD (defined as two consecutive screening testosterone levels of <300 ng/dl and clinical symptoms of TD based on the ADAM questionnaire) who were aged between 18-75 years. The study duration was 9 months, with study 1 lasting 3 months and study 2 lasting 6 months.

In study 1, subjects applied Testavan to the shoulder/upper arm each morning with the applicator. The starting dose for all subjects was 46mg, which could be titrated up to 69 mg or down to 23mg at day 21 or day 56, according to response. The primary efficacy endpoint was the responder rate (defined as the number of subjects with an average serum total testosterone concentration within the physiologic range of 300-1050 ng/dl on day 90.) Secondary efficacy variables included sexual function, evaluated via the IIEF scale, fatigue, assessed using the MAF scale, and quality of life (QoL), assessed using the SF-12, on day 90. The extension study (study 2) evaluated the same efficacy parameters as study 1, and also included pharmacokinetic assessments for testosterone and DHT²⁶.

In study 1, the responder rate at day 90 was 85.5%, and more than half of the subjects responded as early as day 1 of treatment. With continued treatment in study 2, the responder rate was 82.1% at the end of month 6. The overall responder rates for the 110 subjects who completed 9 months of Testavan treatment, were 84.5% in study 1 and 82.7% in study 2²⁶.

Maximum testosterone levels were reached between 2 and 4 hours at months 3 and 9, indicating rapid absorption at the application site, with peak testosterone levels reflecting normal physiological levels. However, 30.2% of subjects had a maximum testosterone concentration >1500 ng/dl on day 90, and 8.1% of those who received the 69mg dose had a maximum testosterone concentration ≥ 2500 ng/dl²⁶.

IIEF scores improved significantly in study 1 (mean improvement of 13.8 ± 17.1 ; $p < 0.0001$) and these benefits were maintained in study 2 (mean improvement of 17.5 ± 17.1 ; $p < 0.0001$). See Table 1. MAF scores showed a significant improvement in fatigue for all four domains and global fatigue index in study 1, and this benefit persisted through study 2 ($p < 0.0001$). See Table 2. QoL also improved significantly, for all 4 domains, in study 1 ($p < 0.0001$), and this also was maintained in study 2 ($p < 0.0001$). Around 44% of subjects

benefitted from significant improvements in symptoms and severity of TD from baseline, according to ADAM questionnaire scores²⁶.

Ninety-five adverse events were experienced by 62 subjects in study 1., of which 22 were considered related to treatment. Forty-nine adverse events were 28 subjects in study 2, of which 14 were considered related to treatment. Most of the reported AEs were mild-to moderate and the majority had resolved by the end of the study²⁶.

The study authors concluded that Testavan was efficacious and well tolerated. They also noted that frequent titration to the highest dose of 69mg could have been reduced, while maintaining the average steady-state serum total testosterone concentration in the normal range and reducing the incidence of maximum testosterone concentrations >1500 ng/dl (> 52 nmol/l)²⁶.

Table 3. Improvement in IIEF* scores from baseline with Testavan in phase III studies

IIEF scores	Study 1 ²⁵		Study 2 ²⁶	
	Day 35	Day 90	3 months	9 months
Sexual desire	1.2	2.2	2.1	2.4
Erectile function	3.4	5.9	5.2	6.7
Orgasmic function	1.3	1.8	1.7	2.2
Intercourse satisfaction	1.3	2.4	2.8	3.6
Overall satisfaction	1.2	2.1	2.1	2.6
	P<0.0001 for all		P <0.0001 for all	

*International Index of Erectile Function

Table 4. Improvement in MAF* scale scores from baseline with Testavan in phase III studies

MAF scale scores	Study 1 ²⁵		Study 2 ²⁶	
	Day 35	Day 90	3 months	9 months
Global fatigue index	8.2	11.8	15.6	12.6
Severity	3.6	5.2	5.3	5.7
Distress	1.7	2.2	2.0	2.2
DIADD**	13.6	16.7	18.9	22.9
Timing	2.6	3.0	2.8	2.9
	P<0.0001 for all		P <0.0001 for all	

*Multidimensional Assessment of Fatigue. **Degree of Interference in Activities of Daily Living Domain

5. Regulatory affairs, dosing and administration

Testavan is available in the UK, Australia, Ireland, Luxembourg, Romania, Netherlands, Belgium, Norway, Sweden, Finland, Denmark, Germany, Italy, Slovakia, Spain, Portugal, Czech Republic, Poland, Switzerland and Austria.

Testavan is a 20mg/g transdermal gel, which comes in a metered dose dispenser with a hands-free cap applicator for precise dispensing and application²⁷. One pump action delivers 1.15g/1.25ml of gel, equivalent to 23 mg testosterone. Testavan is indicated for adult male hypogonadism, when TD is confirmed by clinical features and biochemical evidence, confirmed by two separate blood tests²⁸.

The recommended starting dose is 23mg (1 pump press), applied once daily, preferably in the morning, to clean, dry, intact skin on the upper arm/shoulder, where it would be covered by a short-sleeved T shirt²⁷. Following administration, patients should be advised to let the application dry fully before dressing, wait at least 2 hours before showering, bathing or swimming, and wear clothing that covers the application site²⁸.

It is recommended that the testosterone level is measured 2-4 hours post-dosing on approximately days 14 and 35 after treatment initiation or dose adjustment. If the serum testosterone level is <500 ng/dl (17.3 nmol/L), the daily dose may be increased by 1 pump press. If it is >1050 ng/dl (36.4 nmol/L), the daily dose may be decreased by one pump press. Dose titration should be based on signs and symptoms of TD, and biochemical results. The maximum recommended daily dose is 3.45g gel, containing 69mg testosterone, which is equivalent to 3 pump presses²⁸.

Elderly patients should receive the same dose as adult men, bearing in mind that physiological testosterone levels decrease with advancing age. Risk of pre-existing prostate cancer must be excluded prior to starting Testavan treatment²⁸.

Testavan should be used with caution in patients with²⁸:

- renal and hepatic impairment
- hypertension
- thrombophilia
- Severe cardiac disease
- Ischaemic heart disease

- migraine
- epilepsy
- cancer, who are at risk of hypercalcaemia and associated hypercalciuria due to bone metastases

Caution should also be applied in patients taking oral anticoagulants, adrenocorticotrophic hormone (ACTH) and corticosteroids, because of potential drug interactions²⁸.

The question has arisen, as to whether testosterone therapy is associated with short-term risk of venous thromboembolism (VTE) in men with and without hypogonadism. The FDA issued a warning on this matter in 2014²⁹, and a subsequent warning relating to cardiovascular risk in 2015³⁰, but the data on both these risks is scant and open to interpretation.

A recent case-crossover study published in JAMA, compared 6-month testosterone use for 39,622 men who had a VTE with testosterone use 6 to 12 months before the VTE. Use of testosterone therapy in the 6-month case period was associated with an increased short-term risk of VTE in men with and without hypogonadism³¹.

Risk factor screening should be considered, such as Factor V Leiden (FVL) heterogeneity, the lupus anticoagulant, and high lipoprotein(a) plus a careful enquiry of past VTE events³².

Contraindications to Testavan treatment include hypersensitivity to any of the ingredients and known or suspected carcinoma of the prostate or breast²⁸.

Testosterone levels should be checked at baseline and regularly thereafter, according to evidence-based guidelines. The dose should be adjusted to ensure maintenance of eugonadal testosterone levels. Clinical signs that may indicate excessive androgen exposure and dose adjustment, include nervousness, irritability, weight gain and prolonged or frequent erections²⁸.

Evaluate patients at 3, 6 and 12 months, then every 12 months thereafter to assess serum testosterone levels (therapeutic target mid-upper range: 15–30 nmol/L), confirm symptomatic

improvement and check for any changes in haematocrit (should remain <54%) and PSA (increases >1.4 ng/mL over any 1-year period or a velocity >0.4 ng/mL/year during

sequential measurement over >2 years warrants urological evaluation + more intensive surveillance for prostate cancer

thereafter); 3-monthly follow-up may be necessary in some patients, including those with suboptimal treatment response or safety issues¹².

Patients on long-term treatment should have their haemoglobin, haematocrit, liver function and lipid profile checked regularly. Careful monitoring of the prostate and breast should be performed at least annually, or twice yearly in elderly patients and those at increased risk through clinical or familial factors²⁸.

The most common adverse effects in the phase II and phase III trials were application site reactions (4%), including skin irritation, rash, erythema, pruritus, dermatitis and skin dryness. Most of these reactions were mild to moderate in severity. Hypertension, hypertriglyceridemia, increased PSA and increased haematocrit were also commonly observed (affecting $\geq 1/100$ to $< 1/10$ patients)²⁸.

6. Conclusion

Low testosterone is a real concern for many men, and because three-quarters of men in the EMAS maintained normal testosterone levels into old age⁹, we can assume that, TD is not solely a consequence of ageing, but is often related to underlying co-morbidity.

Testavan's optimal absorption and bioavailability mean that smaller volumes of gel can be used to achieve normalisation of serum testosterone levels, which reduces skin residue. Applicator-application also minimises hand contamination with testosterone, which further reduces the risk of transferring testosterone to a partner or child. Testavan therefore expands the treatment options for men with TD who are not concerned about fertility, and may also aid compliance in those concerned about secondary transference.

7. Expert opinion

International expert guidelines now recognise TD and ED as independent risk factors for CVD. Multiple professional associations recommend screening for TD and ED in high risk groups, such as type 2 diabetes, metabolic syndrome, obesity and regular opiate users^{12,33,34}. Currently, however, few diabetes specialists routinely include assessment of ED and TD as part of routine case. Implementation of these guidelines will uncover many

previously undiagnosed patients who require treatment because of bothersome symptoms. In early 2020, a large double-blind placebo-controlled study from Australia, the T4DM trial³⁵, will report on whether treatment with TRT, in obese men with pre-diabetes and TD, can prevent progression to type 2 diabetes. It is therefore likely that health care professionals will see increasing numbers of patients who are candidates for TRT and have complex treatment needs.

Men with TD, by definition, are symptomatic and require therapy that is usually life-long and effectively relieves those bothersome symptoms. This is a particularly relevant for urologists, who receive referrals for patients requesting therapy sexual dysfunction. In contrast, endocrinologists rarely ask about sexual symptoms and patients seldom complain. Issues of convenience, tolerability and reliable efficacy are therefore of critical importance. The high rates of discontinuation seen with existing therapies clearly demonstrate that patients have important unmet needs.

Oral testosterone is not commonly used in the UK, mainly due to the need for frequent dosing, the need to be taken with a fatty meal and concerns about first pass effects on the liver.

Self-administered short acting injections are cheap but inconvenient as they require training to be safely and reliably administered. This can be a major life change that many men find unacceptable. A major risk is the rapid change in levels that can lead to a patient increasing doses of their own volition due to rebound symptoms leading to rises in haematocrit and possible increased CV risk.

Long acting depot injections, such as Testosterone Undecanoate, usually require appointments with health care professionals with associated costs. Steady state levels within the normal range can usually be achieved but raised haematocrit can still be a problem in around 6% of patients. Injection site pain can be a problem for some men. Pellets of long acting testosterone requiring specialist insertion are popular in the US, but not available in the UK and Europe.

Topical gels are often the most convenient first line treatment, but options are important as patient preference is more important than virtually any other clinical area of medicine. The

chosen therapy must be convenient to use and reach reliable therapeutic levels to effectively and consistently relieve symptoms.

Studies suggest that Testavan may provide more effective in reaching therapeutic levels with a reduced volume of gel and testosterone dose due to improved skin absorption. A 2% gel requires less volume of product but may be associated with a greater risk of skin irritation. There may be an advantage for convenience, and especially in areas or occasions where access to soap and water is limited. Lifestyle issues such as frequent showering, swimming, sun exposure, shift work and frequent flying can be significant issues for some patients. Third party transfer is an important issue for a significant number of men, especially those with small children, and the novel applicator seems to largely overcome the transfer problem.

There are still unmet needs with current regimes. Combination therapies with long acting injections and top-up gels may be a way of reaching therapeutic levels in patients who do not respond to one agent alone, but this is off label use, and expensive. We now know that some men have insensitive androgen receptors with high number of CAG repeats and require much higher doses for clinical benefits³⁶. It is likely that more men will be tested for androgen receptor polymorphism in future to detect these patients requiring higher doses for clinical effect.

Current licensed preparations suppress LH/FSH production and therefore significantly reduce fertility. Many men might state that this is not an issue for them, but as most men present with sexual problems, the chance of marital breakup might lead to fertility becoming a problem in the future. Whilst there is evidence that, for most men, endogenous production might return after 9-12 months, this is unpredictable and cessation of therapy is usually associated with the return of bothersome sexual symptoms, such as loss of desire and ED, which will clearly affect fertility. Many men are therefore condemned to tolerate their symptoms, throwing further strain on their work and relationships.

In primary hypogonadism, there is little alternative to TRT, but for secondary cases, other strategies are possible. Clomiphene³⁷ or Tamoxifen can block the inhibitory effect of oestradiol on pituitary feedback and increase endogenous testosterone production. Both are off-label in men, a considerable problem for GP prescribing and response is less

predictable in older men, especially over 50. HCG (Human Chorionic Gonadotrophin) at 5000 units by subcutaneous injection twice to 3 times weekly can be effective but is expensive for long term use³⁸. There are few published long term studies as to clinical benefits for HCG. Combination therapy with TRT and low dose HCG (500 units twice or 3 times weekly) or Clomiphene can effectively preserve fertility for many men but this is off-label use with little long- term data to support this approach. Unfortunately, such trials, involving these generic products are unlikely to be conducted, due to expense and the limited indications. Sperm storage may be a logical approach before commencing treatment but few patients or physicians consider this, often due to expense and logistic issues. As ED and TD are now widely accepted as independent risk factors for CVD, the next five years is likely to see many more patients presenting for treatment, as the screening recommendations for high risk patients are implemented, according to evidence- based guidelines. The outcome of studies such as T4DM³⁵ and TRAVERSE³⁹ are likely to have considerable impact on future prescribing patterns. As more men with ED are screened and seek treatment and fail to respond to oral therapy in around 50% of cases, many will elect for correction of low/borderline testosterone levels to enhance response to cheaper generic PDE5 inhibitors rather than move to expensive and invasive second line therapies such as intra-cavernosal injection¹². As the patents for testosterone gel preparations expire in the next 12-18 months, these savings will become even more relevant.

Novel products are in development to meet these unmet needs. A new oral testosterone formulation is under development⁴⁰. This is likely to prove more acceptable than current formulations, either alone or in combinations.

A testosterone nasal spray is current licensed in North America and shortly likely to be licensed in Europe. This requires twice daily administration and may be acceptable to many men either alone or in combination with other TRT. The major advantage is the prompt onset of action and the lack of LH/FSH suppression⁴¹.

A long-acting oral Aromatase Inhibitor (AI) is under-development and could represent considerable advantages in blocking the conversion of testosterone to oestrogen, thus increasing endogenous levels. This has the potential to preserve fertility and reduce visceral adiposity, but monitoring will be required as a reduction of oestradiol might potentially increase the risk of osteopenia in the long term⁴².

Enclomiphine (a mixture of 2 isomers of clomiphene) has been under development for several years, targeting the treatment of men with secondary hypogonadism wishing to preserve fertility. This might be useful for younger obese men wishing to preserve fertility, either alone or in combination with existing therapies⁴³.

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Information resources

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