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The long-term efficacy and safety of a testosterone mucoadhesive buccal tablet in testosterone-deficient men

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Striant® sustained-release (SR) is a mucoadhesive buccal tablet (30 mg testosterone, The Urology Company) that adheres to the gum surface in the mouth providing controlled- and sustained-release of testosterone over a 12-h dosing period, offering a unique and rational method of testosterone delivery. Striant SR is indicated for testosterone-replacement therapy (TRT) for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests. Pharmacokinetic studies have shown that testosterone is released from Striant SR in a manner similar to the normal daily rhythm of endogenous testosterone secretion, with serum levels rising rapidly after insertion and peak levels reached by the second 12-hourly dose with no accumulation over time. In clinical trials involving hypogonadal men receiving Striant SR for up to 2 years, mean serum testosterone levels have always remained within the normal range. Striant SR is well tolerated, with gum-related disorders (such as irritation, inflammation and gingivitis) and taste perversion being the most commonly reported adverse events, reported by 5.6–16.3% and 3.0–4.1% of patients, respectively. Once patients have become accustomed to it, Striant SR has a high level of patient acceptance. In a long-term study, 90% of patients rated the twice-daily dosing as acceptable, just under half preferred it to other forms of TRT that they have used and 96% found it to be cosmetically acceptable. There is no clinically significant risk of testosterone transfer from Striant SR, as any testosterone that may be present in the saliva when swallowed is subject to extensive first-pass hepatic metabolism. It is pertinent to note that the saliva of eugonadal men contains similar levels of endogenous testosterone. Buccal delivery is particularly suitable where easy and rapid reversal of treatment might be required (such as in late-onset hypogonadism) and where there is a need to avoid the potential for transfer of testosterone to women and young children.

What's known on the subject? and What does the study add?
Striant® SR is the only available buccal delivery system for testosterone replacement therapy. Previous pharmacokinetic studies have shown that Striant SR effectively produces physiological serum testosterone levels in hypogonadal men. Efficacy and safety data from previously unpublished studies over 2 years of continuous use indicate that Striant SR is effective long term in maintaining serum testosterone within a physiological range, is well tolerated and has a high level of patient acceptance.

KEYWORDS

hypogonadism, late-onset hypogonadism, testosterone deficiency, testosterone replacement, testosterone supplement, buccal delivery

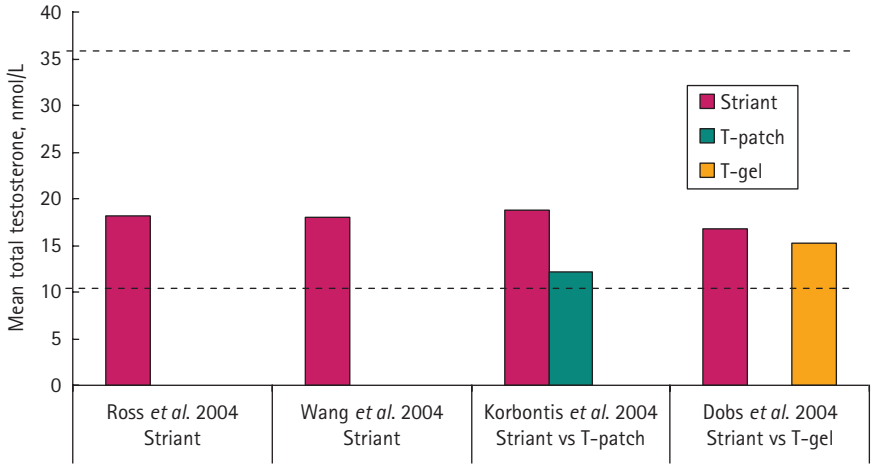
INTRODUCTION

Striant® sustained-release (SR) testosterone buccal system (The Urology Company) is a mucoadhesive tablet that adheres to the gum surface in the mouth providing controlled- and sustained-release of testosterone over a 12-h dosing period. Striant SR is indicated for testosterone-replacement therapy (TRT) for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests [1]. Striant SR was the first buccal system for TRT and remains the only product on the market delivering testosterone by this unique route.

The pharmacokinetics, efficacy and safety data obtained from clinical trials were examined in previous reviews of Striant SR around the time of the product launch [2,3]. This review aims to re-evaluate that data considering developments in treatment guidelines and the experience gained from >7 years of prescribing and access to previously unpublished results from two long-term safety studies.

Male hypogonadism or testosterone-deficiency syndrome has been defined in different ways [4], but the terms are generally used to refer to any state characterised by low blood testosterone levels. The cause may be in the testis (primary or hypergonadotrophic hypogonadism) or a hypothalamic or pituitary disorder (secondary or hypogonadotrophic hypogonadism) [5]. Serum testosterone levels also decline gradually as a consequence of ageing. However, the correlation between testosterone levels and symptoms is poor and surveys have shown that a considerable portion of men with low testosterone are asymptomatic [6]. It is therefore generally accepted that age-related diminishing testosterone levels (also referred to as late-onset hypogonadism), are only considered clinically relevant if symptomatic

FIG. 1. Time-averaged serum concentration at steady state over a 24-h period ($C_{AVG\ (0–24)}$) in clinical trials of Striant [14,15], Striant vs testosterone transdermal patch (T-patch) [16] or testosterone gel (T-gel) [17] in testosterone-deficient men. The region between the dashed lines represents the physiological range of testosterone (10.4–36.4 nmol/L).



[7,8]. Two large USA surveys identified that the prevalence of symptomatic testosterone deficiency in adult males is between 5.6% and 12% of the male population [6,9] and >8% of men aged 50–79 years [10].

The condition can have a significant negative effect on health-related quality of life and can adversely affect the function of multiple organ systems [11]. As the population continues to age, the clinical and economic burden of testosterone-deficiency syndrome will increase [11].

TREATMENT GUIDELINES

In guidelines produced in 2010 by both the British Society for Sexual Medicine [10] and the Endocrine Society [7], testosterone therapy is recommended for men with symptomatic testosterone deficiency to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone density [7,10]. The aim of TRT is to restore serum testosterone to the mid-normal eugonadal levels and minimise signs and symptoms of hypogonadism. However, the ultimate goals are to maintain or regain the highest health-related quality of life, to reduce disability and the development of major illnesses [12].

TESTOSTERONE PREPARATIONS

Various testosterone formulations are available for substitution therapy including implants, injectable, oral, buccal and dermal preparations. Each of the formulations has specific benefits and potential problems [13] and the selection of the preparation should be a joint decision of an informed patient and physician considering the patient's lifestyle, family situation and likelihood of compliance as well as the need to consider the possibility of transference to a child or partner [10].

BUCCAL DELIVERY OF TESTOSTERONE

Striant SR, the only available buccal delivery system for testosterone, is a progressive hydration tablet with a matrix containing 30 mg testosterone [1]. The buccal tablet is placed in position on the gum above the right or left canine, twice daily, ≈12 h apart, and is held in position for ≈30 s. As it absorbs water from the oral cavity it quickly adheres to the buccal mucosa and the matrix of the tablet slowly hydrates to become soft and gelatinous enabling the slow, constant release of testosterone from the convex surface. The dry portion of the system protects the active ingredient from moisture and the environment until it is hydrated and released [14]. Once released the testosterone is immediately absorbed via the buccal mucosa to take advantage of the venous drainage from the oral cavity, which flows directly to the superior vena cava enabling the buccal delivery of testosterone to circumvent hepatic first-pass metabolism [1].

PHARMACOKINETICS OF STRIANT SR

Pharmacokinetic studies (Table 1 [14–17]) have shown that testosterone is released from Striant SR in a manner similar to the normal daily rhythm of endogenous testosterone secretion, with serum levels rising rapidly after insertion and peak levels reached by the second 12-hourly dose with no accumulation over time. Removal of the system results in a rapid drop in testosterone levels allowing for easy reversal if necessary.

TOTAL SERUM TESTOSTERONE

The pharmacokinetics of Striant SR used for 7 days at the recommended twice daily dosing schedule were investigated in 12 testosterone-deficient men [15]. Total serum testosterone levels increased from a mean (SD) baseline of 3.7 (3.6) nmol/L to a peak concentration (C_{max}) of 26.6 (5.8) nmol/L at 4.8 (5.8) h [15]. A steady state for total serum testosterone concentration was achieved within the first 24 h (i.e. by the second dose) [15].

The mean C_{max} over the full 7-day dosing period was 31.5 nmol/L, which was at the high end of the normal range [15]. At 12 h after removal of the final tablet, the mean serum testosterone had returned to baseline levels (3.4 nmol/L) [15].

A similar pharmacokinetic profile was seen in a larger phase III trial of Striant SR in 82 men [14] (Table 1). The mean (SD) total serum testosterone level increased from a baseline of 5.2 (3.1) nmol/L and remained within a range of 20.1–24.9 nmol/L throughout the 12-week treatment period [14]. At steady state, 72.6% of reportable individual patient total testosterone serum concentrations were within the physiological range, as were all the mean serum testosterone concentrations at every sampling point over a 24-h period at week 12 [14]. The time-averaged testosterone level ($C_{AVG\ (0–24)}$) of 18.0 nmol/L was also within the normal range and intra-patient variability was low (Fig. 1 [14–17]).

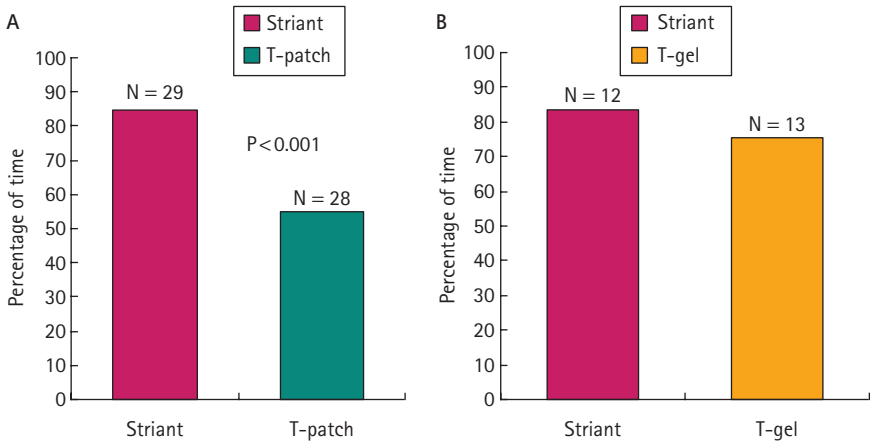
TABLE 1 Pharmacokinetic studies of Striant SR in otherwise healthy testosterone-deficient men

Reference	Study design	Treatment(s)	Blood sampling schedule	Parameter	Mean (sd)
Ross *et al.* 2004 [15] (UK)	Phase I, open-label, single centre	Striant SR twice daily for 7 days	Blood samples taken daily and multiple samples taken over 24 h on days 7 and 8.	n	12
				$C_{max\ 1-7D}$ (nmol/L)	31.5 (7.1)
				$C_{max\ (0-24)}$ (nmol/L)	26.7 (6.0)
				$C_{min\ (0-24)}$ (nmol/L)	11.8 (4.7)
				C_{AVGtot} (nmol/L)	19.3 (3.2)
				$C_{AVG\ (0-24)}$ (nmol/L)	18.2 (5.0)
				$T_{max\ 1-7D}$ (h)	97.1 (55.4)
				T_{max24} (h)	4.8 (5.8)
				T_{min24} (h)	12.0 (5.0)
				$T_{1/2,z}$ (h)	5.7 (2.5)
Wang *et al.* 2004 [14] (USA)	Phase III, open-label, multi-centre	Striant SR twice daily for 12 weeks	Blood samples taken every month and multiple samples taken over 24 h at week 12.	n	82
				$C_{max\ (0-24)}$ (nmol/L)	33.62 (15.3)
				$C_{min\ (0-24)}$ (nmol/L)	10.10 (4.5)
				$C_{AVG\ (0-24)}$ (nmol/L)	18.04 (7.1)
				T_{max24} (h)	10.5 (9.3)
				T_{min24} (h)	10.3 (8.0)
				% $T_{24\ (dur)}$	75.5 (27.7)
				% $T_{24\ (above)}$	80.1 (27.8)
				% $P_{24\ (dur)}$	72.6 (25.9)
Korbontis *et al.* 2004 [16] (Europe) Comparison with Transdermal patch (T-patch)	Phase III, open-label, parallel-arm, multi-centre	67 patients (33 receiving Striant SR and 34 receiving T-patch) for 7 days	Blood samples taken on days 1, 3, 4 and 6, and multiple samples taken over 24 h on days 7 and 8.	**Striant SR**	
				n	29
				$C_{max\ (0-24)}$ (nmol/L)	31.58
				$C_{min\ (0-24)}$ (nmol/L)	11.10
				$C_{AVG\ (0-24)}$ (nmol/L)	18.74 (5.9)
				% $P_{24\ (dur)}$	84.8
				% $P_{24\ (above)}$	88.4
				% $T_{24\ (dur)}$	84.9
				T-patch	
				n	28
				$C_{max\ (0-24)}$ (nmol/L)	20.68
				$C_{min\ (0-24)}$ (nmol/L)	5.76
				$C_{AVG\ (0-24)}$ (nmol/L)	12.15 (5.55)
				% $P_{24\ (dur)}$	55.1
				% $P_{24\ (above)}$	55.1
				% $T_{24\ (dur)}$	54.9
Dobs *et al.* 2004 [17] (USA) Comparison with testosterone gel (T-gel)	Phase III, open-label, parallel-arm, multi-centre	28 patients (13 receiving Striant SR and 15 receiving T-gel) for 14 days	Blood samples taken on days 3–4, 7–8 and 10–11, and multiple samples taken over 24 h on days 14 and 15.	**Striant SR**	
				n	12
				$C_{max\ (0-24)}$ (nmol/L)	29.5 (11.5)
				$C_{min\ (0-24)}$ (nmol/L)	8.7 (2.78)
				$C_{AVG\ (0-24)}$ (nmol/L)	16.66 (4.86)
				% $T_{24\ (dur)}$	83.4 (20.1)
				T gel	
				n	13
				$C_{max\ (0-24)}$ (nmol/L)	26.0 (12.2)
				$C_{min\ (0-24)}$ (nmol/L)	8.7 (3.12)
				$C_{AVG\ (0-24)}$ (nmol/L)	15.27 (4.86)
				% $T_{24\ (dur)}$	75.3 (24.5)

Footnote to table:

Pharmacokinetic parameter	*Definition*
$C_{max\ 1-7D}$	*Maximum observed serum concentration (during the dosing phase, i.e. from first sampling time on day 1 to last sampling time on day 8) [15]*
$C_{max\ (0-24)}$	*Maximum testosterone concentration during the last two consecutive dosing intervals (over 24 h) on days 7/8 [15,16], at week 12 [14], or days 14/15 [17].*
$C_{min\ (0-24)}$	*Minimum testosterone concentration during the last two consecutive dosing intervals on days 7/8 [15,16], over 24 h at week 12 [14], or days 14/15 [17].*
C_{AVGtot}	*Time-averaged serum concentration (during the dosing phase, i.e. from first sampling time on day 1 to last sampling time on day 8)*
$C_{AVG\ (0-24)}$	*The average serum concentration calculated at steady state during the 24-h period on day 7-8 [15], at week 12 [14], or on days 14 and 15 [17]. Calculated as the area under the concentration-time curve over 24 h [$AUC_{(0-24)}$] divided by 24 h.*
$T_{max\ 1-7D}$	*Time to maximum observed serum testosterone concentration (during the dosing phase, i.e. from first sampling time on day 1 to last sampling time on day 8)*
T_{max24}	*Time to maximum observed total serum testosterone concentration during the last two consecutive dosing intervals on days 7/8 [15] or at week 12 [14]*
T_{min24}	*Time to minimum observed serum testosterone concentration during the last two consecutive doing intervals on days 7/8 [15] or at week 12 [14]*
$T_{1/2,z}$	*Apparent terminal elimination half-life determined on day 8 after the last tablet was removed*
% $T_{24\ (dur)}$	*Percentage of time that serum testosterone concentrations were within the physiological range 10.4–36.4 nmol/L [14,23,24]*
% $T_{24\ (above)}$	*Percentage of time that serum testosterone concentrations were > 10.4 nmol/L over the 24-h sampling period [14]*
% $P_{24\ (dur)}$	*Percentage of reportable total testosterone serum concentrations over 24 h that were within the physiological range 10.4–36.4 nmol/L [14]*
% $P_{24\ (above)}$	*Percentage of reportable total testosterone serum concentrations over 24 h that were > 10.4 nmol/L*

FIG. 2. Percentage of the time serum concentrations were within the physiological range of testosterone (10.4–36.4 nmol/L) in two phase III clinical trials comparing Striant SR (30 mg twice daily) with T-patch (5 mg once daily) [16] (A) or T-gel (5 g once daily) [17] (B) in testosterone-deficient men



FREE TESTOSTERONE AND DIHYDROTESTOSTERONE (DHT)

In both the 7-day phase I study and the 12-week study of Striant SR twice daily in hypogonadal men, the pharmacokinetic profile of DHT was similar in pattern to that of total testosterone [14,15]. In addition, in both studies the mean concentration ratio of testosterone/DHT was within the normal male range of 9–12 and remained relatively stable throughout treatment [14,15]. Striant SR does not therefore appear to have a disproportionate effect on DHT levels. DHT is implicated in the development of BPH and prostate cancer, so high DHT blood levels might be regarded undesirable. Scrotal testosterone patches can elevate serum DHT levels by four- to 10-fold [18,19], and higher serum testosterone/DHT ratios have also been reported after the use of transdermal testosterone gels. Although the increases may not always be clinically significant [20], transdermal delivery of testosterone will always have the potential for conversion to DHT via 5α reductase 1 and 2, particularly the former iso-enzyme located within the skin.

The mean serum levels of free testosterone with Striant SR followed the same pattern as for total serum testosterone and DHT and the percentage of free testosterone was also stable over the duration of the study at ≈2.9%, indicating that free testosterone and total testosterone levels increased proportionately during treatment with Striant SR [14].

EFFICACY OF STRIANT SR

TRT is effective in relieving the symptoms of testosterone deficiency when eugonadal levels of testosterone are maintained [21–23]. The various testosterone preparations and delivery systems available can be distinguished by their ability to reproduce physiological testosterone levels and by their safety profile and patient acceptability. The efficacy endpoints of clinical trials of Striant SR have therefore been largely pharmacokinetic.

However, objective and subjective measures of sexual function were assessed in a double-blind, randomised, placebo-controlled pilot trial using an earlier formulation of buccal testosterone [24]. Treatment with buccal testosterone (10–20 mg once daily) for 8 weeks significantly enhanced sexual function compared with placebo across both objective and subjective measures [24].

The efficacy of Striant SR for producing physiological serum testosterone levels in hypogonadal men was established in the two single-arm pharmacokinetic studies [14,15]. Additional pharmacokinetic data has also been obtained from two open-label, parallel-arm multicentre trials in which Striant SR was compared with a testosterone transdermal patch (T-patch) [16] for 7 days, or a testosterone gel (T-gel) for 14 days [17] in testosterone-deficient men.

COMPARISON OF STRIANT SR WITH T-PATCH AND T-GEL

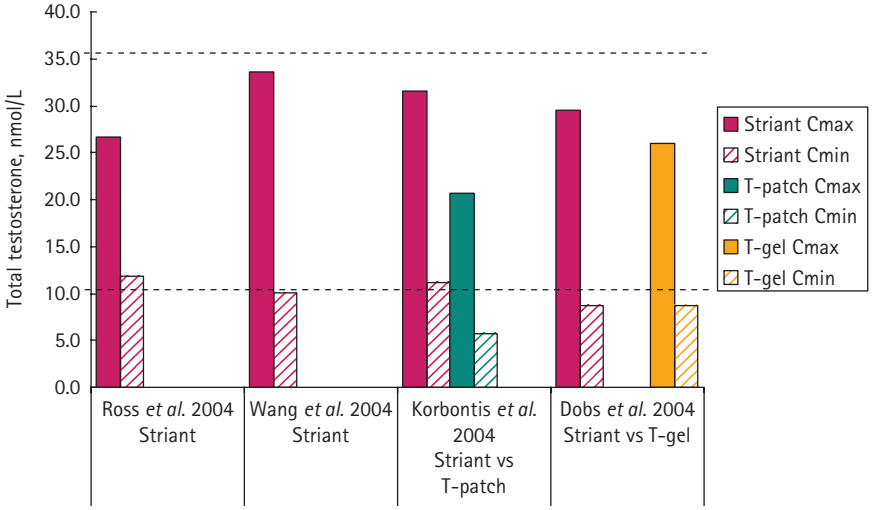
Striant SR has been compared with a T-patch and a T-gel in two comparative non-inferiority studies. Striant SR was compared with Andropatch 5 mg (GlaxoSmithKline, Uxbridge, UK) in a 7-day trial involving men with primary and secondary hypogonadism [16] and Androgel 5 g (Abbott Laboratories, IL, USA), a T-gel (containing 50 mg testosterone) in a 14-day trial [17].

In both comparative studies, the mean total serum testosterone levels remained within the normal physiological range (10.4–36.4 nmol/L) at all sampling points throughout the treatment period for Striant SR, T-patch and T-gel [16,17]. Time-averaged testosterone levels at steady state ($C_{AVG\ (0–24)}$) over the 24-h sampling period were also within the normal physiological range for all treatment groups (Fig. 1), although for T-patch the $C_{AVG\ (0–24)}$ of 12.2 nmol/L was at the low end of the normal range [16].

At steady state, testosterone concentrations were within the normal physiological range for 84–85% of the 24 h sampling time in the Striant SR-treated patients [16,17], compared with 75% of the time with T-gel [17] and 55% with T-patch ($P < 0.001$ for Striant SR vs T-patch) [16] (Fig. 2 [16,17]). In addition, 85% of patients treated with Striant SR had serum testosterone within the physiological range over 24 h compared with 55.1% of patients treated with T-patch [16] (Table 1).

The total testosterone mean maximum and minimum serum concentrations over the 24-h assessment periods ($C_{max\ (0–24)}$ and $C_{min\ (0–24)}$, respectively) of the two comparative clinical trials [16,17] are shown in Fig. 3 [14–17], together with the equivalent data from the two Striant SR clinical trials [14,15]. The mean testosterone $C_{max\ (0–24)}$ for Striant SR was consistently within the normal physiological range across all four clinical trials [14–17], as were the testosterone $C_{max\ (0–24)}$ for T-patch and T-gel in the two comparative trials [16,17]. The $C_{min\ (0–24)}$ for Striant SR varied from 8.7 to 11.8 nmol/L across the four studies [14–17], remaining slightly above the lower physiological range of 10.4 nmol/L in two of the studies [14,17]. In the comparative trial of Striant SR and T-gel, the $C_{min\ (0–24)}$ was

FIG. 3. Maximum (C_{max}) and minimum (C_{min}) mean total testosterone concentration during the last 24 h of treatment in clinical trials of Striant SR 30 mg [14,15], Striant SR 30 mg vs T-patch [16] or T-gel [17] in testosterone-deficient men. The region between the dashed lines represents the physiological range of testosterone (10.4–36.4 nmol/L).



8.7 nmol/L for both treatments [17], whereas treatment with T-patch resulted in a lower $C_{min\ (0–24)}$ of 5.8 nmol/L [16].

FACTORS THAT MAY AFFECT THE EFFICACY OF STRIANT SR

In the 3-month phase III trial, there was no difference between testosterone pharmacokinetic parameters before and after meals [14]. In addition, the pharmacokinetics of Striant SR was not affected by gum abnormalities or medications that could potentially cause dry mouth [14]. In clinical trials, no clinically significant differences were noted on the impact of body mass index (BMI) on testosterone levels although this may not apply to the very obese, as patients with a BMI of >35 kg/m^2 were excluded from the study [14].

EFFICACY OF STRIANT SR WITH LONG-TERM USE

Two long-term open-label studies were carried out to further evaluate the long-term safety, tolerability and efficacy of Striant SR as TRT in testosterone-deficient men. Interim data from these studies were reported in a previous review [3]. The multicentre studies carried out in Europe (study COL-1621-08) and the USA (study COL-1621-09) enrolled a total of 189 patients for up to 12 months with a further 51 patients receiving Striant SR on a compassionate-use basis for ≥2 years of continuous use [25].

In the European and USA studies, up to 62% of subjects in the intention-to-treat populations had ≥80% of their total serum testosterone assessments within the normal range. These results, particularly in the case of the larger USA study, are lower than was seen in previous studies reflecting the lower compliance with dosing and the lack of supervision of dosing around the serum samples [25]. In the previous studies, the primary efficacy parameters were focused on the final 24 h of the study and patients were confined during that time to enable multiple blood sampling, which facilitated compliance [14–17]. However, despite this, the mean total serum testosterone levels for both studies were within the normal range at each assessment after baseline [25].

SAFETY AND TOLERABILITY

Striant SR has been well tolerated in clinical trials lasting up to 12 months. Table 2 shows the incidences of adverse events (AEs) that were at least possibly related to the use of Striant SR and reported by ≥1% of patients in the pivotal 12-week phase III clinical trial [14,26].

TABLE 2 Incidences of AEs that were possibly, probably or definitely related to the use of Striant SR and reported by ≥1% of patients in a 12-week phase III clinical trial [14,26]]

AE	Incidence, % N = 98
Gum or mouth irritation	9.2
Taste bitter	4.1
Gum pain	3.1
Gum tenderness	3.1
Headache	3.1
Gum oedema	2.0
Taste perversion	2.0

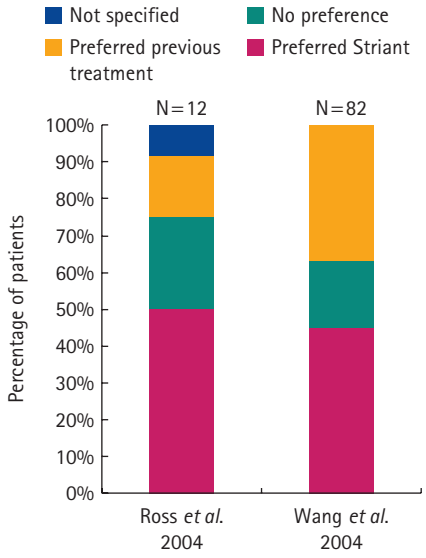
In all, 189 patients were included in the combined safety population in the two long-term extension trials, with 51 patients using Striant SR for ≥2 years (including compassionate-use) [25]. In all, 62 patients (32.8%) reported AEs that were considered to be at least possibly related to the study drug and 22 patients had events that led to discontinuation [25]. The most commonly-reported AEs are described below.

GUM DISORDERS

The most common AEs were gum-related disorders, reported by 16.3% (98 patients) and 18.2% (33) of patients in two phase III trials [14,16]. In all, 19 gum-related AEs (including oedema, gingivitis, inflammation and blister) were reported in 16 men (16.3%) during the study [14]. Most of the gum-related AEs were transient. Two men (3.1%) withdrew from the study due to severe gum irritation and one withdrew due to mouth irritation [14]. There were no cases of ulceration or leukoplakia.

Application-site reactions were also the most frequent AEs considered related to the study drug in the long-term extension studies, reported by 5.6% of patients (162 patients) in the larger study and were stated as reasons for treatment-discontinuation in six cases, with a further additional patient citing gingivitis as a reason for discontinuation [25]. At ≥2 years use of Striant SR, there was no increase in the incidence of gum-related problems; moderate gingivitis and mild gum oedema (one patient each) were the only gum-related disorders reported overall [25].

FIG. 4. Patient preference for Striant SR or previous testosterone treatment in two open-label clinical trials of Striant for 7 days [15] or 12 weeks [14]



Application-site reactions led to only 4.3% of patients discontinuing over 2 years.

PSA LEVEL ELEVATION

There were no clinically relevant changes in PSA levels in the clinical trials lasting up to 3 months. In the long-term extension studies, the changes in the mean values for PSA were all small and not clinically significant except for two patients who discontinued due to increased PSA levels considered related to the study drug [25].

POLYCYTHAEMIA

In the long-term studies, polycythaemia, considered to be at least possibly related to the study drug, occurred in five patients and was given as a reason for treatment discontinuation for one patient. Polycythaemia/erythrocytosis is a known potential complication of long-term TRT [25].

DYSGEUSIA

Treatment with Striant SR can cause mild distortions in taste (dysgeusia) for some patients, but rarely at a level to provoke treatment discontinuation. When asked specifically, up to one quarter of patients in one of the long-term studies reported that they experienced an unacceptable taste when using Striant SR, but taste perversion was spontaneously reported as an AE by only five patients (3.0%; all rated as mild) and was the reason for treatment discontinuation for only one patient (0.6%) [25]. 'Bitter taste' and taste perversion were also spontaneously reported by only three patients (4.1%) and two patients (2.0%), respectively, in the 3-month trial; resulting in treatment-discontinuation for one patient [14].

PATIENT ACCEPTABILITY, PREFERENCE AND EASE OF USE OF STRIANT SR

ADHERENCE OF THE BUCCAL TABLET

Patients have reported occasional problems with non-adherence of Striant SR to the gum, although in clinical trials this improved over time as familiarity increased and did not always require replacement of the tablet [14,15]. Oral ingestion of Striant SR will not result in clinically significant serum testosterone concentrations due to extensive first-pass (hepatic) metabolism [1]. Patients withdrawing from the clinical trials due to application problems and intolerance to the presence of the buccal tablet, have tended to occur in the early weeks of the studies [14].

In the larger of the two long-term studies, 38–53% of patients reported at least one problem with tablet adherence at each 3-monthly visit [25]. Problems with adherence were related mostly to oral care and eating/drinking (experienced at least once by 59% and 54% of patients), despite the fact that patients were instructed to carry out oral care in the interval between removing one tablet and replacing with another [25].

PATIENT ACCEPTABILITY AND PREFERENCE

Once patients have become accustomed to the presence of the buccal table and the application procedure, treatment with Striant SR has a high level of patient acceptance; most subjects (67%) using Striant SR for 3 months rated the treatment as acceptable or very acceptable [14]. In the larger of the two long-term extension studies; 86% of patients rated the buccal tablet as convenient and 90% rated the twice-daily dosing as acceptable [25].

In two open-label clinical trials, 45–50% of patients preferred Striant SR to their previous treatment (Fig. 4 [14,15]). After 52 weeks in the larger of the two long-term extension studies, 11 (50%) and 10 (47.6%) of the 21 and 22 patients with previous experience of i.m. testosterone injections or T-gel respectively, found Striant SR to be more acceptable than their previous therapy [25]. In the same study, most patients (up to 95.9% of 121 patients) also found Striant SR to be cosmetically acceptable [25].

THE PLACE OF STRIANT SR IN TREATMENT GUIDELINES

Treatment guidelines suggest that i.m., subdermal, transdermal, oral and buccal preparations are safe and effective, and that the selection of the preparation should be a joint decision of an informed patient and physician [7,8,10]. For many hypogonadal men, most of the available treatments will be equally suitable, although buccal and transdermal routes of administration appear to offer more stable testosterone levels than i.m. and oral preparations. However, the choice is often made based on the patient's preference, family situation and cost.

Short-acting preparations such as Striant SR are particularly suitable for men with late-onset hypogonadism who may be more likely to experience elevated haematocrit or prostate carcinoma, requiring rapid discontinuation of testosterone substitution [8,10].

The patient's family situation should also be considered. Users of T-gels are instructed to wash their hands after application of the T-gel and to take a shower or cover the application sites before physical contact with another person. Theoretically, once the ethanol has evaporated from the T-gel, the testosterone which remains on the skin (up to 90% of the delivered dose) has a low bioavailability. However, there have been several recent published case reports of testosterone transfer to a child or female partner resulting in the clinical syndrome of hyperandrogenism [27], although in most cases this could be attributed to the user's failure to follow the instructions. A recently published case involved precocious puberty in a 10-month old boy secondary to transfer of topical testosterone from his father, who was treated with a T-gel. Once the father's

therapy was changed from a topical to a buccal dosage form, the symptoms in his son receded [28].

Patients using Striant SR may feel concerned about the potential for transfer of testosterone in saliva. However, this is not considered to be clinically significant, as any testosterone that may be present in the saliva when swallowed is not expected to result in clinically significant testosterone concentrations due to extensive first-pass hepatic metabolism [1]. In addition, the saliva of eugonadal men contains a low level of testosterone equivalent to that in men treated with Striant SR.

CONCLUSIONS

Striant SR has been available in Europe and the USA for >7 years and offers a unique and rational method of testosterone delivery. Physiological levels of testosterone are reached by the second dose and clinical studies of up to 2 years duration indicate that Striant SR is effective long term in maintaining serum testosterone within a physiological range.

Striant SR is also well-tolerated with long-term use, with the most frequent AEs being a low incidence of local irritation at the site of administration and dysgeusia. Striant SR should be considered in particular where easy and rapid reversal of treatment might be required (such as in late-onset hypogonadism) and where there is a need to avoid the potential for transfer of testosterone to women and young children. The consistent testosterone levels achieved, relatively independent of BMI and low intra-patient variability make Striant SR an attractive option for patient and physician alike.

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CONFLICT OF INTEREST

MG Wyllie is a Director and WW Dinsmore an Investigator for Plethora Solutions.

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Abbreviations: **SR**, sustained release; **TRT**, testosterone-replacement therapy; **C**max, peak concentration; **C**AVG(0_24), average serum concentration calculated at steady state during a 24-h period; **DHT**, dihydrotestosterone; **T-patch**, testosterone transdermal patch; **T-gel**, testosterone gel; **BMI**, body mass index; **AE**, adverse event.