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CLINICAL STUDY REPORT

CROSS-OVER COMPARISON OF TESTOSTERONE SERUM LEVELS IN HYPOGONADAL MEN TREATED WITH L0074 TESTOSTERONE PATCH 60 cm² (2 patches/48 h) AND ORAL TESTOSTERONE UNDECANOATE –PANTESTONE® 40 mg – (2 capsules, bid)

(Protocol L00074 TD 301)

Final version: 14 February 2006

CONFIDENTIAL DOCUMENT

1. TITLE PAGE

L0074 TD TESTOSTERONE PATCH 60 cm²

Clinical Study Report

CROSS-OVER COMPARISON OF TESTOSTERONE SERUM LEVELS IN HYPOGONADAL MEN TREATED WITH L0074 TESTOSTERONE PATCH 60 cm² (2 patches/48 h) AND ORAL TESTOSTERONE UNDECANOATE –PANTESTONE® 40 mg – (2 capsules, bid)

A phase-III, international, multicentre, randomised, open-label, cross-over study in hypogonadal men, involving two consecutive periods of 22 days each, separated by a wash-out period of 14 days

Protocol n°:	L00074 TD 301
Date of first enrolment:	16 March 2005
Date of last completed:	19 September 2005
Date of the report:	14 February 2006
Coordinating Investigator:	Dr. Michel COLLE

Study performed in compliance with Good Clinical Practice

2. SYNOPSIS

Name of Company: PIERRE FABRE MEDICAMENT	TABULAR FORMAT Referring to Part IV of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of finished product: Testopatch®		
Name of active substance: Testosterone		

Title of the study:
Cross-over comparison of testosterone serum levels in hypogonadal men treated with L0074 Testosterone patch 60 cm² –Testopatch®– (2 patches/48 h) and oral testosterone undecanoate –Pantestone® 40 mg– (2 capsules, bid).

Investigators:

Coordinating/Main Investigator: Dr. M. COLLE, Paediatrician-endocrinologist, 25, rue Boudet, F-33000 Bordeaux.
Scientific Advisor: Pr. J.-P. RAYNAUD, University Pierre & Marie Curie, 4, place Jussieu, F-75005 Paris.

Study centres:

24 French centres and 1 Spanish centre.

Publication: None at the time of writing this report.

Study period: date of first enrolment: 16 March 2005 date of last completed: 19 September 2005	Clinical Phase: III

Objectives:

To compare average serum total testosterone (TT), bioavailable testosterone (BT), and dihydrotestosterone (DHT) levels over the first and last 48 hours of a 22-day treatment with L0074 TD patch 60 cm² (Testopatch®) versus a 22-day oral treatment with testosterone undecanoate (Pantestone®, two 40-mg capsules twice a day).
To compare the effects of both treatments on serum levels of LH, FSH, and SHBG, as well as their clinical effects (assessed by clinical scores) over a 22-day treatment period.
To assess treatment general and local tolerability and acceptability.

Methodology:

This was an international, multicentre, randomised, open-label, cross-over study, involving two consecutive periods of 22 days each, separated by a wash-out period of 14 days.
During the first treatment period, one group of patients was treated with Testopatch® and the second group received Pantestone® orally for 22 days.
During the second treatment period, the first group received Pantestone® orally and the second group was treated with Testopatch® for 22 days.
Existing testosterone treatments were withdrawn at least 8 days before admission to the study for those administered orally or in gel or at least 3 weeks before admission for those administered intramuscularly.

Number of patients:

Planned: 55. Screened: 62. Included: 53. Completed: 49.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

- men aged > 18 years with known primary or secondary hypogonadism previously treated with androgens or not treated
- total testosterone ≤ 2.5 ng/mL (after withdrawal from androgens for previously treated patients)
- body mass index ≤ 32 kg/m²
- patients having provided written informed consent after having received complete information about the objectives and procedures of the study
- willingness to comply with all the procedures and constraints inherent to the study.

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Diagnosis and main criteria for inclusion: *(continued)*

Non-inclusion criteria:

- known acute or chronic prostate pathology, prostate-specific antigen (PSA) > 2 ng/mL, and/or suspicion of prostate cancer; familial history of prostate cancer
- male breast cancer
- severe cardiovascular, respiratory, hepatic or renal failure, or metabolic diseases/disorders
- non-controlled hypertension (SBP/DBP > 160/90 mmHg)
- generalised dermatological disorders that might affect testosterone absorption or local tolerability assessment (hypertrichosis, psoriasis, eczema)
- alanine-aminotransferase and/or aspartate-aminotransferase activity two-fold greater than the upper limit of the normal or over
- haematocrit > 51%
- uncontrolled diabetes mellitus (type I or II)
- psychiatric disease; organic cerebral disease (epilepsy, migraine)
- sleep apnoea syndrome
- history of allergy to dermal patches
- concurrent treatment in patch or other androgen replacement therapy
- concurrent treatment with barbiturates, ketoconazole, spironolactone, anticoagulants, finasteride, antiandrogens, LH-RH analogues, treatments influencing erection or testosterone blood level, or any other medication known to alter the activity of cytochrome P450 enzymes
- treatment with corticosteroids applied topically or used as immunosuppressants (corticosteroids were authorised when used in physiological doses as replacement therapy for secondary adrenal insufficiency, e.g., cortisone < 30 mg/day or prednisone < 5 mg/day.
- history of alcohol or drug abuse

Non-inclusion criteria according to amendment no. 2:

- men aged 65 or over (due to the risk of benign prostate hypertrophia or adenocarcinoma)
- aggressiveness
- professional athletes (because of positive testing in doping controls).

Test product, dose, and method of administration, batch number(s):

Testopatch®: two patches applied simultaneously and symmetrically either to the upper arm, lower back, upper buttock or thigh, every other day in the morning.
Batch number: 7009034 (expiry date: 01/2006).

Reference therapy, dose and mode of administration, batch number(s):

Pantestone® 40 mg, capsules (testosterone undecanoate): two capsules in the morning (at end of breakfast) and two in the evening (at end of dinner).
Batch number (expiry dates): 00098 (11/2006), 00100 (01/2007) and 00104 (09/2007).

Duration of treatment:

22 days for each treatment period, with a 14-day wash-out period interposed between the two periods.

Criteria for evaluation:

— Primary efficacy criterion:
average level of serum total testosterone (TT) over the last 48 hours of each treatment period, as assessed on four blood samples taken:

. 4 h, 24 h, 28 h and 48 h after the last application of the patches
. 4 h after the morning intake of Pantestone® capsules (just before lunch) at Day 21 and Day 22, and before the morning intake (just before breakfast) at Day 22 and Day 23.

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Criteria for evaluation: *(continued)*

— Secondary efficacy criteria:

- average concentration of serum TT over the first 48 hours of each treatment period, as assessed on four blood samples taken over 48 hours as for the primary efficacy variable, and at trough (before the first morning dosing during the last 48 hours of each treatment period)
- average concentration of serum bioavailable testosterone (BT) (free testosterone + testosterone bound to albumin) over the first and last 48 hours of each treatment period and at trough at the end of the last treatment period
- average concentrations of serum dihydrotestosterone (DHT) and estradiol (E2), the main metabolites of testosterone, over the first and last 48 hours of each treatment period and at trough at the end of the last treatment period
- BT/TT, DHT/TT and E2/TT ratios over the first and last 48 hours of each treatment period and at trough at the end of each treatment period
- number of patients with values for TT, BT, and DHT serum concentrations below or above the corresponding physiological ranges (TT: 3-10 ng/mL; BT: 1-3 ng/mL; DHT: 0.5-1.5 ng/mL) over the first and last 48 hours of each treatment period
- change from baseline in LH, FSH, and SHBG serum levels at the end of each treatment period
- change from baseline in clinical scores (Aging Males Symptoms Rating Scale [AMS], Male Sexual Function questionnaire [MSF-4]) at the end of each treatment period.

— Safety and tolerability criteria:

- vital signs recorded at each study visit
- local tolerability assessed by the FDA skin irritation scoring system at the beginning and end of the patch treatment period
- recording of adverse events (AEs) on a patient diary card throughout the study and at each study visit by patient questioning
- determination of PSA serum concentration at screening and at end of each treatment period
- routine laboratory tests at patient screening and at end of study.

— Acceptability criteria:

- patch adhesiveness as assessed by the investigator on a 5-point scale (≥ 90%, 75-90%, 50-75%, < 50%, patch detached) at the end of the patch treatment period
- percentage of patch detachments over the whole treatment period as captured on the patient's diary card (complete, > 50% but still stuck, ≤ 50% detached)
- patients' global assessment of treatment efficacy on a visual analogue scale scored from "Not efficient at all" to "Very efficient"
- patients' global assessment of safety on a visual analogue scale scored from "Very badly tolerated" to "Very well tolerated"
- ease of patch application and removal on a 4-point rating scale ("Very easy", "Easy", "Difficult", "Very difficult")
- comfort of patch use on a 4-point rating scale ("Very comfortable", "Comfortable", "Rather uncomfortable", "Not comfortable at all")
- ease of capsule swallowing on a 4-point rating scale ("Very easy", "Easy", "Difficult", "Very difficult")
- global acceptability of each treatment as assessed by the patients on a 4-point scale in response to the question: "Would you accept to continue testosterone treatment with these patches/capsules? ("Yes, certainly", "Yes, probably", "No, probably not", "No, surely not") and to the additional question "If no, why?".

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Statistical methods:

Efficacy:

Primary efficacy variable (average level of serum total testosterone over the last 48 hours of treatment):

the primary objective of the study was to ascertain clinical equivalence of the two treatments tested (capsules, patch). Equivalence was accepted if the 95% confidence interval of the difference between treatments (determined using the residual variance of the analysis of variance incorporating the effects: sequence, subject within sequence, period, and treatment) fell entirely within the predefined interval [-0.5 ng/mL;+0.5 ng/mL].

Secondary efficacy variables:

average level of serum TT over the first 48 hours of treatment: same analysis as for the primary efficacy criterion

descriptive analysis of the number of determinations of TT, BT and DHT falling outside the physiological ranges

other criteria: analysis of variance incorporating the effects sequence, subject within sequence, period and treatment (test for difference), or non-parametric analysis, as appropriate.

Safety: descriptive analysis of clinical and biological safety parameters and of incidence of AEs.

Acceptability and patch adhesiveness: parametric or non-parametric analysis, as appropriate.

Sample size: based on previous studies, standard deviation of the primary efficacy variable was estimated at 1.4 ng/mL, correlation coefficient at 0.67, giving a number 44 patients required to demonstrate equivalence of treatments with a two-sided α risk of 0.05 and a test power of 80%. Assuming an attrition rate of 20%, 55 patients were to be included in the study.

SUMMARY – CONCLUSIONS

Disposition of patients - Deviations to study protocol – Populations studied

25 centres recruited 62 patients, of whom 9 were not included (7 not meeting inclusion criteria, 1 for practical reasons, 1 for consent withdrawal). 53 patients entered the 1st treatment period (Testopatch®: 28; Pantestone®: 25). Two patients withdrew from treatment during the 1st period (1 for AE during treatment with Testopatch®; 1 for practical reasons during treatment with Pantestone®), after completing the end-of-period visit. One patient withdrew during the intermediate wash-out period, after treatment with Pantestone®, on patients' decision. 50 patients entered the second period of treatment (Pantestone®: 27; Testopatch®: 23). One patient receiving Pantestone® withdrew during the 2nd period (for insufficient response) without an end-of-period visit. Thus, 49 patients completed the 2nd period and 49 had an end-of-period visit.

155 minor deviations were recorded during the study (chiefly non-respect of time intervals before inclusion and between study phases, changes in treatment duration, poor treatment compliance, use of unauthorised treatment, high testosterone level at inclusion). 23 major deviations were recorded (chiefly missing values for the primary efficacy variable). Finally, 9 patients were excluded from the all-patients-treated (APT) population and 18 from the per-protocol (PP) population. Thus, the APT was constituted of 44 patients and the PP population of 35 patients.

The safety population was constituted of 53 patients of whom 51 received at least one dose of Testopatch® and 52 at least one dose of Pantestone®.

Description of study patients

Mean patient age was 49 years. Mean TT serum concentration before inclusion was 1.99 ng/mL. Hypogonadism was primary in 57% of patients (congenital in 29%, acquired in 71%). 68% of patients had already received a treatment for hypogonadism but 73% of them had no ongoing treatment at the time of screening.

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SUMMARY - CONCLUSIONS (continued)

Efficacy and safety variables at baseline of each treatment period

Analysis of efficacy variables at baseline of each treatment period showed a significant period effect, with lower values for TT, BT and DHT at the beginning of the 2nd treatment period compared with the 1st treatment period, especially when Testopatch® was administered first. However, there was no significant sequence or group effect. A significant period effect was also detected for the clinical score at the AMS questionnaire but not at the MSF-4 questionnaire.

There were no between-group differences at baseline in vital signs and biological variables.

Primary efficacy variable (average TT serum level over the *last* 48 hours of each treatment period)

TT serum level over the last 48 hours of treatment was significantly greater after treatment with Testopatch® than with Pantestone® (means: 4.64 vs 2.58 ng/mL in the APT population, $p < 0.001$). 95% CIs of between-treatment differences indicated that Testopatch® was significantly superior to Pantestone®. Results were similar in the APT and PP populations.

Secondary efficacy variables

Hormonal variables:

Significant differences between treatments were observed for average TT serum levels over the *first* 48 hours of each treatment period (5.13 vs 3.71 ng/mL, $p < 0.001$). 95% CIs of between-treatment differences indicated that Testopatch® was significantly superior to Pantestone®.

Comparison of TT trough levels (before morning treatment) at the end of each treatment period showed significantly higher TT concentrations for Testopatch® than for Pantestone® (3.15 vs 2.45 ng/mL, $p < 0.01$).

Less patients treated with Testopatch® than with Pantestone® had TT values below the physiological range during the first and especially the last 48 hours of treatment (22 vs 27, and 24 vs 36, respectively). Conversely, the number of patients with values above the physiological range was greater with Testopatch® than with Pantestone® (7 vs 2 and 7 vs 1 during the first and last 48 hours of treatment; maximum values: 15.6 and 13.5 ng/mL, respectively).

Similarly to TT, average BT levels over the first and last 48 of treatment were significantly greater with Testopatch® than with Pantestone® ($p=0.001$ and $p < 0.01$, respectively) but were similar at trough.

Conversely, average DHT levels over the first and last 48 hours of treatment (0.71 vs 1.05 ng/mL, and 0.68 vs 0.89 ng/mL, respectively) as well as at trough (0.59 vs 0.96 ng/mL) were found significantly lower with Testopatch® than with Pantestone® ($p < 0.001$, $p < 0.05$, and $p<0.001$, respectively). More patients treated with Pantestone® than Testopatch® showed DHT serum levels greater than the physiological range. Estradiol levels were slightly but significantly higher for Testopatch® than for Pantestone® over the first and last 48 hours of treatment but did not differ between treatments at trough.

BT/TT ratio was slightly higher for Pantestone® over the last 48 h, whereas DHT/TT ratio was markedly higher for Pantestone® over the first and last 48 h. E2/TT ratio was lower for Testopatch®.

Serum SHBG levels decreased with Pantestone® but were not affected by Testopatch® ($p < 0.001$ between treatments). LH and FSH levels decreased during the study with no significant difference between treatments.

Testopatch® (but not Pantestone®) seemed somewhat less active in patients with BMI ≥ 30.

Clinical scores:

Analysis of total score and subscores at the AMS questionnaire showed that Testopatch® was more effective than Pantestone® at improving AMS total score (mean score reduction of -7.9 vs -4.3, respectively; $p < 0.05$), psychological subscore (-1.8 vs -0.6; $p < 0.01$), and sexual subscore (-3.2 vs -1.5; $p < 0.05$). Score at the MSF-4 questionnaire indicated that both treatments were moderately active (mean score reduction of -1.2 vs -0.9, respectively) and not significantly different from each other.

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SUMMARY - CONCLUSIONS (continued)

Safety results

23 patients experienced at least one AE during treatment with Testopatch® versus 14 patients during treatment with Pantestone®. 11 patients experienced at least one treatment-related AE with Testopatch® versus 5 with Pantestone®. 1 serious AE occurred during treatment with Pantestone® and 1 treatment-related AE led to patient withdrawal with Testopatch®. Most AEs occurring during treatment with Testopatch® concerned local reactions (application site disorders in 6 patients). Most AEs observed with Pantestone® concerned the gastrointestinal (4 AEs) and nervous systems (5 AEs). Only 3 AEs were of severe intensity. The AE which led to discontinuation of treatment with Testopatch® was a skin allergic reaction. The serious AE occurring during treatment with Pantestone® was unrelated to treatment (planned surgical intervention).

There was no notable change in mean values of biological safety variables or vital signs and in the results of clinical examination, and no increase in the number of abnormal values suggestive of alteration of erythrocyte production or of lipid metabolism. Mean PSA levels were similar after Testopatch® and Pantestone® at the end of the 1st period of treatment and only 3 patients in each treatment group had a PSA level > 2 ng/mL (maximum value of 3.2 ng/mL after Pantestone®).

Assessment of local patch tolerability indicated the occurrence of few local skin reactions, generally of mild intensity (84% of patients with no local reaction as assessed by investigators; 87% as assessed by patients).

Acceptability results – Patch adhesiveness

Patch adhesiveness as assessed by investigators was found satisfactory in ~75% of patients.

Treatment efficacy as assessed by patients on a VAS was slightly but not significantly higher for Testopatch®. Patients' assessment of treatment tolerability on a VAS showed a significantly higher score for Pantestone®, but estimation of patients' preference showed no significant difference between treatments and comparable numbers of patients stated that they would probably or certainly continue the treatment with Testopatch® or Pantestone®.

Testopatch® was deemed easy to apply and remove by the patients but found somewhat uncomfortable by a low proportion of them, whereas Pantestone® was considered easy or very easy to use. Differences in easiness of use may contribute to the slight differences in acceptability that were noted between the two treatments.

Conclusion

Hormonal efficacy outcomes showed that Testopatch® was more potent than Pantestone® to increase serum levels of total testosterone and bioavailable testosterone in hypogonadal men as early as the first few days and throughout 3 weeks of treatment in the study. Conversely, Pantestone® was more potent to increase DHT and the ratios of bioavailable testosterone and DHT to total testosterone. Overall, the smooth and prolonged release of testosterone by Testopatch® translates into greater improvement in clinical state of hypogonadal patients, as assessed by a more pronounced improvement in AMS score.

Maintenance of patches for two days generally causes no or only very mild skin reactions. Some precautions for use of patches, mild discomfort and certain inconveniencies imposed upon patients by study protocol may have led some of them to prefer oral treatment.

The overall clinical benefit/risk ratio appears clearly in favour of Testopatch®.

Date of the report: 14 February 2006