Pierre Fabre Médicament
Represented by: Institut de Recherche Pierre Fabre
45, Place Abel Gance
F-92100 Boulogne

1. TITLE PAGE

CLINICAL STUDY REPORT

"TRANSDERMAL TESTOSTERONE SUPPLEMENTATION IN ELDERLY HYPOGONADAL MEN WITH SARCOPENIA: EFFECTS ON MUSCLE FUNCTION, PHYSICAL PERFORMANCE, BODY COMPOSITION AND QUALITY OF LIFE."

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROL, PARALLEL-GROUP STUDY ON 150 PATIENTS.

Investigational product: L00074 Testopatch®

EudraCT number: 2006-006354-98

Protocol number: L00074 TD 304

Phase of development: III

Date of first enrolment: December 3rd, 2007

Date of last completed: Not applicable

Coordinating Investigator: Pr Claude JEANDEL

Date of report: 22 October 2019

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

Name of Company: Pierre Fabre Médicament		
Name of finished product: Testopatch®, 2.4mg/24h (60 cm² transdermal device)		
Name of active substance (or ingredient): Testosterone		
Title of study:	"Transdermal testosterone supplementation in elderly hypogonadal men with sarcopenia: effects on muscle function, physical performance, body composition and quality of life." A randomized, double-blind, placebo-control, parallel-group study on 150 patients.	
Coordinating Investigator: ***Investigators:***	Pr Claude JEANDEL Dr Fabien TIGOULET Dr Chokri BOUBAKRI Pr Athanase BENETOS Dr Monique FERRY Dr Philippe DEJARDIN	
Study centre(s):	Four geriatrics centres, located in France (Nancy, Montpellier, Valence and Paris).	
Publication (reference)	None	
Studied period (years, months …): **(date of first enrolment)** **(date of last completed)**	July 2007 to May 2008 December 3rd, 2007 Not applicable	**Phase of development: III**
Objectives: **Primary:** **Secondary:**	To determine whether testosterone replacement in older men, who have low testosterone levels and mild to moderate physical impairment, will modify their body lean mass -To determine whether testosterone will improve their physical performance as assessed by the Short Physical Performance Battery (SPPB) -To determine whether testosterone will increase their muscle strength as measured by the Hand-grip test -To determine whether testosterone will increase their body lean mass as measured by impedancemetry -To determine whether testosterone will improve their quality of life as assessed by Ageing Males Symptoms (AMS) and Short Form Health rating survey (SF-12) -To assess the androgenic and pituitary hormonal profile under treatment -To assess the safety profile of Testopatch in the elderly	
Methodology:	This was a randomized, double-blind, placebo-control, parallel-group study over 6 months, followed by an open extension under Testopatch® during 6 months.	
Number of patients **(planned and analysed):**	150 planned to be enrolled (120 to be completed) 1 patient was included in the study, received study treatment but was withdrawn because of not treatment-related adverse event. 1 patient was screened but not included because of non-inclusion criteria	
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Diagnosis and main criteria for inclusion:

Inclusion criteria

- Elderly men aged 65 and 90 years (included)
- AMS ≥ 37
- Serum BT < 0.90 ng/mL
- Short physical performance battery (SPPB) value between 4 and 9
- Body lean mass evaluation by Impedancemetry < -2 DS from normal value
- Serum total PSA ≤ 3ng/mL
- Able to complete an informed consent.

Non-inclusion criteria

*Criteria related to pathologies

- Known acute or chronic prostate pathology, and/or PSA > 3 ng/mL, and/or suspicion of prostate cancer; familial history of prostate cancer,
- Male breast cancer,
- Severe cardiovascular, respiratory, hepatic, renal failure, or severe metabolic diseases/disorders,
- Unstable angina, NYHA class III or IV congestive heart failure, or myocardial infarction within 3 months of entry,
- Blood pressure > 160/90 mm Hg,
- Haematocrit > 48%,
- ALT and/or AST twice above the upper limit,
- Uncontrolled hyper or hypothyroidism,
- Limiting neuromuscular, joint or bone disease,
- Documented sleep apnoea,
- Dementia, cognitive impairment or any psychiatric disease affecting subject's ability to provide informed consent,
- Rheumatoid arthritis, cirrhosis or active hepatitis,
- History of stroke causing persistent motor deficit,
- Uncontrolled diabetic patients (type I or II),
- Acute illness in the prior 30 days,
- Severe disability limiting strength or physical function testing,
- Inability to perform hand-grip test,
- Generalized dermatological disorders that might affect testosterone absorption or local tolerability assessment (hypertrichosis, psoriasis, eczema)

*Criteria related to treatments

- Use of testosterone, anabolic steroids, DHEA, androstanolone, recombinant growth hormone (rGH), or corticosteroids in the past year,
- Other concomitant patch treatment or other androgen replacement therapy,
- Concomitant treatment with corticosteroids, barbiturates, ketoconazole, spironolactone, anticoagulants, finasteride, dutasteride, anti-androgens, LH-RH analogues, or any treatment influencing testosterone level

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Diagnosis and main criteria for inclusion:	*Criteria related to the way of life • Alcohol (more than 14 drinks per week at V2 (1 drink = 3,5 dL of beer = 1,5 dL of wine = 0,45 dL of strong beverage) or drug abuse (regular use of sedatives, hypnotics, tranquilizers or any addictive agent). • Patient who cannot be contacted in case of emergency, • Patient nor registered with a social security system or health insurance, • Participation to another clinical trial in the previous month or during the study, • Patient who, in the judgments of the investigator, is not likely to be compliant during the study, • Patient who has forfeited her freedom by administrative or legal award, or who is under guardianship, or who has been admitted to a sanitary or social institution, or who is in an emergency situation.
Test product, **Dose,** **Mode of administration,**	Testopatch® 2,4 mg/24 h Two 60-cm² patches applied simultaneously and symmetrically either on the upper arm, lower back/upper buttock or thigh, every 48 hours in the evening
Duration of treatment:	Double-blind phase: 6 months Followed by an open extension under Testopatch® during 6 months
Reference therapy, **Dose,** **Mode of administration,**	L0074 Testosterone Placebo 60-cm² patch placebo Two 60-cm² patches applied simultaneously and symmetrically either on the upper arm, lower back/upper buttock or thigh, every 48 hours in the evening
Criteria for evaluation:	**<u>Main criteria</u>** Changes in body composition assessed by changes of lean body mass using whole body dual x- ray absorptiometry (DEXA). **<u>Secondary criteria (at each visit)</u>** •Changes in physical performance assessed by SPPB evolution. •Changes in muscle strength assessed by modifications in isometric handgrip strength. •Changes in Jean body mass assessed by impedancemetry •Changes in clinical scores (AMS) •Changes in SF-12 •Changes in hormonal levels (TT, BT, DHT, E2, SHBG, FSH, LH, Delta 4 androstenedione, Delta 5 androstenediol). •Number of falls and fractures over the follow-up study period, •Local and systemic tolerability.

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Statistical methods:

Inferential statistical strategy will be based on a closed testing procedure. If one test is not significant in the sequence defined below, subsequent analyses will be regarded as descriptive. The sequence is

1. performs analysis on the primary criterion on FAS at 6 months,
2. performs analysis on key secondary criteria on PP data set at 6 months,
3. performs analysis on key secondary criteria on FAS at 6 months.

Sequences (4,5,6) are the same as (1,2,3) reperformed on data at 3 months.

Primary criterion

The mean difference between groups in Lean Body Mass change will be tested using a covariance analysis model including baseline and treatment effect at a nominal significance level set to α=0.05.

Key secondary criteria

The sum-rank O'brien multiple testing procedure will be performed on the changes of the short physical performance battery, grip strength and the aging male score.

No statistical analysis has been done.

Summary - Conclusions:

2 patients were selected between 16/10/2007 and 26/11/2007.

The first patient was included in the study but was withdrawn because of increased PSA level between V0 and V1 (Sponsor's decision). According to the Investigator, this adverse event was not related to study treatment. The patient received 8 days of treatment.

A second patient was screened but not enrolled due to the "Body Lean Mass" value: 59.1 kg (inclusion criteria: <49.9 kg).

No serious adverse events and deaths were reported during the study.

Due to lack of inclusion, despite 2 selections in one centre, the trial ended officially in May 2008.

Date of report 22 October 2019