2.5 Clinical Overview

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List of Abbreviations

ACTH	Adrenocorticotropic hormone
ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area Under Curve
BfArM	German Federal Institute for Drugs and Medical Devices
BMI	Body Mass Index
BPH	Benign Prostatic Hyperplasia
C_{ave}	Average concentration
CI	Confidence Interval
CV	Cardiovascular
DHT	Dihydrotestosterone
DRE	Digital Rectal Examination
ECG	Electrocardiogram
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GFI	Global Fatigue Index
GGT	Gamma-glutamyl Transferase
Hct	Haematocrit
HPLC	High Performance Liquid Chromatography
ICH	International Council for Harmonisation
IIEF	International Index of Erectile Function
INR	International normalised ratio
IM	Intramuscular
ISS	Integrated Summary of Safety
ITT	Intention-to-Treat
LFT	Liver Function Tests
LH	Luteinising Hormone
LHRH	Luteinising hormone-releasing hormone
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Events
MAF	Multidimensional Assessment of Fatigue
MCS	Mental Component Summary

MedDRA	Medical Dictionary for Regulatory Activities
MEB	Medicines Evaluation Board
MI	Multiple Imputation
PCS	Physical Component Summary
PE	Pulmonary Embolism
PK	Pharmacokinetics
PP	Per Protocol
PSA	Prostate Specific Antigen
SAE	Serious Adverse Event
SF-12	Short Form 12 Health Survey
SHBG	Sex Hormone-binding Globulin
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPA	Special Protocol Assessment
TEAE	Treatment-Emergent Adverse Event
TRT	Testosterone Replacement Therapy

2.5.1 Product Development Rationale

2.5.1.1 Introduction

FE 999303 belongs to the pharmacotherapeutic class of androgens and the intended indication of Testosterone gel (FE 999303) 2% is: "Testosterone replacement therapy (TRT) for adult male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests". Testosterone gel (FE 999303) 2% is delivered as a transdermal gel to be applied to the upper arm and shoulder using a cap applicator.

Testosterone, the primary androgenic hormone, and the metabolite dihydrotestosterone (DHT) are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex and other male characteristics.

Male hypogonadism is a clinical condition characterised by a low serum testosterone level (morning serum total testosterone levels is less than 300 ng/dL [10 nmol/L]) in combination with a diversity of symptoms and signs such as reduced libido and vitality, decreased muscle mass, increased fat mass, depression, and others (1,2). Hypogonadism is caused by insufficient testosterone secretion by the testes, and two basic types of male hypogonadism are identified:

- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle stimulating hormone [FSH], luteinising hormone [LH]) above the normal range
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinising hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

The goal of TRT in hypogonadal men is to restore testosterone levels to approximately the level of healthy men and to alleviate the symptoms associated with testosterone deficiency. Testosterone is a well-known endogenous substance which has been approved and used as replacement therapy worldwide for decades and is available as approved products in several strengths and formulations, including intramuscular (IM) preparations, scrotal and transdermal patches, transdermal gel, and orally administered agents.

The available TRT formulations differ in pharmacokinetics (PK) and safety profiles (3). The IM formulations are associated with testosterone peaks and troughs outside the normal range of healthy men, while oral formulations are achieving variable levels of testosterone with need of several daily doses. With the later developed scrotal and transdermal patches, products with steady-state testosterone levels became available to patients. The patches are associated with high frequency of

application site reactions, therefore testosterone gel formulations present a more favourable mode of testosterone replacement therapy.

In common for the topical formulations, is the risk of secondary exposure to others if appropriate precautions are not taken. Recent development efforts have therefore focused on increasing the bioavailability to minimise the amount of unabsorbed testosterone on the skin.

Testosterone gel (FE 999303) 2%, a topical hydroalcoholic gel formulation with testosterone as the drug substance, has been developed by Ferring Pharmaceuticals for the treatment of male hypogonadism. Testosterone gel (FE 999303) 2% has similar characteristics as other approved testosterone replacement products, especially the 1-2% topical gel products. The similar characteristics with other approved testosterone products is demonstrated versus an active topical comparator in a phase 1 pharmacokinetic study, and by using objective pharmacokinetic testosterone endpoints in phase 2 and 3 clinical trials, which have also been used for approval of other testosterone products

The characteristics of the gel formulation were selected to provide enhanced absorption with a smaller amount of gel than offered by other transdermal testosterone products, and hence with a reduced drug load. In addition, Ferring has developed a cap applicator as part of the primary packaging, i.e., a dispenser cap designed to also serve as the gel applicator, to provide application of the gel without coming in direct contact with the hands (hands-free) and thereby, in combination with the reduced drug load, reducing the likelihood of secondary transfer of testosterone to others.

2.5.1.2 Clinical Development Program

Ferring has completed three phase 1 trials, two phase 2 trials, and three phase 3 trials as part of the clinical development program for Testosterone gel (FE 999303) 2% (Table 1). A graphical presentation of the trials, indicating key development outcomes, is provided in Figure 1.

Results of these trials are presented in Module 5 individual ICH E3 clinical trial reports and summarised in Module 2 summaries. A summary comparison to published results of similar trials of commercial testosterone replacement products is also included in respective safety, efficacy, and clinical pharmacology summaries.

Table 1 Clinical Development Program for Testosterone gel (FE 999303) 2%

Phase	Trial ID *Objective*	Design	Treatment(s) Dose	Subjects	Population
1	FE 999303 CS02 *Relative bioavailability (FE 999303 vs. active comparator)*	Open-label, randomised crossover	Testosterone gel (FE 999303) 1%, 50 mg Testosterone gel (FE 999303) 2%, 50 mg TESTOGEL 1% (Also registered as ANDROGEL 1%), 50 mg	Total: 11	Testosterone down-regulated healthy adult males
1	000065 *Single dose PK after showering*	Open-label, randomised crossover	Testosterone gel (FE 999303) 2%, 69 mg	Total: 16	Adult hypogonadal males
1	000066 *Secondary exposure in non-treated females*	Open-label, fixed-sequence	Testosterone gel (FE 999303) 2%, 69 mg	Total: 30	Healthy males and their healthy female partners
2	000011 *Single dose and steady state PK; testosterone in normal physiologic range*	Open-label, sequential dose escalation	Testosterone gel (FE 999303) 2%, 23, 46, 69 mg	Total: 20	Adult hypogonadal males
2	000024 *Steady state PK; applicator feasibility*	Open-label, sequential dose escalation	Testosterone gel (FE 999303) 2% 46 mg (by hand) 23, 46, 69 mg (with applicator)	Total: 20	Adult hypogonadal males
3	000023 *Efficacy (PK); safety*	Open-label, non-randomised	Testosterone gel (FE 999303) 2%, 23, 46 or 69 mg based on titration criteria	Total: 180	Adult hypogonadal males
3	000077 (extension of 000023) *Efficacy (PK); long term safety*	Open-label, non-randomised	Testosterone gel (FE 999303) 2% Fixed dose established in 000023 (down-titrated if required)	Total: 145	Adult hypogonadal males
3	000127 (pivotal trial) *Efficacy (PK); safety*	Open-label, non-randomised	Testosterone gel (FE 999303) 2% 23, 46 or 69 mg based on titration criteria	Total: 160	Adult hypogonadal males

The applicator proposed for the marketed product has been used in Trials 000065, 000066, 000024, 000023, 000077, and 000127.

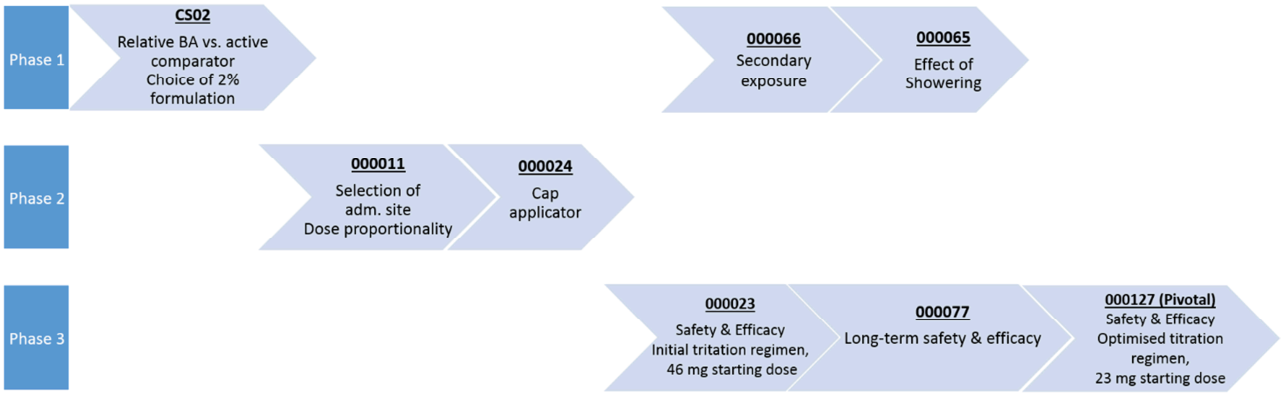

Figure 1 Chronological presentation of clinical development program for Testosterone gel (FE 999303) 2%

Phase 1 program

The first phase 1 trial, Trial FE 999303 CS02 [CS02, 5.3.3.1], was conducted to evaluate the relative bioavailability of two formulations of Testosterone gel (FE 999303) 1% and 2% versus the active comparator TESTOGEL 1% (also registered as ANDROGEL), to select a final formulation for the continued development program. Both Testosterone gel (FE 999303) formulations exhibited greater bioavailability than ANDROGEL 1%, with the 1% formulation showing the highest absorption rate following a single dose. The Testosterone gel (FE 999303) 2% formulation was considered suitable to take forward into further development due to the higher bioavailability compared to ANDROGEL 1%, and was preferred over the 1% formulation because it allowed for achieving the same testosterone concentrations with the lowest volume of gel between the two formulations.

Trial 000065 [000065, 5.3.3.4] was conducted to evaluate the effect of showering on the absorption of testosterone after administration of Testosterone gel (FE 999303) 2%. This trial demonstrated that showering 1 or 2 hours after application resulted in minimal decreases in testosterone bioavailability.

Trial 000066 [000066, 5.3.3.4] was conducted to evaluate secondary transfer of testosterone after administration of Testosterone gel (FE 999303) 2% from males to their healthy female partner. The trial demonstrated that there was no secondary exposure in female subjects following contact with their treated male partner when the male partner was clothed or after showering.

Phase 2 program

Trial 000011 [000011, 5.3.3.2] was conducted to evaluate the site of administration (thigh, abdomen or shoulder/upper arm) of Testosterone gel (FE 999303) 2% based on single dose administration, and multiple dose administrations of 23, 46 and 69 mg to the shoulder. The trial demonstrated that absorption was dose-proportional and that application to the shoulder/upper arm

yielded maximum bioavailability. It was thus decided to use the shoulder/upper arm as application site in the continued development program.

The next phase 2 trial, Trial 000024 [000024, 5.3.3.2], was conducted to evaluate Testosterone gel (FE 999303) 2% multiple dose administrations of 46 mg by hand and 23, 46, and 69 mg by cap applicator. The trial demonstrated that the absorption of testosterone was dose-proportional and similar when applied with applicator or by hand. Furthermore, the applicator allowed easy application of the gel. Based on these results it was decided to use the cap applicator in all later clinical trials.

Phase 3 program

Supporting phase 3 trials

The first phase 3 trial, Trial 000023 [000023, 5.3.5.4] was designed to evaluate the efficacy and safety of three dose levels (23, 46 or 69 mg) of Testosterone gel (FE 999303) 2% in adult hypogonadal male subjects. Subjects were treated for 90 days with Testosterone gel (FE 999303) 2% with a starting dose of 46 mg adjusted using a titration scheme based on a pre-dose testosterone level. The primary endpoint of responder rate ≥75% (defined as percentage of subjects with an average testosterone level between 300 and 1050 ng/dL on Day 90) was met. The trial also demonstrated improved signs and symptoms of testosterone deficiency.

Trial 000077 [000077, 5.3.5.4] was an extension of Trial 000023 with the primary objective to evaluate long term safety of Testosterone gel (FE 999303) 2% and as secondary objective to evaluate the efficacy of Testosterone gel (FE 999303) 2% by responder rate. The trial included subjects who completed Trial 000023; these subjects were treated for up to an additional 6 months. For subjects participating in both trials, the responder rates were similar after completion of 3 months treatment in Trial 000023 and after completion of the extension Trial 000077 (84.5% and 82.7%, respectively).

Pivotal phase 3 trial

Trial 000127 [000127, 5.3.5.2] was the pivotal trial to demonstrate efficacy and safety of Testosterone gel (FE 999303) 2% in achieving therapeutic levels of total testosterone in hypogonadal male subjects. The dosing regimen and titration scheme in Trial 000127 were chosen based on data from previous clinical trials with Testosterone gel (FE 999303). The efficacy criteria in Trial 000127 were based upon established endpoints used in the phase 3 trials 000023 and 000077, and were in line with those previously used for approval of transdermal testosterone products. A total of 159 adult hypogonadal male subjects were treated for 120 days with Testosterone gel (FE 999303) 2% with a starting dose of 23 mg adjusted using a titration scheme based on a testosterone sample collected 4 hours after application of the gel. The primary endpoint of responder rate ≥75% (defined as percentage of subjects with an average testosterone level between 300 and 1050 ng/dL on Day 90) was met and improved signs and symptoms of testosterone deficiency were observed.

2.5.1.3 GCP Compliance

All trials conducted with Testosterone gel (FE 999303) 1% and 2% were conducted under Good Clinical Practice regulations as consolidated under ICH-GCP and Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance.

2.5.1.4 Regulatory Guidance and Advice

The development program was discussed with various regulatory authorities and the pivotal phase 3 Trial 000127 [000127, 5.3.5.2] was performed in accordance with the FDA Special Protocol Assessment agreement. In Europe, the development program was discussed with regulatory authorities in Germany [R-Authority Meetings Minutes-36437] and the Netherlands [R-Authority Meetings Minutes-38420]. Of note, it was agreed that the legal basis for the application is according to article 8(3) of Directive 2001/83/EC as a 'full-mixed' dossier. Hence, this application relies on the generated clinical data as well as literature references, in particular the scientific literature documenting testosterone replacement therapy. A well-established objective endpoint based on serum testosterone concentration measurements within the therapeutic range, in a clearly defined patient population, was used in the Testosterone gel (FE 999303) 2% development program. Furthermore, the application includes a clinical trial with a cross-over design in which a direct comparison with the marketed product ANDROGEL 1% was performed [CS02, 5.3.3.1]. Based on these elements, the clinical documentation can be bridged to the scientific literature on other testosterone replacement therapies, such as other transdermal gels.

2.5.2 Overview of Biopharmaceutics

Several *in vitro* skin permeation studies were used to select the formulation of Testosterone gel (FE 999303) to be studied in the comparative bioavailability trial FE 999303 CS02 [CS02, 5.3.3.1]. As predicted by these *in vitro* studies, comparative bioavailability data demonstrated that both the 1% and 2% Testosterone gel (FE 999303) formulations exhibited greater bioavailability than TESTOGEL 1% (also registered as ANDROGEL 1%). The Testosterone gel (FE 999303) 2% formulation was considered suitable to take forward into further development due to the higher bioavailability compared to ANDROGEL 1%, and was preferred over the 1% formulation because it allowed for achieving the same testosterone concentrations with the lowest volume of gel between the two formulations.

2.5.3 Overview of Clinical Pharmacology

2.5.3.1 Clinical Pharmacology Trials

The clinical pharmacology program includes phase 1 and 2 clinical trials that provided data to support the dose titration scheme to be used in phase 3 clinical trials and the proposed product labelling.

The first phase 1 trial, Trial FE 999303 CS02 [CS02, 5.3.3.1], was conducted to evaluate the safety, relative bioavailability and PK of two formulations of Testosterone gel (FE 999303) 1% and 2%

versus the active comparator ANDROGEL 1%. The results from this trial were used to select a final formulation for the continued development program and to allow for a direct comparison of the to-be-marketed formulation of Testosterone gel (FE 999303) 2% to an already approved testosterone gel product.The bioavailability of Testosterone gel (FE 999303) 1% and 2% relative to ANDROGEL 1% were 200% and 139%, respectively (2.5.3.5.1). As described above in 2.5.2, the Testosterone gel (FE 999303) 2% formulation was considered suitable to take forward into further development.

Two other phase 1 trials were conducted to provide information on the effect of showering on the absorption of Testosterone gel (FE 999303) 2% [000065, 5.3.3.4] and the transfer of testosterone from treated male subjects to their female partners following application of Testosterone gel (FE 999303) 2% [000066, 5.3.3.4].

In Trial 000065, showering 1 and 2 hours after application of Testosterone gel (FE 999303) 2% decreased the 24-hour average total testosterone concentration (C_{ave}) by 19.2% and 14.3%, respectively, compared to not showering after Testosterone gel (FE 999303) 2% administration Showering 6 hours following Testosterone gel (FE 999303) 2% administration did not result in a decrease in C_{ave} [2.7.2.2.2].

The potential for testosterone transfer of Testosterone gel (FE 999303) 2% applied to the intact skin of the shoulder and upper arm was evaluated in Trial 000066 [000066, 5.3.3.4]. No statistically significant differences in secondary exposure to testosterone were noted in female subjects when the male partner was clothed at the time of contact or had showered before contact [2.7.2.2.3].

Two phase 2 trials of Testosterone gel (FE 999303) 2% were conducted in adult hypogonadal male subjects to evaluate the site of administration, evaluate dose response, and to compare application of Testosterone gel (FE 999303) 2% directly by hand *vs.* by cap applicator avoiding direct hand contact.

The shoulder and upper arm was selected as the site of administration of Testosterone gel (FE 999303) 2% based on the results of Trial 000011 [000011, 5.3.3.2], which was conducted in 20 subjects. Application of Testosterone gel (FE 999303) 2% to the shoulder and upper arm resulted in greater absorption than application to the thigh or abdomen, based on difference in C_{ave} ($p < 0.05$) [2.7.2.2.4].

The hands-free cap applicator was first introduced into clinical trials in Trial 000024 [000024, 5.3.3.2], which was conducted in hypogonadal males to compare Testosterone gel (FE 999303) 2% applied by hand *vs.* cap applicator. There was no apparent difference in the PK of testosterone absorption following the administration of 46 mg of testosterone to the shoulder and upper arm once daily for 7 days by hand or by cap applicator. This trial also showed a nearly linear increase in exposure to testosterone following administration of Testosterone gel (FE 999303) 2% 23, 46 or 69 mg once daily for 7 days using the cap applicator.

The results of Trial 000024 [000024, 5.3.3.2] demonstrated that 46 mg of Testosterone gel (FE 999303) 2% applied to the shoulder/upper arm using the cap applicator consistently led to serum testosterone levels within the therapeutic range (between 300 and 1050 ng/dL). In addition,

for evaluation of restoration of testosterone levels to the normal range, the following PK limits based on C_{max} were assessed: at least 85% of subjects with C_{max} below 1500 ng/dL, at most 5% of subjects with C_{max} between 1800 and 2499 ng/dL and no subjects with C_{max} of 2500 ng/dL or more. The 46 mg dose did not result in any subjects with C_{max} >1500 ng/dL, whereas this was the case in 3 (16.7%) subjects treated with the 69 mg dose. The 46 mg testosterone dose was therefore selected as the starting dose for the first phase 3 Trial 000023 [000023, 5.3.5.4].

2.5.3.2 Pharmacokinetics

2.5.3.2.1 Absorption

Due to the well-established nature of testosterone, the PK program for Testosterone gel (FE 999303) 2% focused on the absorption of testosterone, as this variable was known to be affected by the gel formulation. Testosterone gel (FE 999303) 2% provides transdermal delivery of testosterone, mimicking the natural circadian rhythm in terms of temporal changes in testosterone levels, with a median T_{max} of approximately 2-4 hours after dosing. Serum testosterone concentrations return to pre-dose values approximately 12 hours after application and no accumulation occurs after daily application for 10 days. Application on the upper arm and shoulder results in higher serum testosterone concentrations compared to application on the abdomen or the inside of the thigh. Washing the skin 1 or to 2 hours after application can cause a minor decrease in absorption by 19% or 14% respectively, but absorption is not affected by washing 6 hours after application. Skin-to-skin contact without prior showering can cause transfer and subsequent absorption of testosterone [2.7.2].

2.5.3.2.2 Distribution

No trials were conducted to evaluate distribution of Testosterone gel (FE 999303) 2%. All data on the distribution of testosterone was obtained from the literature.

Circulating testosterone is primarily bound in the serum to SHBG and albumin. The albumin-bound fraction of testosterone easily dissociates from albumin and is presumed to be biologically active. The portion of testosterone bound to SHBG is not considered biologically active. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins [2.7.2.4.5].

2.5.3.2.3 Metabolism

No trials were conducted to evaluate distribution of Testosterone gel (FE 999303) 2%. All data on the metabolism of testosterone was obtained from the literature.

Testosterone is metabolised to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT [2.7.2.4.6].

2.5.3.2.4 Excretion

No trials were conducted to evaluate excretion of Testosterone gel (FE 999303) 2%. All data on the excretion of testosterone was obtained from the literature.

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose of testosterone given IM is excreted in the urine as glucuronic and sulphuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the faeces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver [2.7.2.4.7].

2.5.3.3 Drug-Drug Interactions

No drug-drug interaction trials were conducted. All data on drug-drug interactions was obtained from the literature.

In the literature it is described that changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may decrease insulin requirements (4,5,6,7,8,9,10,11).

Changes in anticoagulant activity may be seen with androgens; therefore, more frequent monitoring of international normalised ratio (INR) and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy (12,13,14,15,16,17,18).

The concurrent use of testosterone with adrenocorticotropic hormone (ACTH) or corticosteroids may result in increased fluid retention and requires careful monitoring particularly in patients with cardiac, renal or hepatic disease (19,20,21,22,23,24).

2.5.3.4 Special Populations

2.5.3.4.1 Paediatric Use

Testosterone gel (FE 999303) 2% has not been evaluated in paediatric patients less than 18 years old.

2.5.3.4.2 Geriatric Use

Of the 339 subjects enrolled in the pivotal and supporting phase 3 clinical trials of Testosterone gel (FE 999303), 61 subjects (18%) were of age ≥65 years; 29 of these geriatric patients also participated in the 6-month extension trial.

The factor of age was evaluated as subgroup analysis in Trial 000127 [000127, 3.5.5.2]. The results showed that age had no impact on responder rates in subjects more than 55 years [2.7.2.3.10.1].

2.5.3.4.3 Renal/Hepatic Impairment

Testosterone gel (FE 999303) 2% has not been evaluated in patients with renal or hepatic impairment [2.7.2.3.10.2].

2.5.3.5 Comparison of Testosterone Gel (FE 999303) 2% with Other Testosterone Products (clinical pharmacology trials)

2.5.3.5.1 Comparison to ANDROGEL 1% (Trial FE 999303 CS02)

The safety, relative bioavailability and PK of two formulations of Testosterone gel (FE 999303) 1% and 2% versus ANDROGEL 1% were evaluated in Trial FE 999303 [2.7.2.2.1]. With each formulation, an amount of gel corresponding to 50 mg of testosterone was applied to the abdomen once daily for seven days.

Based on the AUC_{0-24} values on Day 7, the bioavailability of Testosterone gel (FE 999303) 2% relative to ANDROGEL 1% was 139%. The C_{max} value for Testosterone gel (FE 999303) 2% differed to a similar degree between the formulations and was 1.54-fold greater than C_{max} for ANDROGEL 1% on Day 7. These results indicated that a lower mg dose and volume of Testosterone gel (FE 999303) 2% is required for reaching similar testosterone concentrations compared to ANDROGEL 1%. With both formulations, testosterone steady state levels were reached after the first dose. The maximal concentrations occurred on average 6 hours after application for Testosterone gel (FE 999303) 2%, compared to 14 hours for ANDROGEL 1% on Day 7. The T_{max} of Testosterone gel (FE 999303) 2% is however similar to that of TOSTREX 2%, which was reported to be 2-4 hours (25).

2.5.3.5.2 Comparison to Published Literature

The results of the clinical pharmacology trials of Testosterone gel (FE 999303) 2% were compared to published clinical pharmacology trials of other topical products. ANDROGEL 1% (TESTOGEL 1% in Germany and Australia), ANDROGEL 1.62%, TOSTREX 2% (also registered as TOSTRAN, FORTIGEL and FORTESTA), and TESTIM 1% were chosen for comparison as they are approved in EU and have similar posology and characteristics.

A literature search was conducted revealing five comparative bioavailability trials, three trials evaluating the effect of showering on testosterone levels and three trials comparing the effects of application site on testosterone levels. Seven out of 11 publications included ANDROGEL 1%, two publications included ANDROGEL 1.62%, one publication included TOSTREX 2%, and two publications included TESTIM 1% (one of these being a comparative bioavailability trial including also ANDROGEL 1%).

In trials 000065 and 000024, the mean C_{ave} values after application of 46-69 mg Testosterone gel (FE 999303) 2% were similar to the values reported for 50 mg ANDROGEL 1% in four publications. In Trial 000011, the application of 23-46 mg Testosterone gel (FE 999303) 2% resulted in similar mean C_{ave} compared to 50 mg ANDROGEL 1% [2.7.2.3.2].

The effects of showering on absorption of testosterone from Testosterone gel (FE 999303) 2% were similar to the effects of ANDROGEL 1%, ANDROGEL 1.62%, and TOSTREX 2% reported in three publications. The effects of site of application on absorption of testosterone were similar for Testosterone gel (FE 999303) 2% compared to ANDROGEL 1.62% and TESTIM 1%, in that

bioavailability of testosterone was higher after application to shoulder/upper arm than to the abdomen or thighs (two publications) [2.7.2.3.2].

2.5.3.6 Clinical Pharmacology Conclusion

Testosterone gel (FE 999303) 2%, a topical hydroalcoholic gel formulation with testosterone as the active ingredient, is designed for rapid absorption through the skin after application on the shoulders and upper arms. The rate of absorption is similar to that of TOSTREX 2%. The absorption of Testosterone gel (FE 999303) 2% is higher than that of ANDROGEL 1% with a bioavailability of 139% relative to ANDROGEL 1%. The exposure to testosterone in the blood is dose dependent. Application of Testosterone gel (FE 999303) 2% with the hands-free cap applicator provides similar absorption as hand application but lower risk of secondary exposure to others. Application of Testosterone gel (FE 999303) 2% to the shoulder and upper arm results in higher absorption than application to the abdomen or thigh. Showering one hour after application of Testosterone gel (FE 999303) 2% results in some reduction in exposure, after two hours in a minimal reduction and after six hours in no effect. There is no or minimal transfer to other individuals if the male applying Testosterone gel (FE 999303) 2% showers or wears clothing covering the application site. The observed effects of application site and of showering on the absorption of testosterone are similar to the effects reported for other testosterone gel products approved in the EU.

2.5.4 Overview of Efficacy

2.5.4.1 Overview of Clinical Trials Contributing with Efficacy Data

Ferring has conducted one pivotal phase 3 trial [000127, 5.3.5.2], at once daily doses of 23, 46 and 69 mg as determined by titration scheme, to demonstrate the efficacy of Testosterone gel (FE 999303) 2% for the intended indication “TRT for adult male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests”. In addition, two supportive phase 3 trials, Trial 000023 [000023, 5.3.5.4] and its safety extension trial 000077 [000077, 5.3.5.4] were conducted prior to the pivotal Trial 000127.

A well-established, objective PK-based efficacy endpoint (responder rate, defined as percentage of subjects with average testosterone levels of 300-1050 ng/dL), was used in all three phase 3 trials. The trials had an uncontrolled, open-label dose titration design, which was similar to phase 3 trials for other recently approved testosterone replacement products. For bridging of efficacy to the existing testosterone gel products approved in EU, a comparison to published results of similar efficacy trials (reporting C_{ave} values) of commercial products has also been made.

An individualized titrated dose-design aiming to increase the testosterone level to the normal range was used in both Trial 000023 and Trial 000127, to account for subject variability in transdermal absorption. While meeting their efficacy endpoints, and hereby providing supportive evidence of Testosterone gel (FE 999 303) 2% being effective in the treatment of hypogonadal males, the results of Trials 000023 and 000077 also suggested that a modified titration scheme would be

appropriate. Based on these trial results, the starting dose and titration scheme in the pivotal Trial 000127 were adjusted as described in Section 2.5.4.2.1.1. The specified starting dose and titration scheme defined for Trial 000127 is essentially similar to the posology proposed for regulatory approval.

The pivotal Trial 000127 is described in Section 2.5.4.2, the comparison with published literature is described in Section 2.5.4.4 and trials 000023 and 000077 are described in [2.7.3] Clinical Summary of Efficacy.

2.5.4.2 Pivotal Phase 3 Trial

2.5.4.2.1 Background and Methods

Trial 000127 [000127, 5.3.5.2] investigated the safety and efficacy of Testosterone gel (FE 999303) 2% over a 90-day treatment period and a 30 day follow-up period in adult hypogonadal males. The trial was conducted in the US and Canada and included 159 adult hypogonadal males. The diagnosis of hypogonadism was confirmed based on symptoms and two baseline morning serum testosterone concentration measurements (at least 3 days apart within 60 days of initial treatment) less than 300 ng/dL. Eligible subjects were excluded from the trial where TRT would be contraindicated or pre-existing conditions would interfere with the evaluation of the PK of testosterone absorption. The demographics of the population were consistent with the general population of age-related hypogonadism. The mean age of subjects was 54.1 ([redacted] years and 21 (13.2%) of the 159 subjects were ≥65 years of age. The majority of subjects were Caucasian (77.4%), followed by Black/African American (19.5%). The mean BMI was 30.7 (range: 20-35) kg/m^2 [000127, Table 7, 5.3.5.2].

The primary efficacy endpoint was the responder rate, calculated as percentage of subjects at Day 90 whose C_{ave} serum total testosterone levels were between 300 and 1050 ng/dL.

The secondary efficacy endpoints were:

- The percentage of subjects on Days 14, 35 and 56 whose C_{ave} serum total testosterone levels were between 300 and 1050 ng/dL
- Pharmacokinetic parameters (C_{ave}, AUC_{τ}, T_{max}, C_{max}, C_{min}) for total testosterone and DHT on Days 14, 35, 56 and 90
- Change from baseline (Day 1) to Days 35 and 90 in International Index of Erectile Function (IIEF) scores per domain
- Change from baseline (Day 1) to Days 35 and 90 in Multidimensional Assessment of Fatigue (MAF) global score
- Change from baseline (Day 1) to Days 35 and 90 in Short Form-12 Health Survey (SF-12) total score and per domain (Physical Component Summary (PCS), Mental Component Summary [MCS])

- Dose titration decisions made on the 4-hour testosterone values in comparison with hypothetical decisions that would have been made based on 2- and 6-hour testosterone values.

2.5.4.2.1.1 Dose Titration Scheme

The titration scheme that was used in Trial 000127 [000127, 5.3.5.2] was based on the results of previously completed phase 2 and 3 trials. In the first phase 3 trial 000023 [000023, 5.3.5.4], the safety and efficacy of a titrated dose of Testosterone gel (FE 999303) 2% applied with an applicator for 90 days was evaluated. The initial starting dose of Testosterone gel (FE 999303) 2% was 46 mg and, if necessary, the dose could be down-titrated to 23 mg or up-titrated to 69 mg at two time points in the study, based on a single morning pre-dose serum testosterone sample (concentration levels triggering dose adjustments: below 300 and exceeding 600 ng/dL). In safety extension Trial 000077 [000077, 5.3.5.4], subjects initially continued to administer the same dose of Testosterone gel (FE 999303) 2% that they were administering at the end of Trial 000023. At one time point in the trial, the dose could be down-titrated based on a single morning testosterone measurement taken 2 hours after administration of Testosterone gel (FE 999303) 2%. The data from these supporting phase 3 trials suggested that a starting dose of 23 mg (1 pump actuation) with subsequent titration based on a single testosterone level at 4 hours after application of a dose could result in an average testosterone concentration of 300 to 1050 ng/dL. Based on the observation of a relatively low correlation between pre-dose concentrations and C_{ave} on Day 90 it was concluded that using pre-dose concentrations of serum testosterone do not adequately predict the C_{ave} values. If the serum testosterone concentration 4 hours post-dose was below 500 ng/dL in Trial 000127, the daily Testosterone gel (FE999303) 2% dose was increased by 1 pump actuation. If the serum testosterone concentration exceeded 1050 ng/dL, the daily Testosterone gel (FE 999303) 2% dose was decreased by 1 pump actuation [Titration Report, 5.3.5.3]. This titration regimen was therefore used in the pivotal phase 3 Trial 000127.

In Trial 000127, the initial dose of Testosterone gel (FE 999303) 2% was 23 mg testosterone once daily in the morning, delivered as a single pump actuation (23 mg) applied with a cap applicator to one shoulder and upper arm. Two additional dose levels, 46 and 69 mg testosterone, were potentially used if the subject qualified for an increase at the titration visits during the trial. The 46 mg dose was administered as two pump actuations, one to each shoulder and upper arm. The 69 mg dose was administered as three pump actuations using both shoulders and upper arms. Titration decisions were based on serum samples collected on Days 14, 35, and 56 at 4 hours post-dose. The dose of Testosterone gel (FE 999303) 2% was titrated-up or -down within seven business days of the blood draws. If the 4-hour concentration was within 500 to 1050 ng/dL, there was no dose change. A 4-hour testosterone concentration below 500 ng/dL resulted in a one pump actuation dose increase and above 1050 ng/dL, a one pump actuation dose decrease. After Day 63, the dose was fixed for the remainder of the study. While the titration scheme was based on a single serum testosterone sample at 4 hours after dosing, a PK model demonstrated that a therapeutic C_{ave}

could be obtained in >75% of subjects when the titration sample was also collected 2 hours after application of the gel ([2.7.3] and described in detail in the [Titration Report, 5.3.5.3]).

2.5.4.2.2 Primary Efficacy Endpoint

The Full Analysis Set (FAS) Population was used for the primary endpoint analyses and included subjects who had sufficient PK data to determine a C_{ave} on Days 14, 35, 56, or 90 or discontinued the study early due to safety reasons. Missing Day 90 C_{ave} was imputed by last observation carried forward (LOCF).

On Day 90, of the 155 subjects who were included in the FAS population, 76.1% met the predetermined efficacy criteria for success in that they had a C_{ave} on Day 90 between 300 and 1050 ng/dL (95% confidence interval [CI]: 69.4, 82.8%); the predetermined efficacy criteria were a responder rate ≥75% and the lower bound of the 95% CI ≥65%. Sensitivity analyses pre-specified in the statistical analysis plan showed a similar response rate in the Per Protocol (PP) (78.6%) and the PP completer (82.8%) populations (Table 2).

Table 2 Responder Rate - Day 90: Sensitivity Analyses

	Population	Responder Rate (Testosterone C_{ave} between 300 and 1050 ng/dL)	95% CI
Sensitivity Analyses	ITT (n =159)	118 (74.2%)	67.4%, 81.0%
	ITT Multiple Imputation	78.2 %	71.5%, 84.8%
	PP (n =145)	114 (78.6%)	71.9%, 85.3%
	PP Completers (n =134)	111 (82.8%)	76.5%, 89.2%

CI: Confidence Interval; ITT: Intention-to-Treat; PP: Per Protocol
Source: [000127, Table 8, 5.3.5.2]

These results were confirmed with additional sensitivity analyses, including multiple imputation (MI) to impute missing responses for individual C_{ave} values performed on the ITT (Intention-to-Treat) population. The MI results showed that on Day 90, 78.2% of the 159 subjects had serum testosterone C_{ave} levels between 300 and 1050 ng/dL (95% CI, 71.5%, 84.8%).

2.5.4.2.3 Secondary Efficacy Endpoint

One of the secondary efficacy objectives for Trial 000127 [000127, 5.3.5.2] was determination of the percentage of subjects on Days 14, 35 and 56 with C_{ave} serum total testosterone levels between 300 and 1050 ng/dL. The percentages for each of the visits when PK profiles were determined are presented in Table 3. The percentage of subjects within the desired range increased at least 2-fold between Day 14 and Day 35, with the first titration occurring between the PK profile days. Between Day 35 and Day 56, there was a second titration, and the percentage within the desired range increased by approximately 1.25 fold. Between Day 56 and Day 90, there was a third titration, if needed, and the percentage within the desired range increased slightly.

Table 3 Percentage of Subjects with Testosterone C_{ave} Values Between 300 and 1050 ng/dL on Days 14, 35, 56 and 90 (FAS population)

	Day 14	Day 35	Day 56	Day 90
With LOCF	29.1%	58.2%	71.2%	77.8%
Without LOCF	29.1%	60.7%	75.0%	82.0%

FAS: Full Analysis Set; LOCF: Last Observation Carried Forward
Source: [000127, Table 10, 5.3.5.2], [000127, Stat Table 14.2.2.1.3, 5.3.5.2]

The secondary efficacy objectives included also determination of the PK parameters (C_{ave}, AUC_{τ}, T_{max}, C_{max}, C_{min}) for total testosterone and DHT on Days 14, 35, 56 and 90. DHT levels are expected to follow testosterone levels, except in the case of contamination of samples with topical testosterone, causing the ratio testosterone:DHT to increase. A summary of results for testosterone and DHT at Day 90 is presented in Table 4.

Table 4 Pharmacokinetic Parameters for Total Testosterone and DHT – Day 90

Dose on Day 90	C_{max} (ng/dL) Mean ±SD	T_{max} (hr) Median	C_{min} (ng/dL) Mean ±SD	AUC_{τ} (ng•h/dL) Mean ±SD	C_{ave} (ng/dL) Mean ±SD	N
Testosterone parameters						
23 mg	721 ±254	4.02	191 ±49	8831 ±2829	368 ±121	5
46 mg	1228 ±640	2.02	277 ±140	12245 ±5010	506 ±207	45
69 mg	1099 ±595	2.08	229 ±82	10590 ±3979	438 ±164	89
All dose levels	1127 ±606	2.0	244 ±106	11062 ±4372	458 ±180	139
DHT parameters						
23 mg	91.4 ±34.8	4.12	45.1 ±21.0	1579 ±560	65.9 ±24.1	5
46 mg	138 ±66	3.75	62.5 ±26.4	2210 ±956	91.2 ±38.9	45
69 mg	118 ±55	3.95	53.1 ±29.7	1876 ±956	77.7 ±39.7	89
All dose levels	124 ±59	3.9	55.9 ±28.7	1973 ±956	81.6 ±39.4	139

AUC: Area Under the Curve; C_{ave}: Average Concentration; C_{max}: Maximum Concentration; C_{min}: Minimum Concentration; DHT: Dihydrotestosterone; SD: Standard Deviation; T_{max}: Time to Reach Maximum Concentration
Source: [000127, Table 11, 5.3.5.2] [000127, PK Supplement, 5.3.5.2]

On Day 90, the mean value of C_{ave} for testosterone was 458 ng/dL, which is well within the target range of 300-1050 ng/dL.

The values of C_{max}, AUC_{τ}, and C_{ave} for testosterone were similar across dose levels, confirming the effectiveness of the dose titration regimen. For the 23 mg dose, the values tended to be slightly lower but this is based on data from five subjects only. The mean values of C_{min} and C_{max} for testosterone were 244 and 1127 ng/dL, respectively, which is near the boundaries of the normal range of 300-1050 ng/dL. The median T_{max} for testosterone occurred at approximately 2 hours after dosing, except for subjects receiving 23 mg at Day 90, when the median T_{max} was at 4.02 hours. The parameter values of DHT followed those for testosterone. As expected, the median values for T_{max} for DHT tended to be longer than the median values for testosterone, ranging from 2.00 to 4.12 hours.

The use of Testosterone gel (FE 999303) 2% resulted in improvements in the subject reported outcome instruments which were assessed as secondary endpoints in the study population of

hypogonadal males and are considered to support the effectiveness of the product. The change from baseline in subject reported outcome on Days 35 and 90 is presented in Table 5.

The IIEF questionnaire results demonstrated improvement from baseline (Day 1) for all 15 questions and 5 domains at Day 35 and the end of trial (Day 90). All the individual domains for IIEF, i.e. Erectile Function, Intercourse Satisfaction, Orgasmic Function, Sexual Desire, and Overall Satisfaction, showed a significant improvement through the course of trial ($p < 0.0001$). IIEF mean total score demonstrated a significant improvement in sexual function from Day 1 (35.9) at Day 35 (44.0) and at the end of trial (50.3), an improvement of 8.4 ±13.2 and 14.4 ±16.9, respectively ($p < 0.0001$).

There was a significant improvement in fatigue from baseline (Day 1) for all 16 MAF questions at Day 35 and the end of trial (Day 90). There was a significant ($p < 0.0001$) improvement in the mean scores for Severity, Distress, Degree of Interference in Activities of Daily Living, and Timing. Overall, Global Fatigue Index (GFI) mean score demonstrated a significant improvement in fatigue from Day 1 (27.6) at Day 35 (19.4, $p < 0.0001$).

There was a significant improvement from baseline to Day 35, and the end of trial (Day 90) in three of the psychometrically-based PCS domains: General Health ($p \leq 0.0001$), Physical Functioning ($p = 0.0015$), and Role-Physical; $p < 0.0001$). The Bodily Pain domain also showed significant improvement from baseline at Day 35 ($p = 0.0315$) or approached significance ($p = 0.0559$) at Day 90. The mean total PCS score also showed significant improvement from baseline to Day 35 ($p = 0.0343$) and Day 90 ($p = 0.0033$). A significant improvement from baseline at Day 35 and Day 90 was also observed in the MCS in all 4 domains: (Mental Health, Vitality, Role-Emotional and Social Functioning; $p < 0.0001$). The mean total MCS score also showed significant improvement from baseline (Day 1) to Day 35 ($p < 0.0001$) and Day 90 ($p < 0.0001$) and at the end of trial (15.8, $p < 0.0001$).

The treatment satisfaction questionnaire was also used to assess overall subject satisfaction with the Testosterone gel (FE 999303) 2% and the cap applicator. The results presented good satisfaction with the product (83.4% of subjects were very satisfied/satisfied using this testosterone gel product) and supported the use of applicator while applying the gel (93.5% of subjects were very satisfied/satisfied using cap applicator and 87.0% of subjects felt less risk of testosterone transference to his partner or child by using cap applicator) [2.7.3.3.2.2].

Table 5 Change from Baseline in Subject Reported Outcome on Days 35 and 90 (FAS population)

		Change from Baseline		
	Baseline	**Day 35**	**Day 90**	**p value**
IIEF score				
Erectile Function	14.9 ±9.4	3.4 ±6.7	5.9 ±8.1	p <0.0001
Intercourse Satisfaction	5.8 ±4.4	1.3 ±3.2	2.4 ±3.6	
Orgasmic Function	5.4 ±3.6	1.3 ±3.0	1.8 ±3.5	
Sexual Desire	5.2 ±2.1	1.2 ±1.9	2.2 ±2.1	
Overall Satisfaction	4.6 ±2.2	1.2 ±2.3	2.1 ±2.5	
Total Score	35.9 ±18.7	8.4 ±13.2	14.4 ±16.9	
MAF score				
Severity Domain	12.0 ±4.9	-3.6 ±4.8	-5.2 ±4.9	p <0.0001
Distress Domain	5.1 ±2.6	-1.7 ±2.6	-2.2 ±2.5	
Degree of Interference in Activities of Daily Living	48.0 ±22.9	-13.6 ±24.1	-16.7 ±24.5	
Timing Domain	13.1 ±3.0	-2.6 ±3.3	-3.0 ±3.4	
Global Fatigue Index	27.6 ±11.2	-8.3 ±10.1	-12.0 ±11.1	
SF-12 score				
PCS Domain	48.2 ±8.8	1.2 ±7.0	1.8 ±7.1	p <0.05
MCS Domain	43.7 ±11.1	6.3 ±9.5	6.5 ±10.1	p <0.0001

FAS: Full Analysis Set; IIEF: International Index of Erectile Function; MAF: Multidimensional Assessment of Fatigue ; MCS: Mental Component Summary; PCS: Physical Component Summary ; SF-12: Short Form 12 Health Survey
Source: [000127 Stat Table 14.2.2.2.2, 5.3.5.2], [000127 Stat Table 14.2.2.3.2, 5.3.5.2], [000127 Stat Table 14.2.2.4.2, 5.3.5.2]

2.5.4.2.4 Comparison of Results in Sub-populations

Subgroup analyses in Trial 000127 results showed that age had no impact on responder rates in subjects <55 years *vs.* ≥55 years on Days 14, 35, 56 and 90. Neither was there any impact on responder rates observed in Caucasians *vs.* all other races; and in BMI <30 kg/m^2 *vs.* BMI ≥30 kg/m^2 on Days 14, 35, 56 and 90 [2.7.3.3.3].

2.5.4.3 Persistence of Efficacy and/or Tolerance Effects

Subjects in Trial 000023 [000023, 5.3.5.4] continuing treatment in the safety extension Trial 000077 [000077, 5.3.5.4] were treated for a total of 270 days with maintained efficacy based on C_{ave} within the target range of 300-1050 ng/dL [2.7.3.6].

2.5.4.4 Efficacy Comparison of Testosterone Gel (FE 999303) with Other Products (Phase 3 Trials)

To bridge efficacy of Testosterone gel (FE 999303) 2% to existing testosterone gel products approved in EU, the data from Trial 000127 [000127, 5.3.5.2] were compared with phase 3 trials of other topical testosterone products (excluding patches) that have been reported in the published

literature. ANDROGEL 1% (TESTOGEL 1% in Germany and Australia), ANDROGEL 1.62%, TOSTREX 2% (also registered as TOSTRAN, FORTIGEL and FORTESTA), and TESTIM 1% were considered appropriate for comparison. The products are approved in EU and have similar posology and advantage of dose titration based upon skin absorption rates related to metabolism across the stratum corneum (Table 6). The trials selected for comparison also had similar end-points and duration of treatment [2.7.3.4.1].

Table 6 EU Approved Posology for Topical Testosterone Gels

IMP	Starting dose	Gel Weight	Application Method	Approved dosage	Application site	Recommended dose titration time
TESTIM 1%	50 mg/day (one tube)	5 g	By hand	50-100 mg/day	Shoulders and/or upper arms	Early morning before application, 7-14 days after treatment initiation
ANDROGEL 1%	50 mg/day (one sachet)	5 g	By hand	50-100 mg/day	Shoulders and/or upper arms	In morning before application, 3-7 days after treatment initiation
ANDROGEL 1.62%	40.5 mg (two actuations)	2.5 g	By hand	20.25-81 mg/day	Shoulders and/or upper arms	In morning before application, on Day 14 and Day 28 after treatment initiation
TOSTREX 2%	60 mg (3 gm of gel)	3 g	By hand	60-80 mg/day	Abdomen or to both inner thighs	2 hours after dosing, 14 days after treatment initiation
Posology of Testosterone gel (FE 999303) 2% in Trial 000127 for approval						
Testosterone gel (FE 999303) 2%	23 mg/day (one actuation)	1.15 g	By cap applicator	23-69 mg/day[a]	Shoulders and/or upper arms	2-4 hours after dosing, on Day 14 and Day 35 after treatment initiation

[a]1.25 mL/1.15 g (1 pump actuation) =23 mg, 2.50 mL/2.30 g (2 pump actuation) =46 mg, 3.75 mL/3.45 g (3 pump actuation) =69 mg

The comparison of the mean C_{ave} values for Day 90 or Day 180 for the above-mentioned products is presented in Table 7. The mean C_{ave} values for Testosterone gel (FE 999303) 2% were similar to the reported C_{ave} values for ANDROGEL 1%, TOSTREX 2%, and TESTIM 1%. For ANDROGEL 1.62%, no C_{ave} values were reported for treatment of 90 days or more, only changes from baseline. The baseline values plus the changes from baseline indicated that treatment with ANDROGEL 1.62% also produced similar C_{ave} values as the other products, including Testosterone gel (FE 999303) 2%.

Table 7 Comparison of Mean C_{ave} Values Between Products

Reference	Product	Sampling Day	Dose Level of Testosterone	Mean C_{ave} (ng/dL)	N
[000127, 5.3.5.2]	FE 999303	90	23 mg/day	368 ±121	5
			46 mg/day	506 ±207	45
			69 mg/day	438 ±164	89
			All levels	458 ±180	139
Swerdloff et al. (26), and Wang et al. (27)	ANDROGEL 1%	180	50 mg/day	555 ±34	51
			50 to 75 mg/day	450 ±106	20
			100 to 75 mg/day	744 ±74	20
			100 mg/day	713 ±30	52
Steidle et al. (28)	ANDROGEL 1%	90	50 mg/day	398 ±234	99
			100 mg/day	493 ±237	106
Dobs et al. (25)	TOSTREX 2%	90	All levels, 10 to 70 mg/day	439 ±163	149
Seftel et al. (29)	TESTIM 1%	90	50 mg/day	405 ±248	99
			100 mg/day	506 ±234	106

The information on subject reported outcome from Trial 000127 were also compared to the information on studies of other testosterone gel products that have been reported in the published literature. The subject reported outcome with Testosterone gel (FE 999303) 2%, demonstrated significant improvement in sexual function, fatigue parameters, and QoL which were in line with trials with ANDROGEL 1% and TOSTREX 2%. The improvement in QoL were similar to results presented in meta-analysis of TRTs [2.7.3.4.2].

2.5.4.5 Efficacy Conclusion

The pivotal trial data (000127) as well as the supporting data from phase 2 and phase 3 trials demonstrated that Testosterone gel (FE 999303) 2% successfully restores testosterone levels in hypogonadal men to achieve the physiological range of serum testosterone. The proposed dosing regimen, as confirmed in the pivotal phase 3 trial, includes a low starting dose of 23 mg with sequential dose-titration points after the initial starting dose. The dose can be titrated upward (to 46 mg or 69 mg testosterone) based on the single 4-hour post dose total testosterone concentration sample. The effectiveness of the proposed titration scheme is supported by the finding in the pivotal phase 3 Trial 000127 that the primary efficacy objective was achieved with a greater than 76% response rate and the lower bound of the 95% CI to be ≥65%. The number of responders gradually increased during the treatment period. There was no impact of age, BMI, and race on responder rate. The normalisation of total testosterone levels was commensurate with significant improvements sexual functioning, fatigue, and QoL as noted by improvement in subject reported outcomes in the IIEF, MAF, SF-12, and treatment satisfaction questionnaires. The treatment satisfaction was good; almost all patients were satisfied or very satisfied with using the cap

applicator and felt using it decreased the risk of secondary exposure to others. Based on published literature, the adequacy of the proposed titration regimen and the overall efficacy profile of Testosterone gel (FE 999303) 2% including C_{ave} and subject reported outcome, is in line with already marketed testosterone products.

Overall, Testosterone gel (FE 999303) 2% has been demonstrated to be efficacious in normalising the serum testosterone levels and relieving the symptoms of male hypogonadism.

2.5.5 Overview of Safety

2.5.5.1 Clinical Trials – Methods

The safety data supporting the MAA for Testosterone gel (FE 999303) 2% is based on completed phase 1, phase 2, and phase 3 clinical trials conducted by Ferring during development of the product (Table 8); and scientific literature available for other approved TRT products (Section 2.5.5.3.9).

The safety data for Testosterone gel (FE 999303) 2% includes a total of 395 subjects in six trials: one phase 1 (000065 [000065, 5.3.3.4]), two phase 2 (000011 [000011, 5.3.3.2], and 000024 [000024, 5.3.3.2]), and three phase 3 (000023 [000023, 5.3.5.4], 000077 [000077, 5.3.5.4], and 000127 [000127, 5.3.5.2]) trials. Of these, 339 subjects were in the phase 3 trials 000023 and 000127. In Trial 000023, 172 subjects completed 90 days of treatment and in Trial 000127, 139 subjects completed 120 days of treatment. In Trial 000077 [000077, 5.3.5.4], the long term safety extension of Trial 000023, 106 subjects completed an additional 180 days of treatment, for a total of 9 months of exposure to Testosterone gel (FE 999303) 2%. Given that testosterone products, and specifically testosterone transdermal products, have been marketed for years and are widely used, the cumulative exposure represents a sufficient database to evaluate the safety of Testosterone gel (FE 999303) 2%.

The sources of safety data in these trials included reported AEs, clinical laboratory results, physical examinations, and in the pivotal trial an evaluation of application site erythema occurrence and severity.

The summary of clinical safety primarily focuses on the data from clinical trials (Treatment Emergent Adverse Events [TEAEs] [2.7.4.2.1] and Overall Population [ISS Tables, 5.3.5.3]) in males with a clinical diagnosis of hypogonadism based on symptoms and pre-treatment serum total testosterone concentrations. Summaries of safety data from the phase 3 trials (trials 000023, 000077 and 000127), and overall population which includes all adult hypogonadal male subjects enrolled in the six trials (000011 [000011, 5.3.3.2], 000023, 000024 [000024, 5.3.3.2], 000065 [000065, 5.3.3.4], 000077 and 000127) are also presented. For specific analyses, subgroups of subjects are presented to focus on the most relevant safety assessments. The Summary of Clinical Safety [2.7.4.7] also includes scientific literature available for other approved topical TRT gels with similar exposure to treatment, which ranged from 90 to ≥180 days of treatment, and meta-analysis on TRTs.

An analysis (pooled data) of major cardiovascular (CV) events was performed by identifying Medical Dictionary for Regulatory Activities (MedDRA) terms defined under the Standardised MedDRA Query (SMQ) categories: Ischaemic cerebrovascular conditions; Haemorrhagic cerebrovascular conditions; Embolic and thrombotic events, arterial; Myocardial infarction (MI); and Other ischaemic heart disease [2.7.4.5].

2.5.5.2 Clinical Trials – Analyses

Safety variables for Testosterone gel (FE 999303) 2% included treatment-emergent adverse events (TEAEs), changes in vital signs, clinical laboratory safety test results (including haemoglobin and haematocrit [Hct]), hormone test results (LH, FSH and estradiol), insulin and prostate specific antigen (PSA; including percent of subjects with PSA values >4.0 ng/mL) and physical examination (including digital rectal exam and examination for application site reactions). For the summary of safety, changes in Hct, liver function tests (LFT), and PSA values were laboratory changes of special concern.

Application site reactions were assessed in Trial 000127 [000127, 5.3.5.2] using a specific data collection form and skin AEs that were associated with the application site were coded in MedDRA to Application Site specific terms under the General Disorders and Administration Site Conditions System Organ Class (SOC). All application site events were coded in MedDRA 14.0. As the events were coded differently in trials 000023 [000023, 5.3.5.4] and 000127, the events in Trial 000023 were re-coded for the safety analysis so that all events were included in the SOC General Disorders and Administration Site Conditions [2.7.4.4].

In the analysis, AEs that were considered treatment related by the investigator and/or sponsor were classified as adverse drug reactions (ADRs).

Table 8 Summary of Testosterone gel (FE 999303) Trials Providing Safety Information

Trial Number	Trial Objective	Trial Design	Test Product(s) Mode of application Application site	Dosing Regimen[a]	Number of Subjects Exposed to / Completed	Duration of Treatment
Pivotal Phase 3 Clinical Trial						
[000127, 5.3.5.2]	Efficacy and safety in adult hypogonadal male subjects.	Open-label, non-randomised	Testosterone gel (FE 999303) 2% Cap application Shoulder/upper arm in a contralateral fashion	23, 46, or 69 mg daily for 120 days. Titration based on testosterone concentration	159 / 139	120 days
Other Phase 3 Clinical Trials						
[000023, 5.3.5.4]	Safety and efficacy of three dose levels in adult hypogonadal male subjects.	Open-label, non-randomised	Testosterone gel (FE 999303) 2% Cap application Shoulder/upper arm in a contralateral fashion	23, 46, or 69 mg daily for 90 days. Titration based on testosterone concentration	180 / 172	90 days
[000077, 5.3.5.4]	Safety in adult hypogonadal male subjects who completed treatment in Trial 000023.	Open-label, non-randomised	Testosterone gel (FE 999303) 2% Cap application Shoulder/upper arm in a contralateral fashion	Continue same dose as Trial 000023 for 180 days.	145 / 127[b]	180 days
Phase 2 Clinical Trials						
[000011, 5.3.3.2]	PK, safety, and efficacy of three volumes in adult hypogonadal male subjects.	Open-label, sequential dose escalation	Testosterone gel (FE 999303) 2% Hand application Single dose: Day 1 (at inner thigh), Day 7 (at abdomen) and Day 13 (at shoulder/upper arm) Multiple dose: shoulder/upper arm	3 single doses of 46 mg and escalating doses of 23, 46, and 69 mg / daily each for 10 days	20 / 20	3 single doses 7 days apart and 10 days each of 23, 46, and 69 mg doses
[000024, 5.3.3.2]	PK, safety, and efficacy of gel application with an applicator in adult hypogonadal male subjects.	Open-label, sequential dose escalation	Testosterone gel (FE 999303) 2% Hand and cap applicator Shoulder/upper arm in a contralateral fashion	46 mg for 7 days by hand and escalating doses of 23, 46, and 69 mg by applicator	20 / 18	7 days of 46 mg dose 7 days apart and 7 days each of 23, 46, and 69 mg

Trial Number	Trial Objective	Trial Design	Test Product(s) Mode of application Application site	Dosing Regimen[a]	Number of Subjects Exposed to / Completed	Duration of Treatment
				each for 7 days		
Phase 1 Clinical Trials						
[CS02, 5.3.3.1]	Relative bioavailability, safety, and tolerability of gel application (1% and 2%) *vs.* active comparator in healthy testosterone down-regulated male subjects.	Randomised, open-label, active control, multiple dose, 3-way crossover	Testosterone gel (FE 999303) 1% and 2% Hand application Abdomen	1% gel =5.0 g gel daily 2% gel =2.5 g gel daily ANDROGEL 1% =5.0 g gel daily for 7 days	11 / 10	14 days
[000065, 5.3.3.4]	Effects of showering on PK in adult hypogonadal male subjects.	Randomised, open-label, four-way crossover	Testosterone gel (FE 999303) 2% Cap applicator Shoulder/upper arm in a contralateral fashion	Single dose of 69 mg / Showering sequence	16 / 16	Single dose / Showering sequence [c]
[000066, 5.3.3.4]	Secondary exposure from male subjects to female partners (healthy couples in a heterosexual relationship).	Open-label, three parts (Part I, Part II and Part III) with a minimum of 7-days washout between treatments	Testosterone gel (FE 999303) 2% Cap applicator Shoulder/upper arm in a contralateral fashion	Single dose of 69 mg / Part	30 / 30 (15 couples)	Single dose / Part [d]

[a] 1.25 mL (1 pump actuation) =23 mg, 2.50 mL (2 pump actuation) =46 mg, 3.75 mL (3 pump actuation) =69 mg. In the phase 2 trials 000011 and 000024, the 3.75 mL dose of Testosterone gel (FE 999303) 2% (3 pump actuations) is equivalent to 70 mg of testosterone. In phase 3 trials 000023, 000077 and 000127, the 3.75 mL dose of Testosterone gel (FE 999303) 2% (3 pump actuations) is equivalent to 69 mg of testosterone. This is a nominal difference only, due to rounding.
[b] Not unique subjects. They entered the Trial 000077 after completing the Trial 000023;
[c] Showering sequence: Showering at 1, 2 or 6 hours post-dose, and a no-shower condition
[d] Part I: Contact while male subject was clothed; Part II: Skin-to-skin contact with male subject after showering; Part III: Skin-to-skin contact with male subject without showering
PK: Pharmacokinetics

2.5.5.3 Clinical Trials – Safety Results

2.5.5.3.1 Population

Three hundred ninety five (395) subjects treated with Testosterone gel (FE 999303) 2% were included in the safety analysis. The mean age of subjects was 54.8 (range: 25-75) years and 62 (15.7%) subjects were of age ≥65 years [Table 15, 2.7.4]. The majority of subjects were Caucasian (79.7%) and the mean BMI was 30.2 (range: 20-35) kg/m^2. The demographics and clinical characteristics for the for the phase 3 trial population (n =339) were similar for the overall population [2.7.4.1.3].

2.5.5.3.2 Adverse Events

Overall, across the phase 2 and phase 3 trials of Testosterone gel (FE 999303) 2%, 141 (35.7%) subjects experienced 269 treatment emergent adverse events (TEAEs). The majority (258/269) of the AEs were mild or moderate in intensity. Nine subjects from three phase 3 trials experienced 11 AEs which were severe in intensity [2.7.4.2.1].

The most commonly occurring AEs (≥1%) were upper respiratory tract infection reported in 11 (2.8%) subjects, bronchitis, blood triglycerides increased, PSA increased, hypertension and cough each in 7 (1.8%) subjects, nasopharyngitis in 6 (1.5%) subjects, and application site erythema, back pain, epididymitis, rash, GGT (Gamma-glutamyl Transferase) increase and Hct increased each in 4 (1%) subjects [2.7.4.2.1.1].

A total testosterone C_{max} >2500 ng/dL was observed in 28 (2.7%) of the 24 hours PK profiles measured across the phase 3 trials of Testosterone gel (FE 999303) 2% [ISS Table 7.1, 5.3.5.3]. These C_{max} values did not exhibit evidence that the C_{max} values had any impact on incidence of AEs, severity of AEs or relationship to trial drug.

2.5.5.3.3 Serious Adverse Events

Overall, across the phase 3 trials of Testosterone gel (FE 999303) 2%, a total of nine subjects experienced 11 SAEs: lung neoplasm malignant with unreported history of lung nodule at the baseline visit; MI with outcome death [2.7.4.2.1.2]; right limb fracture; diverticulitis (2 incidences) and dehydration; spinal compression fracture; heart rate irregular; angina unstable [redacted] and progression of degenerative osteoarthritis [2.7.4.2.1.3]. Narratives of the SAE's are presented in [2.7.4.2.2].

2.5.5.3.4 Adverse Drug Reactions

In Trial 000127 [000127, 5.3.5.2], ADRs occurred in 24 (15%) subjects. The most frequently reported ADRs that occurred in >2% of subjects were application site reactions reported in 6 (3.8%) subjects, and included application site rash and erythema events [2.7.4.4]. ADRs that occurred in >1% of subjects were blood triglycerides increased/hypertriglyceridemia events reported in 3 (1.9%) subjects and PSA increased reported in 2 (1.3%) subjects (Table 9).

In Trial 000023 [000023, 5.3.5.4], ADRs occurred in 20 (11%) subjects. The ADRs that occurred in >2% of subjects were application site reactions reported in 6 (3.4%) subjects, including application site rash events in 3 (1.7%) subjects, and blood triglycerides increased/hypertriglyceridemia ADRs reported in 5 (2.8%) subjects. Headache was reported in 2 (1.1%) subjects (Table 9).

Table 9 Common Adverse Drug Reactions Occurring in >1% of Subjects

Adverse Drug Reaction	Trial 000127	Trial 000023
	N=159	N=180
Blood triglycerides increased or Hypertriglyceridemia	3 (1.9%)	5 (2.8%)
Application site rash	3 (1.9%)	3 (1.7%)
Application site erythema	5 (3.1%)	0
Prostatic specific antigen increased	2 (1.3%)	1 (0.6%)
Headache	0	2 (1.1%)

Source: [ISS Table 10.1, 5.3.5.3]

In Trial 000077 [000077, 5.3.5.4], ADRs occurred in 10 subjects (5.8%). The most common ADRs that occurred in >2% of subjects, were increases in Hct/haemoglobin reported in 5 (3.4%) subjects.

In general, testosterone transdermal gels are very well tolerated by subjects with the most commonly reported ADRs including acne, headache, emotional lability, nervousness, abnormal dreams, gynecomastia, and mastodynia, all occurring in <8% of subjects (30).

2.5.5.3.5 Serious Adverse Drug Reactions

The only SAE that was considered to have a reasonable possibility of being related to the treatment by the investigator was MI with stents placed in Trial 000127 [000127, 5.3.5.2], The event of non-fatal MI occurred after 3 months of treatment in a late middle-aged male with no CV history, but with risk factors [redacted]

2.5.5.3.6 Cardiovascular Events

Three major adverse cardiovascular events (MACE, defined as per the 1 Apr 2016 EMA draft guideline on clinical investigation of new medicinal products for the treatment of acute coronary syndrome, as non-fatal stroke, non-fatal MI, and CV death (31)) were identified in the Testosterone gel (FE 999303) 2% development program. [redacted] One MI was considered related, but the two other events were not [2.7.4.5].

Taking the most conservative approach, one event of each of non-fatal stroke (old subdural hematoma), non-fatal MI and CV death (MI with outcome death) were reported in the Testosterone gel (FE 999303) 2% development program, with 339 subjects in the phase 3 trials (59755 person-days, or 164 subject year's exposure). The event of subdural hematoma does not seem to be treatment emergent, as the same subdural was in a previous CT scan of the head taken a year prior

to trial enrolment. The event of non-fatal MI occurred after 3 months of treatment in [redacted] male with no CV diagnosis in medical history, but with risk factors [redacted]. The event of CV death occurred after just under one month of treatmen [redacted] The cause of death is stated to have been MI [redacted] These events are described in narratives in [2.7.4.2.2]. The incidence of MACE in the Testosterone gel (FE 999303) 2% development program is comparable to that seen in both testosterone and placebo treated subject in other reported clinical trials [2.7.4.5].

2.5.5.3.7 Application site reactions

Application site reactions were the most frequently reported AEs. Of the 395 subjects, 22 (5.6%) subjects reported 25 skin reactions during the trials; that included 18 (4.6%) subjects who experienced 21 treatment related application site reactions. Seventeen (4.3%) subjects had a mild skin reaction and 5 (1.3%) subjects had a moderate skin reaction [ISS Table 6.1.1, 5.3.5.3]. In one phase 1 trial FE 999303 CS02 [CS02, 5.3.3.1], [redacted] Of 339 subjects in the phase 3 trials, 13 (3.8%) subjects experienced 16 ADRs of application site reactions [2.7.4.4].

2.5.5.3.8 Safety in Geriatric population

Currently, there is no consensus concerning age specific reference values for testosterone. However, it should be taken into consideration that the physiologically testosterone serum levels are lower with increasing age.

Of the 395 subjects included in the pooled safety analysis, 62 (15.7%) were ≥65 years of age. There was a higher frequency of AEs in the age group of ≥65 years than in the age group of <65 years (54.8% and 32.1%, respectively). There was no clear difference in the frequency of SAEs between the age groups (3.2% and 2.1%, respectively). ADRs tended to occur more frequently in the age group of ≥65 years than in the age group of <65 years (16.1% and 13.5%, respectively), [ISS Table 2.1.1.3, 5.3.5.3].

No effect of age was found on the frequency or severity of skin related AEs, PSA levels and LFT. Hct ≥54% was more likely to be observed in subjects of age ≥65 years than in younger subjects [2.7.4.6.1.1].

2.5.5.3.9 Comparison of Testosterone Gel (FE 999303) 2% with Other Testosterone Products

Testosterone, as an active substance of several different TRTs administered by various routes, has been marketed and widely used for several decades with extensive safety experience worldwide also reflected in the scientific literature. The safety of Testosterone gel (FE 999303) 2% is supported by historical comparison with data from phase 3 trials of topical testosterone gels

(ANDROGEL 1.62% and TOSTREX 2%), with similar posology and advantage of dose titration. The trials had similar trial designs as phase 3 trials of Testosterone gel (FE 999303) 2% (open-label, non-randomised), except one trial by Kaufman et al. (32) which was a double-blind, randomised design incorporating a small placebo arm [Table 2, 2.7.4.1.1.2]. The trial data of other TRTs available commercially for decades with different posology and PK profiles like transdermal patches (ANDRODERM 2/4 mg), IM injection (Testosterone Enanthate 250 mg/mL) were also included for safety comparison as there is long-term safety experience and these products are associated with larger variability in exposure to testosterone [2.7.4.7].

The population treated with topical testosterone gels included in comparison was comparable to the overall trial population treated with Testosterone gel (FE 999303) 2% [Table 15, 2.7.4.1.3]. The overall safety profile of Testosterone gel (FE 999303) 2% based on AEs, SAEs, skin tolerability profile, and laboratory parameters such as Hct, PSA, LFT was similar to that of other approved TRTs included in the safety analysis. The safety profile of Testosterone gel (FE 999303) 2% trials as reported in trials with non-randomised, uncontrolled design, and 30 to ≥180 days of treatment was similar to the profile observed in meta-analysis of 16 placebo-controlled trials, with at least 6 months of treatment with TRTs (33). In a meta-analysis of 51 trials with at least 3 months of treatment with TRTs, no significant effects on mortality, prostate, or CV outcomes were reported (34). Based on incidence of these events (mortality [0.3%], PSA >4.0 ng/mL [2.1%], or CV outcomes [MACE: 0.9%]), the results were similar to phase 3 trials included in the clinical development program of Testosterone gel (FE 999303) 2%.

The comparison of the overall safety profile of Testosterone gel (FE 999303) 2% and approved TRTs included in the safety analysis is presented in Table 10.

Table 10 Safety Profile of Testosterone gel (FE 999303) 2% and Approved TRTs in Published Studies Providing Safety Information

Treatment (Duration)	Testosterone gel (FE 999303) 2% (30 to ≥180 days)	ANDROGEL 1.62% (182 days)	ANDROGEL 1.62% (182 days extension trial of 182 days trial)	TOSTREX 2% (90 days)	ANDRODERM 2/4 mg Transdermal Patch (14 days)	Testosterone Enanthate 250 mg/mL IM injection (210 days)
Trial/Study population	395 (Overall Population)[a]	234	191	149	36	20
AEs, n(%)	141 (35.7)	130 (55.6)	79 (41.4)	69 (46.3)	-	4 (20) (related events)
Withdrawal due to AE, n(%)	10 (2.53) (1 report each of lung neoplasm malignant, upper limb fracture, MI, angina unstable, headache, pruritic dermatitis, erectile dysfunction, application site rash, 2 reports of increased Hct)	25 (10.7) (17 reports of increased PSA, others: diarrhoea, fatigue, increased Hct, increased blood pressure, and diabetes)	17 (8.9) (11 reports of increased PSA)	5 (3.4) (1 report each of dermatitis contact, application site reaction, gastric hypomotility, contusion, and dyspnoea)	0 (0)	0 (0)
SAE, n(%)	9 (2.28) (1 report each of MI, MI with stents placed, lung neoplasm malignant, upper limb fracture, compression fracture lumbar spine, diverticulitis, angina unstable, progression of degenerative osteoarthritis, tachyarrhythmia	5 (2.1) (1 report each of MI, tachycardia, back pain, pituitary tumor, and spinal cord and nerve root disorders)	4 (2.1) (1 report each of atrial fibrillation, gastrointestinal haemorrhage, non-cardiac chest pain, and prostate cancer)	5 (3.4) (rectal haemorrhage, colon cancer, dyspnoea, cellulitis, and intestinal obstruction)	0 (0)	0 (0)
Death, n(%)	1 (0.3) (MI)[b]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Major Adverse Events (%)	Upper respiratory tract infection in (2.8), bronchitis, increased blood triglycerides, increased PSA, hypertension and cough (1.8 for each), nasopharyngitis (1.5), and application site erythema,	Increased PSA[c] (9.8), upper respiratory infection (4.7), back pain (3.0), headache (3.0), insomnia (3.0), hypertension (2.6), and increased Hct or haemoglobin, diarrhoea, nasopharyngitis, myalgia, and	Increased PSA[c] and upper respiratory tract infection (5.2 for each), nasopharyngitis (2.6), hypertension (2.1), influenza, sinusitis, and acne (1.6 for each), application site reaction (1.6), increased Hct	Application site reaction (16.8), upper respiratory infection (6.7), sinusitis (4.0), hypertension (2.7), and increased PSA (1.3)	Application site pruritus (17), application site vesicles (6), and back pain (6)	Acne or skin problems (spots) (10), hair loss and pain at the injection site (5 for each)

Treatment (Duration)	Testosterone gel (FE 999303) 2% (30 to ≥180 days)	ANDROGEL 1.62% (182 days)	ANDROGEL 1.62% (182 days extension trial of 182 days trial)	TOSTREX 2% (90 days)	ANDRODERM 2/4 mg Transdermal Patch (14 days)	Testosterone Enanthate 250 mg/mL IM injection (210 days)
	back pain, epididymitis, rash, increased GGT and increased Hct (1)	dermatitis contact (2.1 for each), application site reaction (0.9)	(1)			
Safety / Laboratory assessments	**Haematology:** 5 subjects had Hct >54% **PSA:** 9 subjects had >4 ng/mL. Mean increase form baseline was 0.22 ng/mL **Others:** No clinically significant changes in LFT, 3 reports of MACE (0.9%) and 25 reports of application site reactions (5.6%) were identified.	**Haematology** 5 subjects had Hct >54% **PSA:** 7 subjects had >4 ng/mL. Mean increase form baseline was 0.14 ng/mL (182 days) **Others:** No clinically significant changes in vital signs, ECGs, DRE, IPSS total score, or Irritation Assessment were observed.	**Haematology:** 4 subjects had Hct >54% **PSA**: 3 subjects had >4 ng/mL. Mean increase form baseline was 0.10 ng/mL (182 days) **Others:** No clinically significant changes in vital signs, ECGs, IPSS total score, or Irritation Assessment were observed.	**Haematology:** - **PSA:** - **Others:** No clinically relevant differences were observed from baseline to day 90 in laboratory values, vital signs, bodily functions, or BMI.	**Haematology:** - **PSA:** - **Others:** 13 reports of application site reactions (28%) were identified.	**Haematology:** Increase in haemoglobin (7.9%), and Hct (8%), within normal range. **PSA:** Increased from 0.35 ±0.24 µg/L to 0.53 ±0.36 µg/L, within normal range. **Others:** Significant decrease in total serum cholesterol, LDL cholesterol and triglycerides. No clinically relevant differences in BMI.
References	Testosterone gel (FE 999303) 2% Trials	Kaufman et al (32), NCT00433199 (35), ANDROGEL 1.62% PI (36)	Kaufman et al.(37), NCT00433199 (35), ANDROGEL 1.62% PI (36)	Dobs et al. (25) FORTESTA Gel PI (38) NCT00522431 (39)	ANDRODERM (testosterone transdermal system) PI (40)	Minnemann et al. (41)

[a] Overall Population: All adult hypogonadal male subjects enrolled in the six trials (000011, 000023, 000024, 000065, 000077 and 000127)
[b] The event of death was not considered to be related to the treatment
[c] Average serum PSA >4 ng/mL based on two separate determinations, or an average change from baseline in serum PSA of greater than 0.75 ng/mL on two determinations
AE: Adverse Event; BMI: Body Mass Index ; CV: Cardiovascular; DRE: Digital Rectal Examination; ECG: Electrocardiogram; GGT: Gamma glutamyl Transferase; Hct: Haematocrit; IPSS: International Prostate Symptom Score; MACE: Major Adverse Cardiovascular Events; MI: Myocardial Infarction; PI: Package Insert; PSA: Prostate-Specific Antigen; SAE: Serious Adverse Event

2.5.5.4 Safety Conclusion

There are no safety issues or signals identified in the Testosterone gel (FE 999303) 2% development program. The most commonly occurring AEs (≥1%) were upper respiratory tract infections, bronchitis, blood triglycerides increased, PSA increased, hypertension, cough, nasopharyngitis, application site erythema, back pain, epididymitis, rash, GGT increased and Hct increased. The frequency of individual AEs was overall low. No effect of race or BMI was found with PSA, Hct ≥54% or LFT AEs. Hct ≥54% was more likely to be observed in the age group of ≥65 years than in the age group of <65 years during the trial. The incidence of local administration site reactions was low, and local tolerability is considered favourable also when comparing to other transdermal testosterone products. Subjects' C_{max} values >2500 ng/dL did not exhibit evidence that C_{max} had any impact on the safety profile of the formulation.

Three incidences of MACE were identified in the Testosterone gel (FE 999303) 2% development program; two MI as SAEs and one incidental finding of old subdural haematoma when an MRI was done for a recent fall. One MI was considered treatment related, but the two other events were not. The incidence of CV events are in line with EMA PRAC and a meta-analysis (42,43,44).

On the basis of analysis of safety data from trials in the clinical development program of Testosterone gel (FE 999303) 2% and of safety data in the scientific literature, Testosterone gel (FE 999303) 2% is well tolerated in the treatment of adult hypogonadal males and the overall safety profile is in line with the other commercial testosterone products.

2.5.6 Class Labeling for Warnings and Precautions

Testosterone products have established class labelling for a number of potential safety issues. The following subsections briefly describe each of these issues, and provide links to relevant literature references for each.

2.5.6.1 Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

Androgens may accelerate the progression of sub-clinical prostate cancer and BPH. Evaluation of patients for pre-existing prostate cancer (digital rectal examination and estimation of PSA) prior to initiating and during treatment with androgens is appropriate.

In the clinical trials of Testosterone gel (FE 999303) 2%, of 395 subjects, 7 subjects (1.8%) had PSA increase TEAEs [2.7.4.2.1] and [2.7.4.3.1]. Of these, 3 subjects had events that were assessed by the investigator as possibly related to trial treatment. Overall, in the phase 3 trials, the mean PSA increase from baseline to the last measurement was 0.2 ng/mL, which is in line with similar trials of commercial products (Table 10).

The class labelling is extensively described in the literature (45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66).

2.5.6.2 Polycythemia

Androgens have been reported to stimulate production of red blood cells by enhancing the production of erythropoietin. Increases in Hct, reflective of increases in red blood cell mass, requires regular monitoring on long-term testosterone therapy. As noted previously, 5 AEs related to increase in red blood cell mass were reported in phase 3 clinical trials of Testosterone gel (FE 999303) 2% [ISS Table 2.3.1.1, 5.3.5.3] and [2.7.4.3.2]. An increase in red blood cell mass may increase the risk of thromboembolic events.

The class labelling is extensively described in the literature (67,68,69,70,71).

2.5.6.3 Clotting Disorders

Patients with thrombophilia should be treated using testosterone products with caution. There have been post-marketing reports of thrombotic events, including deep vein thrombosis and pulmonary embolism (PE), in patients during testosterone therapy such as Testosterone gel (FE 999303) 2%.

One subject in the clinical trials of Testosterone gel (FE 999303) 2% had a PE [ISS Table 2.3.1.1, 5.3.5.3] [redacted] in Trial 000127 [000127, 5.3.5.2]; see narrative in [2.7.4.2.2]). This event occurred following surgery [redacted] The event was assessed as not related to trial treatment.

The class labelling is extensively described in the literature: (72,73,74,75,76,77).

2.5.6.4 Cardiovascular Risk

To date, epidemiologic studies and randomised controlled trials have been inconclusive for determining the risk of MACE, such as non-fatal MI, non-fatal stroke, and CV death, with the use of testosterone compared to non-use. Some studies, but not all, have reported a potential increased risk of MACE in association with use of TRT in men. The EMA's PRAC has completed a EU-wide review of testosterone-containing medicines following concerns over serious side effects on the heart and blood vessels, including heart attack. The PRAC review did not find consistent evidence that the use of testosterone in hypogonadal adults increased the risk of heart problems. The committee considered that the benefits of testosterone continue to outweigh its risks (42,78).

No CV safety concerns were identified in the Testosterone gel (FE 999303) 2% clinical program. An analysis of CV SMQs of the data did show an incidence similar to reported for other marketed TRT products. One serious adverse drug reaction of MI, treated [redacted], was reported in Trial 000127 [000127, 5.3.5.2] with Testosterone gel (FE 999303) 2%. The Testosterone gel (FE 999303) 2% MACE incidences are in line with re-categorisation of MACE from the Xu meta-analysis of placebo-controlled randomised trials of testosterone therapy among men lasting 12+ weeks reporting CV-related events (43,44). The testosterone products should be administered with caution in patients with hypertension, as they may cause rise in blood pressure; and severe cardiac insufficiency, or ischaemic heart disease as they may cause severe complication characterised by oedema with or without congestive cardiac failure.

The class labelling is extensively described in the literature (34,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102).

2.5.6.5 Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including Testosterone gel (FE 999303) 2%, spermatogenesis may be suppressed through feedback inhibition of pituitary FSH possibly leading to adverse effects on semen parameters including sperm count.

No events related to spermatogenesis were reported in the trials of Testosterone gel (FE 999303) 2% [ISS Table 2.3.1.1, 5.3.5.3].

The class labelling is extensively described in the literature (103,104,105,106,107,108,109,110,111,112).

2.5.6.6 Females and Males of Reproductive Potential – Effect on Fertility

Testosterone gel (FE 999303) 2% is intended to be used in men only. With large doses of exogenous androgens, spermatogenesis may be suppressed through feedback inhibition of pituitary FSH possibly leading to adverse effects on semen parameters including sperm count.

The class labelling is extensively described in the literature (113,114,115,116,117).

2.5.6.7 Use in Pregnancy and Lactation

Testosterone gel (FE 999303) 2% must not be administered to women who are pregnant or to women who are breastfeeding. Literature has shown that testosterone is teratogenic and may cause foetal harm. Exposure of a foetus to androgens may result in varying degrees of virilisation. Secondary exposure from a male treated with Testosterone gel (FE 999303) 2% was evaluated in Trial 000066 [000066, 5.3.3.4]. Women were protected from transfer if the male wore clothing covering the application site or showered.

The class labelling is extensively described in the literature (118,119,120,121,122,123,124,125).

2.5.6.8 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with IM testosterone enanthate has produced multiple hepatic adenomas. Testosterone gel (FE 999303) 2% is not known to cause these adverse effects. However, testosterone products should be administered with caution in patients with hepatic disease as they may cause severe complication characterised by oedema with or without congestive cardiac failure.

In clinical trials, treatment with Testosterone gel (FE 999303) 2% resulted in a minor mean decrease in alanine aminotransferase and alkaline phosphatase, and small mean increases in aspartate aminotransferase (0.25 U/L), GGT (0.47 U/L), and bilirubin (0.01 mg/dL) [2.7.4.3.3] and [ISS Table 5.1.1, 5.3.5.3].

A total of 7 subjects in the clinical trials of Testosterone gel (FE999303) 2% had AEs related to increases or abnormalities in LFT [ISS Table 2.3.1.1, 5.3.5.3]; for 3 of these subjects, the events were assessed by the investigator as related to trial treatment.

The class labelling is extensively described in the literature (126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147).

2.5.6.9 Oedema

Androgens, including Testosterone gel (FE 999303), may promote retention of sodium and water. Oedema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. In such cases testosterone therapy should be discontinued.

One ADR of peripheral oedema was reported in the clinical trials of Testosterone gel (FE 999303) 2% [ISS Table 2.3.1.1, 5.3.5.3].

The class labelling is extensively described in the literature (148,149,150,151,152,153,154,155,156,157).

2.5.6.10 Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including Testosterone gel (FE 999303) 2%. Careful and regular monitoring of the breasts is required.

[redacted] and two subjects reported nipple pain events (one possibly related, one not related) in the clinical trials of Testosterone gel (FE 999303) 2% [ISS Table 2.3.1.1, 5.3.5.3].

The class labelling is extensively described in the literature (2,30,158,159).

2.5.6.11 Sleep Apnoea

The treatment of hypogonadal men with testosterone may potentiate sleep apnoea in some patients, especially those with risk factors such as obesity or chronic respiratory diseases.

No sleep apnoea events were reported in the clinical trials of Testosterone gel (FE99303) 2% [ISS Table 2.3.1.1, 5.3.5.3]. One subject ([redacted] had an AE of snoring that was assessed by the investigator as possibly related to trial treatment.

The class labelling is extensively described in the literature (160,161,162,163,164,165,166,167,168,169,170,171).

2.5.6.12 Lipids

Changes in serum lipid profile requires regular monitoring on long-term testosterone therapy.

In the clinical trials of Testosterone gel (FE 999303) 2%, 7 subjects (1.8%) had blood triglycerides increased events, 3 subjects (0.8%) had hypertriglyceridemia events, and blood cholesterol

increased and hyperlipidemia events were reported in 1 subject (0.3%) each. [ISS Table 2.3.1.1, 5.3.5.3].

The class labelling is extensively described in the literature (11,172,173,174,175,176,177,178,179,180).

2.5.6.13 Hypercalcemia

Androgens, including Testosterone gel (FE 999303) 2%, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria).

Two subjects were diagnosed with cancer during participation in the clinical trials of Testosterone gel (FE99303). Neither of these subjects, nor any other subject, had a hypercalcaemia event) [ISS Table 2.3.1.1, 5.3.5.3].

The class labelling is extensively described in the literature (181,182,183,184,185,186,187,188).

2.5.6.14 Decreased Thyroxine-binding Globulin

Androgens may decrease concentrations of thyroxin-binding globulins, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, and there is no clinical evidence of thyroid dysfunction.

Only one subject in the clinical trials of Testosterone gel (FE99303) 2% had an AE related to the thyroid) [ISS Table 2.3.1.1, 5.3.5.3], [redacted] was diagnosed with a thyroid neoplasm during participation in Trial 000077 [000077, 5.3.5.4]. This event was assessed as not related to trial treatment.

The class labelling is extensively described in the literature (189,190,191,192,193,194).

2.5.7 Benefits and Risks

The clinical development program for Testosterone gel (FE 999303) 2% has achieved the objectives of providing a comprehensive database to support the key components for labelling based on efficacy and safety, as well as dose response, and evaluation of the parameters of the effect of showering on testosterone absorption and secondary transfer of testosterone. This data is further substantiated by comparing the safety and efficacy with the significant data on comparable products available in the scientific literature. Other components of labelling are supported by the scientific literature for testosterone as well.

2.5.7.1 Target Indication and Patient Population

The proposed indication for Testosterone gel (FE 999303) 2% is “Testosterone replacement therapy for adult male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests”.

Treatment should be initiated only if hypogonadism has been demonstrated and if other aetiology, responsible for the symptoms, has been excluded. Testosterone deficiency should be demonstrated

by clinical features and confirmed by two separate blood testosterone measurements before initiating therapy with Testosterone gel (FE 999303) 2%.

2.5.7.2 Important Alternatives and Medical Need

Testosterone, as an active ingredient of drug products, has been marketed and widely used for several decades with extensive safety experience worldwide. Other approved TRT products includes topical gels and solutions like ANDROGEL, TOSTREX, AXIRON etc.; transdermal patches like ANDRODERM, TESTOPATCH etc.; oral capsules like TESTOCAPS etc., and IM injection like TESTOVIRON, TESTO ENANT etc.

Testosterone gel (FE 999303) 2% is a novel testosterone gel formulation designed for enhanced absorption from the skin, and is safe and efficacious TRT in adult hypogonadal males. The formulation utilises a permeation-enhancing system, which minimises the volume of gel necessary for restoration of normal testosterone levels, thereby reducing the risk of secondary exposure. The product is supplied with a cap applicator that allows patients using the product to avoid direct contact between the gel and the hand, further reducing the risk of secondary exposure.

2.5.7.3 Recommended Dose(s) and Dosing Regimen(s)

Based on results from the pivotal phase 3 clinical trial, Testosterone gel (FE 999303) 2% should be applied once daily to the upper arm/shoulder using 1 pump actuation (23 mg testosterone) as the starting dose. At approximately Day 14 the starting dose is either maintained or up-titrated to 2 pump actuations (46 mg testosterone). Dose titration is repeated on approximately Day 35, where the dose may be decreased, maintained or increased to the maximum dose of 3 pump actuations (69 mg testosterone). The need for further titration should be re-assessed periodically thereafter. Titration decisions should be based on clinical signs and symptoms related to testosterone deficiency and a 2-4 hr post-dose serum testosterone concentration sample with the goal of achieving a testosterone average concentration (C_{ave}) between 300 and 1050 ng/dL. If the serum testosterone concentration is below 500 ng/dL, the daily dose may be increased by 1 pump actuation. If the serum testosterone concentration exceeds 1050 ng/dL, the daily dose may be decreased by 1 pump actuation.

Testosterone gel (FE 999303) 2% should be applied using the applicator. Patients should be instructed not to apply Testosterone gel (FE 999303) 2% with fingers or hands.

2.5.7.4 Key Benefits

- Treatment with Testosterone gel (FE 999303) 2% following the proposed dosing scheme restored the testosterone concentrations in adult hypogonadal males to the eugonadal range [000127, 5.3.5.2].

- The average serum testosterone concentrations observed in the clinical program were in line with those obtained after treatment with already marketed testosterone replacement gels. The high concentration and bioavailability of the product enables a lower gel volume than for other testosterone replacement gels, meaning that less testosterone remains unabsorbed on the skin where it may potentially be transferred to others.
- The product is provided in a dosing pump, capable of dosing the patients with doses of 23 mg, 46 mg or 69 mg of testosterone depending on individual needs. The product is titrated via a dose titration scheme based on a serum testosterone sample which together with an evaluation of clinical signs and symptoms provides a simple, convenient and safe way for patients to achieve and maintain normal endogenous levels of testosterone.
- The benefit to the subject is further supported by significant improvements in quality of life, as demonstrated in the secondary subject reported efficacy endpoints in the IIEF, MAF and SF-12 treatment satisfaction questionnaires.
- The adverse events observed are in line with the established profile for topical TRTs and in line with other testosterone gels. Local tolerability is considered favourable when comparing to other transdermal testosterone products.
- The product is applied with a hands-free cap applicator, meaning that patients can apply the product without coming into direct hand contact with the gel. The results of the pivotal clinical trial demonstrated that almost all patients were satisfied or very satisfied with the cap applicator, and 87.0% of subjects felt that using the cap applicator resulted in less risk of testosterone transference to his partner or child. In line with this, no cases of unintended secondary exposure were reported in the clinical program, except in trial [000066, 5.3.3.4] when treated subjects were instructed to engage in direct skin to skin contact with their female partner without prior showering.

2.5.7.5 Strengths, Limitations, and Uncertainties of Evidence Related to Benefits

- In the pivotal phase 3 Trial 000127 [000127, 5.3.5.2], the primary efficacy endpoint was met by 76.1% (118 of 155 subjects; 95% CI, 69.4%, 82.8%). Sensitivity analyses showed a similar response rate in the PP (78.6%) and the PP completer (82.8%) populations. This result was confirmed with additional sensitivity analyses, including multiple imputation to impute missing values for individual C_{ave} performed on the ITT population.
- The pattern of improvements in the MAF and IIEF is similar to other drugs in the class. All 5 domains of the IIEF as well as total IIEF score improved significantly from baseline following treatment both at Day 35 and Day 90. All 4 domains of the MAF as well as GFI improved significantly from baseline following treatment both at Day 35 and Day 90.

- In the phase 3 trials with treatment durations of 90 and 120 days, the most frequent ADRs were mild application site reactions; all other ADRs occurred in less than 2% of subjects. There was one serious ADR and no deaths attributable to an ADR. No new or unexpected safety signals have been identified in the Testosterone gel (FE 999303) 2% clinical development.
- The existence of an objective, well-established, PK-based efficacy endpoint enabled the phase 3 trials to be designed as open-label trials and without the need for a control arm. This design is well-established and accepted for replacement therapies in general, and has been used to establish the efficacy and safety for other recently approved testosterone replacement gels.
- The titration scheme used in the pivotal trial was developed based on the substantial amounts of PK data obtained in trials 000011, 000023, 000024 and 000077 [Titration Report, 5.3.5.3]. This enabled the design of an optimised titration scheme based on post-dose serum testosterone measurements, which was prospectively tested and confirmed in the pivotal phase 3 trial [000127, 5.3.5.2].

2.5.7.6 Key Risks

Key risks identified with Testosterone gel (FE 999303) 2% based on safety data are worsened hypertension, increased Hct, and secondary exposure. Such risks have also been reported for other marketed topical testosterone products. Based on published safety data other potential risks can be prostate cancer, and ischemic heart disease.

2.5.7.7 Strengths, Limitations, and Uncertainties of Evidence Related to Risks

- It has been described in the literature that testosterone may cause an increase in existing hypertension, however no treatment emergent ADRs of hypertension aggravated or increased blood pressure were reported in the phase 2 and 3 trials of Testosterone gel (FE 999303) 2%.
- Patients may be affected with an increase in the percentage of Hct due to testosterone. An increase in Hct may increase the risk of developing blood clots in the veins and arteries. However, none of the events of Hct increased, reported in the clinical trials of Testosterone gel (FE 999303) 2%, were serious.
- If no precaution is taken, Testosterone gel (FE 999303) 2% can be transferred to other persons by close skin-to-skin contact. If the contact is repeated or prolonged, this may in women cause, unwanted side effects such as growth of facial and/or body hair, acne, deepening of the voice or changes in the menstrual cycles. Similarly, children have naturally low concentrations of testosterone and could be harmed by higher levels. However, no cases of secondary exposure were reported in trials of Testosterone gel (FE 999303) 2%, except in trial [000066, 5.3.3.4] when treated subjects were instructed to engage in direct skin-to-skin contact with their female partner without prior showering.

- Testosterone treatment may accelerate the progression of pre-existing prostate cancer. However, prostate cancer, assessed related, was not reported in the Testosterone gel (FE 999303) 2% clinical development program. Three non-serious cases of possible related PSA increase were recorded.
- Three events of MACE were recorded during the clinical development program; two MIs and one incidental finding of [redacted]. Outcome of the single MI recorded in the clinical database as related was reported as 'recovered'. The pattern of CV events appear to be in line with other testosterone products, as well as the EMA PRAC evaluation and a meta-analysis (195,43,44).
- There are insufficient long term safety data in geriatric subjects to assess the potential risks of CV disease and prostate cancer. There was a higher frequency of AEs in the age group of ≥65 years than in the age group of <65 years, however the frequency of individual AEs was low overall and there were no differences in the frequency of SAEs. However, Hct ≥54% was more likely to be observed in the age group of ≥65 years than in younger subjects.

2.5.7.8 Risk Management

The safety concerns (important identified risks and important potential risks) with Testosterone gel (FE 999303) 2% and its management is presented and described in [P-Risk Management Plan-2491, 1.8.2].

2.5.7.9 Benefit – Risk Conclusions

Testosterone gel (FE 999303) 2% is a novel testosterone gel formulation designed for enhanced absorption from the skin. The efficacy and safety of the product was demonstrated in three phase 3 trials, one of which prospectively tested the proposed dose titration scheme. The primary efficacy was measured by serum testosterone concentrations in the eugonadal range, and in the pivotal trial 76.1% (95% CI, 69.4%, 82.8%) of subjects had serum testosterone concentrations in this range, meeting the pre-specified primary efficacy criteria of responder rate ≥75% and the lower bound of the 95% CI to be ≥ 65%. This benefit was further substantiated by significant improvements in treatment satisfaction questionnaires measuring sexual functioning, fatigue and quality of life. No new or unexpected safety signals were identified in the Testosterone gel (FE 999303) 2% development program and the overall frequency of individual AEs was low. No effect of race or BMI was found with PSA, Hct ≥54% or LFT AEs. Hct ≥54% was more likely to be observed in the age group of ≥65 years than in the age group of <65 years during the trial.

Overall, the safety and efficacy results were in line with other approved gels for TRT.

The formulation utilises a permeation-enhancing system, which minimises the volume of gel and the dose necessary for restoration of normal testosterone levels. This reduces residual amount of testosterone on the skin, which is believed to reduce the risk of secondary exposure, one of the important risks of testosterone gels, in comparison with other testosterone gels. The product is supplied with a cap applicator that allows patients using the product to avoid direct contact between

the gel and the hand, further reducing the risk of secondary exposure. In the pivotal trial, almost all patients were satisfied or very satisfied with using the cap applicator and indicated that they felt it lead to a reduced risk of secondary exposure. In line with this, no cases of unintended secondary exposure were reported, indicating that the application method may represent an important advantage as compared to existing, hand-applied gels.

The dose titration scheme, which is supported by PK data and data from simulations, provides a simple, convenient and safe way for patients to achieve and maintain normal endogenous levels of testosterone.

The overall efficacy profile is comparable to already approved TRT products. The proposed dosing regimen resulted in similar C_{ave} values as existing products, within the eugonadal range. The overall safety profile of Testosterone gel (FE 999303) 2% in terms of AEs and ADRs is in line with currently approved and marketed testosterone products.

In conclusion, Testosterone gel (FE 999303) 2% has been demonstrated to be a safe and efficacious testosterone replacement therapy in hypogonadal men. The significant benefits of Testosterone gel (FE 999303) 2% in the proposed indication outweigh the risks.

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