CBG MEB

Public Assessment Report

Scientific discussion

Androgel 16.2 mg/g, gel

(testosterone)

NL/H/3240/001/DC

Date: 1 August 2016

This module reflects the scientific discussion for the approval of Androgel 16.2 mg/g, gel. The procedure was finalised on 11 November 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Events
BA	Bioavailability
BCF	Bio Concentration Factor
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
DT50	Degradation Time for 50% of a substance to be degraded under laboratory conditions
EC	Effect concentration
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ELS	Early Life Stage
FA	Full Analysis
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-operation and Development
PEC	Predicted Environmental Concentration
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PL	Package Leaflet
PSA	Prostate-Specific Antigen
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Androgel 16.2 mg/g, gel from Besins Healthcare.

The product is indicated in adults as testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.
A comprehensive description of the indications and posology is given in the SmPC.

Testosterone containing products have been marketed for the treatment of primary and secondary hypogonadism in Europe and the rest of the world for decades, initially in injectable, implantable and oral formulations, but more recently in patch and gel formulations. The safety and efficacy of their use is well established in continuous treatment over many years in millions of patients.

This application concerns a line-extension to the current marketing authorisation of Androgel 25 mg and 50 mg, gel in sachets (NL Licence RVG 27740-27741), which has been authorised through a mutual recognition procedure (FR/H/0203/001-002) since 2002 by Laboratoires Besins International. The current RMS for this procedure is the Netherlands (NL/H/3240/002-003).

The new formulation, a 16.2 mg/g testosterone containing gel, is supplied in a gel pump capable of providing 1.25 g gel (equals 20.25 mg testosterone) per actuation. Compared to the already marketed gels, Androgel 25 and 50 mg, gel in sachets, the new product provides a more accurate dosing of testosterone to the patient; the smallest dose that can be applied is 2.5 g of gel containing 25 mg of testosterone. The multi-dose pump contains sufficient gel for one month's treatment.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, Hungary, Ireland, Iceland, Italy, Luxembourg, Poland, Romania, Slovenia and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83. The dossier includes a complete quality module. Regarding the non-clinical and clinical modules, only data relevant for the extension are included. For the non-clinical and clinical data of testosterone, reference is made to the existing marketing authorisations of Androgel 25 mg and 50 mg gel.

Androgel 25 mg and 50 mg are hydroalcoholic gels containing 1% testosterone, packaged in a sachet. Both products are referred to as Androgel 1%. The new product contains 16.2 mg/g testosterone which equals to percentage of 1.62% testosterone. Therefore, the product is also referred to as Androgel 1.62%.

Scientific advice regarding the dossier requirements was given by the German authority in December 2007.

II. QUALITY ASPECTS

II.1 Introduction

Androgel 16.2 mg/g is a transparent or slightly opalescent, colourless gel with an odour of alcohol. The pH range is 4.5 to 6.5. One gram of gel contains 16.2 mg testosterone. One pump actuation delivers 1.25 g of gel containing 20.25 mg of testosterone.

The gel is packed in a multi-dose container (comprised of a polypropylene canister with an LDPE lined pouch) with metering pump that contains 88 g gel and delivers a minimum of 60 doses.

The excipients are: carbomer 980, isopropyl myristate, ethanol 96%, sodium hydroxide and purified water.

II.2 Drug Substance

The active substance is testosterone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Testosterone is a white crystalline powder, or colourless or yellowish-white crystals. It is practically insoluble in water, freely soluble in alcohol and in methylene chloride and practically insoluble in fatty oils. Polymorphism is not relevant for this product since it concerns a gel in which the active substance is dissolved. and that these substances comply with the European Pharmacopoeia.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur, including supplementary tests for any unspecified impurity and residual solvents, as specified by the CEP. Batch analytical data demonstrating compliance with this specification have been provided for four production scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three production scale batches from one manufacturing site that were stored at 25°C/60% RH (60 months), 30°C/35% RH (60 months) and 30°C/70% RH (60 months) and on one production scale batch from the other manufacturing site stored at 25°C/60% RH (12 months). The batches were stored in the proposed packaging.
For most parameters, no specific trends or unexpected results are observed and the data stay well within the specification limits. After storage for 36 months and over at 30°C/70% RH some trends and out-of-specification results were observed. Two full scale batches of drug substance per manufacturing site were stored at 40°C/75% RH (6 months), showing no trends or changes in any of the tested parameters. Based on the available data, the proposed re-test period of 1 year without any special storage requirements is justified.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines, the choice of excipients is justified and their functions explained. The development of the batches leading to the proposed final formulation has been sufficiently discussed. The same excipients are used is the already registered Androgel 25 and 50 mg, gel in sachets. Parameters such as viscosity, pH, and permeability have been investigated in order to reach the anticipated formulation. The aim was to create a formulation with higher viscosity, reduced volume of application and improved skin permeation compared to the available 1% testosterone formulations.
Several studies related to the container closure system were performed, i.e. regarding extractables, leachables, stability and reproducibility of the delivered dose. Reproducibility testing showed that all tested canisters delivered more than 60 doses. All the doses were within ±10% of the label claim (1.25 g) and therefore comply with the Ph.Eur. Uniformity of Dose requirements. The design of the clinical studies were performed in order to form the basis for scale up and preparations of clinical materials. The proposed formulation was also used during clinical testing.

Manufacturing process
The manufacturing process includes mixing, dissolution, dispersion, de-aerating, filling and packaging. It is seen as a standard, as conventional manufacturing techniques are used. The manufacturing process has been validated according to relevant European guidelines. Sufficient process validation

data on the product have been presented for three batches on production scale and two batches on pilot scale.

Control of excipients
All excipients comply with the Ph. Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, pH, viscosity, assay, degradation, uniformity of mass delivered doses, number of delivered doses, extractable, content and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life requirements/limits are identical except for assay of isopropyl mysristate and for related substances. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from twelve batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Microbiological attributes
The release and stability specifications include testing of the microbiological quality of the product to demonstrate compliance with the pH. Eur. monographs for Total Aerobic Microbial Countand Total Yeasts and Moulds Count, as well as for absence of the specified organisms Pseudomonas aeruginosa and Staphyloccocus aureus. The formulation is not prone to microbial spoilage due to the high ethanol content. This level of ethanol provides sufficient antimicrobial activity. Data on several batches demonstrate the microbiological integrity of the product at the end of the shelf-life.

Stability of drug product
Stability data on the product has been provided for twelve batches (nine production scale batches and three pilot scale batches). The batches were stored at 25°C/60% RH (up to 36 months data are available for 8 batches and up 30 months data for one batch) and at 40°C/75% RH (6 months data are available for 6 batches). The batches were stored in the packaging proposed for marketing. The conditions used in the stability studies are according to the ICH stability guideline. The parameters remain relatively stable and stay within the proposed specification limits. Results of a photostability study showed that the product is sensitive to direct light exposure, but the packaging materials provide sufficient protection from light. The proposed shelf-life of 36 months without any special storage requirements is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Androgel 16.2 mg/ml, gel has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The active substance in Androgel 16.2 mg/g, gel (or also referred to as Androgel 1.62%), is testosterone. Testosterone is a very well established endogenous hormone. The pharmacology, pharmacokinetics and toxicology of testosterone at normal concentrations and the pharmacology of hypogonadism are well understood. Therefore it was agreed that no further non-clinical testing is required. The MAH refers to existing non-clinical studies originally conducted, when the testosterone formulation was first established more than 20 years ago, and literature data that support the pharmacology and toxicology of transdermal testosterone.

III.2 Pharmacology

Testosterone at normal concentrations and the pharmacology of hypogonadism are both well understood. Testosterone has different effects on the reproductive system at different stages of life and is essential for the development of the male phenotype. Male hypogonadism results from insufficient secretion of testosterone and is characterised by low serum testosterone concentrations. Treatment with exogenous testosterone alleviates testosterone deficiency by elevating plasma concentrations of testosterone, dihydrotestosterone and androstenedione, resulting in a normalisation of gonadotropin levels. The secondary pharmacological effects of testosterone include anti-inflammatory activity in the prostate, effects on cardiac tissue and blood vessels, effects on the kidneys, activities in auto-immune disease, and enhancement of athletic performance. These secondary pharmacological effects as well as the safety pharmacology and the pharmacodynamics drug interactions of testosterone have been clinically well-established.

III.3 Pharmacokinetics

The pharmacokinetic profile of testosterone in men following transdermal administration from hydroalcoholic gel formulations is extensively documented and well understood.
According to literature, approximately 10% of a testosterone dose applied on the skin is absorbed into the systemic circulation. The key parameter which influences the consistency of the pharmacokinetic profile for transdermal use is the composition of the formulation. The use of an hydroalcoholic base for the formulation and the management of skin cleansing routines to optimise absorption, and subsequent sustained release into the systemic circulation, assures an effective pharmacokinetic profile following application of the drug product.
In vitro percutaneous absorption studies were performed using cadaver human skin to investigate the permeation process of testosterone through the skin to identify factors that influence transdermal transfer. These studies demonstrated that the majority of applied testosterone is associated with the skin surface, and that a solvent is required in the formulation to enhance mobilisation of the hormone across the skin. The transdermal formulations therefore comprise a hydroalcoholic gel containing the drug substance testosterone Ph.Eur. with the solvent ethanol 96% (ethanol Ph.Eur).
The *in vivo* pharmacokinetic profile of transdermal testosterone from gel formulations has been investigated clinically using both the 1% and the 1.62% formulations. Testosterone is converted to dihydrotestosterone by 5 alpha-reductase present in skin and is converted to estradiol through aromatisation. Inactivation of testosterone mainly occurs in the liver where it is metabolised to various 17-ketosteroids. The main elimination pathway is via the urine, with some excretion in the faeces. Blood concentration of testosterone after administration of Androgel 1.62% at the proposed maximal dose do not exceed normal values of 300-1000 ng/dl (dihydrotestosterone 31-193 ng/dl). The geometric mean dihydrotestosterone/testosterone ratio across all doses and study days for subjects on testosterone gel 1.62% treatment was 0.156 and the 95% prediction interval was 0.074-0.330 which is within the normal range of approximately 0.05-0.33 reported in the literature. The pharmacokinetic drug interaction profile of testosterone has been established by its extensive clinical use.

III.4 Toxicology

The need for toxicity data for testosterone is overridden by the extensive clinical safety experience with testosterone. Therefore, the non-clinical overview focuses on published toxicology data. Since testosterone levels after administration of Androgel 1.62% do not exceed normal values and since this product is intended to restore normal levels of testosterone, no increased risk is expected.
Overall the available data indicate that testosterone is of very low acute and repeated dose toxicity to animals. The available genotoxicity data point to a lack of genotoxic risk for testosterone. The potential exists for hyper-proliferative effects due to testosterone, as indicated in animal models, but at exposure levels well in excess of normal physiological levels.
Testosterone exhibits reproductive and developmental toxicity when administered prenatally, however this is of little consequence to the proposed drug product, which is indicated for the treatment of male hypogonadism. The local tolerance studies demonstrated a satisfactory Androgel local tolerance in rabbits and guinea pigs. In the rabbit study, 0.5 ml of Androgel or placebo gel was applied to the skin of male New-Zealand rabbits. No erythema or oedema was observed in any rabbit at any observation time. In the guinea pig study no clinical signs and no deaths related to treatment were reported and,

during the challenge phase of the experiment, neither erythema nor oedema was observed in any animal at any observation time.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Summary of main study results

Substance (INN/Invented Name): testosterone					
CAS-number (if available): 58-22-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	PM			
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	PM			
	BCF	PM			
Persistence	DT50 or ready biodegradability	PM			
Toxicity	NOEC	PM			
PBT-statement :	PM				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	1.42	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	The substance is a hormone that influences both development and reproduction of fish.				(Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	PM			
Ready Biodegradability Test	OECD 301	PM			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	PM			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	PM	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	PM	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	PM	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	PM	µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	PM	L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	PM		
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	PM	mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	PM	mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	PM	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	PM	mg/kg	
Sediment dwelling organism		NOEC	PM	mg/kg	species

Conclusions on studies:
The above data is acceptable, however not yet complete. There are two post-approval commitments linked with the ERA:
- To perform a study to determine the log K_{ow} in compliance with the guideline OECD 107
- To perform a Phase II assessment including the following studies:
    - Adsorption-desorption using a batch equilibrium method (OECD 106) using 3 soil types and 2 types of sewage sludge;
    - Ready biodegradability test (OECD 301);
    - Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308);
    - Algal growth inhibition test (OECD 201);
    - Daphnia sp. reproduction test (OECD 211, use version 2012);
    - Fish, early life stage (ELS) toxicity test (OECD 210, use version 2013);
    - Activated sludge, respiration inhibition test (OECD 209, use version 2010)

The MAH should consider especially that the substance is a hormone that influences both development and reproduction of (in)vertebrates. The fish ELS test does not cover the appropriate life stages and hence cannot be used to focus on, a fish full life cycle test should be submitted. This study should be used to addresses the specific mechanism of action and the set up should be such that a valid NOEC/EC10 value can be derived.

III.6 Discussion on the non-clinical aspects

The submitted non-clinical overview to support the pharmacology, pharmacokinetics and toxicology of transdermal testosterone is adequate. There are four *in vitro* pharmacokinetic studies assessing a percutaneous absorption of testosterone from Androgel in human cadaver skin and two local tolerance studies assessing an acute dermal irritation in rabbits and a skin sensitisation in guinea pigs.
Regarding the testosterone amount transferred across the human skin, the data are consistent with the clinical observations with a bioavailability estimated between 6 to 13%. The local tolerance studies demonstrated a satisfactory Androgel local tolerance in rabbits and guinea pigs. The provided Environmental risk assessment is acceptable however not complete. Commitments were made to provide the missing information.

IV. CLINICAL ASPECTS

IV.1 Introduction

For this line extension, 11 bioavailability and pharmacokinetic studies were submitted. One pivotal phase III safety and efficacy study was submitted. The overview with the characteristics of the studies is presented below.

Table 1. Overview of study performed for Androgel 16.2 mg/ml, gel

Type of study	Study Identifier	Objectives of the study	Study Design and Type of Control; Diagnosis of Patients	Test Product; Dosage Regimen; Route of Administration	Enrolled; Completed; Age Range (years)	Duration of Treatment	Study Status; Type of Report
BA	S176.1.005	To determine the multiple dose PK of testosterone after administration of testosterone gel 1.62% in hypogonadal males with and without Postdose skin washing	Randomized, open-label, three-way crossover hypogonadal males	Testosterone gel 1.62%; 5.00 g, once daily in the AM to the upper arms/shoulders for seven days during each treatment period, topical	24 17 34-77	21 days of exposure	Complete; Full
BA	S176.1.006	To determine the multiple dose PK of testosterone after administration of testosterone gel 1.62% in hypogonadal males with and without	Randomized, open-label, three-way crossover; hypogonadal males	Testosterone gel 1.62%; 2.50 g, once daily in the AM to the upper arms/shoulders for seven days during each treatment period, topical	18 15 31-60	21 days of exposure	Complete; Full

		moisturizer lotion or sunscreen					
BA	S176.1.007	To determine the single and multiple dose relative bioavailability of testosterone after administration of testosterone gel 1.62% to the abdomen, upper arms/shoulders, and a combination of both application sites using a rotation schedule	Randomized, open-label, three-way crossover; hypogonadal males	Testosterone gel 1.62%; 5.00 g, once daily in the AM to the abdomen, upper arms/shoulders, and a combination of both application sites using a rotation schedule, topical	36 32 29-73	31 days of exposure (including 5-day washout period between treatments)	Complete; Full
PK	S176.1.003	To determine the PK of total testosterone concentrations in female patients after single and multiple episodes of contact with a male partner dosed with testosterone gel 1.62%	Randomized, open-label, parallel; healthy male and female patients	Males: testosterone gel 1.62%; 5.00 g once daily in the AM to the abdomen for seven days, topical Females: 15 minutes of contact time; no direct dose application	96 patients (48 couples) 95 patients (47 males, 48 females) 18-65	7 days of exposure	Complete; Full
PK	S176.1.008	To evaluate the effects of dose, Postdose washing, and application site on the transfer potential of testosterone gel 1.62% from dosed males to a non-dosed female partner	Randomized, open-label, parallel group; healthy male and female patients	Males: testosterone gel 1.62%; 2.50 or 5.00 g, two single doses once daily in the AM to the abdomen or upper arms/shoulders, topical Females: 15 minutes of contact time; no direct dose application	48 patients (24 couples) 48 patients (24 couples) 18-59	2 days of exposure, separated by a 1-week washout	Complete; Full
PK	S176.1.004	To evaluate the sensitization and skin irritation potential of testosterone gel 1.62% on intact skin of healthy adult male patients	Randomized, double-blind, placebo controlled; healthy patients	Testosterone gel 1.62%; 100 mg gel/3.14 cm2 patch, topical	235 214 18-79	6 weeks (three phases: 21-day induction; 12-17 day rest; 5 day challenge)	Complete; Full
PK	S176.1.009	To determine the PK of total testosterone concentrations in female patients after a single episode of contact with a male partner dosed with testosterone gel 1.62%	Randomized, open-label, parallel; healthy male and female patients Females: 15 minutes of contact time; no direct dose application	Males: testosterone gel 1.62%; 5.00 g single dose to the upper arms, shoulders and abdomen, topical	24 patients (12 couples) 24 patients (12 males, 12 females) 23-52	Single dose	Complete; Full
PK	S176.1.011	To determine the PK of total testosterone concentrations in female patients after a single episode of contact with a male partner dosed with testosterone gel 1.62%	Randomized, open-label, parallel; healthy male and female patients	Males: testosterone gel 1.62%; 5.00 g single dose to the upper arms, shoulders only, topical Females: 15 minutes of contact time; no direct dose application	24 patients (12 couples) 24 patients (12 males, 12 females) 21-59	Single dose	Complete; Full
PK	S176.1.001 and amendment	To determine the multiple dose PK and comparative bioavailability of testosterone after administration of testosterone gel , 1.22%, 1.42%, and 1.62% at doses of 1.25, 2.50, and 3.75 g	Randomized, open-label, parallel; hypogonadal males	Testosterone gel; once daily in the AM to the abdomen for 5 days at each dose level of 1.25, 2.50, and 3.75 g, topical	38 36 26-72	20 days of exposure (5 days at each dose of testosterone gel and 5 days of Androgel® 1%)	Complete; Full
PK	S176.1.002	To determine the single and multiple dose PK of testosterone after administration of testosterone gel 1.62% at doses of 1.25 g, 2.50 g, 3.75, 5.00, and 6.25 g	Randomized, open-label, parallel; hypogonadal males	Testosterone gel 1.62%; 1.25 g, 2.50 g, 3.75, 5.00, or 6.25 g once daily in the AM to the abdomen or upper arms/shoulders (rotation schedule), topical	56 51 27-69	14 days of exposure	Complete; Full
PK	S176.1.010	To determine the multiple dose PK and comparative	Randomized, open-label, two period,	Testosterone gel 1.62%; 5.00 g once daily A: to the abdomen or upper	62 62 29-74	14 days of exposure	Complete; Full

		bioavailability of testosterone after different sites of administration of testosterone gel 1.62% at a dose of 5.00 g	cross-over; hypogonadal males	arms/shoulders (rotation schedule), B: to a combination of upper arms/shoulders and abdomen, topical			
Efficacy and Safety	**S176.3.104 (pivotal)**	**The primary efficacy parameter was the percentage of patients with serum total testosterone Cav within the normal range of 300-1000 ng/dL. Success in the study was defined as >75% of patients on active treatment within the normal serum testosterone concentration range of 300-1000 ng/dL. In addition, the lower bound of the 95% CI could not be less than 65% based on the Day 112 PK results for the pivotal phase of the trial.**	**Randomized, double-blind, placebo-controlled with an open-label extension; hypogonadal males**	**Testosterone gel 1.62%; 1.25 g, 2.50 g, 3.75, and 5.00 g, once daily, topical**	**274 patients (234 Testosterone-gel 1.62%; 40 placebo) 196 patients (168 Testosterone-gel 1.62%; 28 placebo) (Day 182); 26-79**	**Double-blind phase: 182 days Open-label phase: additional 182 days**	**Complete; Full**

Abbreviations: BA = bioavailability, CSR = clinical study report, N= number of enrolled patients, testosterone-gel = testosterone gel.

IV.2 Pharmacokinetics

Androgel 16.2 mg/g gel was selected based on skin permeation test (human cadaver skin) and phase I pharmacokinetics (PK) data. The MAH has chosen to use a 1.62% strength based on the observation that the PK profile - in patients using 1.62% gel - was similar to the profiles as seen with the currently marketed 1% testosterone gel.
For all phase I to III trials the MAH has measured testosterone, dihydrotestosterone and estradiol in serum. All analytical procedures were accurate, precise, and sensitive. No concerns were noted.

PK studies were performed in hypo-gonadal men with testosterone levels below the normal (i.e. 300 ng/dl). After single dosing (one application to the upper arms-shoulders of 1.25, 2.50, 3.75, 5.00 or 6.25 g testosterone 1.62% gel) testosterone concentration showed a continuous increase up to 8 hours post-dose (Cmax) at all dose levels, after which testosterone concentrations remained consistent and within the eugonadal range (300 to 1000 ng/dl) for the remainder of the 24-hour dosing interval. Eugonadal testosterone concentrations were reached 2-4 hrs post-dose. Baseline concentrations of testosterone were obtained 48-72 hrs after cessation of treatment.
Upon multiple dosing - once daily (conform a rotational scheme) application of 1.25, 2.50, 3.75, 5.00 or 6.25 g testosterone 1.62% gel - Cmax was reached 8 hrs post-dose. Eugonadal testosterone concentration were obtained 2 hrs post-dose and eugonadal concentrations were maintained over the whole 14 days treatment period. No unexpected accumulation was observed. A trend towards dose proportionality for testosterone can be observed at day 14 for 1.25-5.00g when baseline adjusted.
In general it is observed that all metabolites (dihydrotestosterone, estradiol) follow the same trend in concentrations as testosterone.
The calculated bioavailability of testosterone from this gel was 1.0-8.5%. This was lower than the bioavailability from the already marketed 1% gel. However accurate evaluation of true bioavailability for drugs applied by transdermal route of administration is somewhat questionable, due to wide variance and taking into consideration the skin reservoir effect and the slow release of the drug during the full PK curve evaluation.
Data on contact transfer with female partner of testosterone after application 2 hrs post-dose, with or without t-shirt; with or with-out washing demonstrated that best method for avoiding transfer of testosterone to the female partner is to use a t-shirt when physical body contact is involved. This is stated in the proposed SmPC and in line with already registered testosterone 1% gels.

No formal studies of testosterone gel 1.62% have been conducted in patients with renal or hepatic insufficiency. As Androgel is administered topically, first-pass metabolism in the liver is bypassed. The

metabolites of testosterone are renally excreted as inactive glucuronides and sulphates. Therefore, renal or hepatic impairment is unlikely to have significant effects on testosterone levels and no specific dosage recommendations are necessary for these patients.

No *in vitro* interaction studies were performed. This is acceptable as the interactions are well known and the SmPC is brought in line with the approved SmPC of Androgel 1% gel. The MAH has conducted *in vivo* interactions studies with moistening lotion and sunscreen lotion. Applying sunscreen or moistening lotion one hour after applying Androgel 1.62% slightly increased the bioavailability.

IV.3 Clinical efficacy

Main study

Design

The phase III pivotal study (S176.3.104) was a multi-centre, randomised, double-blind, placebo-controlled study with an open-label extension of Androgel 16.2 m/ml, gel for the treatment of hypogonadism in adult males. The study was performed in in 274 hypogonadal adult male patients (aged 18-80 years). The duration of the blinded period was 182 days total. After the blinded periods patients were able to be enrolled in the open label part of the study which also lasted 182 days (total study duration 364 days). In the blinded part of the study 234 patients were treated with Androgel 16.2 mg/g and 40 patients were included in the placebo group. After 182 days of treatment (blinded part), patients could agree to continue into an open-label, active treatment maintenance phase of the study. Placebo-treated patients from the pivotal 182-day phase of the study were started on 2.5 g of testosterone gel 1.62% and titrated to pre-specified serum total testosterone concentrations within the normal range over two clinic visits at Days 196 and 210. These patients continued on a stable dose of testosterone gel 1.62% for the remainder of the 364 day study unless they did not remain within the pre-specified serum total testosterone concentration range. Patients who did not remain within the pre-specified serum total testosterone concentration range could be titrated to a new dose on Day 266.

No differentiation has been made for patients with primary and secondary hypogonadism in the in- and exclusion criteria. The baseline testosterone concentrations in the placebo group were near the lower limit of the eugonadal concentrations (300-1000 ng/dl) of testosterone. Mean testosterone values in the placebo group were 294 ng/dl (sd 126 ng/dl) and in the treatment group these were 282 ng/dl (sd 291 ng/dl).

All patients were started at a mid-range dose level of testosterone gel 1.62% (2.50 g) and were then individually titrated up or down (if necessary) to an optimal dose level (1.25 g – 5.00 g). The optimal dose level was based on periodic measurement of serum testosterone level over the first 42 days, after which they were maintained at this dose level for approximately 140 days.
The gel was applied conform a rotational scheme: 3 days stomach and 4 days upper arms/shoulder. The overall mean compliance for the full analysis (FA) sample was similar for the testosterone gel 1.62% groups and the placebo group (94.29% versus 97.70%).

Endpoints

The primary endpoint is the proportion of patients on active treatment with a Day 112 (double-blind period) or Day 364 (open-label period) C_{av} within the normal serum testosterone concentration range of 300-1000 ng/dL. Success was defined as ≥75% of patients on active treatment within the normal serum testosterone concentration range (300-1000 ng/dL) on these days. Additionally, the lower bound of the 95% CI was to be not less than 65%, based on the Day 112 and 364 PK results.

For the double-blind period, the critical secondary efficacy endpoint was to evaluate total testosterone Cmax values during the first 182 Days of the study. For the open-label period, the critical secondary efficacy endpoint was to evaluate total testosterone Cmax values for each treatment group (Formerly Placebo and Continuing Active) for Days 266 and 364. The individual total testosterone Cmax values were to be in the following ranges:

- Cmax ≤1500 ng/dL in ≥85% of the patients
- Cmax between 1800 – 2500 ng/dL in ≤5% of the patients
- Cmax >2500 ng/dL in none of the patients.

All other secondary efficacy variables were based on change from Baseline to Day 182 (Visit 10) or Day 364 (Visit 14). The primary endpoints as well as the secondary endpoints are acceptable.

Results

During the double blinded period (Day 0-182), a total of 66 subjects were withdrawn from the study: 25 subjects due to adverse events, 19 subjects withdrew consent, 2 subjects experienced lack of efficacy, 3 subjects were lost at follow-up, 10 subjects had protocol violations and 5 patients were lost due to administrative reasons.

In the double blind period A total of 251/274 patients (91.6%) were included in the FA Sample (testosterone gel 1.62%: 214/234 patients, 91.5%; placebo: 37/40 patients, 92.5%). In the open-label phase 191 patients (163 patients previously on active treatment and 28 patients previously on placebo) were allocated to treatment and analysed for safety and included in the FA Sample for efficacy.

The primary efficacy variable in the blinded part of the study was total testosterone C_{av} on Day 112. On Day 112, 81.6% of patients on testosterone treatment (95% CI of 75.1% - 87.0%) had C_{av} values within the target range, which met the criteria for primary efficacy.

Table 2. Number and percentage of patients achieving target range for testosterone C_{av} by day and treatment

Population	Study Day	Testosterone gel 1.62%		Placebo		p-value
		n/N (%)	95% CI	n/N (%)	95% CI	
FA	14	138/210 (65.7)	(58.9, 72.1)	11/37 (29.7)	(15.9, 47.0)	<0.0001
	56	151/183 (82.5)	(76.2, 87.7)	11/32 (34.4)	(18.6, 53.2)	<0.0001
	112	**146/179 (81.6)**	**(75.1, 87.0)**	**10/27 (37.0)**	**(19.4, 57.6)**	**<0.0001**
	182	139/169 (82.2)	(75.6, 87.7)	8/28 (28.6)	(13.2, 48.7)	<0.0001
Efficacy	14	115/175 (65.7)	(58.2, 72.7)	7/27 (25.9)	(11.1, 46.3)	<0.0001
	56	138/165 (83.6)	(77.1, 88.9)	8/26 (30.8)	(14.3, 51.8)	<0.0001
	112	**146/179 (81.6)**	**(75.1, 87.0)**	**10/27 (37.0)**	**(19.4, 57.6)**	**<0.0001**
	182	135/165 (81.8)	(75.1, 87.4)	8/27 (29.6)	(13.8, 50.2)	<0.0001
PP	14	94/147 (63.9)	(55.6, 71.7)	5/27 (18.5)	(6.3, 38.1)	<0.0001
	56	112/131 (85.5)	(78.3, 91.0)	7/24 (29.2)	(12.6, 51.1)	<0.0001
	112	**102/124 (82.3)**	**(74.4, 88.5)**	**7/20 (35.0)**	**(15.4, 59.2)**	**<0.0001**
	182	101/118 (85.6)	(77.9, 91.4)	8/21 (38.1)	(18.1, 61.6)	<0.0001

n = number of patients achieving target range
N = number of patients with evaluable PK parameter for the given study day
CI = Confidence interval
FA = Full Analysis Sample
PP = Per-Protocol Sample
Note: One patient included in the Efficacy Sample did not have sufficient data for Cav determination, but Cmax was identified for this patient.
At Day 112 the Efficacy Sample equals the FA Sample
Note: 95% CI are based on exact binominal distribution. P-values are calculated from Cochran-Mantael-Haenszel tests for equality of the response percentages between testosterone gel 1.62% and placebo, across pooled study sites.

After day 182, patients could continue in an open-label setting for another 182 days. A total of 191 patients continued (163 for the active treatment group and 28 from the former placebo group). The same primary endpoint was used as for the blinded period, however at day 364. On Day 364, 77.9% of patients continuing on active testosterone treatment (95% CI of 70.0% - 84.6%) had C_{av} values within the target range, which meets the criteria for primary efficacy.

Table 3. Number and percentage of patients achieving Cmax ranges by day and treatment for the open-label period (all samples)

Population	Study Day	Continuing active Testosterone gel 1.62%		Formerly Placebo		Combined (CA en FP)	
		n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
FA	266	109/139 (78.4)	(70.6-84.9)	18/26 (69.2)	(48.2-85.7)	127/165 (77.0)	(69.8 – 83.2)
	364	106/136 (77.9)	(70.0-84.6)	20/23 (87.0)	(66.4-97.2)	126/159 (79.2)	(72.1 – 85.3)
Efficacy	266	102/131 (77.9)	(69.8 – 84.6)	16/23 (69.6)	(47.1-86.8)	118/154 (76.6)	(69.1-83.1)
	364	106/136 (77.9)	(70.0 – 84.6)	20/23 (87.0)	(66.4-97.2)	126/159 (79.2)	(72.1-85.3)
PP	266	61/74 (82.4)	(71.8-90.3)	6/12 (50.0)	(21.1-78.9)	67/86 (77.9)	(67.7-86.1)
	364	54/71 (76.1)	(64.5-85.4)	8/9 (88.9)	(51.8-99.7)	62/80 (77.5)	(66.8-86.1)

For the overall results, n= number of observations and N= number of evaluable observations across all study days.
Pop=Population
CA = Continuing Active
FP = Formerly Placebo
FA = Full Analysis Sample
PP = Per-protocol Sample
n = number of patients achieving range
N = number of patients with evaluable PK parameter for the given study day

The secondary endpoints in the blinded part (total testosterone C_{av} on Day 14, 56 and 182) and open label part of the study (total testosterone C_{av} on Day 266) were met. A decrease in luteinizing hormone and follicle-stimulating hormone concentrations is observed in the treatment groups at day 84 and day 182 whereas no change from baseline was observed in the placebo group for both hormones. This also indicates that testosterone treatment is effective in hypogonadal male patients.

IV.4 Clinical safety

Adverse events

In the pivotal study (S176.3.104) treatment-emergent adverse events (TEAE) were reported for 5/234 (2.1%) of the patients in the testosterone gel group versus 1/40 (2.5%) for the placebo group. In the testosterone gel group a higher proportion (25/234, 10.7%) of patients experienced TEAEs that led to permanent discontinuation of the study in comparison with the placebo group (0 patients).

Severe TEAEs were reported in 11/234 (4.7%) patients of the testosterone gel group and in none of the patients in the placebo group. Severe TEAEs included: back pain, myocardial infarction, tachycardia, diarrhoea, dyspepsia, gastroenteritis, pneumonia, fall, diabetes mellitus, pituitary tumour, radicular pain, libido increased, sleep disorder and erection increased. The events concerning back and myalgia were considered unlikely or not related to the study drug. The observed incidences are consistent with an older at-risk patient population.

The most common TEAE leading to discontinuation was PSA (prostate-specific antigen) increased, which was pre-specified in the protocol as a discontinuation criterion. The percentage of patients who experienced at least one TEAE during the study was 58.1% (136/234) for the testosterone gel and 37.5% (15/40) for the placebo group.

The incidence of TEAEs in the 11 phase I studies was as expected in this type of study with a low incidence of moderate or severe TEAEs and no clinically relevant signals emerging. In the contact transfer studies rash and (application site pruritus) were reported.

Serious adverse event and deaths

In the pivotal study (S176.3.104) there were no deaths. 9 treatment-emerged serious adverse events were reported during this study (myocardial infarction, tachycardia, back pain, pituitary tumour, radicular pain, malignant hypertension, atrial fibrillation, gastrointestinal haemorrhage, non-cardiac chest pain, and prostate cancer). These incidents were only reported by patients who had received active treatment.

In the 11 phase I studies and contact transfer studies no deaths were reported. In total, two patients experienced a serious adverse event after receiving the study drug. In a contact transfer study, 2 patients were discontinued from study participation due to rash AEs.

Discontinuation due to AEs
Increased PSA level was the TEAE that led to study discontinuation (conform study protocols). Testosterone has an effect on prostate tumour growth. Tumour growth is related to the higher PSA levels. In the SmPC it is advised to check the patient for (pre-existing) prostate cancer prior to testosterone treatment. PSA levels should be checked twice yearly.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Androgel 16.2 mg/ml, gel.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Transfer events: adverse reactions following secondary exposure to testosterone - Off label use in athletes
Important potential risks	- Prostate events - Cardiovascular events - Serious adverse events in elderly - Adverse reactions following use in women and male children
Missing information	none

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

Androgel 16.2 mg/g gel can be prescribed to hypogonadal patients (testosterone concentration <300 ng/dl) in order to raise testosterone concentrations into the eugonadal range (300-1000 ng/dl). Pharmacokinetic data from the PK studies and the pivotal study in hypogonadal males indicate that after first dosing eugonadal concentrations are reached within 2-4 hours and levels remain within this range for 24 hours. C_{max} is obtained after 8 hours. Patients maintained eugonadal concentrations upon multiple once daily dosing in the phase I/II pivotal studies.

Based on the several bioavailability studies the following can be concluded:
- application of the gel only to upper arms/shoulder demonstrates the highest testosterone levels post dosing.
- application via a rotational scheme (3 days abdomen and 4 days upper arm/shoulders) showed similar PK profiles compared to upper arms/shoulders only.
- no unexpected accumulation of testosterone occurred when applying the gel once daily for a longer time period (multiple dosing).

Based on the submitted efficacy data, efficacy of the new Androgel formulation in the treatment of hypogonadal adult males is proven. After applying testosterone 1.62% gel patients' eugonadal testosterone levels were reached and maintained throughout the study. The primary endpoints were met:
- On Day 112 of the blinded part, 81.6% of patients on testosterone treatment (95% CI of 75.1% - 87.0%) had C_{av} values within the target range.
- On Day 364, 77.9% of patients continuing on active testosterone treatment (95% CI of 70.0% - 84.6%) had C_{av} values within the target range.

Secondary endpoints were met as well.

In the pivotal study it was observed that patients enrolled in the placebo group had testosterone baseline values close to the lower limit of the eugonadal range. These patients reached eugonadal testosterone concentrations within the study. In- and exclusion criteria did not distinguish between patients with primary and secondary hypogonadism. In the FA set this is clearly notable from the large observed variation in both treatment groups. Although the best study population would have been patients with primary hypogonadism, the primary goal of the study was met: it was demonstrated that Androgel 16.2 mg/g restored testosterone levels within eugonadal boundaries.

With respect to safety of the product no notable difference was observed compared to the safety profile already known for the registered testosterone 1% gels. Risk management is adequately addressed.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Androgel 50 mg, gel in sachets NL/H/3240/003. There are a few differences between the PLs. The main difference concerns the description of the method of administration, where it is explained how to use the pump pack. In addition, both PLs are presented in a similar design and house style with similar content across the majority of sections. However, there is a difference in formats; the reference PL is in a four page booklet with two columns of text per page. A bridging study was performed to address the differences in format and content. The testing method of the bridging study is considered acceptable. The design, presentation, font style and size are satisfactory. The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Androgel 16.2 mg/ml, gel has a proven chemical-pharmaceutical quality and is a line-extension of Androgel 25 mg and 50 mg, gel in sachets. These products are well-known medicinal products with an established favourable efficacy and safety profile. The new formulation is considered to be an approvable addition to the original product. The new formulation is considered to provide a better dosing capability compared to the currently approved Androgel testosterone gels in sachet.

Sufficient non-clinical and clinical data relevant for the extension have been provided. The efficacy and safety results were satisfactory, and in line with the known efficacy and safety of the existing testosterone gel formulations.
The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that the benefit/risk balance for Androgel 16.2 mg/ml, gel - intended for the treatment of hypogonadal adult males - is positive , and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 November 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
- Replacement or addition of a manufacturing site for part or all manufacturing process of the finished product; secondary packaging site; primary packaging site; site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal product. - Change in the composition of the inner pouch of the primary packaging. - Change in qualitative and quantitative composition; semi-solid and non-sterile liquid pharmaceutical forms.	NL/H/3240/IB/025/G	IB	12-5-2016	14-6-2016	Approved	N