Decentralised Procedure

Public Assessment Report

Finjuve für Männer 2,275 mg/ml Spray zur Anwendung auf der Haut, Lösung

Finasteride

DE/H/6478/001/DC

Applicant:
Polichem S.A.

Date:
24th March 2021

This module reflects the scientific discussion for the approval of the above-mentioned product. The procedure was finalised on 17th September 2020.

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Finjuve für Männer 2,275 mg/ml Spray zur Anwendung auf der Haut, Lösung
Name of the drug substance (INN name):	Finasteride
Pharmaco-therapeutic group (ATC Code):	D11AX10
Pharmaceutical form(s) and strength(s):	Cutaneous spray, solution, 2.275 mg/mL
Reference Number(s) for the Decentralised Procedure	DE/H/6478/001/DC
Reference Member State:	DE
Concerned Member States:	IT, LU, PT
Legal basis of application:	Full Dossier Art 8.3(i) Dir 2001/83/EC
Applicant (name and address)	Polichem S.A. 50 Val Fleuri 1526 Luxemburg Luxembourg
Names and addresses of all proposed manufacturer(s) responsible for batch release in the EEA	ALMIRALL HERMAL GmbH Scholtzstr. 3 21465 – Reinbek Germany

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for "*Finjuve für Männer 2,275 mg/ml Spray zur Anwendung auf der Haut, Lösung*" (topical finasteride), in the treatment of mild to moderate male androgenetic alopecia (AGA), is approved.

II EXECUTIVE SUMMARY

II.1 Problem statement

The applicant is submitting a Marketing Authorization Application for finasteride 2.275 mg/mL (corresponding to 0.25%) cutaneous spray, solution, according to Article 8.3 of Directive 2001/83/EC (full-mixed dossier with quality, non-clinical and clinical data) for male androgenetic alopecia (AGA). The cutaneous spray, solution, is a new pharmaceutical route to administer finasteride for AGA. The proposed trade name is Finjuve® 2.275 mg/mL Spray.

Finasteride is a well-known active substance that is orally administered for the systemic treatment of AGA (Propecia® 1 mg tablets) and benign prostate hyperplasia (Proscar® 5 mg tablets), and has been sold in the European Union (EU) and many countries worldwide for more than 20 years.

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, the isoenzyme that converts testosterone into dihydrotestosterone (DHT). Although the complete aetiology of AGA has not been definitively established, AGA is known to depend on the presence of the androgen dihydrotestosterone (DHT), which is formed from testosterone by Type I and II 5α-reductase enzymes. In the scalp of men suffering from AGA, an increased rate of conversion of testosterone into DHT has been detected in the bald areas compared to the hair-bearing occipital region. The Type I and II 5α-reductase enzymes are differentially expressed in tissues and developmental stages. In the development of AGA, Type II 5α-reductase appears to be more important than Type I 5α-reductase. Finasteride, as a competitive and specific inhibitor of Type II 5α-reductase, appears to interrupt a key factor in the development of AGA in those patients genetically predisposed.

The mechanism of action of topical finasteride (inhibition of Type II 5α-reductase) is the same as that described for oral finasteride. However, as a topical application, the topical finasteride formulation allows finasteride to act specifically on the Type II 5α-reductase present in the hair follicular portion, while minimizing systemic absorption even after repeated treatments. A lower systemic bioavailability of topical compared to that of oral finasteride is expected to reduce the frequency and severity of systemic side effects associated with oral finasteride, such as sexual dysfunction and psychiatric symptoms that have been associated with more widespread use of oral finasteride post-marketing.

II.2 About the product

Pharmacotherapeutic group: other dermatologicals
ATC code: D11AX10

Therapeutic indication

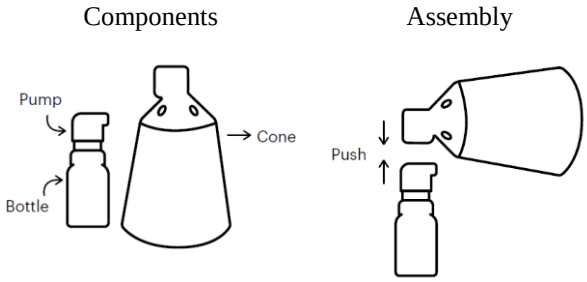
Finjuve is indicated for the topical treatment of adult men from 18 to 41 years of age with mild to moderate male pattern hair loss (androgenetic alopecia) to increase hair growth and prevent further hair loss.

Posology and method of administration

Finjuve is provided as a spray applicator consisting of a plastic bottle containing 18 mL of solution, with a snap-on spray pump and a separate plastic cone.
Finjuve should be applied once daily to bald areas of the scalp. Depending on the size of the baldness, 1 to 4 non-overlapping spray actuations (50 to 200 microliter of solution) can be used.

The bottle contains up to 180 actuations (delivering 50 microliter each), which is sufficient for 45 days of treatment when the maximum dose of 4 actuations once daily is administered, 60 days of treatment for 3 actuations once daily, 90 days of treatment for 2 actuations once daily, and 180 days of treatment for 1 actuation once daily. The bottle should not be used beyond 180 actuations as it could result in the delivery of an insufficient dose. Patients should be advised accordingly.

Assembly of the spray applicator
The presentation of Finjuve contains 2 separate components: a bottle with an attached metering pump, and a plastic cone. These components require assembly prior to first use.



Finjuve should be administered by the patient himself. Hair and scalp should be fully dry prior to application of the solution. When spraying the scalp, the plastic cone must be in contact with the scalp to avoid finasteride dispersion in the air. The bald scalp area covered by the cone limits the maximum treatment area for 1 actuation. To cover an area larger than the cone diameter 2, 3, or 4 actuations may be prescribed. In these cases, before applying the second, third, or fourth actuation, the cone should be moved to an area of the scalp next to, but not touching, the area of any previous actuations to avoid spray overlap.

Immediately after application the patient should avoid contact between the treated scalp and surfaces (e.g. pillows, helmets, hats etc.) until the solution has dried. Once applied, Finjuve should be left in place for at least 6hours.

II.3 General comments on the submitted dossier

A Scientific Advice meeting was held with the BfArM on 16-Mar-2015, a follow up written advice was provided on 14-Apr-2015, and a pre-submission meeting with the BfArM was held on 10-Jan-2019.

The clinical development programme for topical finasteride includes 4 Phase I studies, 1 Phase IIa study, and 1 Phase III study.

During Scientific Advice meeting, 16-Mar-2015, the following regulatory and clinical topics were addressed and subsequently actioned in the development programme:

- The proposal to file with a single Phase III pivotal study (Study PM1541): this was considered to be sufficient for this MAA by BfArM, in light of the wealth of publicly available information on finasteride (see also European Medicines Agency [EMA] guidance CPMP/EWP/2330/99, 2001).
- The design of Study PM1541, including the addition of a third treatment group for oral finasteride, the use of a double-blind, double-dummy design, the treatment duration, and the evaluation of study endpoints.
- The need for the clinical development programme to include a photosensitisation study (Study PM1542) and local tolerability study (Study PM1646).

At pre-submission meeting, on 10-Jan-2019, amongst others the following regulatory and clinical topics were addressed:

- The statistical strategy and need for a post-hoc analyses for the pivotal study PM1541, as the ITT population defined by the Applicant was considered a selected population.
- The small safety database.

The Applicant submitted a paediatric investigation plan for topical finasteride to the EMA on 23-Nov-2015. On 15-Apr-2016, the EMA granted a product specific waiver for all subsets of the paediatric population (EMEA-001878-PIP01-15).

No elderly were studied. In the phase I studies and the phase IIa study males ≥18 to ≤65 years were included. In the phase III trial PM1541 males ≥18 to ≤40 years were included.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

GMP
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU.

GLP
The new non-clinical studies include pivotal GLP-compliant toxicological and local tolerance studies and GLP compliant bioanalytical and analytical procedures for determining finasteride exposure following topical use.

GCP
According to the Applicant, the clinical studies have been conducted in accordance with GCP. The Applicant provided a tabulated overview on inspection by competent authorities.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Finjuve 2.275 mg/mL Spray are of sufficient quality in view of the present European regulatory requirements.
A valid CEP for non-micronized finasteride from the drug substance is provided. This CEP is renewed from 14. August 2014 and issued 14. December 2017. The applicant uses the micronized form so the micronization steps are described in the dossier together with a successful validation.
The control tests and specifications for the drug substance are adequately drawn up.
ICH stability testing of three consecutive batches of micronized finasteride were conducted, and the results obtained showed that the drug substance is stable for the tested period, i.e. 72 months at long-term conditions (25ºC/ 60% relative humidity (RH)), and 6 months at accelerated stability (40ºC/ 75% RH). During formal stability testing no degradation product was observed.
The retest period of 60 months with no special storage conditions is justified.

Drug Product
The product is a clear, slightly viscous and colourless hydro-alcoholic spray solution for cutaneous use to be applied on the scalp. The product solution is filled into a plastic bottle, closed with a snap-on spray pump with actuator and nozzle. The drug product is supplied as packaged spray applicators composed of the bottle and the snap-on spray pump, together with a plastic cone to be clamped by the patient onto the top of the pump actuator.
The designed packaging combination using the cone is capable of delivering a dose on the scalp of 50 µL (0.114 mg finasteride) per actuation/shot.
The development of the product has been adequately and extensively described, the choice of excipients is justified and their functions explained.
The manufacturing process is adequately described and is considered to be a standard process.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on five batches. The batch analysis results show that the finished products meet the specifications proposed.
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.
The extrapolated shelf-life of 24 months with no special storage conditions to be specified for the drug product is considered acceptable.

Medical Device
The medical device and the medicinal product form a single integral product, which is intended exclusively for use in the given combination and which is not reusable. CE marking of the device is therefore optional. The device has no CE mark and no certificate issued by a Notified Body.

III.2 Non-clinical aspects

Pharmacology
Finasteride is a synthetic antiandrogen that acts by inhibiting Type II 5α-reductase, the enzyme that converts testosterone to dihydrotestosterone (DHT). By blocking this enzyme, finasteride inhibits the conversion of testosterone into the more powerful androgen DHT. Within the scalp this reduction in androgenic activity helps treat hair loss where a hormonal factor is involved, such as has been shown for androgenetic alopecia (AGA).
The topical administration of finasteride represents a new route of administration, whereas the mechanism of action of topical finasteride (inhibition of Type II 5α-reductase) is the same as that described for oral finasteride.

Pharmacokinetics
Finasteride is a well-established active substance with a documented pharmacokinetic (PK) profile following oral administration. Therefore, new non-clinical PK data of finasteride topical formulation are limited to investigations on absorption of finasteride after dermal application.
Topical finasteride was shown to penetrate into the skin reaching measurable levels in skin tissue and in the region of the hair follicles, but only small amounts penetrated through the skin.
The pharmacokinetics of finasteride topical solution, administered by the topical route, has been evaluated in three separate dermal toxicity studies (4-weeks, 13-weeks, 39 weeks) in minipigs. The toxicokinetic results of all studies confirmed the low systemic exposure of minipigs to finasteride. Plasma levels of finasteride were higher on Day 28 when compared to Day 1, but in studies with longer duration of repeated topical administration for 13 or 39 weeks, no further accumulation was observed. The time to maximum plasma levels varied highly, as did the calculated elimination half-lives. A possible depot formation in skin tissue may be responsible for these variations.
The potential for local adverse effects by concomitant use of cosmetics, sunscreens and/or other topical medicinal products has not been studied; as a precautionary measure a parallel local use together with Finjuve should be avoided and a respective advice is implemented in the SmPC/PL.

Toxicology
Finasteride is a well-established active substance with a documented toxicology profile following oral administration. Finjuve is the first topical medicinal product containing finasteride for local treatment of androgenetic alopecia (AGA). The topical administration of finasteride 0.25% solution represents a new route of administration.
Local effects and systemic tolerability of topical finasteride 0.25% solution was investigated in rabbits and minipigs with repeated dermal application for 4 weeks in rabbits (on abraded and non-abraded skin) and for up to 39 weeks in minipigs.

No systemic effects were detected in these studies at concentrations up to three times higher (0.75%) compared to the to-be-marketed formulation (0.25%). Only low systemic exposure from the topical route of administration was demonstrated in corresponding toxicokinetic examinations. However, in all animals (treated and control) local effects such as minimal and transient signs of irritation and scaling were observed. Skin discolouration was seen in all groups in the 4- and 13-week, but in no group in the 39-week minipig studies. This was interpreted as a brownish composite of the contained non-volatile excipients. During clinical studies in humans, where a more frequent cleaning procedure with detergents is common, no discolouration was noted.

The genotoxic profile of finasteride is well-characterised and it is known from literature that finasteride exhibits no mutagenic properties in bacteria and does not increase *in vivo* chromosome aberrations in mice.
Published carcinogenicity studies demonstrated that finasteride is devoid of carcinogenic potency based on genotoxic mechanisms, while carcinogenic effects (hyperplasia of Leydig cells) based on induced hormonal imbalance were observed for high finasteride level in rats. Due to the low systemic exposure following topical administration a carcinogenic risk for man can be excluded.

It is known from literature that finasteride exerts effects on male accessory reproductive organs including prostate and seminal vesicles, and it is considered to cause a reduction of male fertility by this mechanism. Following administration of finasteride during pregnancy, severe effects on the intrauterine development of the sexual organs in male foetuses were seen over a wide dose range, leading, at higher dose level, to a feminization of male offspring.
Similar to oral finasteride medicinal products, Finjuve is not intended for use in women and contraindicated in women who are pregnant or may become pregnant. A respective warning not to come into contact with Finjuve due to the known potential risk to a male foetus is implemented in the SmPC/PL.

Topical finasteride 0.25% solution was not irritating to skin and eyes in standard tests and did not cause contact sensitization. Based on the results obtained in guinea pigs following dermal exposure in association with light, it can be concluded that finasteride topical solution does not elicit a photoirritant response, but may elicit photosensitization in the guinea pig. However, clinical data from a randomised controlled clinical study are negative, i.e. no potential for the induction of photosensitization was noted in healthy subjects.

The excipient HPCH (hydroxypropyl chitosan) was toxicologically qualified in an extensive non-clinical testing program, including single- and repeated-dose toxicity, genotoxicity, toxicity to reproduction, and local tolerance. Based on the performed dermal toxicity studies with HPCH and determined NOAELs (1% and 5%), there are no safety concerns regarding the clinically used formulation that includes 1% HPCH.

Environmental Risk Assessment (ERA)
The applicant provided a Phase I ERA resulting in a $PEC_{surfacewater}$ of 0.00105 µg/l which is below the action limit of 0.01 µg/l. Accordingly, the ERA can stop in Phase I and a Phase II ERA is not required.
The experimentally derived n-octanol/water partition coefficient (log D) of 3.7 for finasteride is below the trigger value of 4.5 and a PBT assessment is not required. Finasteride is not a potential PBT substance.

Summary of main study results

Substance (INN/Invented Name): Finasteride			
CAS-number (if available): 98319-26-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.7	No PBT substance ~~(N)~~
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.00105 µg/l	µg/L	Not > 0.01 threshold
her concerns (e.g. chemical class)	-/-	-/-	No

Conclusions on studies:
Based on the data provided it can be expected that finasteride will not pose a risk to the environment when used in accordance with the SmPC.

III.3 Clinical aspects

Pharmacokinetics

Standard methods such as total and peak exposure were used in order to describe biopharmaceutic disposition comparing topical and oral finasteride administration.

The pharmacokinetic parameters used in the relative bioavailability studies for descriptive pharmacokinetic data analysis are considered adequate.

Descriptive statistics rather than formal confirmatory statistical analysis are considered acceptable.

Bioavailability has been investigated in comparison to the oral drug available on the market. The expected rather low systemic availability could be confirmed by considering results of respective studies in male patients with AGA. In the pivotal phase III study after administration of topical finasteride at the intended dose (i.e., up to 200 microliter = up to 4 sprays once daily), mean maximum plasma finasteride concentrations were > 100-times lower than after 1 mg once daily oral finasteride administration at all sampling times over 6 months of treatment.
PK-data are available for 36.9% of the 458 originally randomized patients of the pivotal study.

Table 2.7.2-3 Summary of Mean (SD) Maximum Finasteride Plasma Concentration by Visit (Study PM1541, PK Population)

Visit	Topical finasteride Up to 200 µL (0.455 mg) o.d. (N=71)			Vehicle (N=64)			Oral finasteride 1 mg o.d. (N=34)			Oral/ topical fold [a]
	n	Mean (pg/mL)	SD (pg/mL)	n	Mean (pg/mL)	SD (pg/mL)	n	Mean (pg/mL)	SD (pg/mL)	
Baseline	69	BLQL [b]	-	60	BLQL	-	34	BLQL	-	-
Week 4	67	27.0	28.0	61	BLQL	-	34	3376	3046	125
Week 8	69	26.9	26.7	61	BLQL	-	34	4421	3393	164
Week 12	71	36.5	45.9	58	BLQL	-	34	7166	12745	196
Week 24	69	48.0	87.2	63	BLQL	-	33	5029	4182	105

- BLQL=below lower quantification limit; N=total number of patients in a treatment group; PK=pharmacokinetic(s); SD=standard deviation.
- a) The oral/topical (finasteride) fold ratio was manually calculated.
- b) 4 pre-dose samples had quantified finasteride and were therefore excluded from the baseline calculations. The mean (SD) finasteride plasma concentration at baseline including these 4 pre-dose values was 6 pg/mL (36 pg/mL).
- Note: BLQL: <4 pg/mL.

Source: Section 5.3.5.1, Clinical Study Report PM1541, Table 14.2.17.1.1 and Listing 16.2.6.5.

Pharmacodynamics

The pharmacodynamics of topical finasteride were evaluated in two phase I studies, one phase IIa study and in the pivotal phase III study (please see also tabulated overview of these studies in section II (Clinical Pharmacology) of the AR:

Overview of the Clinical Studies Used for the Pharmacological Evaluation of Topical Finasteride

Study	No. of study centres Location	Study design and type of control	Objective	Test product(s); dosage regimen; route of administration	No. of patients randomised by treatment group	Key inclusion criteria [a]	Duration of treatment	PK/PD assessments
PM 1024	1 Switzerland	Phase I, single-centre, open-label, rand., parallel-group, active-controlled, **PK/PD study**	PK, PD	*Topical finasteride*: 1 mL (2.275 mg) topical finasteride b.i.d. *Oral finasteride*: 1 mg oral finasteride o.d.	***Topical finasteride***: 12 [b] ***Oral finasteride***: 12	Male ≥18 to ≤65 years AGA (≥Type II on the Norwood-Hamilton scale)	1 week	**PK:** plasma concentration of finasteride after single- and multiple-dose administration **PD:** plasma concentrations of testosterone and DHT after single- and multiple-dose administration
PM 1227	1 Switzerland	Phase I, single-centre, open-label, rand., parallel-group, active-controlled, **PD study**	PD	*Topical finasteride b.i.d.* or *o.d.*: 1 mL (2.275 mg) topical finasteride b.i.d. or o.d. *Oral finasteride*: 1 mg oral finasteride o.d.	***Topical finasteride*** *b.i.d.*: 6 *Topical finasteride o.d.*: 6 ***Oral finasteride***: 6	Male ≥18 to ≤65 years AGA (≥Type II on the Norwood-Hamilton scale)	1 week	**PD:** scalp and serum concentrations of testosterone and DHT after multiple-dose administration

Study	No. of study centres Location	Study design and type of control	Objective	Test product(s); dosage regimen; route of administration	No. of patients randomised by treatment group	Key inclusion criteria [a]	Duration of treatment	PK/PD assessments
PM 1332	1 Switzerland	Phase IIa, single-centre, DB, rand. ,parallel-group, dose-response, placebo-controlled, **PK/PD study**	PK, PD	*Topical finasteride or vehicle: **100 µL** (0.228 mg), **200 µL** (0.455 mg), **300 µL** (0.683 mg), or **400 µL** (0.910 mg) topical finasteride or vehicle o.d.*	***Topical finasteride**: 6 per dose group (24 total)* ***Vehicle**: 2 per dose group (8 total)*	Male ≥18 to ≤65 years AGA (≥Type II on the Norwood-Hamilton scale)	1 week	**PK**: plasma concentration of finasteride, concentration of unabsorbed finasteride, and finasteride uptake in stratum corneum c after multiple-dose administration **PD:** scalp and serum concentrations of testosterone and DHT after multiple-dose administration
PM 1541	52 Belgium, Germany, Spain, Hungary, Russian Federation	Phase III, multi-centre, DB, double-dummy, rand., parallel-group, placebo- and active-controlled efficacy and safety study	Efficacy	*Topical finasteride: Up to 4 sprays (i.e., **up to 200 µL**, 0.455 mg) topical finasteride o.d. + oral placebo* *Vehicle: topical vehicle + oral placebo o.d.* *Oral finasteride: topical vehicle + 1 mg oral finasteride o.d.*	***Topical finasteride**: 189* ***Vehicle**: 184* ***Oral finasteride**: 85*	Male ≥18 to ≤40 years AGA (Type III vertex, IV, or V on the Norwood-Hamilton scale)	24 weeks	**PK:** plasma concentration of finasteride after multiple-dose administration **PD:** serum concentration of DHT after multiple-dose administration

AGA=androgenic alopecia; b.i.d.=twice daily; DHT=dihydrotestosterone; o.d.=once daily; PD=pharmacodynamic(s); PK=pharmacokinetic(s).

The mechanism of action for finasteride is to inhibit Type II 5α-reductase, which converts testosterone into DHT. Therefore, DHT concentrations in the scalp, serum, or plasma were the key PD endpoints measured in all 4 studies providing clinical pharmacology data (Studies PM1024, PM1227, PM1332, and PM1541). In Studies PM1024, PM1227, PM1332, and PM1541 testosterone concentrations were also measured to ensure that there were no clinically meaningfully changes from baseline.

The optimal dose of topical finasteride was based on the ratio of the changes from baseline in DHT scalp concentrations to DHT serum concentrations in Studies PM1227 and PM1332. Scalp concentrations of DHT were used as a surrogate marker for efficacy, as the scalp is the target tissue. Serum or plasma concentrations of DHT were used as a surrogate marker for safety, as decreased systemic concentrations of DHT have been associated with the adverse reactions of oral finasteride. Therefore, the higher the ratio of scalp to serum DHT reduction, the more favourable the predicted benefit-risk profile (due to greater scalp DHT reduction and less serum DHT reduction).

In the 2 studies that assessed both DHT scalp and serum concentrations (Studies PM1227 and PM1332), the percentage of scalp DHT reduction was similar for oral finasteride and the tested topical finasteride doses, indicating a potentially similar efficacy profile - apart from the topical 300 µL finasteride dose, which showed a less pronounced effect on DHT scalp concentration.

On the other hand, the percentage of serum DHT reduction increased with increasing dose, indicating the potential for fewer safety risks at lower doses of topical finasteride. The highest ratios of scalp to serum DHT reduction, indicating the best benefit/risk ratio, were observed for the 100 µL (0.228 mg) and 200 µL (0.455 mg) o.d. doses of topical finasteride in the phase IIa Study PM1332. Although the 100 µL dose demonstrated the most favourable benefit-risk profile, a dose of up to 200 µL (up to 4 sprays of 50 µL each) o.d. of topical finasteride was chosen as maximal dosage regimen, as this dose provides coverage of a greater area (up to 200 cm^2 [each spray covers an area of 50 cm^2]), thus allowing for more extensive treatment of greater levels of baldness severity.

Of note, in the pivotal phase III study, at week 24, the percentage decrease in mean DHT serum concentration from baseline was higher in the oral finasteride group but decrease was significant both with topical finasteride and oral finasteride: -34.5% for topical finasteride compared to -55.6% for oral finasteride – thus indicating possibly systemic adverse reactions of a sexual nature related to a decrease in DHT, though with less probability for topical finasteride than with oral finasteride .
The following table and figure displays the significant mean DHT serum concentration decrease both in the oral finasteride group and topical finasteride group:

Phase III Study PM1541
Topical finasteride o.d. (up to 4 sprays, i.e. 50 µL [0.138 mg] up to 200 µL [0.455 mg]) vs. placebo (vehicle) vs. oral finasteride 1 mg o.d

Table 2.7.2-4 Summary of Mean (SD) DHT Serum Concentration by Visit (Study PM1541, PD Population)

Visit	Topical finasteride Up to 200 µL (0.455 mg) o.d. (N=65)			Vehicle (N=55)			Oral finasteride 1 mg o.d. (N=31)		
	n	Mean (ng/dL)	SD (ng/dL)	n	Mean (ng/dL)	SD (ng/dL)	n	Mean (ng/dL)	SD (ng/dL)
Baseline	65	39.3	16.0	54 [a]	38.5	21.5	31	35.5	14.5
Week 4	62	25.2	12.7	54	39.8	23.8	30	14.2	10.4
Week 8	59	27.0	13.4	52	39.8	23.4	31	13.6	9.0
Week 12	64	26.5	13.4	52	38.5	15.8	29	14.0	8.6
Week 24	62	25.7	12.2	53	39.3	18.5	30	15.8	10.1
% difference									
Week 24 vs. baseline [b]		-34.52			2.25			-55.63	

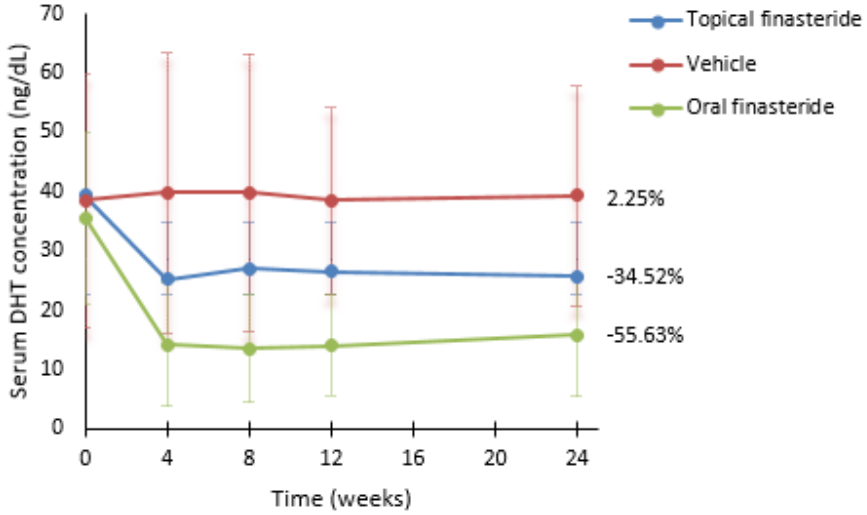
DHT=dihydrotestosterone; N=total number of patients; n=number of patients with available data; PD=pharmacodynamic(s); SD=standard deviation.

a) Excludes 1 patient with a baseline serum DHT value of 1050 ng/dL.

b) Percentage difference between Week 24 and baseline was manually calculated.

Source: Clinical Study Report PM1541

Figure 1 DHT Serum Concentrations after Multiple-dose Administration of Topical Finasteride up to 200 µL (0.455 mg) o.d., Vehicle, or Oral Finasteride 1 mg o.d. (Study PM1541, PD Population)



DHT=dihydrotestosterone; o.d.=once daily; PD=pharmacodynamic(s); SD=standard deviation.

Note: Error bars indicate the SD. Percentage difference between Week 24 and baseline is shown at the end of each line.

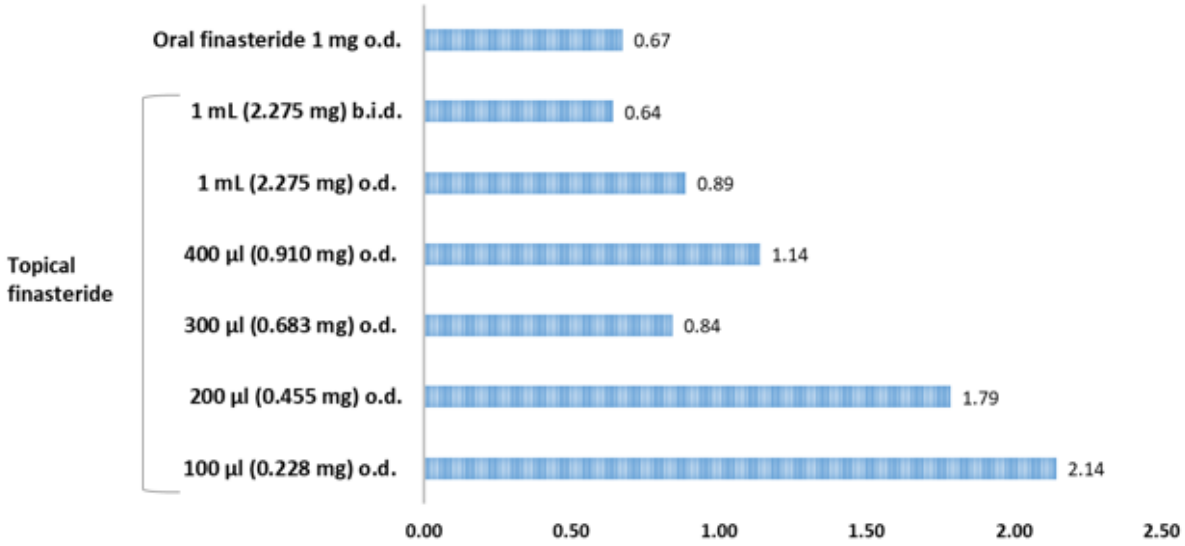
Source:Table 2.7.2.4.

Clinical efficacy

Dose-finding

The optimal dose of topical finasteride was based on the ratio of the changes from baseline in DHT scalp concentrations to DHT serum concentrations in phase I study PM1227 (n=18) and phase IIa study PM1332 (n=32).
In the phase IIa study, with a treatment duration of 1 week, multiple-dose administration with 100 µL or 200 µL topical finasteride o.d. achieved the best balance between scalp and serum concentrations of DHT, maximising the decrease in mean DHT scalp concentrations (surrogate PD marker for efficacy) and minimising the decrease in mean DHT serum concentrations (surrogate PD marker for safety).
Therefore, in order to cover a greater scalp area (allowing for the treatment of more severe AGA), the results indicated that the optimal dosage of topical finasteride for the pivotal phase III study is up to 200 µL o.d. (i.e., up to 4 sprays of 50 µL each), which would cover 200 cm^2 of scalp (each spray covering an area of 50 cm^2).

Figure 2.5-1 Efficacy/Safety Ratio Based on Relative Scalp/Serum DHT Reduction (Study PM1227 and Study PM1332, PD Populations)



b.i.d.=twice daily; DHT=dihydrotestosterone; o.d.=once daily; PD=pharmacodynamic(s).

Note: For both Studies PM1227 and PM1332, the number of patients in each treatment group was 6. Ratios were calculated by dividing the percentage change from baseline in DHT scalp concentration by the percentage change from baseline in DHT serum concentration.

Pivotal Phase III Study PM1541

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects/ patients [a]	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Efficacy	PM1541	Determine whether a daily treatment of 24 weeks with topical finasteride increased hair count in male patients with AGA compared to vehicle	Phase III, multi-centre, double-blind, double-dummy, randomised, parallel-group, placebo- and active-controlled, efficacy and safety study	*Topical finasteride*: Up to 4 sprays (i.e., up to 200 µL, 0.455 mg) topical finasteride o.d. + oral placebo *Vehicle*: topical vehicle + oral placebo o.d. *Oral finasteride*: topical vehicle + 1 mg oral finasteride o.d.	*Topical finasteride*: 181 *Vehicle*: 181 *Oral finasteride*: 84	Male patients with AGA	24 weeks	Complete; full

Study title: Multicenter, randomized, double-blind, parallel-group, controlled study, to assess the efficacy and safety of P-3074 cutaneous spray, solution (topical finasteride), in the treatment of male pattern baldness.

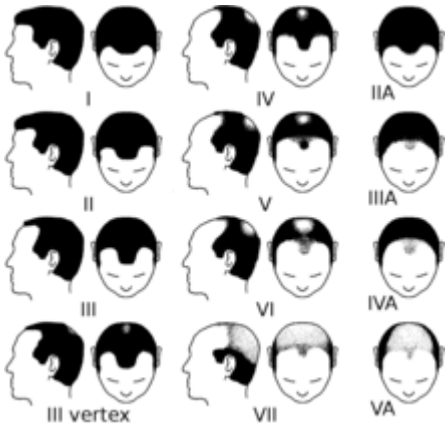
Study centres: 52 sites in 5 countries: 4 sites in Belgium, 20 sites in Germany, 10 sites in Spain, 8 sites in Hungary, and 10 sites in the Russian Federation.

One pivotal phase III study PM1541 was submitted. A Scientific Advice meeting was held with the BfArM on 16-Mar-2015. To file with a single Phase III pivotal study was considered to be sufficient, in light of the wealth of publicly available information on finasteride. A positive benefit-risk relationship will have to be established including convincing proof of clinical relevant superiority (see also *European Medicines Agency [EMA] guidance CPMP/EWP/2330/99, 2001 [Points to consider on Application with 1. Meta-analysis; 2. One Pivotal Study]*). Furthermore, it was advised to include a treatment arm with oral finasteride in the phase III study. A descriptive comparison of topical vs. oral finasteride was considered to be of interest to provide context for the clinical efficacy of topical finasteride (P-3074) observed in the trial and in view of safety and tolerability.

Methods

This was a multicentre, randomized, double-blind, double-dummy, parallel-group, placebo-controlled study of topical finasteride (P-3074) in men with AGA (n=458). A treatment arm with oral finasteride 1 mg was included for descriptive comparison. Male patients between the ages of 18 and 40 years inclusive with mild to moderate vertex male pattern hair loss were enrolled in the study, according to a modified Norwood/Hamilton classification scale (III vertex, IV or V).

Hamilton Norwood Scale (de.wikipedia.org):



Treatment

Treatment duration was 24 weeks. In order to keep a full blinding, a double-dummy technique was used. Three groups of patients were treated once daily each with either
1) Topical finasteride and the oral placebo (n=181),
2) Topical vehicle and oral placebo (n=181), or
3) Topical vehicle and oral finasteride 1 mg tablet over-encapsulated (n=84)

Test product: Finjuve 2.275 mg/mL spray (P-3074, topical finasteride)
Administration route/ dosage form: topical, spray pump
Dose and regimen: 1-4 sprays once daily, i.e. 50 µL [0.114 mg], 100 µL [0.228 mg], 150 µL [0.342 mg] or 200 µL [0.455 mg] o.d.

Reference product: Topical vehicle control
Administration route/ dosage form: topical, spray pump
Dose and regimen: 1-4 sprays once daily

Reference product: Propecia® 1 mg, (oral finasteride), MSD Sharp & Dohme GmbH.
Administration route/ dosage form: oral, film-coated tablet
Dose and regimen: 1mg once daily

Oral placebo control for the reference drug
The oral placebo control was prepared by Eclisse Euromed Clinical Supply Services (formerly THERAmetrics).

Topical finasteride (P-3074) or topical vehicle was applied in the morning onto dry scalp only, following the dose recommended by the study doctor (up to 4 puffs). The first puff was sprayed over the target 1 cm2 circular area, identified by a small dot tattoo as a reference point. The others, if prescribed, covered the rest of the baldness area. The cutaneous spray solution was left in place for at least 6 to 8 hours (after that, the patient had to wash carefully the scalp with shampoo). In addition, patients had to take oral finasteride 1 mg tablet, overencapsulated (or its placebo) daily, until the end of treatment (week 24).
Because of PK/PD assessments patients applied topical finasteride (or its vehicle) and took oral finasteride (or the corresponding placebo) directly at the clinical site no more than 1.5 hours before the sample collection.

Assessments and study procedures were performed at Weeks 4, 8, 12, and 24 (Visits 3, 4, 5, and 6). A follow-up visit took place at Week 28 (Visit 7).

Photography evaluation
Digital photographs were taken (for global and macrophotography assessment of patients).
Global photographs were taken at screening, at Visit 5 (after 12 weeks of treatment), and at the end of treatment (at Visit 6, Week 24) or at the ETV (Early Termination Visit). Global photographs Standardised colour global photographs of the vertex scalp were taken, after which the Investigator selected a 1 cm2 target area in the anterior leading edge of the vertex thinning area between 10 and 2 o'clock. Initially a small dot tattoo was placed in the centre of the circle, and this was used subsequently to locate the same area. A digital macrophotograph was taken of this circular area which was analysed to allow a count of the terminal hairs present. The change in this target area hair-count measurement (TAHC) from baseline at week 24 was the primary efficacy parameter of the study.

Disallowed medication during the trial
The use of systemic corticosteroids, topical corticosteroids in the balding area studied, anabolic steroids, or over-the-counter "hair restorers" were not allowed.
The use of any of the following drugs - flutamide, cyproterone acetate, oestrogen, progesterone, cimetidine, spironolactone, ketoconazole, minoxidil (topical or oral), zidovudine, cyclosporine, diazoxide, phenytoin, systemic interferon, psoralens, streptomycin, penicillamine, benoxaprofen, tamoxifen, phenothiazines or cytotoxic agents - were not allowed for the entire duration of the trial.

Objectives
The primary objective of this pivotal phase III study was to determine whether a daily treatment of 24 weeks with P-3074 solution (topical finasteride), increased hair count in men with AGA compared to vehicle solution (testing for superiority).

Outcomes/endpoints
Appropriate endpoints had been used in the pivotal study.

Efficacy:
Primary efficacy parameter
Total hair count (i.e., target area hair count [TAHC] in the vertex) at week 24

Secondary efficacy parameters
- Total hair count (i.e., TAHC in the vertex) at week 12
- Hair width (i.e., target area hair width [TAHW] in the vertex) at week 12 and week 24;
- Self-administered MHGQ (Male Hair Growth Questionnaire) as assessed by the patient at week 12 and 24;
  The MHGQ administered by the patient assessed 7 parameters: bald spot getting smaller; appearance of your hair; growth of hair; effectiveness in slowing down hair loss; hair line at the front of your head; the hair on top of your head; and overall. A higher score indicated a worse assessment.
- Investigator assessment of patient hair growth/loss change (i.e., improvement) from baseline to week 12 and week 24 , assessed for the vertex;
- Blind assessor assessment of patient hair growth/loss change (i.e., improvement) from baseline to week 12 and week 24, assessed for the vertex.

Pharmacokinetics / Pharmacodynamics:
PK and PD parameters

- Plasma concentrations of finasteride after multiple drug application and intake (randomisation, Week 4, Week 8, Week 12, Week 24, Week 28);
- Descriptive pharmacodynamics analysis: Baseline-corrected serum concentrations of DHT after multiple drug application and intake (randomisation, Week 4, Week 8, Week 12, Week 24, Week 28).

Clinical laboratory tests:
Blood chemistry

In addition to standard safety laboratory testing, the plasma concentration of testosterone after multiple drug application and intake was determined at randomisation, Week -2, Week 8, and Week 24, respectively.

Safety:
Safety variables

- TEAEs;
- Medical history
- Physical examinations;
- Vital signs and body weight;
- Routine haematology, blood chemistry and urinalysis laboratory tests;
- Local tolerability (via the Severity Score for Skin Irritation scale);
- Sexual dysfunction (via the Sexual Dysfunction Questionnaire [IIEF-2]); The self-administered Sexual Dysfunction Questionnaire (IIEF-2) was completed by the patient at each visit from Visit 3 to the end of study (Visit 7 or ETV):

Function Domain	Associated Questions	Max Score
Erectile Function	1, 2, 3, 4, 5, 15	30
Orgasmic Function	9, 10	10
Sexual Desire	11, 12	10
Intercourse Satisfaction	6, 7, 8	15
Overall Satisfaction	13, 14	10

Local tolerability at the application site:
Local tolerability at the application site was assessed to rate the severity of any skin irritation from Week 4 (V3) to Week 28 (V7, End of study), or at the early discontinuation visit. The Investigator used the Severity Score for Skin Irritation scale to assess local tolerability.

Statistical methods
The primary analysis set for efficacy evaluations is the ITT analysis set defined as all patients who had hair count (TAHC) measurements both at baseline and on treatment. This definition raises concerns as about 45% of randomized patients were excluded from the ITT analysis set. However, despite the large proportion of patients excluded, the ITT population may still be considered representative for the overall study population, as the vast majority of patients was excluded due to missing baseline hair count (likely not impacted by treatment, treatment assignment and outcome) and baseline characteristics for those included and excluded were overall similar. The macrophotograph to assess the baseline hair count was taken on the same day as a patient was randomized and started treatment. Hence, it was not possible to do reshoots in case of a non-evaluable macrophotograph.

The issues with exclusion from ITT were already raised in the pre-submission meeting with BfArM (10Jan2019) and the applicant did define an additional analysis set – the modified ITT analysis set (mITT) – as all randomized patients that did take at least one dose of study treatment. This analysis set is considered of special importance as it properly reflects the study population and maintains benefits of randomization.

The primary efficacy analysis tested the null hypothesis, that there was no difference between topical finasteride and the vehicle group in the mean change from baseline for the TAHC at Week 24. The analysis was performed using a mixed model for repeated measures with treatment (topical finasteride or placebo), centre, visit, and the treatment-by-visit interaction as fixed effects, and baseline hair count as a covariate. An unstructured variance-covariance matrix was used to take into account correlations among repeated measures within a patient. This is not the most appropriate analysis for efficacy evaluations as it is based on the missing-at-random (MAR) assumption and targets the hypothetical effect that would have been observed if all patients had continued study treatment as planned. It completely ignores that the treatment effect is probably lost after premature treatment discontinuation and consequently results in overoptimistic effect estimates. Considering that around 27% of week 24 data are missing in the ITT analysis set, sensitivity analysis are required to assess the robustness of results. In addition to the pre-specified sensitivity analyses based on single imputation approaches (LOCF, best case, and worst case imputation), requested additional sensitivity analyses based on multiple imputation approaches were conducted (tipping point analyses and placebo-based imputation (Jump-to-Reference; J2R)). These analysis overall support the robustness of results. Placebo-based multiple imputation analyses were also conducted for the secondary endpoints for which a similar mixed model as for the primary endpoint was the pre-specified analysis.

Post-hoc the primary and secondary endpoints were evaluated based on the mITT analysis set. While for the primary endpoint a single imputation approach (imputing a zero for patients with missing baseline or missing post-baseline measurements and LOCF imputation for patients with available baseline and week 12 measurement) was used, for secondary endpoints evaluations were based on observed cases. This is not acceptable as bias may be introduced. Upon request, additional analysis for secondary endpoints using placebo-based multiple imputation (J2R) was used to handle missing data. The most appropriate approach to handle missing data for primary and secondary endpoints in the ITT population and secondary endpoints in the mITT population is considered to be the Jump-to-Reference approach. For the mITT analysis set a pure Jump-to-Reference approach is likely too conservative for the primary endpoint as it is known that many patients excluded from the ITT population due to missing baseline data for the primary endpoints stayed on treatment throughout the whole study. Hence, the analysis using Jump-to-Reference-based imputations for patients prematurely discontinuing treatment and MAR-based imputations for patients staying on treatment provided by the applicant is considered more appropriate for evaluation of the primary endpoint in the mITT population.

For the primary endpoint, the range of different analysis (different missing data handling) conducted for the ITT, mITT and PP population overall support the robustness of results and show that superiority of topical finasteride over vehicle could be convincingly shown from a statistical perspective.

<u>Participant Flow/ Analysis Populations</u>
Planned: 450
Randomised: 458
Completed study: 323 (70.5% of randomized patients)
never treated patients= 12
Evaluated for safety: 446
Evaluated for efficacy (ITT analysis): 250 (54.6% of randomized patients)
=patients who had hair count measurements both at baseline and on treatment
Evaluated for efficacy (mITT analysis): 446 (97.4% of randomized patients))
=post-hoc analysis: Modified ITT (mITT) Population: *the same as the Safety Population*
=all randomised patients who received at least 1 application of the study treatment.
Evaluated for efficacy (PP analysis): 217

Of the 458 randomised patients, 446 (97.4%) received at least 1 dose of the IMP and were included in the Safety population. Two hundred and fifty patients (54.6%) overall (with a similar proportion of patients in each of the treatment groups) had hair count measurements both at baseline and on treatment and therefore qualified for inclusion in the ITT Population Efficacy analysis.
Of the 458 randomized patients, 323 (70.5%) completed the study. Thus, drop-out was high (29.5%). The exclusion of almost half the patients from the efficacy evaluations raised concerns whether the selected ITT population is representative of the overall study population. However, the vast majority of patients were excluded from the ITT population due to missing baseline hair counts (due to technical issues with the macrophotograph), which is likely not impacted by treatment, treatment assignment or outcome, and baseline characteristics of those included and excluded from the ITT population were overall similar. Therefore, exclusion of almost half the patients may not have relevantly impacted the representativeness of the ITT population. Also please see further above, Statistical methods.

Results
Of the 181 patients treated with topical finasteride o.d. in the study (Safety Population / mITT Population), 12 patients were prescribed to use 1 spray (50 µL, 0.114 mg of finasteride), 6 patients to use 2 sprays (100 µL, 0.228 mg), 34 patients to use 3 sprays (150 µL, 0.342 mg), and 129 patients to use 4 sprays (200 µL, 0.455 mg).
In the ITT Population, of the 105 patients treated with topical finasteride o.d., 10 patients were prescribed to use 1 spray (50 µL, 0.114 mg of finasteride), 3 patients to use 2 sprays (100 µL, 0.228 mg), 19 patients to use 3 sprays (150 µL, 0.342 mg), and 73 patients to use 4 sprays (200 µL, 0.455 mg).

Table 2.7.3-1 Analysis of Change in Target Area Hair Count from Baseline after 12 and 24 Weeks of Treatment (Study PM1541, ITT and mITT Populations)

Analysis	Topical finasteride	Vehicle	Oral finasteride
Baseline unadjusted mean (SD), ITT	201.0 (67.63)	204.8 (67.15)	201.9 (72.94)
Baseline unadjusted mean (SD), mITT	200.3 (67.56)	205.1 (66.30)	198.7 (71.95)
12-week visit (ITT)	**N=105**	**N=97**	**N=48**
Unadjusted mean (SD)	223.3 (74.10)	211.2 (68.14)	224.0 (78.00)
Unadjusted mean change from baseline (SE)	21.5 (2.28)	9.1 (2.17)	22.8 (3.38)
LS mean change from baseline (SE) [a]	20.4 (2.41)	7.6 (2.46)	22.5 (3.31)
Versus vehicle group			
LS mean difference (SE) [a]	12.8 (3.19)	-	-
95% confidence interval [a]	(6.5, 19.1)	-	-
p-value [a]	<0.001	-	-
24-week visit (primary endpoint, ITT)	**N=105**	**N=97**	**N=48**
Unadjusted mean (SD)	229.1 (75.28)	204.4 (71.87)	208.8 (68.35)
Unadjusted mean change from baseline (SE)	22.3 (3.05)	7.2 (2.65)	20.2 (3.38)
LS mean change from baseline (SE) [a]	20.2 (2.88)	6.7 (3.01)	21.1 (3.90)
Versus vehicle group			
LS mean difference (SE) [a]	13.6 (3.94)	-	-
95% confidence interval [a]	(5.8, 21.3)	-	-
p-value [a]	<0.001	-	-
24-week visit (post-hoc analysis, mITT)	**N=181**	**N=181**	**N=84**
Unadjusted mean (SD)	227.4 (74.21)	2014.3 (70.99)	207.2 (66.69)
Unadjusted mean change from baseline (SD)	12.2 (21.85)	5.0 (17.77)	12.5 (21.39)
LS mean change from baseline (SE) [b]	11.6 (1.49)	4.8 (1.48)	12.2 (2.12)
Versus vehicle group			
LS mean difference (SE) [b]	6.8 (2.00)	-	-
95% confidence interval [b]	(2.9, 10.7)	-	-
p-value [b]	<0.001	-	-

ITT=intent-to-treat; LS=least squares; mITT=modified ITT; N=total number of patients per treatment group; SD=standard deviation; SE=standard error.

Primary Efficacy Parameter, ITT population

Based on the primary pre-specified analysis (MMRM), the LS mean change (i.e., adjusted mean change) in TAHC (total hair count assessed in 1 cm^2 circular target area) from baseline in the ITT Population at 24 weeks (primary endpoint) was statistically significantly greater in the topical finasteride group (+20.2 hairs) than in the vehicle group (+6.7 hairs; LS mean difference of 13.6 hairs; $p<0.001$), and was similar to the oral finasteride group (+21.1 hairs) (please see table above).

Based on the Jump-to-Reference multiple imputation approach, which is considered more appropriate to handle missing data than the primary analysis (MMRM), the LS mean change in TAHC from baseline at week 24 was statistically significantly greater in the topical finasteride group (+16.3 hairs) than in the vehicle group (+6.3 hairs; LS mean difference of 10.0 hairs; $p=0.012$), and was numerically only slightly smaller as compared to the oral finasteride group (+18.7 hairs).
The mean difference in hair count (10.0 hairs/cm^2) for topical finasteride compared to vehicle by Jump-to-Reference analysis may be still considered clinically relevant but is clearly smaller than mean differences estimated in the meta-analysis by Adil et al. (2017) for oral finasteride (18.4 hairs/cm^2) and topical 5% minoxidil (14.9 hairs/cm^2).

Primary Efficacy Parameter, mITT population (post-hoc analysis)

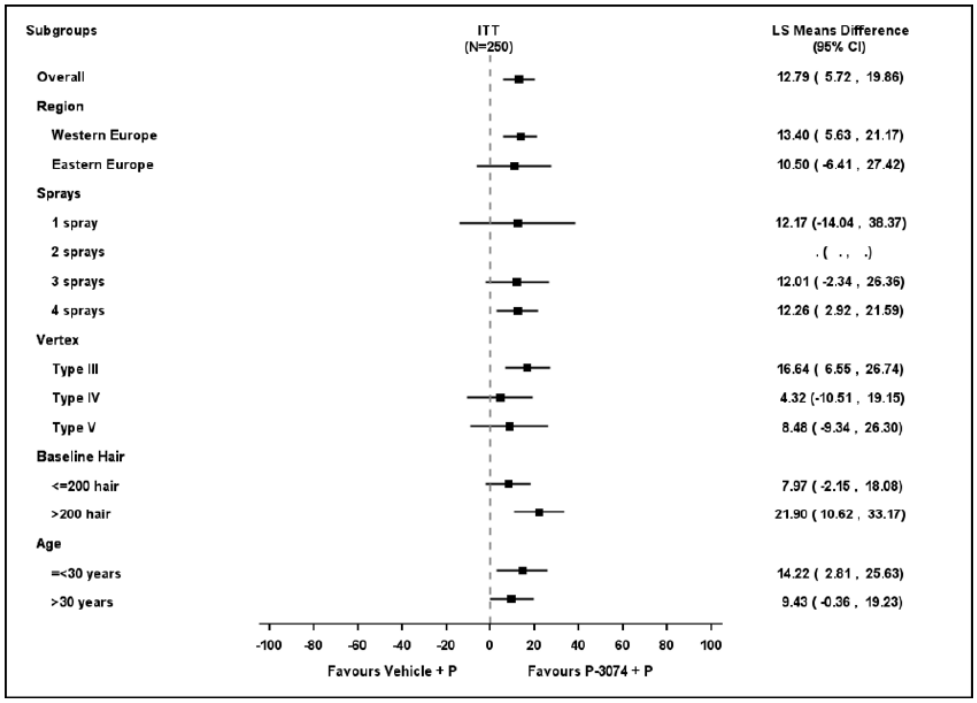
In a post-hoc analysis of TAHC in the mITT Population, the LS mean change was smaller in all treatment groups than that seen in the ITT Population. However, the difference at Week 24 was still statistically significantly greater in the topical finasteride group than in the vehicle group, and was similar to the oral finasteride group.

Using the most appropriate Jump-to-Reference imputations for missing data for analysis of the primary endpoint in the mITT population, these results were similar to the Jump-to-Reference-based analysis for the primary endpoint in the ITT population.

Subgroup evaluation for the primary endpoint

Requested subgroup analyses were provided for the ITT (Figure 6 from the D106 Response to efficacy question 6) and mITT population.

Figure 6 **Forest Plot Subgroup Analyses for the Primary Endpoint, ITT and mITT Populations.**



Point estimates for the mITT population are overall smaller (more missing data that are imputed as no change in hair count) as compared to the results in the ITT population, but results and conclusions are overall similar for both analysis populations.

Effects in subgroups are rather consistent in particular when looking at region and number of sprays. Some differences in point estimates were observed for baseline hair count and vertex type. Increase in hair growth by TAHC was more pronounced in patients with mild alopecia (vertex type III) compared to those with vertex type IV and V. Also the effect was more pronounced in patients with a baseline hair count > 200 hairs compared to those with ≤ 200 hairs/cm². This might be a hint that the overall modest clinical effect of topical finasteride is due to a poor effect in moderate alopecia. Still, overall confidence intervals are largely overlapping and within each subgroup point estimates are in favour of finasteride.

Secondary Efficacy Parameters
The following secondary efficacy parameters were evaluated:

- Target area hair count (TAHC, number of hairs) after 12 weeks of treatment
- Target area hair width (TAHW, width of hair) after 24 weeks of treatment
- IGA (Investigator Assessment) of patient hair growth/loss at week 24
- Blinded Assessor Assessment Score of patient hair growth/loss at week 24
- Male Hair Growth Questionnaire (Patient Self-Assessment) [MHGQ]:The MHGQ administered by the patient assessed 7 parameters: "bald spot getting smaller"; "appearance of your hair"; "growth of hair"; "effectiveness in slowing down hair loss"; "hair line at the front of your head"; "the hair on top of your head"; and "overall".

Secondary Efficacy Parameters, mITT population
Results for secondary endpoints based on the mITT population using Jump-to-Reference analysis are listed in the table below and overall conclusion are similar compared to the ITT population.

As the LS mean score differences in the table below are not easily to be interpreted, in addition a post-hoc responder analysis in regard to these parameters was requested and provided. The post-hoc responder analyses of the secondary endpoints of IGA, Blinded Assessor Assessment and MHGQ are reported in the SmPC section 5.1.

Endpoint	**Treatment group**	**N**	**LS mean (SE)**	**LS mean diff. to vehicle (SE)**	**(95% CI) p-value**
TAHC, hairs (week 12)	Topical finasteride	181	17.6 (2.24)	8.7 (8.82)	(3.2, 14.2) 0.002
	Vehicle	181	8.8 (2.33)	-	-
	Oral finasteride	84	18.0 (3.07)	-	-
TAHW, µm (week 24)	Topical finasteride	181	-1.2 (0.33)	0.5 (0.39)	(-0.3, 1.2) 0.238
	Vehicle	181	-1.7 (0.34)	-	-
	Oral finasteride	84	-0.3 (0.45)	-	-
Investigator assessment, score (week 24)	Topical finasteride	181	0.7 (0.08)	0.3 (0.11)	(0.1, 0.5) 0.010
	Vehicle	181	0.4 (0.08)	-	-
	Oral finasteride	84	0.7 (0.12)	-	-
Blinded Assessor Assessment, score (week 24)	Topical finasteride	181	0.2 (0.07)	0.2 (0.09)	(-0.0, 0.4) 0.072
	Vehicle	181	0.0 (0.07)	-	-
	Oral finasteride	84	0.3 (0.10)	-	-
MHGQ: Smaller Bald Spot (week 24)	Topical finasteride	181	2.9 (0.10)	-0.2 (0.13)	(-0.4, 0.1) 0.218
	Vehicle	181	3.1 (0.09)		
	Oral finasteride	84	3.0 (0.14)		
MHGQ: Hair Appearance (week 24)	Topical finasteride	181	3.3 (0.09)	-0.2 (0.11)	(-0.4, 0.0) 0.060
	Vehicle	181	3.5 (0.08)		
	Oral finasteride	84	3.3 (0.12)		
MHGQ: Hair Growth (week 24)	Topical finasteride	181	3.4 (0.08)	-0.2 (0.11)	(-0.4, -0.0) 0.046
	Vehicle	181	3.6 (0.08)		
	Oral finasteride	84	3.4 (0.12)		
MHGQ: Slow Down Hair Loss (week 24)	Topical finasteride	181	2.5 (0.08)	-0.2 (0.10)	(-0.4; -0.0) 0.034
	Vehicle	181	2.7 (0.08)		
	Oral finasteride	84	2.6 (0.11)		

MHGQ: Front Head Hairline (week 24)	Topical finasteride	181	3.0 (0.08)	-0.3 (0.10)	(-0.5; -0.1) 0.004
	Vehicle	181	3.2 (0.08)		
	Oral finasteride	84	3.0 (0.11)		
MHGQ: Head Top (week 24)	Topical finasteride	181	2.9 (0.08)	-0.1 (0.11)	(-0.4; 0.1) 0.171
	Vehicle	181	3.0 (0.08)		
	Oral finasteride	84	2.9 (0.11)		
MHGQ: Hair Overall (week 24)	Topical finasteride	181	2.8 (0.08)	-0.2 (0.10)	(-0.4; 0.0) 0.084
	Vehicle	181	3.0 (0.07)		
	Oral finasteride	84	2.9 (0.11)		

Summary of Clinical Efficacy

Various statistical assessments of the primary efficacy endpoint, including the pre-specified MMRM analysis in both the ITT and mITT/Safety Populations, all consistently showed statistical significance of topical finasteride vs vehicle and numerically similar efficacy to oral finasteride. The size of the treatment effect, estimated by difference to placebo, is considered modest.

According to the most appropriate analysis of the primary endpoint by the Jump-to-reference (J2R) approach applied to all missing data resulted in an estimated difference of 10.0 hairs/cm^2 between topical finasteride and placebo, statistically significant ($p<0.012$) and numerically similar to the oral finasteride group.

Results of most secondary efficacy parameters seemed clinically not compelling. Hair growth by the investigator's assessment improved a little bit both in the topical and oral finasteride group, but also in the placebo group and the difference to placebo was small: LS mean difference at week 24 compared to placebo 0.3; p-value =0.01. The same was observed in regard to the blinded investigator assessment of hair growth at week 24 and the patient's self-assessment by MHGQ (Male hair Growth Questionnaire) at week 24. The difference to placebo was small.

Also the post-hoc responder analysis showed that the results for the secondary parameters in the topical finasteride group were numerically similar to the oral finasteride group and there was a remarkable placebo response. The difference of the response rates of topical finasteride vs. placebo was modest.

The response rates for IGA were 42.0 %, 35.7% and 27.6% for the topical finasteride, oral finasteride and placebo group, p= 0.00041.

For the blinded Investigator Assessment, which was based on the scalp photographs, responder rates in the different groups were lower: 26.0%, 28.6% and 16.0%, p= 0.0202.

In regard to the Patient's Self-Assessment by MHGQ, responder rates were even lower. In regard to "Overall Change" response rates were 26.5% 25.0% and 19.9% for the topical finasteride, oral finasteride and placebo group, with only a very small difference to placebo and not statistically significant. Response rates in regard to "Hair growth" were 39.8%, 31.0% and 32.0% for the topical finasteride, oral finasteride and placebo group, again only very small difference to placebo and not statistically significant. Response rates in regard to "Appearance of hair" were 40.9%, 36.9% and 28.7%, p= 0.0152. The treatment effect is considered modest.

Clinical safety

A total of 326 subjects were exposed to topical finasteride in the clinical development programme studies; 229 were patients with AGA (study PM1541, PM1332, PM1227, and PM1024) and 97 were healthy subjects (study PM1542 and PM1646).

As mentioned in the Scientific Advice Meetings with BfArM in 2015 and 2019 the Safety Database is considered small. Indeed, relevant safety information is available from the phase III study only, with 181 patients exposed to up to 200 µL (= 0.46 mg) topical finasteride for up to 6 months. Nevertheless, drop-out in the pivotal study was high in all groups, 32.3% (of the randomized patients) in the topical finasteride group. In regard to the safety evaluation the phase I studies

PM1227 and PM1024 and the phase IIa are considered supportive only, as treatment duration was 1 week only each.

The safety profile from oral finasteride 1 mg/day is well-known. Therefore the clinical trial program did not include patients treated for 1 year as per ICH E1, where it is stated that "*…the number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterise the pattern of AEs over time…Usually 300-600 patients should be adequate*." Furthermore in regard to long-term effects it is stated that "*…100 patients exposed for a minimum of one-year is considered to be acceptable as part of the safety data base…*" (ICH Topic E 1, Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety, CPMP/ICH/375/95).

It is reassuring that in the pivotal phase III study after administration of Finjuve at the intended dose (i.e., up to 200 microliter= up to 4 sprays once daily), mean maximum plasma finasteride concentrations were > 100-times lower than after 1 mg once daily oral finasteride administration at all sampling times over 6 months of treatment in the PK-population.

Of note, on the other hand, in the pivotal phase III study, at week 24, the percentage decrease in mean DHT serum concentration from baseline was higher in the oral finasteride group but decrease was significant both with topical finasteride and oral finasteride:-34.5% for topical finasteride compared to -55.6% for oral finasteride – thus indicating possibly systemic adverse reactions of a sexual nature related to a decrease in DHT, though with less probability for topical finasteride than with oral finasteride..

In the pivotal phase III study the overall incidence of AEs in the topical finasteride group was similar to the vehicle group (41.4% vs. 42.0%) and slightly lower than in the oral finasteride group (48.8%). Most of the AEs in the different groups were of mild or moderate intensity. Only 2.2% of the AEs in the topical finasteride group were severe. The rate of patients with AEs leading to study discontinuation in the topical finasteride group (2.8%) was similar to the vehicle group (2.2%) and lower than in the oral finasteride group (7.1%). The incidence of SAEs was low and similar in the different treatment groups. At least 1 SAE occurred in only 2.2% of the patients in the topical finasteride group. No SAE was considered as related to study treatment.

AEs were most frequently reported in the SOC of infections and infestations, followed by nervous system disorders, skin and subcutaneous tissue disorders, with similar incidences in all 3 treatment groups. For the SOC "psychiatric disorders" a higher incidence was reported in the oral finasteride group (8.3%) than in the topical finasteride group (1.7%) or vehicle group (4.4%). The SOC "Reproductive system and breast disorders" was reported for 3.6% of the patients in the oral finasteride group, 2.2% (4 patients= 2x erectile dysfunction, 2x sexual dysfunction) in the topical finasteride group and 1.1% in the vehicle group (see table 2.7.4-18 below).

Table 2.7.4-18 Summary of Treatment-emergent Adverse Events by Most Frequent MedDRA System Organ Class (at Least 3% of Patients per Treatment Group; Study PM1541, Safety Population)

System organ class	Number (%) of patients		
	Topical finasteride (N=181)	Vehicle (N=181)	Oral finasteride (N=84)
Any TEAE	75 (41.4)	76 (42.0)	41 (48.8)
Infections and infestations	45 (24.9)	38 (21.0)	18 (21.4)
Nervous system disorders	18 (9.9)	24 (13.3)	9 (10.7)
Skin and subcutaneous tissue disorders	12 (6.6)	8 (4.4)	5 (6.0)
Gastrointestinal disorders	11 (6.1)	16 (8.8)	6 (7.1)
Injury, poisoning and procedural complications	8 (4.4)	5 (2.8)	1 (1.2)
Respiratory, thoracic and mediastinal disorders	7 (3.9)	11 (6.1)	3 (3.6)
General disorders and administration site conditions	5 (2.8)	4 (2.2)	4 (4.8)
Investigations	5 (2.8)	3 (1.7)	4 (4.8)
Musculoskeletal and connective tissue disorders	5 (2.8)	9 (5.0)	3 (3.6)
Reproductive system and breast disorders	4 (2.2)	2 (1.1)	3 (3.6)
Psychiatric disorders	3 (1.7)	8 (4.4)	7 (8.3)

MedDRA=Medical Dictionary for Regulatory Activities; N=total number of patients per treatment group.
Note: Version 19.0 of MedDRA was used to code the adverse events.
Source: Section 5.3.5.1

Table 2.7.4-20 Treatment-emergent Adverse Events Reported in More than 1 Patient of Any Group (Phase III Study PM1541)

Preferred term	Number (%) of patients		
	Topical finasteride (N=181)	Vehicle (N=181)	Oral finasteride (N=84)
Any TEAE	75 (41.4)	76 (42.0)	41 (48.8)
Nasopharyngitis	28 (15.5)	24 (13.3)	15 (17.9)
Headache	17 (9.4)	20 (11.0)	8 (9.5)
Pruritus	5 (2.8)	1 (0.6)	1 (1.2)
Influenza	4 (2.2)	2 (1.1)	1 (1.2)
Erythema	4 (2.2)	0	0
Pyrexia	3 (1.7)	1 (0.6)	1 (1.2)
Respiratory tract infection viral	3 (1.7)	0	0
Toothache	3 (1.7)	3 (1.7)	2 (2.4)
Back pain	2 (1.1)	5 (2.8)	1 (1.2)
Diarrhoea	2 (1.1)	2 (1.1)	2 (2.4)
Erectile dysfunction	2 (1.1)	2 (1.1)	2 (2.4)
Gastritis	2 (1.1)	1 (0.6)	0
Gastroenteritis	2 (1.1)	4 (2.2)	1 (1.2)
Rash papular	2 (1.1)	0	0
Rhinorrhoea	2 (1.1)	0	0
Sexual dysfunction	2 (1.1)	0	0
Urinary tract infection	2 (1.1)	1 (0.6)	0
Bronchitis	1 (0.6)	2 (1.1)	0
Cough	1 (0.6)	2 (1.1)	0
Dizziness	1 (0.6)	2 (1.1)	0
Libido decreased	1 (0.6)	3 (1.7)	1 (1.2)
Oropharyngeal pain	1 (0.6)	7 (3.9)	3 (3.6)
Pain in extremity	1 (0.6)	2 (1.1)	0
Sinusitis	1 (0.6)	2 (1.1)	1 (1.2)
Gamma-glutamyltransferase increased	0	0	2 (2.4)
Dyspepsia	0	2 (1.1)	1 (1.2)
Hordeolum	0	2 (1.1)	0
Loss of libido	0	2 (1.1)	3 (3.6)
Nausea	0	3 (1.7)	0
Seborrhoic dermatitis	0	2 (1.1)	0
Tonsillitis	0	3 (1.7)	0

N=total number of patients per treatment group;

TEAE=treatment-emergent adverse event = all AEs that occurred or worsened after the first dose of study treatment

Source: Module 5.3.5.1

To conclude, in the phase III study, the overall rate of any AE was similar between all treatment groups, slightly higher in the oral finasteride group (see table 2.7.4-20, above).

Considering all TEAEs of a sexual nature (erectile dysfunction, sexual dysfunction, libido decreased and loss of libido) in the phase III study, the incidence of these events was lowest in the topical finasteride group (5 patients, 2.8%) and vehicle group (7 patients, 3.9%), and highest in the oral finasteride group (5 patients, 6.0%) (see Table 2.7.4-20, above).

Treatment-related adverse events (=*considered as related or possibly related to study treatment*) Pruritus and erythema (4 patients [2.2%] each in Study PM1541) were identified as treatment-related adverse events; both of which were of common frequency (≥1/100 to <1/10). These adverse reactions

were mild or moderate in severity, the majority resolved by the end of the study without discontinuation of the treatment, and none were serious.
Table 2.7.4-21 below displays these AEs that were considered as related or possibly related to study treatment by the investigator:

Table 2.7.4-21 Treatment-related Adverse Events Reported in More than 1 Patient of Any Group (Phase III Study PM1541)

Preferred term	Number (%) of patients		
	Topical finasteride (N=181)	Vehicle (N=181)	Oral finasteride (N=84)
Any treatment-related TEAE [a]	18 (9.9)	12 (6.6)	10 (11.9)
Erythema	4 (2.2)	0	0
Pruritus	4 (2.2)	1 (0.6)	1 (1.2)
Erectile dysfunction	2 (1.1)	1 (0.6)	1 (1.2)
Rash papular	2 (1.1)	0	0
Sexual dysfunction	2 (1.1)	0	0
Libido decreased	1 (0.6)	3 (1.7)	1 (1.2)
Loss of libido	0	2 (1.1)	3 (3.6)

N=total number of patients per treatment group; TEAE=treatment-emergent adverse event= all AEs that occurred or worsened after the first dose of study treatment

a) Includes TEAEs considered as related or possibly related to study treatment by the investigator.

Source: Module 5.3.5.1, Clinical Study Report PM1541

Treatment-related adverse events of a sexual nature

Adverse events, like erectile dyfunction, sexual dysfunction or loss of libido cannot be excluded with use of topical finasteride. Two cases of sexual dysfunction occurred in the topical finasteride group [1.1%] (compared to 0% in the vehicle and in the oral finasteride groups), two cases of erectile dysfunction [1.1%] (compared to 0.6% in the vehicle and 1.2% in the oral finasteride group), one case of libido decrease [0.6%] (compared to 1.7% in the vehicle and 1.2% in the oral finasteride group) occurred in the topical finasteride group), and 0 cases of loss of libido with topical finasteride [0%] (compared to 1.1% for vehicle and 3.6% for oral finasteride). In the phase III study the overall frequency of treatment-related adverse events of a sexual nature (including the PTs “sexual dysfunction”, “erectile disorder”, “loss of libido”, “decreased libido”), this was reported as 2.8% of patients in the topical finasteride group, 3.3% in patients treated with vehicle, and 4.8% of patients treated with oral finasteride 1 mg. This means the frequency of treatment-related adverse events of a sexual nature was similar in the topical finasteride and vehicle group.

Of note, in the pivotal phase III study, at week 24, the percentage decrease in mean DHT serum concentration from baseline was higher in the oral finasteride group but decrease was significant both with topical finasteride and oral finasteride:-34.5% for topical finasteride compared to -55.6% for oral finasteride – thus indicating possibly systemic adverse reactions of a sexual nature related to a decrease in DHT, though with less probability for topical finasteride than with oral finasteride.

The 5 patients on topical finasteride with ADRs of a sexual nature continued to have DHT levels within the normal range throughout the study. By contrast, for the 4 patients randomized to oral finasteride who experienced ADRs of a sexual nature serum DHT dropped below the normal range (<14 ng/dL) and in 3 patients this was already noted at week 4.

Moreover, the number of exposed patients in the pivotal study is too low to draw any definite conclusions, particularly in regard to long-term safety. 181 patients were randomized to the topical finasteride arm, but the drop-out rate was high at 32.3% in the topical finasteride group.

In the phase I studies PM1541 (skin photosensitisation) and PM1646 (skin irritation) skin patches with 200 µL (0.46 mg) topical finasteride were applied for 3 weeks. There were no incidences of photosensitisation in any subject. And in the skin irritation study, after 21days of patch application, the mean cumulative irritation score was 0 for topical finasteride, HPCH, and the negative control, which was statistically significantly less than the mean score for the positive control (45.7; $p<0.05$).

Legal Status
Subject to medical prescription

User Testing
The package leaflet of Finjuve 2.275 mg/mL cutaneous spray, solution passed the readability user test successfully. The interviews showed that the information of the PL was clear, readable and well understood by potential users.

Summary Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's and/or Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The Applicant 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 Finjuve Spray.

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Abnormalities of the external genitalia of a male foetus following exposure of a pregnant woman • Sexual dysfunction (decreased libido, erectile dysfunction and ejaculation disorders) • Depressive disorders
Missing information	None

Pharmacovigilance Plan
The Applicant provided specific adverse drug reaction (ADR) follow-up questionnaires for the important potential risks "sexual dysfunction (decreased libido, erectile dysfunction and ejaculation disorders)" and "depressive disorders", respectively. The questionnaires will become part of the routine pharmacovigilance activities in order to further characterise these potential risks.
No additional pharmacovigilance activities are proposed. This is accepted.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the Applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.6, date of final sign off 15-Sept-2020 is approvable.

The Applicant shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV BENEFIT RISK ASSESSMENT

In the pivotal phase III trial all the various statistical assessments of the primary efficacy endpoint consistently showed statistical significance of topical finasteride vs. vehicle and numerically similar efficacy to oral finasteride. However, the size of the treatment effect, estimated by difference to placebo, and also considering investigator's and patient's self-assessment is considered modest.
The safety profile of oral finasteride 1 mg/day is well-known. At week 24 there was a decrease in mean DHT serum concentration after exposure to both topical and oral finasteride, although higher in the oral finasteride group. Thus, systemic adverse reactions including adverse events of a sexual nature related to a decrease in DHT may also possibly occur with topical finasteride, although the probability is considered lower compared to oral finasteride.
The benefit/ risk ratio of the treatment with Finjuve in mild to moderate AGA in male patients is considered positive.
The application is approved. For intermediate amendments see current product information.