POLICHEM

P-3074

A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, CONTROLLED STUDY, TO ASSESS THE EFFICACY AND SAFETY OF P-3074 CUTANEOUS SPRAY, SOLUTION, IN THE TREATMENT OF MALE PATTERN BALDNESS

Sponsor:	Polichem S.A. - 50, Val Fleuri, 1526 Luxembourg hereby legally represented by its branch located in Via Senago 42D Lugano-Pazzallo CH-6912, Switzerland Phone: +41.91.986.40.00 Fax: +41.91.986.40.01
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PROTOCOL APPROVAL FORM - SPONSOR

PROTOCOL No.: PM1541 **TEST DRUG:** P-3074

PROTOCOL TITLE: A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, CONTROLLED STUDY, TO ASSESS THE EFFICACY AND SAFETY OF P-3074 CUTANEOUS SPRAY, SOLUTION, IN THE TREATMENT OF MALE PATTERN BALDNESS

DATE OF ISSUE: PPD

SPONSOR: Polichem S.A.

Prepared by:

PPD
Polichem SA

PPD
Signature

PPD
Date

Approved by:

PPD
Polichem SA

PPD
Signature

PPD
Date

Statistician
PPD

PPD
Signature

Date

These signatures constitute approval of this revised protocol and provide the necessary assurance that this study will be conducted according to all stipulations of the protocol.

INVESTIGATOR'S STATEMENT: CONFIDENTIALITY AND PUBLICATION POLICY

I, the undersigned, after having read protocol PM1541 entitled "A multicentre, randomized, double-blind, parallel-group, controlled study, to assess the efficacy and safety of P-3074 cutaneous spray, solution, in the treatment of male pattern baldness", agree and accept that all information communicated to me by Polichem S.A., 50, Val Fleuri, L-1526 Luxembourg and their representatives (hereinafter called "Polichem S.A.") is the exclusive property of Polichem S.A., and I will ensure that the same shall be kept strictly confidential by me or any other person involved in the study and shall not be disclosed by me or such person to any third party without the prior written authorization of Polichem S.A..

I agree to conduct the trial in accordance with the protocol and with all applicable government regulations and Good Clinical Practice Guidance.

All data generated in this study are the exclusive property of Polichem S.A. No disclosure of results shall be made without the prior written authorisation of Polichem S.A.

Therefore, any proposed publication or presentation (e.g., manuscript, abstract or poster) for submission to a journal or scientific meeting will be mutually agreed with scientists from Polichem S.A. If the publication/presentation is allowed by Polichem S.A., scientists from Polichem S.A. will be co-authors and the publication shall be jointly prepared. In particular, Polichem S.A. scientists shall review the manuscript to prevent forfeiture of patent rights to data not in the public domain.

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Country: _____ Site number: _____

_____	_____	_____
Principal Investigator	Signature	Date

REFERENCE STUDY PERSONNEL:

Sponsor's Representative: Study Director – PPD

PPD is the Study Director of the clinical trial.
Polichem SA
Via Senago 42 D
6912 Lugano-Pazzallo (Switzerland)

Sponsor's Representative: Clinical Project Manager – PPD

PPD is in charge of coordinating all involved CROs and supervising the study related activities at Sponsor's headquarters.
Polichem SA
Via Senago 42 D
6912 Lugano-Pazzallo (Switzerland)
Phone PPD
Fax: PPD
Email: PPD

Safety Manager: PPD

PPD, is in charge of collecting and evaluating any ADR/SAE that will occur during the study. He is responsible for requesting any follow-up information and compliant reporting to Regulatory Agencies.
Phone: PPD (office) or PPD (mobile phone)
Fax: PPD
E-mail: PPD
PPD

CRO involvement/Outsourced Activities:

Polichem will outsource the following tasks/duties to qualified vendors:

- design of the electronic CRF and all study documents
- identification of Investigators/sites
- submission of study documentation to local Authorities
- random codes generation
- monitoring
- drug labelling, packaging, accountability and destruction
- data management
- statistics
- ICH-GCP clinical study report

Central Laboratory (CCI [redacted])

PPD

Central Laboratory (for Safety analyses)

PPD

Imaging Company

PPD

Blind Assessor:
A Central Blinded Evaluator (CBE) will be in charge to assess the images of the patients enrolled and to assess change in their hair growth.

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Synopsis

Study title	A multicentre, randomized, double-blind, parallel-group, controlled study, to assess the efficacy and safety of P-3074 cutaneous spray, solution, in the treatment of male pattern baldness
Study code	PM1541
Development phase	Phase III study
EudraCT number	2015-002877-40
Sponsor	Polichem S.A.
Number of Study Sites / Countries	Approximately 50 sites in EU and Russia
Study rationale	Androgenetic alopecia (AGA or male pattern baldness) is a genetically determined disorder due to an underlying susceptibility of hair follicles to androgenic miniaturization, affecting more than 50% of men under 50 years of age. Both genetic and environmental factors play a role in its development, and many aetiologies remain unknown. AGA is known to depend on the presence of the androgen dihydrotestosterone (DHT) and on genetic predisposition. DHT is formed by testosterone through the action of the type II 5α-reductase enzyme. In the scalp of men suffering from AGA, an increased rate of conversion of testosterone into DHT has been detected. The basis of androgenetic alopecia in men is a progressive decrease in the density of terminal hairs and a concurrent increase in the density of short, non-pigmented hairs. The Hamilton-Norwood scale has been developed to grade AGA in males: it ranges from stages I to VII. Medically, AGA is viewed as a relatively mild dermatological condition. However, as hair is an important component of identity and self-image, patients with AGA may experience a distorted body image and negative feelings of social disadvantages including depression, low self-esteem, an altered self-image, and less frequent social engagement. Notably, even clinically imperceptible hair loss has been correlated with a decreased quality of life (QoL). Treatment of androgenetic alopecia has the main aim of preventing further progression of the disease and of reversing the miniaturisation (promoting re-growth of hair). Although the market offers a wide choice of treatments, to date there are only two effective drugs authorised by the FDA for the treatment of male pattern baldness, i.e. minoxidil and finasteride 1 mg tablet.

	In the androgenetic alopecia, the target is the inhibition of the type II 5α-reductase isoenzyme present in the scalp to reverse the signs and symptoms of alopecia avoiding the inhibition of the plasmatic type II 5α-reductase isoenzyme. Generally, 1 mg oral finasteride is well tolerated with long-term use, although evidence from preclinical and clinical studies points to significant adverse effects of 5α-reductase inhibitors on health and overall quality of life. Sexual adverse effects have been consistently reported. In multiple double-blind randomised controlled trials, 1 mg oral finasteride has been associated with a significant amount of sexual dysfunctions, including decreased libido (1.8%), erectile dysfunction (1.3%), ejaculation disorders (0.8 – 1.2%) and orgasm disorders (0.4%). However, the use of 1 mg oral finasteride for the treatment of male pattern hair loss has recently been the focus of media and internet attention for potential irreversible sexual dysfunction and severe depression. Reports of potential irreversible sexual dysfunction and severe depression do raise concerns about the safety of 1 mg oral finasteride. It is likely that a lack of plasmatic DHT or another 5 alpha-reduced hormone is responsible for the reported decrease in libido and/or orgasm. Clinical studies with oral finasteride were conducted in 1879 men aged 18 to 41 with mild to moderate, but not complete, vertex hair loss and/or frontal/mid-area hair loss. In the two studies in men with vertex hair loss (n=1553), 290 men completed a 5-year treatment with finasteride vs. 16 patients on placebo. In these two studies, efficacy was assessed by the following methods: hair count in a representative area of scalp, patient self-assessment questionnaire, investigator assessment using a seven-point scale, and photographic assessment of standardised paired photographs by a blinded expert panel of dermatologists using a seven-point scale. In long-term 5-year studies, men treated with finasteride improved their condition, compared to both baseline and placebo beginning as early as 3 months, as determined by both the patient and investigator assessments of efficacy. With regard to hair count, the primary endpoint in these studies, increases compared to baseline were demonstrated starting at 6 months (the earliest time point assessed) through to the end of the study. In men treated with finasteride these increases were greatest at 2 years and gradually declined thereafter to the end of 5 years, whereas hair loss in the placebo group progressively worsened compared to baseline over the entire 5-year period. In finasteride treated patients, a mean increase from baseline of 88 hairs [$p < 0.01$; N=433] in the representative area, was observed at 2 years. An increase from baseline of 38 hairs [$p < 0.01$; N=219] was observed at 5 years, compared with

	a decrease from baseline of 50 hairs [p <0.01; N=47] at 2 years and a decrease from baseline of 239 hairs [p <0.01; N=15] at 5 years in patients who received placebo. Standardized photographic assessment of efficacy demonstrated that 48% of men treated with finasteride for 5 years were rated as improved, and an additional 42% were rated as unchanged. This is in comparison to 25% of men treated with placebo for 5 years who were rated as improved or unchanged. These data demonstrate that a treatment with Finasteride for 5 years resulted in a stabilisation of the hair loss that occurred in men treated with placebo. Van Neste et al (2000) showed that a treatment with 1 mg oral finasteride for 48 weeks led to a net improvement in total hair count of 17.3 ± 2.5 hairs (8.3% ± 1.4%) in a target area of 1 cm^2, compared with placebo ($p < 0.001$). This effect is already present after six months of treatment and is maintained for the following six months. Considering the well-known efficacy of oral finasteride but also a concerning side effect profile, Polichem decided to develop a formulation of finasteride 0.25% in Polichem patented Hydroxypropyl Chitosan Technology (P-3074), that allows finasteride to act on the follicular portion to promote a cutaneous depot of finasteride in the region of hair bulbs, thus minimizing systemic absorption even after repeated treatments. The scope was to achieve consistent inhibitory effects on scalp DHT inhibition, minimizing the systemic effect on serum. Polichem investigated the pharmacodynamic profile of P-3074 o.d. and b.i.d. comparing them to oral finasteride 1 mg, in male subjects, after single and a 7-day administration. Change from baseline in scalp DHT was -70% for P-3074 o.d. and approximately -50% for P-3074 b.i.d. and the oral tablet. Serum DHT decreased by 60-70%. The results proved that P-3074, administered topically at 0.25% o.d. for seven days, is able to effectively penetrate the scalp skin, to reach the bulb and to effectively and already maximally inhibit the type II 5α-reductase isoenzyme directly at bulb level, blocking the local DHT more effectively and more consistently than oral finasteride, finally suggesting that the achievement of comparable levels of DHT inhibition (vs the oral form), could be attained via a lower dose of P-3074. A following dose-finding study evaluated therefore whether P-3074 lower doses (100, 200, 300 and 400 µL) vs vehicle, could achieve consistent inhibitory effects on scalp DHT inhibition (accepted as surrogate end-point), minimizing the systemic effect on serum.

	The doses of 100 and 200 µL P-3074 resulted in a -47/-52% scalp DHT reduction, similar to the 300 and 400 µL doses (i.e. -37/-54%). A -5.6% inhibition was observed for the vehicle. Serum DHT was reduced by only -24/-26% with 100 and 200 µL P-3074 and by -44/-48% with 300 and 400 µL P-3074. In conclusion, at doses up to 200 µL, P-3074 applied topically, allowed to significantly decrease DHT in scalp and only marginally in serum potentially minimizing the untoward side-effects linked to a systemic DHT reduction.
Aim of the study	The primary objective of this pivotal phase III study is to determine whether a daily treatment with P-3074 for 24 weeks increases hair count in men with male pattern baldness (MPB) compared to the vehicle.
Study Population	Not less than 450 male patients (aged 18 to 40 years) with a mild to moderate vertex hair loss (classified as type III vertex, IV or V), classified according to the modified Norwood/Hamilton Scale, will be recruited in the trial.
Study medication	• P-3074 topically administered once a day (o.d.) • P-3074 vehicle topically administered once a day (o.d.) • 1 mg oral finasteride active, once a day (o.d.) • 1 mg oral finasteride placebo, once a day (o.d.)
Duration of treatment	24 weeks
Method of administration	All patients randomised should topically apply P-3074 or its Vehicle once a day for the 6 months of treatment. P-3074 or Vehicle (Placebo) has to be applied in the morning onto dry scalp only, following the dose recommended by the study doctor (up to 4 puffs). The first puff has to be sprayed over the target 1cm^2 circular area, identified by a small dot tattoo as a reference point. The others, if prescribed, shall cover the rest of the baldness area. The cutaneous spray solution has to be left it in place for at least 6-8 hours (after that, the patient has to wash carefully the scalp with shampoo). In the same context, patients has to take in oral finasteride 1 mg tablet, over-encapsulated (or its placebo) daily, until the end of treatment (Visit 6). Therapy with P-3074 (or its Vehicle) has to be continued on a daily basis in order to maintain or increase the hair growth achieved. At Visits 3, 4, 5 and 6, the patient has to administer P-3074 (or its Vehicle) and to take the last capsule, not more than 1.5 hour before the sample collection.

Study end-points	Primary end-point: • Hair growth assessed by Target Area Hair Count (TAHC) in the vertex at 24 weeks. Secondary end-points: • Hair growth assessed by TAHC in the vertex at 12 Weeks; • Target Area Hair Width (TAHW) in the vertex at Weeks 12 and 24; • Patient assessment in Male Hair Growth questionnaire (MHGQ) at Weeks 12 and 24; • Investigator Assessment of Improvement from Baseline to Week 12 and from Baseline to Week 24, assessed for vertex; • Blind Assessor Assessment of Improvement from Baseline to Week 12 and from Baseline to Week 24, assessed for vertex; • Assessment of sexual function at every visit (Sexual Function Index); • Assessment of adverse events (AEs) throughout the study; • Assessment of the local tolerability by means of severity scores for skin irritation; Exploratory end-points • CCI [redacted]; • CCI [redacted].
Experimental design	This is a phase III, multicentre, randomized, double-blind, double-dummy, parallel-group study aimed at evaluate the efficacy and safety of P-3074 cutaneous topical solution in the treatment of the male pattern baldness versus an active comparator of oral finasteride with three treatment arms, in a ratio of 2:2:1 (A:B:C). Group A: P-3074 o.d. + placebo of oral finasteride 1 mg o.d. or Group B: P-3074 Vehicle + placebo of oral finasteride 1 mg o.d. or Group C: finasteride 1 mg o.d. + P-3074 Vehicle The study consists of a screening visit (Visit 1), a randomization visit (Visit 2), a treatment phase of 24 weeks and a 1-month follow-up. At screening (V1), after signing and dating the informed consent form, the patients' demographic data, lifestyle information, surgical history and physical abnormalities will be assessed and recorded. Patients will be instructed not to alter their hairstyle or dye their hair during the study.

	Patients will undergo a full physical examination including the measurement of vital signs (BP, HR), body weight (BW) and height. The patients will be questioned about previous/concomitant pharmacological medications. Then, the local Investigator will perform the clinical diagnosis of mild to moderate vertex hair loss (grade III vertex, IV and V of the modified Norwood/Hamilton Scale). Once the patient fulfils all the inclusion/exclusion criteria, the investigator will take digital photographs (for global assessment) of patients. Global photographs will be taken at screening, at V4 (after 12 weeks of treatment) and at the end of treatment (at Week 24) or at the Early Termination Visit (ETV). Standardized color global photographs of the vertex scalp will be taken with the head in a stereotactic positioning device. Before taking the global photographs, the patient's hair is combed away from the vertex bald spot as the entire balding area must be viewed. Global photographs will be taken prior to preparing the patient for macrophotography. For the macrophotography (V2, V5, V6 or at the ETV), a circular area approximately 1.9 cm in diameter is to be identified in the anterior leading edge of the vertex thinning area between 10 and 2 o'clock. The area will be clipped to approximately 1 mm in length. A small dot tattoo will be placed in the centre of the circle of the clipped hairs. Using the tattoo as a reference point, the circular area will be photographed and a 1 cm^2 circular area within the target area will be analysed. In case of any quality issues with global or macro photos, the patient may be requested to return to the site for reshoot until the images are considered evaluable. A self-administered Male Hair Growth Questionnaire (MHGQ) will be given to patients at V5 (Week 12) and V6 (Week 24), to subjectively measure their perception of hair growth. A Sexual Function Questionnaire (International Index of Erectile Function, IIEF-2) will be given to evaluate any changes in sexual function and activity, at Weeks 4, 8, 12, 24 and 28 or at the ETV. A blind assessor will assess change in hair growth from Baseline to Week 12 and from Baseline to Week 24. An investigator assessment of change in patient hair growth will be done from Baseline to Week 12 and from Baseline to Week 24. Blood and urine samples will be taken at V1, V4 (Week 8) and at the end of treatment (Week 24 or at the ETV) to perform safety laboratory tests (biochemistry, haematology and urinalysis). At all visits (except the screening

	visit) blood samples will also be collected to measure CCI [redacted]. Safety will be monitored throughout the whole study period by recording any adverse event occurrence. Vital signs and weight will be measured at screening V1, Week 24 and Week 28 (or at the ETV); the height will be measured only at screening. Local tolerability will be evaluated from Week 4 (V3) to Week 28 (V7, End of study), or at the ETV, by means of severity scores for skin irritation. Patients who terminate prematurely the study will be asked to complete the early termination visit for the final assessments. Patients who are discontinued from the study will not be replaced. The duration of the entire study for each patient is about 29 weeks.
Criteria for evaluation	**Efficacy Measurements** The change from baseline in the Target Area Hair Count (TAHC) within 1 cm^2 at the Vertex at week 12 and 24, will be determined by a validated computer assisted image analysis method. The change from baseline in the Target Area Hair Width (TAHW) in the vertex at Weeks 12 and 24 will be determinate by the local investigators and by the blind assessor. The local investigators will assess change in hair growth from baseline to Week 12 and Baseline to Week 24, using a 7-point scale. The evaluation will be done by the Investigator or designee, by comparing the global vertex view photograph obtained at Baseline with the patient's actual scalp at Week 12 and Week 24. This assessment will made separately based on changes to the vertex view. The change from Baseline in hair growth will be assessed using the following 7-point scale: -3 = greatly decreased, -2 = moderately decreased, -1 = slightly decreased, 0 = no change, +1 = slightly increased, +2 = moderately increased, +3 = greatly increased. A blind assessor will assess change in hair growth from Baseline to Week 12 and Baseline to Week 24, using a 7-point scale: greatly decreased (-3), moderately decreased (-2), slightly decreased (-1), no change (0), slightly increased (1), moderately increased (2), and greatly increased (3). This assessment will be performed by comparing the global photographs obtained at Baseline with those subsequently obtained at Weeks 12 and 24. MHGQ will be administered at Weeks 12 and 24 or at the ETV.

Participant satisfaction with hair appearance will be assessed by a few questions, covering many specific aspects of male-pattern hair loss.

Safety Measurements

Adverse Events

All adverse events (AEs) experienced by a patient during the entire study period must be recorded in the patient's eCRF. An AE is any untoward occurrence for a patient undergoing a clinical investigation while receiving a medicinal product, irrespective of whether or not the untoward occurrence is considered related to the product. Any clinically significant changes in vital signs or laboratory test results should also be recorded as an AE.

Physical examination

A complete physical examination will be performed at the screening visit (V1), at Week 24 (V6 – End of treatment), at Week 28 (V7 – End of study) or at the ETV. Height (at screening only) and weight will also be measured.

Vital signs

Sitting systolic and diastolic blood pressure from the same arm, heart rate (after 5 minutes sitting) and temperature will be measured at the screening visit (V1), at Week 24 (V6 – End of treatment), at Week 28 (V7 – End of study) or at the ETV.

Safety Laboratory Test

Safety laboratory tests will be performed at Screening (V1), at Week 8 (V4) and at Week 24 (V6 – End of treatment) or at the ETV.

Any abnormal laboratory parameter at any study visit should be followed until the value normalizes or the aetiology is identified.

The safety laboratory tests will include: haematology, clinical chemistry and urinalysis. The following parameters will be measured:

Haematology: haemoglobin concentration, haematocrit, red blood cell count and white blood cell count with differential and platelet count.

Clinical Chemistry: transaminases (AST, ALT), total serum bilirubin (direct and indirect), γ-GT, alkaline phosphatase, serum creatinine, blood urea nitrogen, uric acid, glucose, potassium, calcium, chloride, testosterone, protein and albumin.

Urinalysis: protein content, glucose content, haemoglobin content, WBC content in sediment, RBC content in sediment, crystals content in sediment, casts content in sediment.

	CCI [redacted] Local Tolerability Local tolerability at the application site will be assessed to rate the severity of any skin irritation from Week 4 (V3) to Week 28 (V7, End of study), or at the ETV, through a Severity Score for Skin Irritation. Assessment of potential Sexual Dysfunction The assessment of the potential sexual dysfunction will be done from Week 4 (V3) to Week 28 (V7, End of study), or at the ETV, through a Sexual Dysfunction Questionnaire (IIEF-2).
Inclusion criteria	• Written informed consent before starting any study related procedures; • Men 18 to 40 years of age; • Men with mild to moderate vertex male pattern hair loss according to a modified Norwood/Hamilton classification scale (III vertex, IV or V); • Patients willing to have a tattoo in the target area; • Outpatients; • Ability to comprehend the full nature and purpose of the study, including possible risks and side effects; • Ability to co-operate with the Investigator and to comply with the requirements of the entire study.
Exclusion criteria	• Clinically relevant abnormal skin scalp findings which could interfere with the aim of the study; in particular, abrasion, actinic keratosis, inflammatory disorders or any other abnormality; • Patients who had had hair transplant surgery or hair weaving; • Clinically relevant abnormal laboratory values indicative of physical illness; • Ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study; • History of local infections of skin and subcutaneous tissues of the head in the 3-months period before the trial inclusion;

	• Relevant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases, that may interfere with the aim of the study; • Suspicion of malignancy, including prostate cancer; • History of infertility or difficulty fathering children; • Patients who wish to conceive children during the study or whose sexual partner(s) is pregnant; • Patients with active seborrheic dermatitis; • History of varicocele; • Concurrent use of systemic corticosteroids, topical corticosteroids in the balding area studied, anabolic steroids, or over-the-counter "hair restorers"; • Use of the following drugs with antiandrogenic properties within 6 months of study entry: flutamide, cyproterone acetate, estrogen, progesterone, cimetidine, spironolactone or ketoconazole; • Patients who had been treated with any of the following drugs within the past year: minoxidil (topical or oral), zidovudine, cyclosporine, diazoxide, phenytoin, systemic interferon, psoralens, streptomycin, penicillamine, benoxaprofen, tamoxifen, phenothiazines or cytotoxic agents; • Use of finasteride or dutasteride within previous 12 months; • Light or laser treatment of scalp within previous 3 months; • Participation in the evaluation of any drug for 3 months before this study, calculated from the first day of the month following the last visit of the previous study; • History of drug, alcohol [>2 drinks/day defined according to USDA Dietary Guidelines 2010], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day).
Randomization	The randomization process will be carried-out under blinded conditions, using a web-based system through an IXRS vendor. Eligible patients will be randomized to one treatment group according to a permutated blocks random code generated by the IXRS vendor.
Study procedures	Seven clinical examinations are planned for each patients, as follows: - Screening, Visit 1 (Week -2) - Randomization: Visit 2 (Day 1) - Treatment: Visit 3, 4, 5 and 6 (Week 4, 8, 12 and 24) - Follow-up period: Visit 7 (Week 28)
Not allowed medications	Finasteride is metabolized primarily via, but does not affect, the cytochrome P450 3A4 system. Although the risk for finasteride to affect the pharmacokinetics of other drugs is estimated to be small, it is probable that

	inhibitors and inducers of cytochrome P450 3A4, will affect the plasma concentration of finasteride. The use of systemic corticosteroids, topical corticosteroids in the balding area studied, anabolic steroids, or over-the-counter "hair restorers" is not allowed. The use of any of the following drugs - flutamide, cyproterone acetate, oestrogen, progesterone, cimetidine, spironolactone, or ketoconazole, minoxidil (topical or oral), zidovudine, cyclosporine, diazoxide, phenytoin, systemic interferon, psoralens, streptomycin, penicillamine, benoxaprofen, tamoxifen, phenothiazines or cytotoxic agents - is not allowed for the entire duration of the trial.
Patient Diary	A study diary will be provided to each patient upon randomizing the patient at the randomization visit (V2) and will cover the entire study duration. It will be returned at the end of the study (V7) or at the ETV (if applicable). The patient will record the daily treatment administration (number of puffs and the administration hour), any concomitant medication (topical and/or systemic) during the study period and/or any experienced adverse event. The patient will be required to attend each study visit from V3 to V7 (or ETV) with his diary in order to check with the Investigator any concomitant medication or any adverse event occurred, and the treatment compliance (only for V5, V6 or ETV). The Investigator will report the data on the eCRF. The data recorded in the diary will be considered source data.
Sample size	Group sample sizes of 144 patients randomized to P-3074 and 144 patients randomized to Placebo achieve 99% power to detect superiority using a one-sided, two-sample t-test with a significance level (alpha) of the test equal to 0,025. The margin of superiority, i.e. the distance above the reference (Placebo) mean that is required to be considered superior, is set to 41 hair count whilst the true difference between P-3074 and Placebo is assumed to be 82 hair count and is estimated assuming a mean change from baseline to 6 months in hair count equal to -14 and +68 in Placebo and P-3074 respectively. The data are drawn from populations with standard deviations of 88 in P-3074 and 75 in Placebo. In addition, approximately 72 patients will be randomised to the active comparator arm (oral finasteride 1 mg). Group sample sizes of 144 patients randomized to P-3074 and 72 patients randomized to oral Finasteride achieve a power close to one to reject the null hypothesis of equal serum CCI inhibition assuming a mean serum CCI inhibition equal to 45,6 and 26,2 in oral Finasteride and P-3074 respectively with a standard deviation for both groups of 19,0 (2) and with a significance level (alpha) of 0,050 using a two-sided two-sample equal-variance t-test. Assuming an attrition rate equal to 20%, the total number of patients should be no less than 450 patients randomized to P-3074, Placebo and oral Finasteride in

	a 2:2:1 allocation ratio. All computations were performed using PASS 13 Software.
Study Population	All Randomized Population: all enrolled patients who are randomized to a treatment group. Safety Population: all randomized patients who receive at least one application of the investigational drug. Intention To Treat (ITT) Population: all patients who will have measurements both at baseline and on treatment. Per Protocol Population: all patients in the ITT population • who did not take forbidden medications; • who complete the entire study without any major protocol violations. Analyses done on the Per Protocol will be considered supportive. CCI [redacted]
Statistical Methods	The primary efficacy variable, i.e. the change in the hair count from baseline, will be analysed using the SAS PROC MIXED procedure. The null hypothesis to be tested will be that there is no difference between P-3074 and placebo in the mean change from baseline for the hair count at Visit 6. The alternative hypothesis will be that there is a difference between P-3074 and placebo in the mean change from baseline for the hair count at Visit 6. The primary efficacy data will be fitted by a mixed linear model with treatment (P-3074 or placebo), centre, visit and the treatment-by-visit interaction as fixed effects and baseline as covariate. The variance-covariance matrix of unstructured form will be used in order to model the correlation, within each patient, between the two repeated measurements (over the post-baseline visits). Maximum likelihood estimates of the treatment mean difference computed at visit 5 together with the associated two-sided 95% CI will be calculated by resorting to the Newton-Raphson algorithm implemented in the SAS® Mixed Procedure. A two-sided test with a p-value less than or equal to 0.05 will be considered statistically significant. The secondary efficacy variables, MHGQ, Blind assessor and local investigator assessments of patient hair growth/loss, will be analysed using the same mixed linear model for repeated measures (MMRM) employed for the analysis of primary efficacy data.

LIST OF ABBREVIATIONS

γ-GT	γ-Glutamyl transpeptidase
ADR	Adverse Drug Reaction
AE	Adverse Event
AGA	Androgenetic Alopecia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BLQL	Below Lower Quantification Limit
BMI	Body Mass Index
BP	Blood Pressure
BW	Body Weight
CA	Competent Authority
CPL	Clinical Project Leader
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CS	Clinically significant
DHT	Dihydrotestosterone
EC	Ethics Committee
eCRF	Electronic Case Report Form
ETV	Early Termination Visit
FDA	Food and Drug Administration
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	Heart Rate
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IIEF-2	International Index of Erectile Function
IRB/IEC	Institutional Review Board/Independent Ethics Committee
LPLV	Last Patient Last Visit
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MHGQ	Male Hair Growth Questionnaire
MPB	Male Pattern Baldness
N	Normal
NC	Not Calculated
NCS	Not Clinically Significant
o.d.	Once a day
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
SAE	Serious Adverse Event
SD	Standard Deviation

SOC	System Organ Class
SOP	Standard Operating Procedure
SDTM	Study Data Tabulation Model
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAHC	Target Area Hair Count
TAHW	Target Area Hair Width
TEAE	Treatment-Emergent Adverse Event
V	Visit

1 Introduction

1.1 Background

Androgenetic alopecia (AGA or male pattern baldness) is a genetically determined disorder due to an underlying susceptibility of hair follicles to androgenic miniaturization[1], affecting more than 50% of men under 50 years of age[2]. Both genetic and environmental factors play a role in its development, and many aetiologies remain unknown. The basis of androgenetic alopecia in men is a progressive decrease in the density of terminal hairs and a concurrent increase in the density of short, non-pigmented hairs.

AGA is known to depend on the presence of the androgen dihydrotestosterone (DHT) and on genetic predisposition[3]. DHT is formed by testosterone through the action of the type II 5α-reductase enzyme. In the scalp of men suffering from AGA, an increased rate of conversion of testosterone into DHT has been detected[4].
The basis of androgenetic alopecia in men is a progressive decrease in the density of terminal hairs and a concurrent increase in the density of short, non-pigmented hairs.

The clinical manifestation and severity of androgenetic alopecia are influenced by the distribution in the scalp of the androgens receptors and androgens metabolising enzymes[5].
The Hamilton-Norwood scale has been developed to grade AGA in males: it ranges from stages I to VII[6] (Appendix 1).

Medically, AGA is viewed as a relatively mild dermatological condition. However, as hair is an important component of identity and self-image, patients with AGA may experience a distorted body image and negative feelings of social disadvantages including depression, low self-esteem, an altered self-image, and less frequent social engagement. Notably, even clinically imperceptible hair loss has been correlated with a decreased quality of life (QoL)[7].

Treatment of androgenetic alopecia has the main aim of preventing further progression of the disease and of reversing the miniaturisation (promoting re-growth of hair). Although the market offers a wide choice of treatments, to date there are only two effective drugs authorised by the FDA for the treatment of male pattern baldness, i.e. minoxidil and finasteride 1 mg tablet.
In the androgenetic alopecia, the target is the inhibition of the type II 5α-reductase isoenzyme present into the scalp to reverse the alopecia signs and symptoms avoiding the inhibition of the plasmatic type II 5α-reductase isoenzyme.

Generally, 1 mg oral finasteride is well tolerated with long-term use, although evidence from preclinical and clinical studies points to significant adverse effects of 5α-reductase inhibitors on health and overall quality of life. Sexual adverse effects have been consistently reported[8-10]. In multiple double-blind randomised controlled trials, 1 mg oral finasteride has been associated with a significant amount of sexual dysfunctions, including decreased libido (1.8%), erectile dysfunction (1.3%), ejaculation disorders (0.8 – 1.2%) and orgasm disorders (0.4%)[1,10]. However, the use of 1 mg oral finasteride for the treatment of male pattern hair loss has recently been the

focus of media and internet attention for potential irreversible sexual dysfunction and severe depression. Reports of potential irreversible sexual dysfunction and severe depression do raise concerns about the safety of 1 mg oral finasteride[11,12]. It is likely that a lack of plasmatic DHT or another 5 alpha-reduced hormone is responsible for the reported decrease in libido and/or orgasm[13].

If a limited, variable amount of blood reaches the scalp, only a limited amount of circulating finasteride is able to reach the bulbs. As a consequence, we have to administer an exaggerated dose of oral finasteride to obtain at least a partial inhibition of the type II 5α-reductase isoenzyme (and thus blocks the conversion of testosterone to dihydrotestosterone) at scalp level; on the other hand this oral load produces a very high inhibition of serum DHT, leading to the well-known side effects of oral finasteride.

1.2 Finasteride

Finasteride is a synthetic anti-androgen compound that acts by inhibiting type II 5α-reductase. By blocking this enzyme, finasteride blocks the conversion of testosterone into the more powerful androgen DHT. This reduces androgenic activity in the scalp, treating hair loss at its hormonal source. Its clinical efficacy was demonstrated in well-controlled clinical trials.

A double-blind, randomised, placebo controlled, clinical trial conducted in 249 men orally treated once a day for 42 days with placebo or different doses of finasteride demonstrated that finasteride treatment reduced DHT levels in both serum and scalp, with a dose-response effect[14]. On the basis of the data of this trial, it was concluded that the effect of finasteride on scalp DHT is due to its effect on both follicular DHT levels as well as serum DHT levels. Similar results were obtained in a previous preliminary trial that evaluated the effects of finasteride on scalp skin DHT levels in balding versus non-balding areas of scalp skin[15].

Clinical studies with oral finasteride were conducted in 1879 men aged 18 to 41 with mild to moderate, but not complete, vertex hair loss and/or frontal/mid-area hair loss. In the two studies in men with vertex hair loss (n=1553), 290 men completed a 5-year treatment with finasteride vs. 16 patients on placebo. In these two studies, efficacy was assessed by the following methods: hair count in a representative area of scalp, patient self-assessment questionnaire, investigator assessment using a seven-point scale, and photographic assessment of standardised paired photographs by a blinded expert panel of dermatologists using a seven-point scale.

In long-term 5-year studies, men treated with finasteride improved their condition, compared to both baseline and placebo beginning as early as 3 months, as determined by both the patient and investigator assessments of efficacy. With regard to hair count, the primary endpoint in these studies, increases compared to baseline were demonstrated starting at 6 months (the earliest time point assessed) through to the end of the study. In men treated with finasteride these increases were greatest at 2 years and gradually declined thereafter to the end of 5 years, whereas hair loss in the placebo group progressively worsened compared to baseline over the entire 5-year period.

In finasteride treated patients, a mean increase from baseline of 88 hairs [p <0.01; N=433] in the representative area, was observed at 2 years. An increase from baseline of 38 hairs [p <0.01; N=219] was observed at 5 years, compared with a decrease from baseline of 50 hairs [p <0.01; N=47] at 2 years and a decrease from baseline of 239 hairs [p <0.01; N=15] at 5 years in patients who received placebo. Standardized photographic assessment of efficacy demonstrated that 48% of men treated with finasteride for 5 years were rated as improved, and an additional 42% were rated as unchanged. This is in comparison to 25% of men treated with placebo for 5 years who were rated as improved or unchanged. These data demonstrate that a treatment with Finasteride for 5 years resulted in a stabilisation of the hair loss that occurred in men treated with placebo.

Van Neste et al (2000) showed that a treatment with 1 mg oral finasteride for 48 weeks led to a net improvement in total hair count of 17.3 ± 2.5 hairs (8.3% ± 1.4%) in a target area of 1 cm^2, compared with placebo ($p < 0.001$). This effect is already present after six months of treatment and is maintained for the following six months[16].

The first study conducted using a topical finasteride formulation (0.005% solution applied twice daily for 16-months) showed a progressive decrease in the rate of hair loss in the finasteride group compared to placebo, starting from the 6th month of treatment[17]. A second trial compared the effects of a topical finasteride 1% gel, applied twice daily, with finasteride tablets 1 mg and showed that the therapeutic effect of finasteride gel and tablets were relatively similar to each other[18].

Considering the well-known efficacy of oral finasteride but also a concerning side effect profile, Polichem decided to develop a formulation of finasteride 0.25% in Polichem patented Hydroxypropyl Chitosan Technology (P-3074), that allows finasteride to act on the follicular portion[19] to promote a cutaneous depot of finasteride in the region of hair bulbs, thus minimizing systemic absorption even after repeated treatments[20]. The scope was to achieve consistent inhibitory effects on scalp DHT inhibition, minimizing the systemic effect on serum.

A parallel-group, pharmacokinetic and pharmacodynamic study in male volunteers with androgenetic alopecia[3] showed that the new solution of P-3074 (finasteride 0.25%) administered b.i.d. topically on the scalp for 1 week decreased the serum concentration of DHT to levels comparable to those obtained with the reference finasteride mg tablet administered o.d., albeit finasteride rate and extent of absorption were about 15 and 9 times lower for the topical solution than for the tablet. Serum DHT was reduced by approximately 70 – 75% after administration of P-3074 (finasteride 0.25%) topical solution b.i.d. and by approximately 62 – 72% after administration of 1 mg tablet o.d, confirming a considerable and similar inhibition of DHT with the two formulations.

A more recent pharmacodynamic (PD) study in male volunteers with androgenetic alopecia[21], aimed at comparing two dose regimens (o. d. and b.i.d.) of 1 mL P-3074 (finasteride 0.25%) topical solution (Polichem S.A. Switzerland), demonstrated that once daily applications (i.e. 1 mL/day) for one week exerts already a maximal effect on scalp DHT concentrations (approx. 70% inhibition), suggesting that the final dose of topical solution applied to the scalp could be

significantly lower than the doses used in the two PK and PD studies in healthy volunteers described above.

The safety profile of finasteride, administered as multiple doses of finasteride 0.25% topical solution b.i.d. or oral finasteride 1 mg tablet o.d. for 1 week, in the above mentioned study, was favourable. Local tolerability of P-3074 (finasteride 0.25%) topical solution b.i.d. was excellent, with no signs or symptoms detected at the application site.

A following dose-finding study[21] evaluated therefore whether P-3074 lower doses (100, 200, 300 and 400 µL) vs vehicle, could achieve consistent inhibitory effects on scalp DHT inhibition (accepted as surrogate end-point), minimizing the systemic effect on serum.
The doses of 100 and 200 µL P-3074 resulted in a -47/-52% scalp DHT reduction, similar to the 300 and 400 µL doses (i.e. -37/-54%). A -5.6% inhibition was observed for the vehicle. Serum DHT was reduced by only -24/-26% with 100 and 200 µL P-3074 and by -44/-48% with 300 and 400 µL P-3074. In conclusion, at doses up to 200 µL, P-3074 applied topically, allowed to significantly decrease DHT in scalp and only marginally in serum potentially minimizing the untoward side-effects linked to a systemic DHT reduction.

1.3 Rationale

DHT inhibition in the scalp was accepted as robust surrogate end-point of finasteride efficacy for the treatment of men with male pattern hair loss (androgenetic alopecia) to increase hair growth and prevent further hair loss. On the basis of the results of the Phase II pharmacodynamic studies in male volunteers[21], the present pivotal Phase III study has been designed to determine the efficacy of P-3074 in terms of increasing of total hair count, after a 24-week treatment, vs vehicle, in men with male pattern baldness.

1.4 Risk and benefits

Potential risks of multiple dose topical applications of finasteride are expected to be limited to the known drug-related adverse experiences of the substance, as reported for the product available on the market, or less considering that treatment with the investigational product will be 6 months as opposed to the long term treatment reported in the literature or clinical practice with the marketed 1 mg tablet for androgenetic alopecia or the 5 mg finasteride tablet indicated for benign prostatic hyperplasia, for which safety data are available.

Reported finasteride side effects during oral treatment are mainly linked to the sexual impairments[22] and are:

- decrease of libido, reported in ≥ 1% of men treated with finasteride 1 mg (frequency: finasteride 1.8%, placebo 1.3%);
- erectile dysfunction (frequency: finasteride 1.3%, placebo 0.7%);
- decreased volume of ejaculate (frequency: finasteride 0.8%, placebo 0.4%).

Other adverse reactions reported during clinical trials and/or post-marketing are the following:

- hypersensitivity reactions, including rash, pruritus, urticaria and swelling of the lips and face;
- severe depression;
- palpitation;
- increased hepatic enzymes;
- breast tenderness and enlargement;
- testicular pain, infertility.

In published clinical trials, a total of 97 patients have been treated with finasteride topical formulations up to 16-months, and no patient experienced any local or systemic untoward effect. The tolerability of the treatment was good[17,18].

The doses used in this trial are expected to be safe and tolerable to the patients on the basis of the known safety profile of finasteride (oral marketed formulation) and of previous studies performed with the same formulation[3,21]: in both studies the safety profile of finasteride 0.25% topical solution administered as multiple doses b.i.d. was favourable. Local tolerability was excellent with no signs or symptoms detected at the application site.

In the first PK study, three AEs were experienced by 3 of the 12 subjects randomised in the group treated with finasteride 0.25% topical solution: headache (2 subjects) and ALT increase (1 subject). All AEs were mild to moderate.

In the PD study, three TEAEs were reported by two subjects (one in the b.i.d. treatment group and two in the o.d. treatment group): ALT increase, pollakiuria and testicular pain. All TEAEs were of mild intensity.

In the dose-response study, 5 treatment-emergent AEs (TEAEs) occurred in 5 subjects (15.6%). The reported TEAEs were presyncope (2 events, 2 [6.3%] subjects overall), conjunctivitis, headache and oropharyngeal pain (for each TEAE: 1 event, 1 [3.1%] subject overall). All reported TEAEs were of mild intensity, were not deemed related to study treatment and resolved by the end of the study. No serious adverse events, other significant AEs or deaths occurred during the study. No clinically significant effects of the study treatments on blood pressure, heart rate, ECG or laboratory parameters were observed.

Overall, the safety data revealed the occurrence of adverse events of mild intensity, not deemed related to study treatment. Moreover, neither serious adverse events occurred, nor clinically significant effects of P-3074 on blood pressure, heart rate, ECG and other laboratory parameters were observed, confirming the excellent safety profile of P-3074[23].

2 Study objectives

The primary objective of this pivotal phase III study is to determine whether a daily treatment of 24 weeks with P-3074, increases hair count in men with MPB compared to the vehicle.

2.1 Primary end-point

- Hair growth assessed by Target Area Hair Count (TAHC) in the vertex at 24 weeks.

2.2 Secondary end-points

- Hair growth assessed by TAHC in the vertex at 12 Weeks;
- Target Area Hair Width (TAHW) in the vertex at Weeks 12 and 24;
- Patient assessment in Male Hair Growth Questionnaire (MHGQ) at Weeks 12 and 24;
- Investigator Assessment of Improvement from Baseline to Week 12 and from Baseline to Week 24, assessed for vertex;
- Blind Assessor Assessment of Improvement from Baseline to Week 12 and from Baseline to Week 24, assessed for vertex;
- Assessment of sexual function at every visit (Sexual Function Index);
- Assessment of adverse events (AEs) throughout the study;
- Assessment of the local tolerability by means of severity scores for skin irritation;

For the purpose of assessment of changes in hair growth by investigators and blind assessor screening visits (where global photos are taken) will act as baseline.

2.3 Exploratory end-points

- CCI [redacted]
- CCI [redacted].

3 Investigational Plan

3.1 Overall study design

This is a multicentre, randomized, double-blind, double-dummy, parallel-group, controlled study.

3.2 Randomization

All screened subjects will be assigned a unique number. The Investigator will maintain a list of these numbers and subject names to allow records to be found at a later date.

The randomisation list will be computer-generated by an IXRS vendor, using SAS Version 9.1.3 or higher (version will be stated in the final clinical study report). The randomization process will be carried-out under blinded conditions, using a web-based system through the IXRS vendor. The randomisation list will be attached to the final clinical study report.

Eligible patients will be randomized to one treatment group according to a permutated blocks random code generated by the IXRS vendor.
Randomization will be balanced in a ratio of 2:2:1 (A:B:C). Each participating site will receive treatments randomized in blocks in order to guarantee a balanced distribution. No stratification factor is considered.
Randomisation number will be given to the patients on study Day 1, and will be used to assign the treatment according to the randomisation list, as detailed above.
Eligible patients will be randomized to one of the three treatment groups as follows:

Group A: P-3074 o.d. + placebo of oral finasteride 1 mg o.d.
or
Group B: P-3074 Vehicle o.d. + placebo of oral finasteride 1 mg o.d.
or
Group C: oral finasteride 1 mg o.d. + P-3074 Vehicle o.d.

All patients randomised should topically apply P-3074 (or its Vehicle) in the morning to dry scalp only, and leave it in place for at least 6-8 hours (after that, the patient has to wash carefully the scalp with shampoo). In the same context, patients have to take in 1 mg oral finasteride (or its placebo) daily until the end of a 24-week treatment course (Visit 6). Therapy with P-3074 (or its Vehicle) has to be continued on a daily basis in order to maintain or increase the hair growth achieved. At Visits 3, 4, 5 and 6, the patient has to administer P-3074 (or its Vehicle) and to take the last capsule, not more than 1.5 hour before the sample collection.

3.3 Blinding

Both the investigator and the patients will not be aware of the treatment administered due to the double-blind, double-dummy design.

The randomization list will be generated by IXRS vendor and implemented in IXRS system. Additionally, IXRS vendor will generate treatment kit number list that will be provided to the drug supply vendor for the preparation of the treatment kits.

Neither the members of the clinical unit nor the CPL or the CRA/monitor will have access to the randomisation data or to the treatment kit number list. Upon DB lock, all subjects will be unblinded through IXRS.

The IXRS vendor will notify breaking of the randomisation list to the sponsor and CRO.

3.3.1 Emergency code and unblinding procedures

Unblinding of the code for specific patients will be fully documented in the source documents and in the CSR.

Unblinding may occur for emergency purposes only and when the unblinding result is needed for clinical management of the patient. Sponsor will not require or insist on being involved in the decision to unblind, stall or delay in any way the unblinding of trial subject treatment in emergency situations. The Investigator will be able to break the blind for an individual patient via IXRS according to the unblinding procedure or via code envelope supplied with each treatment kit.
If unblinding occurs without the knowledge of the Sponsor and/or designee, the Investigator must notify the Sponsor and/or designee as soon as possible and no later than 24 hours. All circumstances surrounding the premature unblinding must be clearly documented in the source records.
Any patient who is unblinded will be permanently discontinued from study treatment and should attend an early termination visit.

3.4 Discussion of design

The trial has been designed to determine whether a treatment of 24 weeks with P-3074, applied once daily onto the scalp of patients with androgenetic alopecia, increases hair count, compared to the vehicle.

Safety and tolerability will also be evaluated.
On the basis of the results of a previous study in male healthy volunteers (dose-response study)[21], suggesting that with o.d. application up to 4 puffs (200 µL=0.455 mg of finasteride) of P-3074, a maximal inhibitory effect on DHT level (at scalp level) was reached, the present phase III study aims at evaluating whether P-3074, applied onto the scalp, could exert an increasing in the hair count, after a 24-week treatment. Moreover, there is a safety purpose aimed at comparing the serum DHT inhibition and the finasteride exposure among the arms.

The doses used in the present study have been chosen according to the results of the previous phase IIa study that was aimed at evaluating which was the lower dose of P-3074, applied onto

the scalp, able to maintain the same inhibitory effect of oral finasteride on scalp DHT levels, minimizing the systemic effects on serum DHT.

The treatment period will last 24 weeks as the Van Neste paper showed a statistical significant increase of oral finasteride vs placebo, in the hair count already after 24 weeks of treatment[16].

A double-blind, double-dummy, parallel-group design has been chosen for the study to avoid any bias linked to the route of administration.

3.5 Study Flowchart

	Screening	Treatment Phase					Follow up Phase (End of Study)	Early Termination Visit
Visit	**Visit 1**	**Random Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	
	-Week 2	**Day 1± 5d**	**Week 4±3d**	**Week 8±3d**	**Week 12±3d**	**Week 24±3d**	**Week 28±3d**	
Patient's Informed Consent Form signature	X							
Demographic and habits information	X							
Physical examination§	X					X	X	X
Medical history/current diseases	X							
Prior and concomitant medication	X							
Vital signs	X					X	X	X
Check all Inclusion/exclusion criteria	X	X						
Enrolment	X							
Dispense patient's card	X							
Global Photograph	X				X	X		X
Investigator assessment	X*				X	X		X
Blind Assessor (entry eligibility)	X							
Blind Assessor (efficacy)	X*				X	X		X
Safety Laboratory examinations	X			X		X		X
Check record concomitant medication		X	X	X	X	X	X	X

CCI								
Macrophotography (hair count)		X			X	X		X
MHGQ Questionnaire					X	X		X
Sexual Dysfunction Questionnaire (IIEF-2)			X	X	X	X	X	X
Randomization		X						
Dispense study medication		X			X			
Collect / return study medication			X#	X#	X	X		X
Drug Application at site			X	X	X	X		
Drug Compliance					X	X		X
Dispense study diary to the patient		X						
Check of patient's study diary			X	X	X	X	X	X
Collect / return study diary							X	X
Severity score for skin irritation			X	X	X	X	X	X
Record AEs		X	X	X	X	X	X	X

***** Assessment of hair growth will be performed by investigator and blinded assessor at visits 5 and 6/EOT using global photographs as baseline

[redacted] CCI [redacted]

§ Height will be measured only at screening

4 STUDY POPULATION

4.1 Target population

Not less than 450 male patients, 18-40 year-old inclusive, with mild to moderate vertex male pattern hair loss, according to a modified Norwood/Hamilton classification scale (III vertex, IV or V), will be recruited in the trial.

4.2 Inclusion criteria

To be enrolled in this study, patients must fulfil all of these criteria:

1. Written informed consent before starting any study related procedures;
2. Men 18 to 40 years of age;
3. Men with mild to moderate vertex male pattern hair loss according to a modified Norwood/Hamilton classification scale (III vertex, IV or V);
4. Patients willing to have a tattoo in the target area;
5. Outpatients;
6. Ability to comprehend the full nature and purpose of the study, including possible risks and side effects;
7. Ability to co-operate with the Investigator and to comply with the requirements of the entire study.

4.3 Exclusion criteria

Patients meeting any of these criteria at screening will not be enrolled in the study:

1. Clinically relevant abnormal physical findings which could interfere with the aim of the study; in particular, skin damage such as abrasion, actinic keratosis or any abnormal findings in the scalp;
2. Patients who had had hair transplant surgery or hair weaving;
3. Clinically relevant abnormal laboratory values indicative of physical illness;
4. Ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study;
5. History of local infections of skin and subcutaneous tissues of the head in the 3-month period before the trial inclusion;
6. Relevant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases, that may interfere with the aim of the study;
7. Suspicion of malignancy, including prostate cancer;
8. History of infertility or difficulty fathering children;
9. Patients who wish to conceive children during the study or whose sexual partner(s) is pregnant;

10. Patients with active seborrheic dermatitis;
11. History of varicocele;
12. Concurrent use of systemic corticosteroids, topical corticosteroids in the balding area studied, anabolic steroids, or over-the-counter "hair restorers";
13. Use of the following drugs with antiandrogenic properties within 6 months of study entry: flutamide, cyproterone acetate, estrogen, progesterone, cimetidine, spironolactone, or ketoconazole;
14. Patients who had been treated with any of the following drugs within the past year: minoxidil (topical or oral), zidovudine, cyclosporine, diazoxide, phenytoin, systemic interferon, psoralens, streptomycin, penicillamine, benoxaprofen, tamoxifen, phenothiazines or cytotoxic agents;
15. Use of finasteride or dutasteride within previous 12 months;
16. Light or laser treatment of scalp within previous 3 months;
17. Participation in the evaluation of any drug for 3 months before this study, calculated from the first day of the month following the last visit of the previous study;
18. History of drug, alcohol [>2 drinks/day defined according to USDA Dietary Guidelines 2010], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day).

4.3.1 Disallowed treatments

Finasteride is metabolized primarily via, but does not affect, the cytochrome P450 3A4 system. Although the risk for finasteride to affect the pharmacokinetics of other drugs is estimated to be small, it is probable that inhibitors and inducers of cytochrome P450 3A4, will affect the plasma concentration of finasteride.

The use of systemic corticosteroids, topical corticosteroids in the balding area studied, anabolic steroids, or over-the-counter "hair restorers" is not allowed.

The use of any of the following drugs - flutamide, cyproterone acetate, oestrogen, progesterone, cimetidine, spironolactone, or ketoconazole, minoxidil (topical or oral), zidovudine, cyclosporine, diazoxide, phenytoin, systemic interferon, psoralens, streptomycin, penicillamine, benoxaprofen, tamoxifen, phenothiazines or cytotoxic agents - is not allowed for the entire duration of the trial.

4.3.2 Discontinuation criteria

Patients who withdraw their consent, those with clinically relevant deterioration of the scalp baldness, non-compliant patients and patients who develop clinically significant adverse events during the study may be discontinued from the study. Patients withdrawn from the trial will not be replaced.

4.3.3 Behaviour with sexual partners

During the whole study period, active sexual patients have to use any reliable contraceptive method (mechanical barrier or oral contraceptive).
Moreover, childbearing women should avoid to get in contact with the treated target area of the scalp.

5 STUDY SCHEDULE

The schedule of the study is summarised below.

5.1 Study visits and procedures

Each study patient will undergo 7 visits.
The study duration will last about 30 weeks. A written informed consent will be obtained before any study assessment or procedure.
The first patient first visit (FPFV) is defined as the 1st visit performed at one of the clinical centre by the 1st screened patient. The last patient last visit (LPLV) is defined as the last visit performed at one of the clinical centre by the last patient, i.e. the last visit foreseen by the study protocol, independently of the fact that the patient is a completed or a withdrawn patient.
The following phases, visits and procedures will be performed:

- **Screening**

  - Screening: Visit 1 (-2 weeks)

- **Randomization**

  - Randomization: Visit 2 (Day 1 +/- 5 days)

- **Interventional phase**

  - Treatment: Visit 3, 4, 5 and 6 (Weeks 4, 8, 12 and 24)

- **Final phase**

  - Early termination visit (ETV). In case of early discontinuation, discontinued patients will undergo an ETV;

  - Follow-up period: Visit 7 (Week 28)

Visit	Day	Procedures/Assessments
Visit 1	*-2 Weeks*	➢ Explanation to the patient of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number ➢ Dispense patient card ➢ Demographic data and life style recording ➢ Medical/surgical history ➢ Previous/concomitant medications ➢ Full physical examination (weight, height, vital signs and physical abnormalities) ➢ Laboratory analyses: haematology, blood chemistry, urinalysis ➢ Evaluation of Inclusion/Exclusion criteria for eligibility ➢ Global Photograph ➢ Investigator & blind assessor assessment ➢ AE monitoring
Visit 2	*Day 1*	➢ Check concomitant medication ➢ [redacted] ➢ [redacted] ➢ Hair count macrophotography – baseline evaluation ➢ Inclusion/Exclusion criteria for eligibility ➢ Randomization ➢ Dispense study medication ➢ Dispense study diary ➢ AE monitoring
Visit 3	*Week 4*	➢ Return study medication for application at site ➢ [redacted] ➢ [redacted] ➢ Severity score for skin irritation ➢ Check of patient diary ➢ Sexual Dysfunction Questionnaire (IIEF-2) ➢ AE monitoring and concomitant medications
Visit 4	*Week 8*	➢ Return study medication for application at site ➢ Laboratory analyses: haematology, blood chemistry, urinalysis ➢ [redacted] ➢ [redacted] ➢ Sexual Dysfunction Questionnaire (IIEF-2) ➢ Severity score for skin irritation ➢ Check of patient diary ➢ AE monitoring and concomitant medications

Visit 5	*Week 12*	➢ Return study medication for application at site ➢ [redacted] ➢ [redacted] ➢ Global Photograph & hair count macrophotography ➢ Investigator & blind assessor assessment ➢ MHGQ questionnaires ➢ Sexual Dysfunction Questionnaire (IIEF-2) ➢ Severity score for skin irritation ➢ Study drug collection and new dispensing ➢ Drug Compliance ➢ Check of patient diary ➢ AE monitoring and concomitant medications
Visit 6	*Week 24*	➢ Return study medication for application at site ➢ Physical examination (weight, vital signs and physical abnormalities) ➢ Laboratory analyses: haematology, blood chemistry, urinalysis ➢ [redacted] ➢ [redacted] ➢ Global Photograph & hair count macrophotography ➢ Investigator assessment ➢ MHGQ questionnaires ➢ Sexual Dysfunction Questionnaire (IIEF-2) ➢ Study drug collection ➢ Drug Compliance ➢ Severity score for skin irritation ➢ Checking of patient diary ➢ AE monitoring and concomitant medications
Visit 7 **FU Visit**	*Week 28*	➢ Physical examination (weight, vital signs and physical abnormalities) ➢ Sexual Dysfunction Questionnaire (IIEF-2) ➢ [redacted] ➢ [redacted] ➢ Collection & checking of patient diary ➢ Severity score for skin irritation ➢ AE monitoring and concomitant medications
ET Visit	-	➢ Physical examination (weight, vital signs and physical abnormalities) ➢ Laboratory analyses: haematology, blood chemistry, urinalysis ➢ [redacted] ➢ [redacted] ➢ Global and hair count macrophotography ➢ Investigator assessment ➢ MHGQ questionnaires ➢ Sexual Dysfunction Questionnaire (IIEF-2) ➢ Study drug collection ➢ Drug Compliance check ➢ Severity score for skin irritation ➢ Collection & checking of patient diary ➢ AE monitoring and concomitant medications

In case of any quality issue with global or macro photos, the patient may be requested to return to the site for reshoot until the images are considered evaluable.

6 Efficacy Procedures

6.1 Photography Evaluation

Once the patient fulfils all the inclusion/exclusion criteria, the investigator will take digital photographs (for global and macrophotography assessment) of patients.

Global photographs will be taken at screening, at V5 (after 12 weeks of treatment), and at the end of treatment (at week 24) or at the ETV. Global photographs will be taken prior to preparing the patient for macrophotography. Standardized color global photographs of the vertex scalp will be taken with the head in a stereotactic positioning device. Before taking the global photographs, the patient's hair is combed away from the vertex bald spot as the entire balding area could be viewed.

The change from baseline in the target area hair count within a 1 cm^2 of baldness area at week 24, will be assessed by macrophotographic techniques analysis.

After global photographs are taken the investigator has to select a target area in the anterior leading edge of the vertex thinning area between 10 and 2 o'clock. Using a plastic template, approximately 1.9 cm diameter the area will be clipped to approximately 1 mm in length. A small dot tattoo will be placed in the centre of the circle of the clipped hairs. Using the tattoo as a reference point, the circular area will be photographed and a 1 cm^2 circular area within the target area will be analysed. The procedures will be detailed in an external manual.

6.2 Investigator assessment

The local investigator will assess change in hair growth from baseline to Week 12 and from Baseline to Week 24, using a 7-point scale. The evaluation will be done by the Investigator or designee, by comparing the global vertex view photograph obtained at baseline visit with the patient's actual scalp at Week 12 and Week 24. This assessment will made separately based on changes to the vertex view.

For the purpose of assessment of changes in hair growth by investigators and blind assessor screening visits (where global photos are taken) will act as Baseline.

The change from Baseline in hair growth will be assessed using the following 7-point scale: -3 = greatly decreased, -2 = moderately decreased, -1 = slightly decreased, 0 = no change, +1 = slightly increased, +2 = moderately increased, +3 = greatly increased.

6.3 Blind Assessor

An independent blinded assessor will be responsible to evaluate, under blinded conditions, the screening global photographs of the target area for all patients. (S)he will evaluate the eligibility

of each patient according to the clinical inclusion criteria. The independent blinded assessor will assess the change of the hair growth from baseline to Week 12 and from baseline to Week 24, using a 7-point scale: greatly decreased (-3), moderately decreased (-2), slightly decreased (-1), no change (0), slightly increased (1), moderately increased (2), and greatly increased (3).

This assessment will be performed by comparing the global photographs obtained at screening visit with those subsequently obtained at Weeks 12 and 24.

6.4 Quality of Life Questionnaire

Patients have to assess their scalp hair using a validated, self-administered Male Hair Growth Questionnaire (MHGQ), consisting of 4 questions in the patient's language on treatment efficacy and 3 questions on satisfaction with appearance[24].

The questionnaire will be administered to each eligible patient at Weeks 12 and 24, V5 and V6 respectively or at the ETV, to subjectively measure their perception of hair growth.

Participant satisfaction with hair appearance/growth will be assessed by a few questions.

A Sexual Functioning Questionnaire (IIEF-2)[25] will be administered to all recruited patients at Weeks 4, 8, 12, 24 and 28 or at the ETV.

The Investigator will report the data on the eCRF. The data recorded in the QoL questionnaires will be considered the source document.

6.5 Patient diary

A study diary will be provided to each patient upon randomizing the patient at the randomization visit and will cover the entire study duration. It will be returned at the end of the study (V7) or at the ETV (if applicable).
The patient will record the daily treatment administration (number of puffs and administration hour), any concomitant medication (topical and/or systemic) during the entire study period and/or any experienced adverse event. The patient will be required to attend each study visit with his diary in order to check with the Investigator the treatment compliance and any concomitant medication or any adverse event occurred. The Investigator will report the data on the eCRF. The data recorded in the diary will be considered source data.

7 Safety Procedures

7.1 Physical examination

Full physical examination will be performed at Visit 1, at Week 24 and at Week 28/ETV. Information about the physical examination will be recorded by the investigator. Any abnormalities will be recorded as well.

7.1.1 Body weight

Body weight (BW) will be recorded at Visit 1, at Week 24 and at Week 28/ETV.
Patients will be weighed (kg) lightly clothed without shoes. Height will be measured at screening only and BMI will be recorded. BMI will be calculated as weight [kg]/(height [m] x height [m]).

7.1.2 Vital signs

Patients' blood pressure (BP), heart rate (HR) and temperature will be measured by the investigator or his/her deputy after 5 min at rest in the sitting position at Visit 1, at Week 24 and at Week 28/ETV.

7.2 Clinical laboratory assays

Samples of blood (4.5 mL at each time point) and urine will be collected. The following laboratory analyses will be performed at Visits 1, 4 and 6 (ETV if applicable):

HAEMATOLOGY

Leukocytes and leukocyte differential count (percentage values and absolute values), erythrocytes, haemoglobin (conv. units), haemoglobin (IS units), haematocrit, MCV, MCH, MCHC, thrombocytes.

BLOOD CHEMISTRY

Electrolytes: sodium, potassium, calcium, chloride, inorganic phosphorus
Enzymes: alkaline phosphatase, γ-GT, AST, ALT
Substrates/metabolites: total bilirubin, creatinine, glucose, urea, uric acid, total cholesterol, triglycerides
Hormones: testosterone
Proteins: albumin, globulin, total proteins

URINE ANALYSIS

Macroscopic analysis: pH, specific weight, appearance, colour, nitrites, proteins, glucose, urobilinogen, bilirubin, ketones, haematic pigments, leukocytes

Microscopic analysis: leukocytes, erythrocytes, flat cells, round cells, crystals, cylinders, mucus, bacteria

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7.3.2 Analytics

All the analyses foreseen by the protocol, i.e. CCI [redacted] will be performed at PPD .

The analytical methods will be described in the corresponding analytical protocols and reports.

Analyses will be performed according to the general Principles of "OECD Good Laboratory Practices for testing of chemicals" C(81) 30 (final).

7.3.3 Labelling, storage and transport of samples

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[redacted]

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7.4 Total number of samples and blood withdrawn

During the study, the following volume of blood will be collected:

For routine laboratories analysis:
Visit 1, 4 and 6, or at the ETV: 4.5 mL x 3 collections (excluding ETV: 4.5 mL) = about 13.5 mL

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In total, a maximum of about 55.5 mL of blood (not exceeding a normal blood donation) will be withdrawn from each patient during the entire study (about 30 weeks).

7.5 Local Tolerability

Local tolerability at the application site will be assessed to rate the severity of any skin irritation from Week 4 (V3) to Week 28 (V7, End of study), or at the ETV, through a Severity Score for Skin Irritation. Investigator will use the Severity Scores and will report the score in e-CRF.

Score	Dermal response
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal oedema or minimal papular response
3	Erythema and papules
4	Definite oedema
5	Erythema, oedema and papules
6	Vescicular eruption
7	Strong reaction spreading beyond test site
Score	**Other effects**
A	Slight glazed appearance
B	Marked glazing
C	Glazing with peeling and cracking
D	Glazing with fissures
F	Film of dried serous exudate covering all or part of the patch site
G	Small petechial erosions or scabs

8 CLINICAL SUPPLIES

8.1 Treatment

8.1.1 Description of products

The analytical certificates will be enclosed with the investigational medicinal products (IMPs). In order to keep a full blinding, a double-dummy technique will be used, by administering daily, the test product (P-3074) and the relevant placebo of oral finasteride (powder filled capsules) [A], or P-3074 Vehicle and the relevant placebo capsule of oral finasteride [B] or the active oral finasteride 1 mg tablet, over-encapsulated and P-3074 Vehicle [C], according to the scheme below:

	P-3074	Vehicle P-3074	Oral Finasteride	Placebo Oral Finasteride
Group A	**X**			**X**
Group B		**X**		**X**
Group C		**X**	**X**	

8.1.1.1 Test product

The test drug is a topical formulation (P-3074) with finasteride as the sole active ingredient. The active treatment P-3074 will contain finasteride 0.25% w/w with a relative density of 0.91, i.e. final finasteride concentration ~2.275 mg/mL. P-3074 will be supplied in HDPE plastic bottles, containing 17 mL of solution, with a mechanical spray pump.

8.1.1.2 Control

P-3074 Vehicle topical solution will be used in the trial as the control: it is identical in appearance and indistinguishable from the active treatment.

8.1.1.3 Active comparator

The active comparator is represented by oral finasteride 1 mg, as film-coated tablets (Propecia®), to prevent contact with the active ingredient during normal handling, but blinded by means of over-encapsulation. As Propecia® is provided in the form of over-encapsulated oral tablet, it may be taken with or without food.
Crushed or broken capsules of oral finasteride 1 mg (or its placebo) should not be handled by women when they are or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus.
In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months (n=71) did not result in dose-related undesirable effects.
No specific treatment of overdosage with Propecia®, as well as for P-3074, is recommended.

8.1.1.4 Placebo comparator

The placebo of active comparator is represented by an inert powder filled capsule, indistinguishable from the active comparator, as both are presented in capsules.

8.1.2 Dose regimen

P-3074 (finasteride 0.25% topical solution) or P-3074 Vehicle topical solution will be applied o.d. in the morning for 24 weeks onto the scalp according to a computer generated randomisation list. In these 2 arms, the oral finasteride placebo o.d. will be taken by all the patients enrolled.
Patients randomized to the third arm of oral finasteride 1 mg, will take the oral over-encapsulated tablet once a day for the entire duration of the study. In the same context, they will apply also P-3074 Vehicle topical solution.

8.1.3 Route and method of administration

Both P-3074 and its Vehicle are provided as a spray (mechanical spray pump) that allows an easy distribution of a measurable quantity of solution (50 µL each spray) on the scalp, for a maximum of 4 sprays per day, depending by the target area to be treated. After the application on clean, dry scalp, both topical solutions (P-3074 or its Vehicle) evaporate quickly leaving a water-permeable, transpiring, non-shining and almost invisible layer. This layer maintains a high concentration of finasteride at the surface of the scalp.

All patients randomised should topically apply P-3074 or its Vehicle once a day for the 6 months of treatment. P-3074 or Vehicle (Placebo) has to be applied in the morning onto dry scalp only, following the dose recommended by the study doctor (up to 4 puffs). The first puff has to be sprayed over the target 1 cm^2 circular area, identified by a small dot tattoo as a reference point. The others, if prescribed, shall cover the rest of the baldness area. The cutaneous spray solution has to be left it in place for at least 6-8 hours (after that, the patient has to wash carefully the scalp with shampoo). In the same context, patients has to take in oral finasteride 1 mg tablet, over-encapsulated (or its placebo) daily, until the end of treatment (Visit 6). In case of missing administration of any test products in the morning, it will not be allowed any administration during the day.

Patients will bring with them to the clinical site the investigational products the days of visits 3, 4, 5, 6, to comply with the scheduled daily administration. Patients will topically apply P-3074 (or its Vehicle) and will take oral finasteride (or their corresponding placebo) directly at the clinical site no more than 1.5 hour before the sample collection.

Therapy with P-3074 or its Vehicle has to be continued on a daily basis in order to maintain or increase the hair growth achieved.
Actual timing of each application will be recorded in the patient diary.

8.1.4 Investigational product distribution

All treatment kits will be provided by the investigator or by his/her deputy. They will be exclusively used for the present clinical study and will only be administered to the patients enrolled in the study.

8.2 Packaging and labelling

The Sponsor will provide each site with individually numbered treatment kits. The solution manufacture, the packaging, and the labelling will be performed according to GMP procedures. The sites will be provided with drug required for the 24-week treatment period in periodic shipments. Each pack will be identified by a label bearing the frequency of administration, the treatment code and the number of bottles and capsules contained; each label will be filled in with the site number, the randomization number and visit number by the Investigator. Labels will be provided in local language. The drug will be dispensed to the patients as follows:

- One kit at Day 1 (V2) for once daily administration;
- One kit at Week 12 (V5) for once daily administration till Week 24 (V6).

The overall treatment period is 24 Weeks.

Each patient kit includes:

- 3 bottles of P-3074 (or its Vehicle) and 17 blisters (102 capsules) of oral finasteride (or its placebo) enough to cover a therapeutic period of 12 weeks.

It is required to change the bottle of P-3074 (or its Vehicle) every 4 weeks of treatment.

Patients must return the used/unused study medication at Week 12 (V5) and Week 24 (V6) or at ETV.

If the patient prematurely discontinues the study, the used/unused study medication must be returned at the discontinuation visit.

The study medication will not be available to patients after study termination or to those prematurely withdrawn from the study.

8.3 Storage conditions

The trial medications will be stored in a dry locked place according to the storage temperature recorded on the respective labels.

8.4 Treatment Compliance

Data documentation in the diary
The patients enrolled will be asked to keep a diary also for recording the drug compliance on a daily basis. The start and end date as well as the duration of any interruption of drug intake will be documented, as well as the use of any other concomitant treatment.

Return of plastic bottles/capsules
The patient will be instructed to return the used/unused plastic bottles, as well as the blisters with the over box, together with the diary to the investigator, at visits V3 to V6/ETV (at Visit 3 and Visit 4 for the administration on site, at Visit 5, Visit 6 or ETV also for compliance check)

The number of unused capsules left in the returned blisters will be documented by the investigator in the eCRF and on the separate Drug Accountability Form.
With regards to the topical solution, each bottle of each treatment kit will be weighed centrally before the shipment to the investigational sites. The returned bottles will be weighed again centrally and the net weight of used solution will be calculated.

The investigator will maintain a drug log form with details of bottles dispensed to the patient and the bottles returned.

The patient compliance should be in the range 80-120%, based on the number of days treated.

The decision of statistical evaluation regarding treatment compliance will be decided at the blinded report planning/data analysis meeting before unblinding the treatment code.

8.5 Drug accountability

All the study treatments will be provided directly to the investigator by the Sponsor.
After the receipt of the drug supply, the Pharmacist (if applicable) or the Investigator will confirm in writing by signing and dating standard drug accountability forms.

At the end of the study, unused supplies of all formulations, will either be destroyed (upon written authorisation) or returned to the Sponsor, after assessment of drug accountability.

9 EVALUATION PARAMETERS

9.1 Study variables

9.1.1 Primary variable

- Total hair count after 24 weeks of treatment.

9.1.2 Secondary variables

Efficacy

- Total hair count after 12 weeks of treatment;
- Hair width after 12 and 24 weeks of treatment;
- Self-administered Male Hair Growth Questionnaire (MHGQ) as assessed by the patient at Weeks 12 and 24;
- Investigator assessment of patient hair growth/loss change from baseline to 12 and 24 weeks;
- Blind assessor assessment of patient hair growth/loss change from baseline to 12 and 24 weeks;

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9.2 Safety assessments

Safety and general tolerability of the IMP will be based on TEAEs, physical examinations including BW, vital signs, and routine haematology, blood chemistry and urinalysis laboratory tests.

Local tolerability at the application site will be assessed to rate the severity of any skin irritation from Week 4 (V3) to Week 28 (V7, End of study), or at early discontinuation visit, through a Severity Score for Skin Irritation.

In addition, the self-administered Sexual Dysfunction Questionnaire (IIEF-2) will be assessed by the patient from V3 to the end of study (V7 or ETV).

10 Statistical methods

10.1 Analysis Sets

10.1.1 Definitions

All Randomized Population: all enrolled patients who are randomized to a treatment group.

Safety Population: all randomized patients who receive at least one application of the investigational drug.

Intention To Treat (ITT) Population: all patients who will have measurements both at baseline and on treatment.

Per Protocol Population: all patients in the ITT population

- who did not take forbidden medications;
- who complete the entire study without any major protocol violations.

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Analyses done on the Per Protocol will be considered supportive.
A patient will be defined as screened after the signature of the informed consent, regardless of the completion of all the screening procedures.
A patient will be defined as eligible if he respects all the inclusion/exclusion criteria. Otherwise he/she will be defined as a screening failure.
A patient will be defined as enrolled in the study if he is included into the interventional phase of the study. The enrolment will be performed through randomised allocation to a treatment arm/ treatments sequence.

10.2 Analysis of efficacy

10.2.1 Analysis of Primary Efficacy Endpoint

The primary efficacy variable, i.e. the change in the hair count from baseline, will be analysed using the SAS PROC MIXED procedure.

The null hypothesis to be tested will be that there is no difference between P-3074 and placebo in the mean change from baseline for the hair count at Visit 6.
The alternative hypothesis will be that there is a difference between P-3074 and placebo in the mean change from baseline for the hair count at Visit 6.

The primary efficacy data will be fitted by a mixed linear model with treatment (P-3074 or placebo), centre, visit and the treatment-by-visit interaction as fixed effects and baseline as covariate. The variance-covariance matrix of unstructured form will be used in order to model the correlation, within each patient, between the two repeated measurements (over the post-baseline visits). Maximum likelihood estimates of the treatment mean difference computed at Visit 6

together with the associated two-sided 95% CI will be calculated by resorting to the Newton-Raphson algorithm implemented in the SAS® Mixed Procedure. A two-sided test with a p-value less than or equal to 0.05 will be considered statistically significant. The interaction between treatment and centre will be assessed. A two-sided p-value less than or equal to 0.10 will be considered statistically significant for the test of interaction between treatment and centre. If a statistically significant interaction is observed, efforts will be made to determine whether and how the interaction may affect the treatment comparisons.

10.2.2 Analysis of Secondary Efficacy Endpoints

- **Total hair count after 12 weeks of treatment:** the statistical model described above for the primary endpoint analysis will also provide the maximum likelihood estimate of the treatment mean difference computed at Visit 5 (Week 12) together with the associated two-sided 95% CI and p-value.
- **Hair width after 12 and 24 weeks of treatment:** data will be fitted by a mixed linear model for repeated measures with treatment group, centre, visit and treatment-by-visit interaction as fixed effects, baseline value as covariate, and with an unstructured variance-covariance matrix to take into account correlations among repeated measures within patient. Results will be reported as maximum likelihood estimates of the treatment difference at Weeks 12 and 24 together with associated two-tailed 95% CI. A two-sided test with a p-value less than or equal to 0.05 will be considered statistically significant.
- **Self-administered Male Hair Growth Questionnaire (MHGQ) as assessed by the patient at Weeks 12 and 24:** data will be fitted by a mixed linear model for repeated measures with treatment group, centre, visit and treatment-by-visit interaction as fixed effects, and with an unstructured variance-covariance matrix to take into account correlations among repeated measures within patient. Results will be reported as maximum likelihood estimates of the treatment difference at Weeks 12 and 24 together with associated two-tailed 95% CI. A two-sided test with a p-value less than or equal to 0.05 will be considered statistically significant.
- **Blind assessor assessment of patient hair growth/loss change from baseline:** data will be fitted by a mixed linear model for repeated measures with treatment group, centre, visit and treatment-by-visit interaction as fixed effects and with an unstructured variance-covariance matrix to take into account correlations among repeated measures within patient. Results will be reported as maximum likelihood estimates of the treatment difference at Weeks 12 and 24 together with associated two-tailed 95% CI. A two-sided test with a p-value less than or equal to 0.05 will be considered statistically significant.
- **Change from baseline in Investigator Assessment at 12 and 24 weeks:** data will be fitted by a mixed linear model for repeated measures with treatment group, centre, visit and treatment-by-visit interaction as fixed effects and with an unstructured variance-covariance matrix to take into account correlations among repeated measures within

patient. Results will be reported as maximum likelihood estimates of the treatment difference at Weeks 12 and 24 together with associated two-tailed 95% CI. A two-sided test with a p-value less than or equal to 0.05 will be considered statistically significant.

10.2.3 Handling of Missing Data

Taking into account that maximum likelihood estimates have less bias then classic imputation methods such as LOCF for Informative missingness and are by definition unbiased under a Missing Completely At Random (MCAR) and a Missing At Random (MAR) mechanism of missingness, the mixed linear models described above represent a suitable choice in handling missing data and correcting for the bias potentially caused by drop-outs in this study[26].

To assess the sensitivity of the results obtained using maximum likelihood approach to the presence of missing values, three supplemental analyses will be performed on the primary endpoint:

1. Last Observation Carried Forward (LOCF): Missing outcomes will be replaced by the last non-missing, post-baseline value.
2. Best Case Analysis: Missing outcomes will be replaced by the best outcome.
3. Worst Case Analysis: Missing outcomes will be replaced by the worst outcome.

For each of the three sensitivity analyses (LOCF, BCA and WCA), the change in the hair count from baseline to visit 5 will be fitted by a linear model with treatment (P-3074 or placebo) and centre as fixed effects and baseline as covariate (ANCOVA Analyses).

10.3 Interim Analyses

No interim analysis is planned.

10.4 Sample size and Power

Group sample sizes of 144 patients randomized to P-3074 and 144 patients randomized to Placebo achieve 99% power to detect superiority using a one-sided, two-sample t-test with a significance level (alpha) of the test equal to 0,025. The margin of superiority, i.e. the distance above the reference (Placebo) mean that is required to be considered superior, is set to 41 hair count whilst the true difference between P-3074 and Placebo is assumed to be 82 hair count and is estimated assuming a mean change from baseline to 6 months in hair count equal to -14 and +68 in Placebo and P-3074 respectively[27]. The data are drawn from populations with standard deviations of 88 in P-3074 and 75 in Placebo[27].

Literature[28,29] shows that the mean change from baseline of hair count estimated in 1 $inch^2$ (= 6.25 cm^2) and 1 cm^2 is correlated. For the above reason, the use of 1 $inch^2$ or 1 cm^2, as vertex target area, doesn't affect the sample size calculation.

In addition, approximately 72 patients will be randomised to the active comparator arm (oral finasteride 1 mg). Group sample sizes of 144 patients randomized to P-3074 and 72 patients randomized to oral Finasteride achieve a power close to one to reject the null hypothesis of equal serum CCI inhibition assuming a mean serum CCI inhibition equal to 45,6 and 26,2 in oral Finasteride and P-3074 respectively[14,21] with a standard deviation for both groups of 19,0(2) and with a significance level (alpha) of 0,050 using a two-sided two-sample equal-variance t-test.

Assuming an attrition rate equal to 20%, the total number of patients should be no less than 450 patients randomized to P-3074, Placebo and oral Finasteride in a 2:2:1 allocation ratio. All computations were performed using PASS 13 Software.

10.5 Demographic, baseline and background characteristics

Critical demographic characteristics will be examined according to qualitative or quantitative data. Qualitative data will be summarised in contingency tables. Quantitative data will be summarised using classic descriptive statistics for continuous variables (means, medians, percentiles, standard deviations etc.).

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10.8 Safety and tolerability evaluation

➢ **AEs**

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be classified as pre-treatment AEs (PTAEs) and treatment-emergent AEs (TEAEs), according to the period of occurrence, as follows:

- PTAEs: all AEs occurring before the first dose of the IMP and not worsening after the first dose of the IMP
- TEAEs: all AEs occurring or worsening after the first dose of the IMP

Individual PTAEs and TEAEs will be listed in patient data listings. No summary table will be provided for PTAEs. TEAEs will be summarised by treatment and overall. The number and

percentage of patients with any TEAE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship to treatment and severity.

- **Physical examination**

Significant findings/illnesses, reported after the start of the study and that meet the definition of an AE, will be recorded in the patient source documents. Date of the physical examination and overall investigator's interpretation (as normal [N], abnormal not clinically significant [NCS] or abnormal clinically significant [CS]) will be reported in the CRF.

- **Laboratory data**

Date/time of samples collection and overall investigator's interpretation (as normal [N], abnormal not clinically significant [NCS] or abnormal clinically significant [CS]) will be recorded in the CRF and listed in the final clinical study report. Hard copies of the laboratory print-outs will be attached to the CRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs.

All safety laboratory data will be listed in the clinical study report and a table of all abnormal laboratory values will be presented. All laboratory tests (haematology, blood chemistry and urine analysis) will be summarised by shift tables.

- **Vital signs**

Values of vital signs will be listed and summarised by descriptive statistics.

- **Body weight**

Values of body weight will be listed and summarised by descriptive statistics.

- **Self-administered Sexual Dysfunction Questionnaire (IIEF-2)**

Data will be analysed through a mixed linear model for repeated measures with treatment group, centre and visit and treatment-by-visit interaction as fixed effects, baseline value as covariate, and with an unstructured variance-covariance matrix.

11 DEFINITION AND HANDLING OF AES AND SAES

11.1 Applicable SOPs

AEs definition, classification and management will follow the CRO SOPs, based upon applicable local and international regulations. The full SOP or an operative summary will be made available to the clinical centre.
A brief summary of AE definition, classification and management is reported below.

11.2 Definitions

- **Adverse event (AE)**

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment.

- **Adverse Drug Reaction (ADR)**

An AE that is drug related.

- **Pre-treatment AE (PTAE)**

AEs occurring before the first dose of IMP and not worsening after the first IMP dose. The following medical occurrences and clinical investigations are the only clinically significant events which, according to the investigator judgement, can be defined and recorded as PTAEs:

- trauma (fractures, sprains, strains, falls, domestic accidents, car accidents, etc.) occurred after the signature of the informed consent and before the first IMP administration
- new measurements (vital signs, ECG, laboratory parameters, etc.), performed after the signature of the informed consent and before the first IMP administration, which show a clinically significant worsening in comparison with a previous (baseline) measurement performed after the signature of the informed consent
- any disease diagnosed after the anamnesis recorded at visit 1 and before the first IMP administration in a non-screen failure patient
- physical and mental status changes (pre-syncope, anxiety, dizziness, fainting, etc.) occurred after the signature of the informed consent and before the first IMP administration

- **Treatment-emergent AE (TEAE)**

AE occurring or worsening after the first IMP administration.

- **Serious Adverse Event (SAE)**

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation, i.e. an unplanned overnight hospitalisation, or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

- Medically significant event (may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the above listed conditions).

A non-serious adverse event is any adverse event that does not meet the criteria listed above for a serious adverse event (i.e., death, life-threatening condition, hospitalization, etc.).

Reports of overdose with no associated SAE will be reported in the AE page of the CRF. They will be routinely followed up to ensure that if the overdose leads to a SAE, this will be reported in the SAE report form within the appropriate timelines.

- **Suspected Unexpected Serious Adverse Reaction (SUSAR)**

A suspected ADR that is both unexpected and serious.

11.3 AEs monitoring window

- Start of monitoring: from immediately after the signature of the informed consent
- End of monitoring: follow up visit (observation window)

An AE occurring after the follow up visit 7 (week 28) and coming to knowledge of the investigator (e.g. during a follow-up assessment or by spontaneous reporting by study patients) must be recorded only if it is an ADR, according to the investigator's judgment.

11.4 AEs recording

Any AE experienced by an enrolled patient, independently of its seriousness and its relationship with the investigational product, reported by the patient or observed by the investigator, will be recorded in the patient source documents, copied in the CRF and reported in the clinical study report including time of onset, nature, duration, intensity and any action taken. If the writing of the CRFs of not enrolled patients is foreseen, also the AEs of these patients will be recorded in the CRFs and reported in the clinical study report.

The following minimal information will be recorded for an AE (detailed explanation for each element is available in the SOP or in the operative summary made available to the clinical centre):

<u>Numbering</u>
Each AE must be identified by a progressive number.

<u>Onset</u>
For each AE, it must be reported if it started before or after the first study drug dose. If more doses are foreseen in the study protocol, the progressive number of dose must be specified.

<u>Record date</u>

For each AE, the date when the investigator has detected the AE or was informed by the patient about the AE must be reported.

Description
A clear description of the AE must be reported. Combination of different symptoms must be avoided, e.g. "nausea and vomiting" should be replaced by 2 different AEs, "nausea" and "vomiting".

Seriousness
It is reported if the AE qualifies as a SAE.

Frequency
Single event
Intermittent
Continuous

Intensity
Mild
Moderate
Severe

Relationship to study drug
The relationship to study drug can be either assessable or not assessable. If assessable, one of the following relationships must be chosen:
Not related
Unlikely related
Possibly related
Related
For Unassessable adverse events relationship will remain blank.
By definition, PTAEs are not related to study treatment.

Action taken with study treatment
Dose increased
Dose not changed
Dose reduced
Drug interrupted
Drug withdrawn
Not applicable
Unknown

Other actions taken
Concomitant medication taken
Non drug therapy given
Other

Outcome
Fatal
Not recovered/not resolved
Recovered/resolved
Recovered/resolved with sequelae
Recovering/Resolving
Unknown

An AE can be ongoing at the study end only if its outcome is "Not Recovered/Not Resolved", "Recovering/Resolving" or "Unknown".

Start date

End date

Study discontinuation
It is reported whether the AE has resulted in discontinuation of the patient from the study.

Comments
Any relevant additional information according to investigator's judgement is reported.

11.5 SAEs reporting

The investigator must report any SAE to PPD . The SAE report form must be completed and sent by fax within 24 hours of knowledge of the event by the site using PPD .

The investigator immediately reports also whether or not these SAEs have a clear causal relation with the treatment. Events that do not need to be reported immediately according to the protocol or the investigator's brochure are excluded.

PPD might require additional information be reported immediately or during the course of the trial if necessary.

Subjects experiencing SAEs should be followed up clinically until their health has returned to baseline status or until all parameters have returned to normal or have otherwise been explained.

11.6 SAEs reporting time-frame

Fatal or life-threatening SUSARs must be reported by the sponsor (through CRO) to the concerned Competent Authorities (CA) and EC as soon as possible and no later than 7 calendar days from becoming aware of it.

All other SUSARs and safety issues must be reported by the sponsor (through CRO) to the concerned CA and EC as soon as possible and no later than 15 calendar days from becoming aware of it.

The investigator should decide, on the basis of his/her medical knowledge, whether expedited reporting is appropriate also in other situations, such as medically significant serious events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. Examples are cancer, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

11.7 SAEs: contacts

The CRO can be notified for SAE reporting purposes using the fax numbers stated in this protocol (+44 1628540028 - operative 24-h/day, 365 days/year).

For urgent notifications occurred outside the working hours, the Sponsor is available 24-h/day, 365 days/year, at the following contacts:

12 Ethics, confidential and administrative aspects

12.1 Ethics and Good Clinical Practice (GCP)

The study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) Guidelines and local laws of the Countries in which the study centre are situated. The patient information document and the consent form, both in the local language, must be submitted to and be approved by the Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) of the participating centre. No study-related procedures may begin until the patient has signed the consent form. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

12.2 Direct access to Source Data/Documents

The Investigator(s)/Institution(s) will permit trial-related monitoring, audits from Auditor and/or Sponsor's Representative, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents that will remain confidential.
Sponsor plans to perform at least 2 audits, by giving 2 weeks written notice to each participating centre.

12.3 Unique patient identifier

All the patients who sign the informed consent form for the present study will be coded with "unique patient identifiers" when data are extracted from the study database into the domains of the CDISC SDTM model. The unique patient identifier consists of the sponsor study code (i.e. PM1541), the 3-digit site number (e.g. 001, 002, 003), the 4-digit screening number (e.g. S001, S002, etc.) and, if applicable, the 3-digit patient randomisation number (e.g. 001, 002, etc.). Study code, site number, screening number and patient randomisation number are separated by dashes ("-"). The last 12 digits of the unique patient identifier (enrolled patients), corresponding to the site number, patient screening and patient randomisation numbers separated by a slash, will appear as patient identifier in the individual listings and figures of the clinical study report and will be used to identify the patients in in-text tables or wording (if applicable).

12.4 Informed consent

Before being enrolled into the clinical study, the patients must have expressed their consent to participate, after the investigator has explained to them, clearly and in details, the scope, the procedures and the possible consequences of the clinical study. Information will be given in both oral and written form. The information sheet and informed consent form will be prepared in the local language by the CRO and must be approved by the ECs and regulatory authorities. It will include all the elements required by law according to the ICH-GCP recommendations.

In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- a description of the aims of the study and how it will be organised
- the type of treatment
- any potential negative effects attributable to the study treatment
- the freedom to ask for further information at any time
- the patients' right to withdraw from the clinical study at any time without giving reasons and without jeopardising their further course of medical treatment
- the existence of patient insurance cover and obligations following from this cover

Adequate time and opportunity to satisfy questions will be given to the patients and the time will be recorded.

The investigator will be supplied with an adequate number of blank informed consent forms to be used. The forms will be signed and dated by both the investigator and the patient.

A copy of the signed form will be given to the patient.

To ensure medical confidentiality and data protection, the signed informed consent forms will be stored in the investigator's study file according to the regulatory requirements. The investigator will allow inspection of the forms by authorised representatives of the sponsor, EC members and regulatory authorities. He will confirm, by signing and dating the forms, that informed consent has been obtained.

12.4.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

For the eCRF all data must be derived from source documents (i.e. hospital or clinical records containing all demographic and medical information). Data without a written or electronic record will be defined before trial start and will be recorded directly on the eCRF, which will be documented as being the source data.

The following items (at a minimum) have to be collected as source documents in the patient's file:

- Study code;
- Patient's full name, date of birth, sex, weight and height;
- Medical history;
- Concomitant medications;
- Date of inclusion and patient identification (randomisation) number;
- Date of patient's written informed consent;
- Study drug administration (e.g. start and end of study treatment);
- Date of the visits;
- AEs and SAEs occurring during the study;

- Date of withdrawal and reason.

Specific items required as source documents will be reviewed with the Investigator before the trial.

12.5 Monitoring of the study

Before study initiation, the study protocol, eCRF and study procedures will be reviewed by the Sponsor's representative or by the CRA with the Investigator and staff involved in the study.

During the study, the clinical Monitor will regularly visit the centre, upon previous agreement with the centre, in order to check the accuracy of data entered in the eCRF with respect to the source data, the compliance with the study protocol and with the ICH-GCP guidelines, the progress of patient's enrolment, study drug storage and accountability and clinical facilities. The CRA should have access to patient's hospital notes to verify source data, by maintaining patient's information confidential. CRA should have enough time to perform these checks and must be assisted by the staff involved in the study.

12.6 Data Collection

The study will be carried out in Europe: the data collection will be done through an electronic Case Record Forms using the fully validated EDC system.
The EDC procedure will allow the Investigator to enter study data directly into the database through a personal username and password with the support of on-line checks and detailed instructions for data entry delivered to each centre. The personal username and password will be delivered after ethical and administrative approvals.

12.7 Withdrawal of patients

It will be documented whether or not each patient completed the clinical study. If, for a patient, study treatment or observations are discontinued, the primary reason for discontinuation will be recorded.

12.7.1 Primary reason for discontinuation

- **Adverse event**: Any significant adverse event that in the opinion of the investigator or concerned patient is not compatible with study continuation. For the definition of AE, please refer to § 11.2.
- **death**: the absence of life or state of being dead
- **lack of efficacy**: the lack of expected or desired effect related to a therapy
- **lost to follow-up**: the loss or lack of continuation of a patient to follow-up
- **non-compliance with study drug**: an indication that a patient has not agreed with or followed the instructions related to the study medication

- **physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the patient
- **protocol deviation:** an event or decision that stands in contrast to the guidelines set out by the protocol
- **study terminated by sponsor**: an indication that a clinical study was stopped by its sponsor
- **site terminated by sponsor**: an indication that a clinical site was stopped by the study sponsor
- **technical problems**: a problem with some technical aspect of a clinical study, usually related to an instrument
- **withdrawal by patient**: study discontinuation requested by a patient for whatever reason
- **other**: different than the ones previously specified

12.7.2 Discontinuation procedures

For any patient discontinuing the study, the investigator will:

- ask the patient to undergo, as far as possible, a final medical visit (ETV) to examine the patient's health conditions and perform the required blood sampling for the laboratory assays. This examination will verify that all values tested at screening have remained within a clinically acceptable range (i.e. not clinically significant changes compared to screening);
- arrange for alternative medical care of the withdrawn patient, if necessary;
- record the patient decision about the use of collected biological samples;
- report in the CRF date of the last dose administration, and date and primary reason of study discontinuation;
- record in the CRF any follow-up, if the patient is withdrawn for an AE.

Discontinued patients will not be replaced.

12.8 Study termination – End of Trial

The study will be considered terminated at the date of the last visit of the last patient or upon completion of any follow-up procedure described in the protocol. The investigator and the sponsor have the right to discontinue the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation. Reasons for discontinuation have to be documented appropriately.

12.9 Data Management and Quality Control

To ensure the quality of the data, expected data cleaning checks will be applied to these data. The Data Management team will perform data review using the automatic Edit Checks programmed into EDC system and SAS Edit Checks/ Listings programmed for Manual Data Review. During this process, if clarifications are needed, the Data Manager will raise manual queries within the EDC Database. The full details of procedures for data handling will be documented in the Data Management Plan and associated documents.

Concomitant medications will be coded using the most recent version of WHO Drug Reference List which employs the Anatomical Therapeutic Chemical classification system. Concomitant diseases and adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) terminology.

When the database is declared complete and accurate, it will be locked and unblinded. Any changes to the database after that time can only be made by joint agreement between the Sponsor, the trial Statistician and the Data Manager.

12.10 Data Handling and Record Keeping

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the eCRF and the source documents.

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf) is confidential. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

Investigators must conserve all original study documents for at least 15 years after the completion of the study. If an Investigator cannot guarantee conservation for that time, in agreement with local Institution, then all documentation related to the study (patient's consent, laboratory data and any other instrumental data records) can be forwarded to the Sponsor in sealed packs, accompanied by a checklist. In such cases, the Sponsor will assume full responsibility for safe storage and the Investigator and CRO will be freed from that responsibility.

12.11 Publication Policy

The data produced in the course of the study are the property of POLICHEM SA. No data can be published without the authorisation of POLICHEM SA. Study results will be communicated to the competent Health Authorities by the submission of a synopsis of the clinical study report.

12.12 Financing and Insurance

The Sponsor will take out appropriate civil liability insurance policies in accordance with local regulation and with the requirements of the Health Authorities, to cover patients against any injuries arising from their participation in the study.

12.13 Confidentiality and data protection

By signing this protocol, the investigator and the CRO agree to keep all the information provided by the sponsor in strict confidentiality and to request similar confidentiality from his/her staff. Study documents provided by the sponsor (protocols, IB, CRFs and other materials) will be stored

appropriately to ensure confidentiality. The information provided by the sponsor to the investigator and to the CRO cannot be disclosed to others without direct written authorisation from the sponsor, except for the extent necessary to obtain the informed consent from the patients wishing to participate in the study.

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Appendix 1

Hamilton-Norwood classification of male balding.