NON SUBSTANTIAL AMENDMENT	
Amendment No.	N° 1
Version No.	FINAL
Study Code	PM1541
EudraCT n°	2015-002877-40
Date	8th March 2017

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 SA,

50 Val Fleuri Luxembourg,

hereby legally represented by its branch located in:

Lugano-Pazzallo CH-6912 (Switzerland), Via Senago, 42 D

Tel. +41-91-986.40.00
Fax +41-91-986.40.01

Centres affected by the amendment:

All the centres involved in the study

AMENDMENT APPROVAL FORM

PROTOCOL No.: PM541

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: Non Substantial Amendment 1 – Final Version – 8th March 2017

PPD

Polichem S.A.

PPD

PPD

Signature

PPD

Date

PPD

Polichem S.A.

PPD

PPD

Signature

PPD

PPD

Date

COUNTRY: _____ ***CENTRE N°:*** _____

Principal Investigator

_____	_____	_____
Printed Name	Signature	Date

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

RATIONALE FOR NON-SUBSTANTIAL AMENDMENT

This non-substantial amendment concerns the increasing of the screening period, initially planned in the study protocol, as 1 week ± 3 days. After the signature of the Informed Consent Form by patient, the severity of the baldness condition has to be evaluated by a global photography of the scalp, made by the Study Blind Assessor. However, before sending the photos to the Blind Assessor, a quality check has to be performed by the Image Company responsible of this study, aimed at detecting potential exposure errors, the presence of oil/wet on the hair or hair combing style leading the photo not evaluable. In case of the occurrence of any of these issues, the Image Company may ask for a reshooting of the target baldness area, prolonging in this way the screening period and leading to an out of window visit. Therefore, due to this technical period of evaluation, the Sponsor decided to have 2 weeks ± 5 days as screening period. For this reason, and following the European Directive 2010/C 82/01 with regards to a minor increase in the duration of the trial (< 10 % of the overall time of the trial), the Sponsor decided to implement this protocol change as not-substantial.

Other minor clarifications, comments, text deletions, typo corrections and a general adjustment to the protocol, not impacting on the safety or physical or mental integrity of the clinical trial participants, or the scientific value of the trial, have been included in this not-substantial amendment.

Therefore, the Sponsor submits the below consolidated protocol versions reflecting the aforementioned changes:

- Protocol PM1541 Version 4.0, track changes and clean dated 8th March 2017

In the same context, the Sponsor notifies the update of the Investigator's Brochure, Version 6 dated 17 Feb 2017 and the EudraCT form with the change of the legal representative and the change of the company's name of Therametrics Clinical Supply Services Srl into Euromed Clinical Supply Services Srl (enclosed also the authorization of the Italian Authority).

The most relevant sections changed are displayed below, with corrections/additions/deletions in red bold text. The same changes will be applied throughout the document.

Table of contents
The pages' numbers were updated.

Synopsis
Experimental Design:
….omissis…….
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.
….omissis…….

Study Procedures
Seven clinical examinations are planned for each patients, as follows:
- Screening, Visit 1 (Week ~~-1~~ **2**)

Statistical Methods
….omissis…….
The variance-covariance matrix of unstructured form will be used in order to model the correlation, within each patient, between the ~~three~~ **two** repeated measurements (over the post-baseline visits).
….omissis…….
The secondary efficacy variables, MHGQ ~~scores~~, 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.

Study Protocol
2.2 Secondary end-points
….omissis…….
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.

3.2 Randomization
….omissis…….
In the same context, patients have to take in 1 mg ~~tablet~~ oral finasteride (or its placebo) daily until the end of a 24-week treatment course (Visit 6).
….omissis…….

3.3 Blinding
….omissis…….
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.

~~**Two (2) copies of the list are generated and securely provided as follows:**~~

~~➢ one copy is sent to the manufacturer for the preparation of the individual treatment boxes~~
~~➢ one copy is sent to the IXRS vendor for management of drug supply and emergency unblinding.~~

Neither the members of the clinical unit nor the CPL or the CRA/monitor will have access to the randomisation ~~code~~ **data or to the treatment kit number list**. Upon DB lock, ~~the randomization file will be transferred to CRO for analysis~~ **all subjects will be unblinded through IXRS**.

….omissis…….

3.3.1 Emergency code and unblinding procedures

….omissis…….

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.**

….omissis…….

3.5 Study flow-chart

	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**	
	-Weeks ~~-1~~2	**Day 1±~~3~~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		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								

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

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

CCI

Due to the blood samplings for PK/PD analyses, the patients have to bring with them the study drug also at Visits 3 and 4, for an administration on site

§ Height will be measured only at screening

5.1 Study visits and procedures

….omissis…….

~~Maximum~~**The** study duration will be ~~**29**~~ **about 30** weeks. A written informed consent will be obtained before any study assessment or procedure.

….omissis…….

- **Screening**

  - Screening: Visit 1 (-~~**1**~~ **2** week**s**)

- **Randomization**

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

….omissis…….

Visit	Day	Procedures/Assessments
Visit 1	-~~*1*~~ *2 Week**s***	➢ 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 ~~➢ Global Photograph (if needed a reshoot)~~ ➢ Inclusion/Exclusion criteria for eligibility ➢ Randomization ➢ Dispense study medication ➢ Dispense study diary ➢ AE monitoring

….omissis…….

For all visits including global photo or hair count macrophotography, the patient may be asked to return to the site for reshoot if originally taken images are rejected by imaging vendor due to quality issues.

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**~~ **screening 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.

….omissis…….

6.3 Blind Assessor

….omissis…….

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

7.2 Clinical laboratory assays

Samples of blood (**about** 12.5 mL) and urine will be collected. The following laboratory analyses will be performed at Visits 1, 4 and 6 (ETV if applicable):

CCI [redacted]

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: ~~**12**~~ **4.5** x 3 collections **(excluding** ETV: **4.5 ml)** = **about** ~~**37**~~ **13.5** mL

CCI [redacted]

In total, a maximum of **about** ~~**121**~~ **55.5 mL** of blood (not exceeding a normal blood donation) will be withdrawn from each patient during the entire study (about ~~**28**~~ **30** weeks).

8.1.3 Route and method of administration

….omissis…….

After the application on clean, dry scalp, both topical solutions (P-3074 or its Vehicle) evaporate quickly leaving a water-permeable, ~~transpirant~~ **transpiring**, non-shining and almost invisible layer.
….omissis…….

8.1.4 Investigational product distribution

All ~~groups~~ **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 ~~treatment packs for each patient~~ **numbered treatment kits**.
….omissis…….
Each pack will be identified by a label bearing the frequency of administration, the treatment code and the number of bottles and ~~tablets~~ **capsules** contained; each label will be filled in with the site number, the randomization number and visit number by the Investigator

9.1.2 Secondary variables

….omissis…….

- Self-administered Male Hair Growth Questionnaire (MHGQ) ~~score~~ as assessed by the patient at Weeks 12 and 24

….omissis…….

10.2.1 Analysis of Primary Efficacy Endpoint

….omissis…….
The variance-covariance matrix of unstructured form will be used in order to model the correlation, within each patient, between the ~~three~~ **two** repeated measurements (over the post-baseline visits).
….omissis…….

10.2.2 Analysis of Secondary Efficacy Endpoints

….omissis…….

- **Self-administered Male Hair Growth Questionnaire (MHGQ) ~~Score~~ as assessed by the patient at Weeks 12 and 24**
- **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, ~~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.
- **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, ~~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.

10.4 Sample size and Power

….omissis…….

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.

….omissis…….

11.2 Definitions

….omissis…….

~~➢ events occurred after biopsies performed at Visit 2 (from day – 14 to day – 7)~~

….omissis…….

11.3 AEs monitoring window

….omissis…….

An AE occurring after the follow up visit **7** (~~**day 14±2**~~ **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.

13 References

….omissis…….

28. Gubelin Harcha W, Barboza Martínez J, Tsai TF, Katsuoka K, Kawashima M, Tsuboi R, Barnes A, Ferron-Brady G, Chetty D. A randomized, active- and placebo-controlled study of the efficacy and safety of different doses of dutasteride versus placebo and finasteride in the treatment of male subjects with androgenetic alopecia. J Am Acad Dermatol. 2014 Mar;70(3):489-498.

29. Blume-Peytavi U, Hillmann K, Dietz E, Canfield D, Garcia Bartels N. A randomized, single-blind trial of 5% minoxidil foam once daily versus 2% minoxidil solution twice daily in the treatment of androgenetic alopecia in women. J Am Acad Dermatol. 2011 Dec;65(6):1126-1134.