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PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Clinical Investigation Final Report FR01C/P047B20

The main goal of this clinical investigation is to confirm the absence of acute cutaneous irritation potential of the investigational product after a single application under occlusion, in 10 subjects, by clinical evaluation of the skin sites after 30 minutes and 24 hours of the patch removal in a double blinded fashion.
This clinical investigation was performed in accordance with the respective Clinical Investigation Plan and consistent with the main principles of ICH GCP, Helsinki declaration and Portuguese legal requirements.

Identification of the Clinical Investigation

CIP n./ Study Plan n.	PPT6A17 (v01)	**Study beginning date:**	18/05/2020	**Study conclusion/ suspension date:**	29/05/2020
Report Date:	03/07/2020	**Report Author**	Bárbara Tavares		

Identification of Study Parties

Sponsor	Fancystage Unipessoal Lda
	Rua da Cumieira 31, 4785-618 Trofa
Clinical Investigation Site(s)	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Science and Technology Park of University of Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL
Principal Investigator	Marta de Oliveira Ferreira
Investigator(s)	Ana Luísa Fonseca, Bárbara Tavares
Technical Assistant (s)	Joana Alves, Maria João Vieira, Marta Monteiro, Liliana Ferraz
Administrative assistant (s)	-
Study Coordinator(s)	Márcia Rodrigues

Identification of Investigational Product

Investigational Product (s)			Comparator Product (s)		
Designation	Reference	Batch number	Designation	Reference	Batch number
Pain Relief - Relief&Go - Innocan Pharma	317	A2729	Sodium lauryl sulphate at 2%	-	W1I34
			Type II water	-	T6F67

Clinical Investigation Report ~~prepared~~/changed by

INOVAPOTEK

Bárbara Tavares, Responsible for ~~preparing~~/changing the Clinical Investigation Report

Signature/Date:

Bárbara Tavares 2020.07.03 16:10:45 +01'00'

Clinical Investigation Report approved by

INOVAPOTEK

Bárbara Tavares, Study Director

Signature/Date:

Bárbara Tavares 2020.07.03 16:11:02 +01'00'

SPONSOR

Teresa Neves, Sponsor representative

Signature/Date:

Clinical Investigation Report verified by

INOVAPOTEK

Yogeeta Rocha, Quality Assurance Manager

Signature/Date: Yogeeta Rocha 2020.07.03 16:26:59 +01'00'

HISTORY OF THE DOCUMENT

Revision	Amendment/Deviation	Date
A	First issue	29/05/2020
B	Update product's name	01/07/2020
C	Product's name alteration	03/07/2020

Table of Contents

Abbreviated terms and definitions

µl	Microliter
CEC	Competent Ethics Committee
CIP	Clinical Investigational Plan
CIR	Clinical Investigational Report
CRO	Contract Research Organization
CV	Curriculum Vitae
EC	Ethics Committee
g	Gram
GHQ	General Health Questionnaire
h	Hour(s)
ICH GCP	International Conference on Harmonisation-Good Clinical Practice
INFARMED	National Authority of Medicines and Health Products I.P.
min	Minute(s)
mm	Millimeter
ºC	Celsius degrees
PI	Principal Investigator
RH	Relative Humidity
RNEC	National Registry for Clinical Studies
SD	Standard Deviation
t	Time
T	Temperature

1 – Ethics and Quality Assurance

The CIP was approved by inovapotek Ethical Committee on the 14/06/2017.

This clinical investigation was submitted to INFARMED, I.P. on the 29/05/2017 through the RNEC (National Registry for Clinical Studies) platform under the number 5743.

During trial conduct periodic monitoring was conducted to ensure that the protocol was being followed.

2 – Summary

CIP n./Study Plan n.	PPT6A17 (v01)	**Study beginning date:**	18/05/2020	**Study conclusion/ suspension date:**	29/05/2020
Title	Double blinded randomized controlled study for the evaluation of the acute cutaneous irritation potential of cosmetic products (patch test).				

The primary objective of this clinical investigation is to confirm the absence of acute cutaneous irritation potential of the investigational product. The hypothesis of the investigation is that the investigational product does not induce any skin irritation reaction. According to the results obtained, the investigational product is classified as Non-irritating, Slightly irritating, Moderately irritating or Irritating.

The study is conducted in a double-blinded fashion, in 10 female/male subjects of ages between 18 and 65 years old, with Fitzpatrick skin phototype between I and IV and without skin diseases or other conditions that might interfere with the study.

1 investigational product and 2 comparative products are applied under occlusion with an 8 mm Finn chambers® on Scanpor, using a hypoallergenic adhesive containing occlusion chambers. Investigational and comparative products are applied in the referred occlusion chambers and the adhesive is maintained on the skin for 48 hours until the next visit. After 48 hours, the adhesive is removed and the skin sites are evaluated after 30 minutes by the investigator and potential skin reactions are recorded. The last visit is carried out 24 hours after removal of the adhesive (patch) for the final evaluation of the skin.

The investigational product (Pain Relief - Relief&Go - Innocan Pharma) tested as is, demonstrated to be non-irritating under the test conditions, with an acute irritation index of 0.00.

3 – Introduction

The primary objective of this double blinded randomized controlled study is to confirm the absence of acute cutaneous irritation potential of the investigational product. The hypothesis of the investigation is that the investigational product does not induce any skin irritation reaction.

4 – Clinical Investigation Plan

This double blinded randomized controlled clinical investigation aims to confirm the absence of acute cutaneous irritation potential of the investigational products after a 48 hours patch test performed in a group of 10 subjects, by clinical evaluation after 30 minutes and 24 hours of the patch removal.

10 female/male subjects respecting all the inclusion and exclusion study criteria are enrolled.

Investigational and comparative products are applied under occlusion with an 8 mm Finn chambers® on Scanpor, using a hypoallergenic adhesive (patch) containing occlusion chambers. Products are applied in the respective chamber and the adhesive is maintained on the skin for 48 hours until the next visit. After 48 hours, the adhesive is removed and the skin sites are evaluated after 30 minutes by the investigator and potential skin reactions are recorded. The last visit is carried out 24 hours after removal of the patch for the final evaluation of the skin. According to the results obtained the investigational product is classified as Non-irritating, Slightly irritating, Moderately irritating or Irritating.

Test sites are not randomized, but each product is given randomly a numeric code and each product is applied in the test site with the same code, namely product code 1 is applied in test site 1, product code 2 is applied in test site 2, and so on. Therefore, the position of the test products on the test sites is randomized.

The complete Clinical Investigational Plan (CIP) is presented on Annex V. The CIP was approved by inovapotek Ethical Committee on the 14/06/2017. One subsequent amendment was performed to the CIP, to alter the Principal Investigator, amend the subject sample and product number.

5 – Results and Discussion

5.1 CIP compliance

No CIP deviations have occurred that can have affected the rights, safety or wellbeing of the subject or the scientific integrity of the clinical investigation.

5.2 Test subjects

5.2.1 Subject demographics

10 subjects were included in the clinical investigation and performed the measurements at time-point 30 minutes after the patch removal and 24 hours after the patch removal.
9 female and 1 male healthy subjects with ages between 18 and 65 years old, with Fitzpatrick skin phototype between I and IV and without skin diseases or other conditions that might interfere with the study were enrolled in this clinical investigation.
Full subject demographics data collected through the General Health Questionnaire and concomitant medications and treatments collected through the Concomitant Medications Log are presented on Annex II.

5.2.2 Subject withdrawal and dropouts

30 subjects were screened via telephone having effectively been screened 13 subjects for this clinical investigation. 3 of these subjects were screening failures as 2 subjects had excessive body hair and/or cutaneous alterations on the tested body region (back) which would interfere with the evaluation of the skin reaction and 1 subject missed the patch application.

5.3 Investigational Products

5.3.1 Changes to the investigational products & Product deficiencies

No changes to the investigational/comparator products were observed during the clinical investigation.

5.3.2 Treatment adhesion

The investigational/comparator product were dispensed with a micropipette, 20 µL, over filter paper discs, placed onto the Finn chamber 8mm.

5.3.3. Product codification

Table 1. Codification of the investigational and of the comparator products

Investigational and Comparator Products	Product code
Sodium lauryl sulphate at 2%	2
Water type II	6
Pain Relief - Relief&Go - Innocan Pharma	19

5.4 Measurements

5.4.1 Room conditions

All the study procedures were performed by trained and experienced personnel under controlled atmospheric conditions at all time points. The mean values of temperature (T) and relative humidity (RH) in acclimatization room and in the measurement rooms are presented in the following tables. Complete values are presented in Annex III.
All the values of temperature and relative humidity recorded during the study complied with the specifications.

Table 2. Mean temperature and relative humidity values recorded during the acclimatization period

	30 min after patch removal		24 h after patch removal	
	T (°C)	RH (%)	T (°C)	RH (%)
Mean	22.9	53.0	22.8	55.2
SD	0.5	1.6	0.6	1.1

Table 3. Mean temperature and relative humidity values recorded during the measurements

	Patch application		30 min after patch removal		24 h after patch removal	
	T (°C)	RH (%)	T (°C)	RH (%)	T (°C)	RH (%)
Mean	23.2	49.5	23.0	52.6	22.9	54.8
SD	0.3	2.0	0.5	0.6	0.6	0.5

5.4.2 Control measurements (if applicable)

Not applicable

5.4.3 Tolerance evaluations

The acute cutaneous irritation potential is evaluated by clinical scoring 30 minutes and 24 hours after the adhesive removal.

The clinical scoring of erythema and oedema are done according to a 4-point scale (Table 4) and other clinical signs and symptoms felt by the subjects during the study are also recorded (Table 5).

Table 4. Clinical Scoring of erythema and oedema

CLINICAL SCORING	DESCRIPTION	
	ERYTHEMA	OEDEMA
0	No erythema	No oedema
1	Slight erythema (quiet pinked coloration of the complete tested area or rather visible on one part of the tested area)	Slight oedema (palpable and visible)
2	Obvious erythema (clear erythema covering all the tested area)	Obvious oedema with or without papule(s) or vesicle(s)
3	Important erythema (severe erythema covering all the tested area or erythema diffusing outside the tested area)	Important oedema (extended area outside the tested area) with or without papule(s) or vesicle(s)

Table 5. Clinical coding skin signs and symptoms

Code	Description
D	Desquamation
S	Dryness
P	Papule
V	Vesicle
PRU	Itching
PIC	Tingling
ARD	Burning
ADE	Marked reaction to the adhesive

For the analysis of the results, the scoring of the negative control is deducted to the scoring of the test products and positive control. Based on these deducted results, the

calculation of the acute irritation index (M.I.I.) for the test products and positive control is performed. The M.I.I. is an index calculated according to the following formula:

$$\textbf{M.I.I.} = \frac{\sum \text{ of the grade (erythema + oedema)}}{\text{Number of subjects}}$$

The obtained index is used to classify the test products according to the following scale:

Table 6. Classification of the products according to the obtained index

M.I.I.	CLASS
M.I.I. ≤ 0.20	Non irritating
0.20 < M.I.I. ≤ 0.50	Slightly irritating
0.50 < M.I.I. ≤ 1	Moderately irritating
M.I.I. > 1	Irritating

5.4.3.1 Clinical signs

The results obtained 30 minutes and 24 hours after the patch removal regarding clinical signs are presented on Tables 7 to 9 and the raw data is presented on Annex IV.

Table 7. Skin reactions of the positive control 30 min and 24h after patch removal (negative control deducted)

	30min after patch removal			24h after patch removal		
Subject ID	**Erythema**	**Oedema**	**Other symptoms**	**Erythema**	**Oedema**	**Other symptoms**
13	2	0	PRU, S	2	1	PIC, PRU
15	1	0	PRU	1	0	-
20	2	0	ARD, PRU, S	2	0	PRU, S
21	2	1	PRU, S	2	0	S
24	2	1	PRU, S	1	0	PRU
25	1	0	PRU	1	0	PRU
26	0	0	-	1	0	-
29	2	0	S	2	0	-
30	1	0	ADE	2	0	-
33	2	1	S	2	0	PRU, S

Table 8. Skin reactions of the investigational product 19 (Pain Relief - Relief&Go - Innocan Pharma) tested as is, 30 min and 24h after patch removal (negative control deducted)

	30min after patch removal			24h after patch removal		
Subject ID	Erythema	Oedema	Other symptoms	Erythema	Oedema	Other symptoms
13	0	0	-	0	0	-
15	0	0	-	0	0	-
20	0	0	-	0	0	-
21	0	0	-	0	0	PRU
24	0	0	-	0	0	PRU
25	0	0	-	0	0	-
26	0	0	-	0	0	-
29	0	0	-	0	0	-
30	1	0	ADE	0	0	-
33	1	0	ADE	0	0	-

Table 9. Acute irritation index for investigational product and positive control

M.I.I.		
Investigational and comparator products	Time after patch removal	
	30 min	24 h
Positive control (SLS at 2%)	1.80	1.70
Pain Relief - Relief&Go - Innocan Pharma	0.20	0.00

The skin irritation reaction reaches its maximum 24 hours after the patch removal. And for that reason, the results at this time (24 hours) show better the real reactions and are more meaningful than at 30 minutes, and therefore M.I.I. calculations at 24 hours should be considered over the M.I.I. calculations at 30 minutes. Analysing the M.I.I. calculated (Table 9) 24 hours after patch removal, and according to the scale adopted, it can be concluded that the investigational product (Pain Relief - Relief&Go - Innocan Pharma) tested as is, is non-irritating with an acute skin irritation index of 0.00.

5.5 Adverse Events

No adverse events or significant adverse products effects were verified. Only mild and transient irritant reactions to the investigational and control products were observed, as expected for this type of methodology.

6 – Conclusion

This clinical investigation aimed to confirm the absence of acute cutaneous irritation potential of the investigational products after a 48 hours patch test performed in a group of 10 subjects, by clinical evaluation after 30 minutes and 24 hours of the patch removal.
Regarding the study results, the investigational product tested as is and demonstrated to be non-irritating under the test conditions, with an acute irritation index of 0.00.
The benefits of the investigation superposed the risks, as the tolerance degree of the products was assessed and no adverse events were observed. Only mild and transient irritant reactions to the investigational and control products were observed, as expected for this type of methodology.
In conclusion, the investigational product (Pain Relief - Relief&Go - Innocan Pharma) was concluded to be non-irritating.

7 – Bibliographic References

1	"Product Test Guidelines for the Assessment of Human Skin Compatibility", Colipa Guidelines, 1997.
2	Clinical investigation of medical devices for human subjects — Good clinical practice. International Standard ISO 14155. 2nd edition. 01/02/2011
3	Guideline for Good Clinical Practice – ICH harmonised tripartite guideline E6 (R1). International Conference on Harmonization (ICH). 10 June 1996
4	Goossens, An "Art and science of patch testing". Indian J Dermatol Venereol Leprol (2007); 73 (5): 289-291.
5	Wahlberg, J.E., Lindberg, M. "Patch Testing". Contact Dermatitis (2006); 4th Edition; pp 365-390.
6	An, S. M., Ham, H., et.al. "Primary irritation index and safety zone of cosmetics: retrospective analysis of skin patch tests in 7440 Korean women during 12 year". International Journal of Cosmetic Science (2013); 36: 62-67.
7	Safety Attestation of the product Aqueous solution of sodium lauryl sulfate at 2%; Proposition no. P126C15P173A15P243C16P270C16; 12/01/2017.
8	Tupker, R. A., et al. "Guidelines on sodium lauryl sulfate (SLS) exposure tests". Contact Dermatitis (1997); 37: 53-69.
9	SCCNFP. "Basic Criteria of the Protocols for the skin Compatibility Testing of Potentially Cutaneous Irritant Cosmetic Ingredients or Mixtures of Ingredients on Human Volunteers". (December 1999).
10	Information leaftet; SmartPractice®. "Finn Chambers on Scanpor®". (2011).

8 – Data Handling and Record Keeping

The documents and records supporting the clinical investigation will be archived in the Study Master File at CRO for 10 years. The CRO must obtain Sponsor written permission before disposing of any records even if the retention requirements have been met.

ANNEXES

ANNEX I – CV OF THE INVESTIGATORS

ANNEX II - SUBJECT DEMOGRAPHICS, CONCOMITANT MEDICATION & TREATMENTS

ANNEX III – TEMPERATURES AND RELATIVE HUMIDITY

ANNEX IV – CLINICAL EVALUATION RESULTS

ANNEX V – CLINICAL INVESTIGATION PLAN