inovapotek
PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Clinical Investigation Final Report FR02A/P140D20

This blinded randomized clinical study aimed to assess *in vivo* the hydrating efficacy of one cosmetic serum by measuring the skin capacitance with the equipment Corneometer® CM825 (Courage+Khazaka electronic GmbH, Germany) before and 2, 4, 8 and 24 hours after a single product's application on the forearm compared to one negative control (type II water) and one positive control (glycerine at 85%, aqueous solution).

This clinical investigation was performed in accordance with the respective Clinical Investigation Plan and Study 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.	EC002_v04/ P140D20_v00	**Study beginning date:**	09/07/2020	**Study conclusion/ suspension date:**	03/09/2020
Report Date:	03/09/2020	**Report Author**	Bárbara Tavares		

Identification of Study Parties

Sponsor	Fancystage Unipessoal Lda. Rua da Cumieira, nº 31 4786-681 Trofa – PORTUGAL
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	Bárbara Tavares
Investigator(s)	Ana Luísa Fonseca, Nádia Santos
Technical Assistant (s)	Liliana Ferraz, Maria João Vieira, Marta Monteiro
Study Coordinator	Márcia Rodrigues
Administrative assistant (s)	Andreia Carvalho

Identification of Investigational Product

Investigational Product (s)			Comparator Product (s)		
Designation	Reference	Batch number	Designation	Reference	Batch number
Facial Serum 300mg CBD - SHIR - Innocan Pharma	316	2806	Type II water (negative control)	-	F7M51
			Aqueous solution of glycerine at 85% (positive control)	-	I8K55

Clinical Investigation Report prepared/~~changed~~ by

INOVAPOTEK

Marta Monteiro, Responsible for preparing/~~changing~~ the Clinical Investigation Report

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Clinical Investigation Report approved by

INOVAPOTEK

Bárbara Tavares, Principal Investigator/Study Director

Signature/Date:

Bárbara Tavares 2020.09.03 18:11:09 +01'00'

SPONSOR

Teresa Neves, Sponsor representative

Signature/Date:

Clinical Investigation Report verified by

INOVAPOTEK

Marta de Oliveira Ferreira, on behalf of the Quality Assurance Manager

Signature/Date: Marta de Oliveira Ferreira 2020.09.04 08:21:29 +01'00'

HISTORY OF THE DOCUMENT

Revision	Amendment/Deviation	Date
A	First issue	03/09/2020

Table of Contents

Abbreviated terms and definitions

µl	Microliter
A.U.	Arbitrary Units
CEC	Competent Ethics Committee
CIP	Clinical Investigational Plan
CIR	Clinical Investigational Report
cm	Centimeter
CM	Corneometer
cm^2	Square Centimeter
CRO	Contract Research Organization
CV	Curriculum Vitae
EC	Ethics Committee
g	Gram
GHQ	General Health Questionnaire
ICH GCP	International Conference on Harmonisation-Good Clinical Practice
INFARMED	National Authority of Medicines and Health Products I.P.
mg	Milligram
No	Number
ºC	Celsius degrees
PI	Principal Investigator
RH	Relative Humidity
RNEC	National Registry for Clinical Studies
s	Seconds
SD	Standard Deviation
t	Time
T	Temperature
vs	Versus

1 – Ethics and Quality Assurance

The CIP EC002 was approved by Ethics Committee for Health of inovapotek on the 17/07/2019. Four subsequent amendments were performed to the CIP, the first one to perform a revision of the Detailed Procedure; the second one to perform recommended alterations by the Ethics Committee of inovapotek; the third one to alter the Principal Investigator and include additional possible test areas and measurements; the fourth to include new recommended alterations by the Ethics Committee of inovapotek.

The CIP code EC002 was submitted to INFARMED, I.P. on the 30/05/2019 through the RNEC (National Registry for Clinical Studies) platform under the number 102124.

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

2 – Summary

CIP n./Study Plan n.	EC002_v04/ P140D20_v00	**Study beginning date:**	09/07/2020	**Study conclusion/ suspension date:**	03/09/2020
Title	Blinded Randomized Clinical Study For The Evaluation Of Hydrating Efficacy Of One Cosmetic Serum				

This blinded randomized clinical study aimed to assess in vivo the hydrating efficacy of one cosmetic serum by measuring the skin capacitance with the equipment Corneometer® CM825 (Courage+Khazaka electronic GmbH, Germany) before and 2, 4, 8 and 24 hours after a single product's application on the forearm compared to one negative control (type II water) and one positive control (glycerine at 85%, aqueous solution).

Regarding the study results, the investigational product induced statistically significant hydration increases of up to 164.66%, 141.63%, 146.15% and 121.17% (with mean values of 107.81%, 87.28%, 66.67% and 31.29%) after 2, 4, 8 and 24 hours of a single product's application, respectively, in comparison with the negative control.

The product was well tolerated by the subjects with no uncomfortable symptoms or feelings reported by the subjects.

The benefits of the investigation superposed the risks, as the efficacy degree of the product was assessed and no adverse events were observed.

In conclusion, the investigational product **Facial Serum 300mg CBD - SHIR - Innocan Pharma** demonstrated to have a significant hydrating effect that lasts up to 24 hours after one single application.

3 – Introduction

This blinded randomized clinical study aimed to assess *in vivo* the hydrating efficacy of one cosmetic serum by measuring the skin capacitance with the equipment Corneometer® CM825 (Courage+Khazaka electronic GmbH, Germany) before and 2, 4, 8 and 24 hours after a single product's application on the forearm compared to one negative control (type II water) and one positive control (glycerine at 85%, aqueous solution).

In order to perform this study, one group of 20 healthy female subjects with 18 years old and older were enrolled. Each subject tested a total of three products: the investigational product and two comparator products – one negative control (type II water) and one positive control (aqueous solution of glycerine at 85%).

A plastic marker was applied on a randomized subjects' forearm to outline three test areas, where 2 mg/cm^2 of the investigational product and 2 µl/cm^2 of the comparator products were applied directly on the respective test area.

The skin hydration was evaluated by measuring the skin capacitance, in triplicate, in the previously randomized forearm (volar part), with the equipment Corneometer® CM825 (Courage+Khazaka electronic GmbH, Germany) before (t00) and 2 (t02), 4 (t04), 8 (t08) and 24 (t24) hours after a single product's application on each specific test site of the forearm.

4 – Results and Discussion

4.1 CIP compliance

CIP n./Study Plan no.	EC002_v04/ P140D20_v00	**Study beginning date:**	09/07/2020	**Study conclusion/ suspension date:**	03/09/2020
Title	Blinded Randomized Clinical Study For The Evaluation Of The Hydrating Efficacy Of One Cosmetic Serum				

No CIP/Study Plan deviations have occurred that can have affected the rights, safety or wellbeing of the subject or the scientific integrity of the clinical investigation.
Some temperature and relative humidity (RH) values recorded both for acclimatization and measurements were out of the specifications (23.0 +/- 1.0 °C and 50 +/- 10% RH) as it can be observed in Annex V.
After performing the results analysis, it was concluded that these deviations had not a significant impact on the integrity of the study and therefore all participants completed the study.

4.2 Test subjects

4.2.1 Subject demographics

20 female subjects were included in the clinical investigation and performed the measurements at time-point t00, t02, t04, t08 and t124.
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 III.

4.2.2 Subject withdrawal and dropouts

105 subjects were screened via telephone and 21 subjects were screened in person for this clinical investigation. Of these, 1 was screening failures because the subject was not available for the entire study duration.

4.3 Investigational Products

4.3.1 Changes to the investigational products & Product deficiencies

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

4.3.2 Treatment adhesion

The mean amount of the investigational product Facial Serum 300mg CBD - SHIR - Innocan Pharma weighed during the study was 14.00 mg ± 0.08 mg, and the mean amount applied per skin area on each single application was 1.99 mg/cm^2 ± 0.01 mg/cm^2.

Complete values are presented in Annex IV.

4.3.3. Product codification

The products were coded by inovapotek's personnel not involved in the clinical study, according to the following table:

Table 1. Codification of the investigational and comparator products

Batch	Product Name	Product Codification
2806	Facial Serum 300mg CBD - SHIR - Innocan Pharma	A
F7M51	Type II water	C
I8K55	Aqueous solution of glycerine at 85%	B

4.4 Measurements

4.4.1 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 table. Complete values are presented in Annex V.

Some temperature values recorded were out of the specifications (please see section 4.1 for details), but, after performing the results analysis, it was concluded that these temperature deviations had not a significant impact on the study results.

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

	t00		t24	
	T (°C)	RH (%)	T (°C)	RH (%)
Mean	23.7	49.6	23.3	51.1
SD	0.8	3.7	0.6	2.9

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

	t00		t02		t04		t08		t24	
	T (°C)	RH (%)	T (°C)	RH (%)	T (°C)	RH (%)	T (°C)	RH (%)	T (°C)	RH (%)
Mean	23.0	50.3	22.8	49.4	23.0	48.6	22.5	50.4	22.6	52.3
SD	0.5	3.0	0.6	2.2	0.5	1.9	0.4	2.0	0.5	1.5

4.4.2 Control measurements (if applicable)

Not applicable.

4.4.3 Efficacy evaluations

4.4.3.1 Skin hydration evaluation

Skin capacitance was measured with a Corneometer® CM825 (Courage+Khazaka electronic GmbH, Germany) applying slight pressure in each test site, in triplicate, before application of the products (t00), 2 hours (t02), 4 hours (t04), 8 hours (t08) and 24 hours (t24) after one single application of the products.

The probe head is placed vertically on the skin area to be measured according to the pressure of the spring in the probe. A beep signal is heard if the measurement has been carried out successfully. The probe head is cleaned thoroughly between measurements with a dry paper. Any dirt, water or alcohol on the probe head might influence the measurement values.

Each skin site is measured 3 times not on exactly the same spot but in a neighbouring skin area. Repeated measurements on the same skin area lead to a moisture increase due to occlusion, as water is accumulated under the probe head and cannot evaporate.

The measurement of the skin hydration is based on the internationally recognized capacitance method. This measurement is based on the completely different dielectric

constant of water and other substances. The measuring capacitor shows changes of capacitance according to the moisture content of the samples. The changes in capacitance are converted in hydration units varying from 0 to 120, where 0 units correspond to very dry and 120 units to very humid skin areas. The results are given in arbitrary units (A. U.).

The results obtained at all time-points for the skin hydration with each investigational/control products are presented on Tables 4 to 6 and Figures 1 to 2. The *p-values* obtained in the statistical analysis performed are also presented in these tables and the complete statistical tables of each statistical test performed are presented in Annex VII.

Table 2. Skin hydration results obtained before (t00) and after 2 hours (t02), 4 hours (t04), 8 hours (t08) and 24 hours (t24) of product's application for the investigational product Facial Serum 300mg CBD - SHIR - Innocan Pharma (Product code: A)

	t00 (n=20)	t02 (n=20)	t04 (n=20)	t08 (n=20)	t24 (n=20)
Hydration mean values (A.U.)	33.27	68.51	62.69	55.74	43.87
±SD (A.U.)	4.92	12.75	15.40	17.03	14.89
Mean differences		35.24	29.42	22.47	10.59
±SD		11.87	12.28	14.71	12.89
Mean differences (%)		107.81%	87.28%	66.67%	31.29%
±SD (%)		37.42%	33.72%	41.52%	35.15%
Number of subjects with skin hydration increase		20	20	20	18
Number of subjects with skin hydration increase (%)		100.00%	100.00%	100.00%	90.00%
Maximum increase (%)		164.66%	141.63%	146.15%	121.17%
Mean increase of the subjects who presented positive effects (%)		107.81%	87.28%	66.67%	35.16%
p value (A vs C)		<0.001*	<0.001*	<0.001*	0.006*

* Wilcoxon test

Table 3. Skin hydration results obtained before (t00) and after 2 hours (t02), 4 hours (t04), 8 hours (t08) and 24 hours (t24) of product's application for the positive control (Product code: B)

	t00 (n=20)	t02 (n=20)	t04 (n=20)	t08 (n=20)	t24 (n=20)
Hydration mean values (A.U.)	31.43	74.46	70.13	61.12	45.85
±SD (A.U.)	6.22	7.81	13.23	16.38	17.05
Mean differences		43.03	38.70	29.69	14.42
±SD		7.55	11.93	13.55	14.82
Mean differences (%)		143.37%	127.08%	95.02%	46.21%
±SD (%)		44.94%	46.63%	42.34%	48.25%
Number of subjects with skin hydration increase		20	20	20	19
Number of subjects with skin hydration increase (%)		100.00%	100.00%	100.00%	95.00%
Maximum increase (%)		255.89%	219.26%	168.27%	176.38%
Mean increase of the subjects who presented positive effects (%)		143.37%	127.08%	95.02%	48.67%
P value (B vs C)		<0.001*	<0.001*	<0.001*	<0.001*

* Wilcoxon test

Table 4. Skin hydration results obtained before (t00) and after 2 hours (t02), 4 hours (t04), 8 hours (t08) and 24 hours (t24) of product's application for the negative control (Product code: C)

	t00 (n=20)	t02 (n=20)	t04 (n=20)	t08 (n=20)	t24 (n=20)
Hydration mean values (A.U.)	35.66	37.07	39.65	36.19	37.69
±SD (A.U.)	11.11	10.37	13.20	6.87	11.45
Mean differences		1.41	3.99	0.52	2.03
±SD		13.83	13.15	9.23	11.88
Mean differences (%)		8.41%	13.26%	5.01%	7.92%
±SD (%)		28.18%	26.71%	18.93%	22.86%
Number of subjects with skin hydration increase		13	15	12	14
Number of subjects with skin hydration increase (%)		65.00%	75.00%	60.00%	70.00%
Maximum increase (%)		82.63%	83.28%	38.54%	66.86%
Mean increase of the subjects who presented positive effects (%)		22.66%	23.19%	16.45%	18.44%

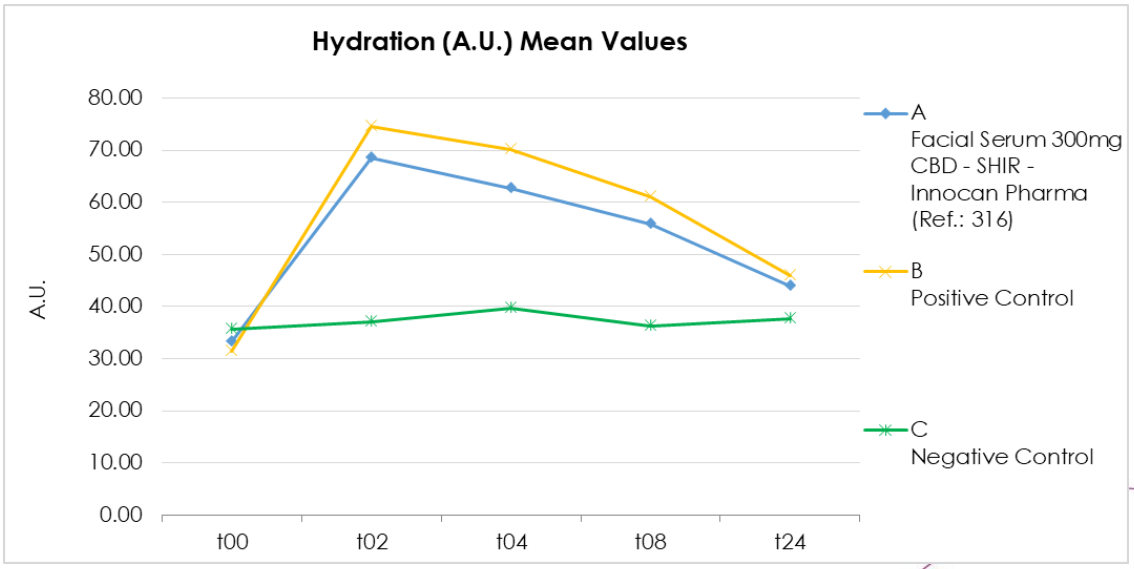

Figure 1. Skin hydration mean results obtained before (t00) and after 2 hours (t02), 4 hours (t04), 8 hours (t08) and 24 hours (t24) of products' application (investigational product, positive control and negative control).

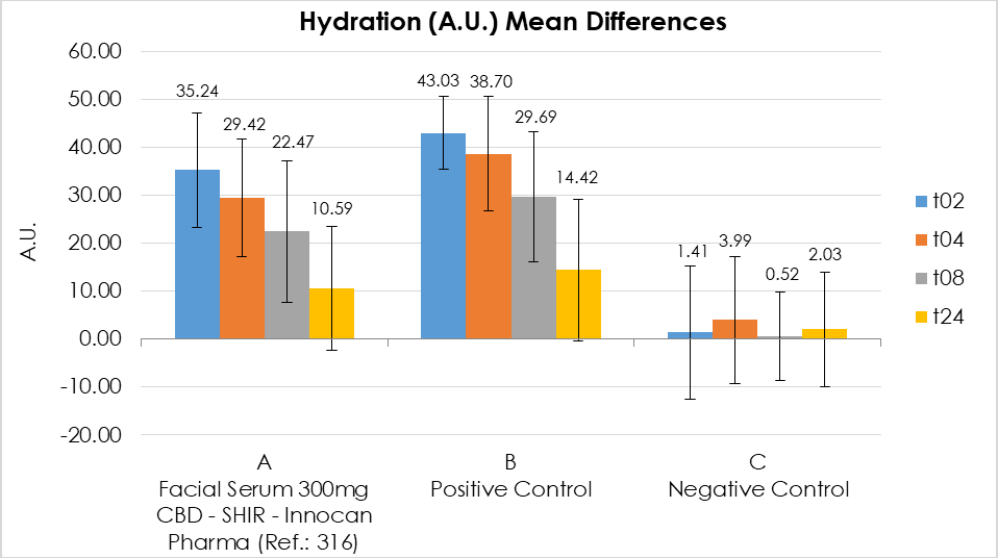

Figure 2. Skin hydration mean differences to the baseline obtained after 2 hours (t02), 4 hours (t04), 8 hours (t08) and 24 hours (t24) of products' application (investigational product, positive control and negative control).

The hydration values obtained for the negative control showed some fluctuations during the entire study duration that were considered normal as the skin hydration variates naturally throughout the day. It was observed an increase of the skin hydration for 100% of the subjects at all time-points for the positive control. These results validate and support the purpose of the positive control. Regarding the results of the statistical analysis it was observed a statistically significant difference between the positive control and the negative control at all evaluated time-points, thus validating the methodology of the study.

The investigational product Facial Serum 300mg CBD - SHIR - Innocan Pharma induced hydration increases up to 164.66%, 141.63%, 146.15% and 121.17% (with mean values of 107.81%, 87.28%, 66.67% and 31.29%) after 2, 4, 8 and 24 hours of the application, respectively. Statistically significant differences between the investigational product and the negative control were observed at t02, t04, t08 and t24 ($p \leq 0.05$) it can therefore be concluded that the investigational product increases significantly the skin hydration, showing a long-lasting effect up to 24 hours with consistent results.

4.4.4 Tolerance evaluations

Not applicable.

4.5 Adverse Events

No adverse events were reported during the study.

5 – Conclusion

This blinded randomized clinical study aimed to assess *in vivo* the hydrating efficacy of one cosmetic serum by measuring the skin capacitance with the equipment Corneometer® CM825 (Courage+Khazaka electronic GmbH, Germany) before and 2, 4, 8 and 24 hours after a single product's application on the forearm compared to one negative control (type II water) and one positive control (glycerine at 85%, aqueous solution).

Regarding the study results, the investigational product induced statistically significant hydration increases of up to 164.66%, 141.63%, 146.15% and 121.17% (with mean values of 107.81%, 87.28%, 66.67% and 31.29%) after 2, 4, 8 and 24 hours of a single product's application, respectively, in comparison with the negative control.

The product was well tolerated by the subjects with no uncomfortable symptoms or feelings reported by the subjects.

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In conclusion, the investigational product **Facial Serum 300mg CBD - SHIR - Innocan Pharma** demonstrated to have a significant hydrating effect that lasts up to 24 hours after one single application.

6 – Bibliographic References

1	Clinical investigation of medical devices for human subjects — Good clinical practice. International Standard ISO 14155. 2nd edition. 01/02/2011
2	Guideline for Good Clinical Practice – ICH harmonised tripartite guideline E6 (R2). International Conference on Harmonization (ICH). 9 November 2016
3	Regulation (EC) no 1223/2009 of the European Parliament and of the Council; 30/11/2009
4	Mod.225.00_Study Plan_v01_PHDTA20, inovapotek, 25/05/2020

7 – 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 - CVs of the Investigators

ANNEX II - Randomization table

ANNEX III - Subject Demographics, Concomitant Medication & Treatments

ANNEX IV – Investigational Product Weight

ANNEX V - Temperatures and Relative Humidity

ANNEX VI – Skin Hydration Results

ANNEX VII - Statistical Analysis Results

ANNEX VIII - Study Plan