CONFIDENTIAL

REPORT: ACCEPTABILITY STUDY (IEC BULGARIA)

IN-USE TEST UNDER ODONTOLOGICAL CONTROL

Clinical study for the appraisal of the oral and dental acceptability of a cosmetic investigational product, after repeated applications under normal conditions of use, in the adult subject

Investigational product	:	**SMOKETREE HYDROLINA BY INA ESSENTIALS** (ref.: 3220901 - Batch n° Lot 6 - 2021)
Standard Study Protocol	:	PEG-TUDRSTD-3.0-GB-of 17 February 2020
Specific Study Protocol	:	N° B220449PE - Version 1, of 29 April 2022
Report	:	N° B220449RD – Version 2, of 02 August 2022
Sponsor	:	**"Ina Trade" Ltd.** 13, Rayna Knyaginya Street 4500 Panagiurishte, Bulgaria
Study monitor	:	Mrs Maria RALCHEVA
Beginning of observations	:	04 May 2022
End of observations	:	01 June 2022
Address of investigation	:	**I.E.C. Bulgaria** -17, Henrik Ibsen Street, Hladilnika, Lozenetz, 1407 Sofia – BULGARIA
Investigator	:	Mr Svilen MITEV, D.D.S. – Dental Surgeon
Responsible for study	:	Mr Valeri KRASTEV

TABLE OF CONTENTS

AUTHENTICATION

The study subject of the present report was conducted under my responsibility, in compliance with the study protocol, in accordance with the standard operating procedures of I.E.C., and in the spirit of the general principles of the Good Clinical Practice published by I.C.H. (Topic E6(R2): EMA/CHMP/ICH/135/1995).

I assume the responsibility of the validity of all raw data obtained during this study and mentioned in the present report.

Svilen MITEV, D.D.S
Dental Surgeon Investigator

I have read this report, I certify that these data are an accurate reflection of the results obtained and I agree with its content.

Valeri KRASTEV
Responsible for study

PERSONNEL INVOLVED IN THE STUDY

I.E.C. FRANCE, 88 boulevard des Belges, 69006 Lyon - France

- **President**
  ETIENNE CAMEL
  Pharm. D., D.E.A. in Skin Biology and Cosmetology, Senior Toxicologist
  (European Registered Toxicologist)

- **General Director**
  FRÉDÉRIC GUILLOT
  Toxicologist, Masters in Management and International Law

- **Scientific Director**
  JEAN-ROBERT CAMPOS
  Post-Graduate in Dermocosmetology
  Ph.D in Cellular Biology and Microbiology

- **Head of Clinical Safety Studies**
  NICOLAS RENTERO
  Ph.D. in Physiology, Industrial and Agribusiness Biochemistry Engineer

- **Responsible for the Study**
  MARINE CHEYMOL
  Master's degree in Microbiology – Microbial Bioprocess

- **Responsible for the Data Management and Statistical Analysis**
  YVES CHIPIER
  Senior technician in Biochemistry

I.E.C. BULGARIE, 17, rue Henrik Ibsen, Hladilnika, Lozenetz - 1407 Sofia - Bulgaria

- **Executive Director**
  GUENTCHO VELEV
  Master in Economics and International Trade

- **Administrative Manager**
  IRINA TOTEVA
  Master in French

- **Operational, Technical and Scientific Laboratory Director**
  BORYANA HRISSIMOVA
  Master in Biology and Chemistry

- **Investigator**
  SVILEN MITEV, D.D.S.
  Post-Graduate in Dental Surgery

- **Technician**
  MARIA VALCHANOVA
  Nurse

- **Responsible for the Study**
  VALERI KRASTEV
  Bachelor's degree in Molecular Biology

QUALITY CONTROL

This study is performed in compliance with the Standard Operating Procedures of the Institut d'Expertise Clinique, the protocol signed with the sponsor and in the spirit of the general principles of the Good Clinical Practices published by I.C.H. (Topic E6(R2): EMA/CHMP/ICH/135/1995).

Audits of clinical studies are conducted every 6 months on each type of study. They are intended to verify the good compliance with the procedures during the study. The results of these audits are reported to the investigator(s) and to the responsible of the laboratories.

The I.E.C. Bulgaria Quality Unit ensures the compliance of the report with the data generated during the study.

Sofia,
On 02 August 2022

Evgeniya RUSEVA
Quality Auditor

1. INTRODUCTION

The study consists in the application of an investigational product under normal conditions of use, to adult subjects. The target panel of the study depends on the tested investigational product nature.

2. STUDY DESIGN

2.1. Study objective

Appraise the oral and dental acceptability of a cosmetic investigational product, after repeated applications under normal conditions of use, in the adult subject.
Claims to be justified: "Tolerance tested under Odontological control", "Suitable for sensitive gums".

2.2. Study type and regulation

2.2.1. Study type

Acceptability study ("in-use test"), under Odontological control, in "open"

2.2.2. Regulation

The study is performed in agreement with the most recent recommendations of the World Medical Association (Declaration of Helsinki - 1964, and last amendment in force, except principle n° 35 related to study registration in a publicly accessible database) and in the spirit of the general principles of the Good Clinical Practice published by I.C.H. (Topic E6(R2): EMA/CHMP/ICH/135/1995).

Moreover, this study is carried out in accordance with the following requirement:
• EU regulation 2016/679 of 27 April 2016 (General Data Protection Regulation) on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC.

2.3. Study relevance

In man, the "in-use" ("acceptability") test performed under Odontological control (subjects individually examined by a Dental Surgeon Investigator) enables to check the absence of discomfort and/or irritation reactions (functional and physical signs) linked to the investigational product.

A directed and adapted questionnaire also enables to appreciate the cosmetic acceptability and the efficacy of the investigational product on the basis of answers given by the subjects.

2.4. Study principle

ACTIONS	D0	D28
Inclusion by the Dental Surgeon Investigator		
Individual clinical examination by the Dental Surgeon Investigator (checking of functional and physical signs)		
Clinical evaluation by the Dental Surgeon investigator (scoring)		
Applications of the investigational product by the subject		
Subject filling in a questionnaire concerning the safety of the investigational product		
Subject filling in a questionnaire concerning the cosmetic acceptability and efficacy of the investigational product		
Appraisal of the cosmetic acceptability and efficacy of the investigational productby the subject, in presence of the Dental Surgeon Investigator		

Grey boxes = actions done

2.5. Investigational product

Designation of the Sponsor	SMOKETREE HYDROLINA BY INA ESSENTIALS
Formula / Reference	3220901
Batch	Lot 6 - 2021
Physical form / Colour	Liquid / transparent
I.E.C. identification code	B220449 09005003
Packaging	Plastic bottle
Quantity supplied *(packaging included)*	25 x 231g + 44 x 231 g
Date of receipt	28/04/2022 + 13/05/2022

Analytical control
The Sponsor guarantees the conformity of the investigational product with the labeling and provides the investigational laboratory with information (designation, formula).
For this type of study, no analytical dosage is made and neither stability, nor absorption of the investigational product are evaluated by I.E.C.

Storage
. Under lock and key, protected from heat, at room temperature.
. The investigational products are destroyed at the end of the study. A sample of the investigational product is kept in the concerned facility for 4 months as of the date of dispatch of the final report. From this date and unless otherwise specified by the Sponsor, the investigational product is destroyed by a specialized company.

2.6. Subjects

2.6.1. Initial inclusion in I.E.C.'s database

To enter the panel of I.E.C., each candidate should undergo a medical examination in the facilities of I.E.C.. This medical examination is performed to ensure that the subject is healthy.
In particular, is not included:

- subject having undergone organ excision, organ transplant, skull concussion with extended loss of consciousness in the last 5 years or with present after-effects;
- subject having a weight out of limits given in our procedures (based on the classification of the Body Mass Index (B.M.I.) defined by the World Health Organization);
- subject having a disease of the immune system or under immunosuppressive treatment;
- subject having treated asthma crisis;
- subject having at least one of the following disorders: cardiovascular, pulmonary, digestive, neurologic, psychiatric, genital, urinary, haematological, endocrine;
- subject having or being in the course of a long-term treatment, in particular with aspirin, products containing aspirin, anti-inflammatories, antibiotics, antihistamines, corticoids, beta-blockers (including eye lotion) and/or desensitisation drugs;
- subject having a skin disease, and in particular: urticaria, œdema, eczema, recurrent herpes, herpes zoster having erupted in the last 3 months, pityriasis versicolor, common acne with a sudden rise of inflammation or nodular or cystic acne, psoriasis, ichthyosis, lichen planus, chronic lupus erythematosus, cheloid scars, severe pigmentation disorders (vitiligo, chloasma, multiple lentigines, numerous or congenital nevi, especially if they are of large size), hyperhidrosis, dorsal hyperpilosity;
- subject having drug or cosmetic intolerance.

Beside the examination and questioning, the subject signs a general consent form, certifying, in particular, that he/she:

- understands the language used in the research center;
- has a health care insurance (private medical aid, social welfare, government health service…) or, if not, a fixed abode;
- can be contacted in case of emergency;
- is not deprived from liberty by a judiciary or administrative decision nor sick in situation of emergency;
- is not admitted to sanitary or social facilities.

The subject commits him/herself to inform I.E.C. of any modification regarding these inclusion criteria and these criteria are reminded to the subject in the informed consent form of the study.

2.6.2. Principle of selection, recruitment and inclusion

The procedure for selection, recruitment and inclusion of the subjects accepting to participate in the study, after having signed an informed consent form, is elaborated to give them clear and precise information, enabling them to appraise the aim and the consequences of their consent.

This procedure includes, in particular:

- a preliminary interview (with the help of an information sheet) during which the objective and the protocol of the study (methodology, duration, study timetable etc...) are explained to the subject, as well as the indemnity amount, the possible benefits, the constraints linked to the study and the foreseeable risks, even in case of stop of the study before its normal end, the non-inclusion period, the possibility for him/herself to check the exactitude of the data contained in his/her medical file;
- the notification of his/her taking over by the insurance in civil liability subscribed independently by the Sponsor and I.E.C., once the subject is definitely admitted in the study by the investigator;
- the signature of an informed consent form by the subject: he/she is thus able to make his/her decision completely freely taking the conditions proposed into account.

Prior to a subject's participation in a study, the subject dates and signs the information sheet and the informed consent form, with full knowledge of the facts. The investigator dates and signs the participation consent form. The information sheet and an original copy of the signed and dated informed consent form are kept by the subject and by the investigator.

The final inclusion of the subject in the study is determined by the investigator, from a clinical examination specific to the study, performed just before the its start, and on the basis of the inclusion and non-inclusion criteria of the study.

2.6.3. Number of subjects requested for the study

The number of valid cases expected is 25 on demand of the Sponsor. A valid case is defined as a subject who has completed a full procedure (complete application duration with all examinations planned).
At least 20 subjects are frequently used for in-use tests and it is considered as a sufficient number to draw valid conclusions.
The subjects are registered and a number in the study is allocated in progressive order of their arrival and selection.

2.6.4. Characteristics of subjects (inclusion and non-inclusion criteria)

This criterion is evaluated on the basis of a questionnaire and clinical examinations listed in the case report form.

100% of subjects with "sensitive" gums were included in the study. This percentage corresponds to a currently admitted proportion for this population.
This criterion shall be put in concrete form by a positive answer to the following question: "do you have any abnormal and repeated reactions to the gums (prickling, itching, redness…)?"
- to oral and dental products;
- to teeth brushing.

Unless specifications given by the Sponsor, a maximum of 25% of "healthy subjects with family or personal history of atopy, without any progressive or recent clinical features of atopic disease" can be included in the study. This percentage corresponds to a currently admitted proportion for this population.
To be considered as a subject with history of atopy, the subject shall present with:
- either TWO cases of familial past history (among: mother, father, brother(s) and sister(s)) for the following affections: (1) atopic dermatitis, (2) allergic asthma in the 1st part of life, (3) recognized pollinosis, (4) dermo-respiratory syndrome;
- or personal past history (at least ONE criterion) among the following affections: (1) constitutional eczema, mostly appearing during the childhood and mostly located into the skin folds, (2) recurrent periodic asthma in the childhood or pre-teenage years (no asthma crisis should have occurred during the last 6 months), (3) recurrent periodic (chronic) conjunctivitis, (4) documented (allergological examination + prick tests) or non-documented pneumallergen related (pollens, acaridae, animals) allergic rhinitis.

2.6.4.1. Inclusion criteria

. Number of subjects: 20

. Origin: Caucasian

. Gender: female or male

. Age: 18 to 70 years old

. Good oral health with at least 20 natural teeth (excluding third molar)

. Mean Modified Gingival Index (MGI) of at least 2

. Mean Bleeding Index (BI) of at least 2

. 100% Sensitive gums

2.6.4.2. Non-inclusion criteria

The following non-inclusion criteria are controlled by the I.E.C. Subject database and thus are not subject to a specific documentation in the case report form:
- Subjects not having respected the restriction concerning the simultaneous acceptance of several biomedical research projects;
- Subjects not having respected the wash-out period during which a person may not be involved in any other biomedical research projects;

The following criteria are evaluated on the basis of a questionnaire and clinical examinations listed in the case report form:
- Subjects not giving their consent;
- Subjects not complying with protocol requirements;

HEALTH OF THE SUBJECT

- Subject of whom the health condition has changed since the inclusion visit in the I.E.C. database and makes the subject ineligible or places him/her at undue risk;
- Subject pregnant, breastfeeding, or not willing to take necessary precautions to avoid a pregnancy during the study (for female subjects only);
- Subject having a medical treatment or being vaccinated or expecting to be vaccinated during the study, that makes the subject ineligible or places him/her at undue risk;
- Subject having a background of intolerance or allergy to cosmetics to drugs or to other substances that makes the subject ineligible or places him/her at undue risk;
- Subject with an oral or dental pathology;

CONTROL OF THE CONCERNED AREA OF THE PRODUCT APPLICATION

- Subject having visible traces of irritation or any other abnormality;
- Subject having undergone a surgery, a chemical or physical treatment to the concerned areas in the last 12 months;

COSMETIC HABITS AND WASH OUT
- Subject having modified his/her cosmetic habits (on the areas concerned by the study) during the last 2 weeks, which makes him/her ineligible;
- Subject having applied a product on the areas concerned by the study, on the inclusion day of the study.

2.6.5. Removal of subjects from study or data analysis

Reasons for which a subject can be discontinued from the study or withdrawn from the data analysis, are one of the following:
- Adverse event,
- Serious adverse event,
- Concomitant treatment incompatible with the study,
- Consent withdrawal by the subject*,
- Lost to follow up,
- Emergence of a non inclusion criterion,
- Decision of the Investigator,
- Violation of the protocol.

** All the subjects are informed of the fact that they can willingly and freely withdraw their consent for participating in the study, if they wish to do so.*

Any discontinuation in the participation of a subject during the study is mentioned in the report and the reasons for this discontinuation are precised. Any premature discontinuation linked to an adverse event or a serious adverse event is followed-up (until final outcome).

If the number of discontinuation or non presentations at the beginning of the study is higher than 10%, the subjects are replaced so that the data are available in at least 90% of the expected valid cases number, except if this discontinuation is due to a severe intolerance to the investigational product.

2.6.6. Constraint and Restriction during the study

Are not authorized:

Drugs / Medical treatments / Vaccination	- Aspirin and derivates - Anti-inflammatory - Antibiotics - Antihistamines - Systemic steroids - Vaccination
Environmental conditions	Any solar exposure, apart from their usual habits
Others	- Product replaced by the investigational product - Changes in cosmetics habits - The investigational product should not be applied on the last day of the study

2.7. Methodology

2.7.1. Mode of application

The applications of the investigational product are performed by the subject at home (starting on D0 and ending on D27 in replacement of the one he/she generally uses and according to the following indications:

Application area	Oral cavity (teeth + gums)
Quantity	As much as necessary
Duration	4 consecutive weeks
Frequency	At least twice a day (in the morning and evening)
Application Conditions	Under normal conditions of use

2.7.2. Appraisal of the oral and dental acceptability by the Dental Surgeon Investigator

The clinical examinations were carried out by the Dental Surgeon Investigator, before the start of use (D0) of the investigational product and after the 4 weeks of application (D28).

The oral and dental acceptability was assessed, by the Dental Surgeon Investigator, on the basis of clinical examinations of the oral and dental cavity (teeth, gums, mucous membranes) *enabling* to observe the physical signs (inflammation, œdema, ulceration…) and of a questioning making possible to evaluate the functional signs (prickling, tightness, heating sensation…) linked to the use of the investigational product. Those data were completed by a questionnaire filled in by the subject and given back to the Dental Surgeon Investigator the last day of the study, detailing the application frequency and application number as well as the nature, location, intensity, duration, period of appearance and emergence after application, of the reactions if any.

2.7.3. Clinical evaluation (scoring) by the investigator

Environment	Using standard controlled conditions			
Criterion	*Area*	*Principle* [(1)]	*Mode*	*Evaluation time point(s)*
MODIFIED GINGIVAL INDEX (MGI)	4 to 6 teeth	5 point scale (0 to 4)	visual	D0 (baseline), and D28

0 = absence of inflammation

1 = mild inflammation; slight change in color, little change in color; little change in texture of any portion of the marginal or papillary gingival unit

2 = mild inflammation; criteria as above but involving the entire marginal or papillar gingival unit

3 = moderate inflammation; glazing, redness, oedema, and / or hypertrophy of the marginal or papillary gingival unit

4 = severe inflammation; marked redness, oedema and / or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

Environment	Using standard controlled conditions			
Criterion	*Area*	*Principle* [(1)]	*Mode*	*Evaluation time point(s)*
BLEEDING INDEX (BI)*	4 to 6 teeth	3 point scale (0 to 2)	visual	D0 (baseline), and D28

0 = no bleeding after 30 seconds

1 = bleeding upon probing after 30 seconds

2 = immediate bleeding observed

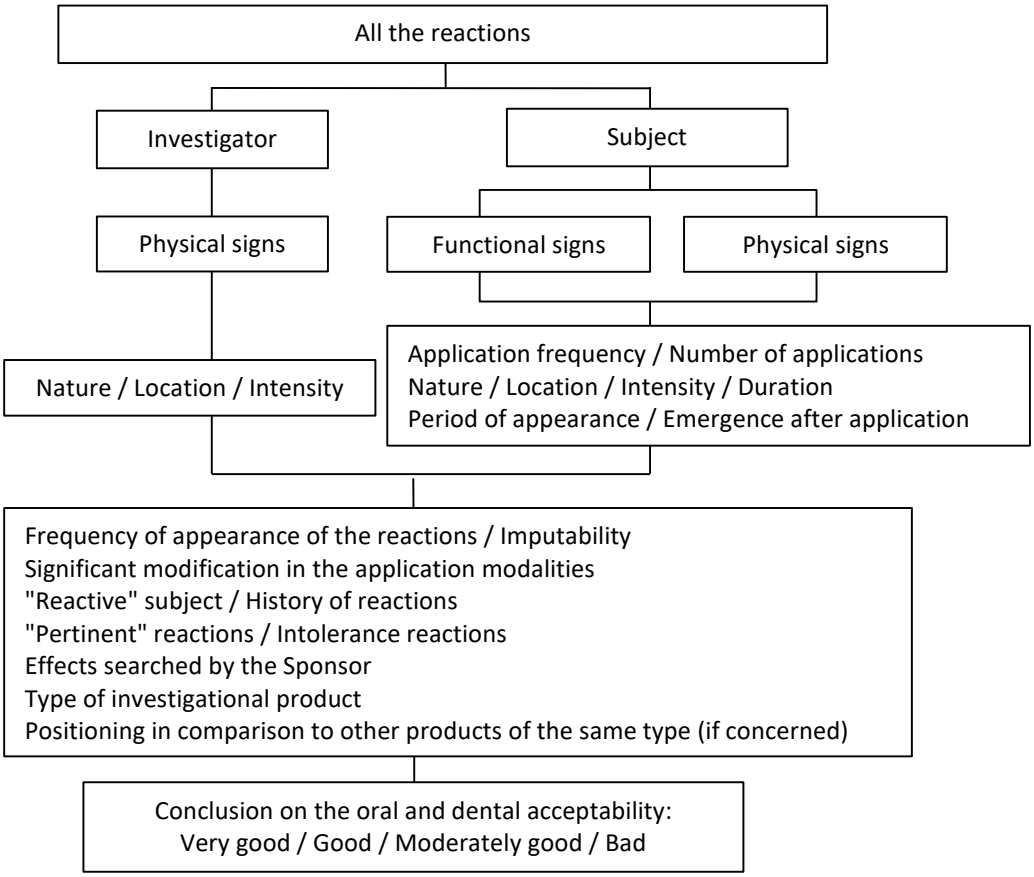
** Using a colour coded periodontal probe. The probe is engaged approximately 1 millimeter (mm) into the gingival crevice. A moderate pressure is used whilst sweeping along the sulcular epithelium gingiva*

The values obtained after application of the investigational products (D28) are compared to initial values (D0) by the paired Wilcoxon test ("two-tail", significativity: $p < 0.05$) after determination of means and standard deviations (sd). In case of statistically significant variation, calculation of the average variation percentage of each criterion at each time point of the study, compared to initial values, from the mean values.

The values obtained after application of the investigational products (D28) are compared between both investigational products by the Mann-Whitney test ("two-tail", significativity: $p < 0.05$). In case of statistically significant difference, calculation of the corresponding variation percentage and mean difference values.

2.7.4. Data analysis and interpretation of the results

The results obtained were collected, analyzed and interpreted by the Investigator, based on the normal conditions of use and the effects searched by the Study Monitor, according to the following schematic drawing.



2.7.5. Appraisal of the cosmetic acceptability and efficacy of the investigational product by the subject

The cosmetic acceptability and efficacy of the investigational product are assessed from a questionnaire adapted to the investigational product, elaborated in collaboration with the Study Monitor and filled in by the subject. The questionnaire is completed by an appraisal of the investigational product given in the presence of the Investigator.

2.8. Adverse events

2.8.1. Definition

An adverse event (A.E.) is defined as:

- any unfavorable and unintended event or degradation of the medical conditions (in comparison with those noted during the initial examination), occurring during the period of application of the investigational product (between the inclusion in the study and the end of the study), not related to the investigational product application: e.g. disease, accident, food intoxication, …
- any reaction or event related to the application of the investigational product (definitely related (very probable or certain), probably related, possibly related or unlikely related (doubtful)) or unrelated to investigational product application, which by its nature, intensity or frequency of appearance leads to a significant modification in the application modalities of the investigational product (rhythm, quantity, application area, …), and/or a discontinuation from the study (withdrawal of the consent by the subject or discontinuation on decision of the Investigator).

As of I.E.C. knows that an adverse event occurred, the Sponsor is informed of the adverse event either immediately for a serious adverse event (see below) or within 48 hours for a non-serious adverse event.

The adverse event shall be collected in an appropriate way in the form provided for this purpose at the end of the case report form, precising the date of onset, location, duration of the event, any action taken, outcome and evaluation of imputability and severity. If the adverse event is ongoing on the final visit, the Investigator has to follow-up the event until complete outcome.

2.8.2. Causality

The Investigator assesses the relationship (causality) of an adverse event to the investigational product according to the following definitions.

- **Definitely related (very probable or certain)**

No uncertainty about the relationship between the event and investigational product application.
The event follows a definite reasonable temporal sequence from the time of the investigational product application and improves upon stopping the dose of the investigational product. A re-challenge is positive. The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject. The event follows a known response pattern to the investigational product.

- **Probably related**

High degree of certainty about the relationship between the event and investigational product application.
The event follows a reasonable temporal sequence from the time of the investigational product application and improves upon stopping the dose of the investigational product. The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject.

- **Possibly related**

Unlikely but cannot rule out with certainty the relationship between the event and investigational product application.
The event may follow a reasonable temporal sequence from the time of the investigational product application. The event may have been produced by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.

- **Unlikely related (doubtful)**

Clinical event has an unlikely relationship with the investigational product application.
There is no reasonable temporal association between the investigational product and the suspected event and the event could have been reasonably produced by the subject's clinical state or other modes of therapy administered to the subject.

- **Unrelated (not linked)**

Clinical event is clearly due to one or several other factors.
There is no reasonable temporal relationship between the investigational product application and the suspected event (e.g., event that occurred before investigational product applications) or no reasonable causality, such as an accident, which cannot remotely be related to study participation (e.g. injuries sustained in a car accident).

2.8.3. Severity

The Investigator assesses the severity of each adverse event according to the following definitions:

- **Slight**

Subject is aware (fully or partly) of the sign or symptom, but it is easily tolerated and does not interfere at all with the subject’s daily activity.

- **Mild**

Subject is aware of the sign or symptom, but it is rather well tolerated and does not interfere with the subject’s daily activity.

- **Moderate**

Event causes discomfort enough to interfere with the subject’s usual activities.

- **Severe**

Incapacitating; subject is unable to perform usual activity.

2.8.4. Serious Adverse Events

A serious adverse event (S.A.E.) is defined as any adverse event, regardless of cause or relationship to the investigational product, which:

- Resulted in death;
- Was life-threatening (i.e., an event which, in the view of the Investigator, placed the subject at immediate risk of death from the reaction as it occurred; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Required hospitalization or prolonged hospitalization;
- Resulted in persistent or significant disability/incapacity;
- Was a congenital anomaly;
- Also considered a serious adverse event is any other important medical event that jeopardized the subject or required intervention to prevent one of the outcomes listed in this definition above.

3. CONFIDENTIALITY - LEGAL FORMALITIES

3.1. Confidentiality

Any information regarding the health condition of the subjects and the results of the clinical examinations, performed before the start of study, for their recruitment, their selection and inclusion, is submitted to the rules of the medical secrecy. In no case this information can be given to the Sponsor with their identity.

To ensure preservation of the subjects' anonymity, the subjects are identified by unique codes and numbers.
For the study, they are identified by a number corresponding to the order of their inclusion in the study.

Should the raw data be sent to the Sponsor, the confidential data of the informed consent form, as well as of the information sheet, are masked.
The Investigator/Institution permits monitoring and auditing by the Sponsor as well as inspection by the appropriate regulatory authorities.
The Monitor(s), the Auditor(s) and the Regulatory Authorities are granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

3.2. Legal formalities

3.2.1. Insurance of I.E.C.

I.E.C. has an insurance to guarantee its civil liability vis-à-vis the subjects.

3.2.2. Insurance of the Sponsor

The Sponsor subscribes an insurance to guarantee its general liability vis-à-vis the subjects.

4. DATA RECORDING AND ARCHIVING

Raw data are defined as original records and certified copies of original records of clinical/instrumental findings and observations (hand-written data, printing tickets, pictures, digital recordings, samples…) directly input in the case report form (constituted, paginated and stapled before the start of the study) or in another specific software/folder/file. Raw data are then synthesized in compilation documents, which are mainly electronic files and enable either direct analysis of the data or transferred to more specific software (video/image analysis, statistical analysis…). If corrections of the raw data or of the compilation are required, the person in charge of the correction shall state the reason, date and sign, according to our procedure (the original entry must remain legible).

All raw data (case report forms, questionnaires if any), as well as the original documents of the compilation, of the final protocol (amendments if any), of the final report (all different versions and/or amendments if any) and of the statistical analysis if any, are kept in the archives for 10 years at the following addresses:

. For the 2 to 6 months following despatch of report:
Lozenetz - 17, Henrik Ibsen street - 1407 SOFIA - BULGARIA
. For the following years: ”Reisswolf - Bulgaria” S.A.
Logistics Park Bozhurishte, 10 Evropa Blvd.
2227 Bozhurishte – Bulgaria.

The traceability of the documents is the responsibility of I.E.C., who keeps updated records of their archiving address. Once this period is over, the Sponsor is contacted regarding its archives. No archive destruction is done without the written and signed agreement from the Sponsor.

5. GUIDELINES

- Declaration of Helsinki (World Medical Association - 1964, and last amendment in force)

- I.C.H. Topic E6(R2) "Guideline for good clinical practices (EMA/CHMP/ICH/135/95)", I.C.H. Harmonised tripartite Guideline for Good Clinical Practices; published on 15 December 2016

- I.C.H. Topic E3 "Structure and content of clinical study reports (CPMP/ICH/137/95)", I.C.H. Harmonised tripartite Guideline for Good Clinical Practices; published of 1st July 1996

- EU regulation 2016/679 of 27 April 2016 (General Data Protection Regulation) repealing Directive 95/46/EC.

6. RESULTS

6.1. Amendment and protocol compliance

6.1.1. Amendment

No amendment to the protocol was issued during the course of this study.

6.1.2. Protocol Compliance

Criterion(a)	Deviation(s) noted	Criterion(a) indicated in the protocol
Number of subjects	22 subjects on D0 21 subjects on D28	25 subjects
Inclusion criteria . Bleeding Index score	. between 1 and 1.5 for 7 subjects (n° 02, 08, 10, 13, 14, 18, 22)	. at least a score of 2

These deviations did not affect, in a notable way, the quality or the interpretation of the results obtained.

6.1.3. Studied population

Number of subjects recruited	26
Number of subjects who came to I.E.C.	22
Number of subjects included in the study	22
Number of subjects discontinued from the study - Consent withdrawal by the subject	1 1 (n° 01)
Number of subjects for the analysis of the results	21

6.1.4. Subjects' characteristics

The characteristics of the subjects are summarized in the following table

Subjects	Sensitivity	Healthy subjects with history of atopy	Users of this type of product°
Number : 21 Females : 11 (52 %) Males : 10 (48 %) Mean age : 43.8 Age min : 22 Age max : 57	Gums : 21 (100 %)	1 (5 %)	21 (100%) *Regular users* 18 (86 %)

°mouthwash

All these subjects also presented with at least 20 natural teeth and a mean Modified Gingival Index (MGI) ≥ 2.

6.2. Appraisal of the oral and dental acceptability of the investigational product

No abnormal clinical sign was noted, by the Dental Surgeon Investigator, after the 4 weeks of use. All the subjects also indicated not having felt and/or observed any discomfort and/or irritation signs during the study.

These results allow to conclude to a very good tolerance at the oral and dental levels for this type of product studied in these conditions.

6.3. Clinical evaluation by the investigator

		Means and standard deviations (Sd)		Probability p: Wilcoxon test	Variation percentage #	Delta on the mean
	n	**D0 Initial value**	**D28**			
Modified Gingival Index-mean score	**21**	2.06 ± 0.23	1.93 ± 0.23	***0.004***	**-6%**	-0.13
Bleeding Index-mean score*	**21**	1.72 ± 0.42	1.21 ± 0.38	***<0.001***	**-30%**	-0.51

 # Variation with regard to the initial values; ***bold type %: variation ≥ 5% (statistically and clinically significant)***

Delta: difference(s) between the means on the considered time point(s) and the initial values

Statistically significant probability: p < 0.05
Probability close to significativity: 0.05 ≦ p < 0.10
Not significant probability: p ≥ 0.10.

6.4. Appraisal by the subject of the cosmetic acceptability and efficacy of the investigational product

6.4.1. Appraisal in the presence of the Odontologist Investigator

Cosmetic acceptability	→	good to very good	:	**100%**
Efficacy	→	good to very good	:	**100%**

6.4.2. Questionnaire

APPRAISAL *(2 or 4 point scale - answers given by "somewhat agree" to "agree" or by "yes")*	**D28** *(n = 21)*
The product is suitable for the subject's gums*	**95%**
From a cosmetic point of view, the investigational product was considered as "good" to "very good"	**90%**
On the whole, the product is pleasant (*"Agree to Somewhat Agree")*	**90%**
Product rating by the subjects (on a scale of 0 to 10)	Mean 7.5
The subject would like to continue using the product *	**71%**
Purchase intention (regardless of its price)*	**52%**

Bold type : % ≥ 50%

**regular users of this type of product*

IN COMPARISON WITH THE USUAL PRODUCT	**D28** *(n = 18)*
By comparing with the product generally used, the subject found his gums "just as good" to "better"	**94%** *(17/18*)*
Preferred product: . the usual product . the investigational product . no preference	 17% *(3/18*)* 22% *(4/18*)* **61%** *(11/18*)*
Comparison of the efficiency of the investigational product with the one normally used: . the usual product was more efficient . the investigational product was more efficient . no preference	 17% *(3/18*)* 22% *(4/18*)* **61%** *(11/18*)*

Bold type : % ≥ 50%

**regular users of this type of product*

7. CONCLUSION

The ORAL AND DENTAL ACCEPTABILITY of the investigational product designated as "SMOKETREE HYDROLINA BY INA ESSENTIALS (ref.: 3220901 - Batch n° Lot 6 - 2021)" can be judged VERY GOOD, after repeated applications under normal conditions of use, twice a day for 4 consecutive weeks, to the oral cavity, by 21 adult subjects, of both genders, from 22 to 57 years old and all with "sensitive" gums.

Moreover, the repeated applications of this investigational product by these subjects led to:

A STATISTICALLY SIGNIFICANT DECREASE of mean BLEEDING INDEX and MODIFIED GINGIVAL INDEX, after 4 weeks of application, in comparison with the initial values, on the basis of a clinical scoring performed by the Dental Surgeon Investigator.

The claims such as "TOLERANCE TESTED UNDER ODONTOLOGICAL CONTROL" and "SUITABLE FOR SENSITIVE GUMS" can thus be justified.

Sofia,
On 02 August 2022

Svilen MITEV, D.D.S
Dental Surgeon Investigator

Valeri KRASTEV
Responsible for study

This study was conducted by INSTITUT D'EXPERTISE CLINIQUE - BULGARIE,
registered by the Bulgarian Health Authorities
Professor Rumyana YANKOVA, MD., Ph. D., Head, Dermatology and Allergy Center,
PULMED University Hospital of Plovdiv, Bulgaria

APPENDICES

APPENDIX 1: SUMMARY OF THE REPORT

APPENDIX 2: PANEL DATA

APPENDIX 3: APPRAISAL OF THE INDIVIDUAL ACCEPTABILITY BY THE INVESTIGATOR

APPENDIX 4: APPRAISAL OF THE ACCEPTABILITY BY THE SUBJECT

APPENDIX 5: APPRAISAL OF THE COSMETIC ACCEPTABILITY AND EFFICACY BY THE SUBJECT

APPENDIX 6: ADVERSE EVENTS

APPENDIX 7: CLINICAL EVALUATION – INDIVIDUAL DATA & STATISTICS

APPENDIX 1

SUMMARY OF THE REPORT

INSTITUT D'EXPERTISE CLINIQUE

17, Henrik Ibsen street, Hladilnika, Lozenetz, 1407 Sofia – BULGARIA

SUMMARY OF THE REPORT: ACCEPTABILITY AND OBJECTIVATION STUDY IN-USE TEST UNDER ODONTOLOGICAL CONTROL (IEC BULGARIA)

Clinical Study	:	Clinical study for the appraisal of the oral and dental acceptability and for the evaluation of the efficacy of an investigational product, after repeated use under normal conditions, in the adult subject
Investigational Product	:	**SMOKETREE HYDROLINA BY INA ESSENTIALS** (ref.: 3220901 - Batch n° Lot 6 - 2021)
Standard Study Protocol	:	PEG-TUDRSTD-3.0-GB-of 17 February 2020
Specific Study Protocol	:	N° B220449PE - Version 1, of 29 April 2022
Report	:	N° B220449RD – Version 2, of 2 August 2022
Beginning of observations	:	04 May 2022
End of observations	:	01 June 2022
Address of investigation	:	**I.E.C. Bulgaria** 17, Henrik Ibsen Street, Hladilnika, Lozenetz, 1407 Sofia – BULGARIA

Protocol

Specific inclusion criteria :

. Number of subjects: 25
. Origin: Indifferent
. Gender: Indifferent
. Age: 18 to 70 years old

. Other:
. Subject presenting with a mean Bleeding Index (BI) of at least 2
. Subject presenting with a mean Modified Gingival Index (MGI) of at least 2
. At least 20 natural teeth

Methodology :

. Application modalities of the investigational product:
. area: oral cavity
. frequency and duration: at least twice a day (in the morning and evening) for 4 consecutive weeks
. conditions of application: by the subject, at home, under the normal conditions of use.

. Modalities of evaluations:
. oral and dental acceptability: clinical examinations by the Dental Surgeon Investigator (D0 and D28) and questionnaire filled in by the subject
. clinical evaluation (scoring) by the Dental Surgeon investigator: clinical evaluation of the MODIFIED GINGIVAL INDEX and BLEEDING INDEX on D0 and D28.
. cosmetic qualities and efficacy: questionnaire filled in by the subject.

Results and conclusion

The claims such as "TOLERANCE TESTED UNDER ODONTOLOGICAL CONTROL" and "SUITABLE FOR SENSITIVE GUMS" can thus be justified.

Sofia,
On 02 August 2022

Svilen MITEV, D.D.S
Dental Surgeon Investigator

Valeri KRASTEV
Responsible for study

This study was conducted by INSTITUT D'EXPERTISE CLINIQUE - BULGARIE,
registered by the Bulgarian Health Authorities
Professor Rumyana YANKOVA, MD., Ph. D., Head, Dermatology and Allergy Center,
PULMED University Hospital of Plovdiv, Bulgaria

APPENDIX 2
PANEL DATA

Code	Subject	Gender	Age	Origin	Healthy subject with history of atopy	Past history of reactions to cosmetics	Past history of reactions to this kind of product	sensitive gums	Subject presenting a good oral heaith with at least 20 natural teeth	bleeding to brushing presently	bleeding to brushing in the past	anterior gingival treatment	Subejct having brushed his/her teeths before the visit (D0 morning)	Subject presenting with a mean Modified Gingival Index(MGI) at least 2	Subject presenting with a mean Bleeding Index (BI) of 1 to 2	Subject who is not a smoker	Subject committing to follow the specific instructions related to the Covid-19 outbreak	Subject who doesn't present or has not presented within the last 15 days symptoms
ARAVA02	01	M	43	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
KOSST06	02	F	38	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
KANEL03	03	F	35	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
MILST06	04	F	57	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
GRIZD	05	M	42	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
DANSA	06	M	42	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
IVAIV02	07	M	22	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
HRIDO04	08	F	25	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
LOZNI	09	M	54	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
CHAAN05	10	F	33	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
MITHR02	11	M	51	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
MARNI06	12	F	45	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
HRIBO09	13	F	49	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
YOVMA	14	F	57	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
GEOYA06	15	M	49	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
STAIV	16	M	38	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
NIKDI11	17	F	42	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
TOTIR	18	F	52	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
TROIV	19	M	47	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
ILINI02	20	M	47	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
DIMPL	21	M	52	Caucasian	-	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes
MITBO07	22	F	44	Caucasian	yes	-	-	yes	yes	-	-	-	yes	yes	yes	yes	yes	yes

APPENDIX 3
APPRAISAL OF THE INDIVIDUAL ACCEPTABILITY BY THE INVESTIGATOR

Nothing to report.

APPENDIX 4
APPRAISAL OF THE ACCEPTABILITY BY THE SUBJECT

Nothing to report.

APPENDIX 5
APPRAISAL OF THE COSMETIC ACCEPTABILITY AND EFFICACY BY THE SUBJECT

COSMETIC ACCEPTABILITY

04	very good	17	good
0	rather good	0	mediocre
0	bad		

EFFICACY as a "MOUTHWASH"

4	very good	17	good
0	rather good	0	mediocre
0	bad		

APPENDIX 6
ADVERSE EVENTS

Subject number	Adverse Event	Serious	Intensity	Action taken	Outcome
/	/	/	/	/	/

APPENDIX 7
INDIVIDUAL DATA and RESULTS OF STATISTICAL ANALYSIS: CLINICAL EVALUATION by a trained assessor

NOMENCLATURE:

Time point 0	:	D0 *(baseline)*
Time point 1	:	D28
Product 0	:	Investigational product
Measure 1	:	MGI-mean score
Measure 2	:	BI-mean score
PC	:	*Variation percentage (with regard to the initial values)*
DMα Tx or Px	:	*Difference on time point(s) or product(s) for measure α*

Individual Data

vol	temps	m1p0	m1pcp0	m2p0	m2pcp0
2	0	2,00		1,50	
	1	1,83	-8,50%	1,33	-11,33%
3	0	2,00		2,00	
	1	2,00	0,00%	2,00	0,00%
4	0	3,00		2,00	
	1	2,67	-11,00%	1,67	-16,50%
5	0	2,00		2,00	
	1	2,00	0,00%	1,30	-35,00%
6	0	2,00		2,00	
	1	1,67	-16,50%	1,17	-41,50%
7	0	2,00		2,00	
	1	1,67	-16,50%	0,67	-66,50%
8	0	2,00		1,33	
	1	1,83	-8,50%	1,33	0,00%
9	0	2,00		2,00	
	1	1,67	-16,50%	1,50	-25,00%
10	0	2,00		1,33	
	1	2,00	0,00%	1,00	-24,81%
11	0	2,00		2,00	
	1	1,67	-16,50%	1,67	-16,50%
12	0	2,33		2,00	
	1	2,00	-14,16%	1,50	-25,00%
13	0	2,00		1,00	
	1	2,00	0,00%	0,67	-33,00%
14	0	2,00		1,00	
	1	2,00	0,00%	1,00	0,00%
15	0	2,00		2,00	

vol	temps	m1p0	m1pcp0	m2p0	m2pcp0
	1	2,00	0,00%	1,00	-50,00%
16	0	2,00		2,00	
	1	2,00	0,00%	1,67	-16,50%
17	0	2,00		2,00	
	1	2,00	0,00%	1,50	-25,00%
18	0	2,00		1,00	
	1	1,50	-25,00%	0,50	-50,00%
19	0	2,00		2,00	
	1	2,00	0,00%	1,00	-50,00%
20	0	2,00		2,00	
	1	2,00	0,00%	1,00	-50,00%
21	0	2,00		2,00	
	1	2,00	0,00%	1,00	-50,00%
22	0	2,00		1,00	
	1	2,00	0,00%	1,00	0,00%

Measure 1 Product 0 Time 1

Shapiro-Wilk Test

	Statistic	ddl	Signification
Product 0 dm1t0t1	0.733	21	0

Wilcoxon Test

Descriptive statistics

	N	Mean	Std deviation	SEM	Minimum	Maximum
Product 0 m1t0	21	2.063	0.226	0.049	2	3
Product 0 m1t1	21	1.929	0.233	0.051	1.5	2.67

Ranks

	N	Mean ranks	Sum of ranks
m1t1p0 - m1t0p0 : Negative ranks	9	5	45
m1t1p0 - m1t0p0 : Positive ranks	0	0	0
m1t1p0 - m1t0p0 : Ex aequo ranks	12		
m1t1p0 - m1t0p0 : Total	21		

Test paired samples

	Z	Sig asympt (bilaterale)	Sig exact (bilaterale)	Sig exact (unilaterale)
m1t1p0 - m1t0p0	-2.754	0.006	0.004	0.002

Measure 2 Product 0 Time 1

Shapiro-Wilk Test

	Statistic	ddl	Signification
Product 0 dm2t0t1	0.92	21	0.086

Wilcoxon Test

Descriptive statistics

	N	Mean	Std deviation	SEM	Minimum	Maximum
Product 0 m2t0	21	1.722	0.42	0.092	1	2
Product 0 m2t1	21	1.213	0.384	0.084	0.5	2

Ranks

	N	Mean ranks	Sum of ranks
m2t1p0 - m2t0p0 : Negative ranks	17	9	153
m2t1p0 - m2t0p0 : Positive ranks	0	0	0
m2t1p0 - m2t0p0 : Ex aequo ranks	4		
m2t1p0 - m2t0p0 : Total	21		

Test paired samples

	Z	Sig asympt (bilaterale)	Sig exact (bilaterale)	Sig exact (unilaterale)
m2t1p0 - m2t0p0	-3.642	0.000	0	0.000