PROTOCOL

STUDY TITLE: **Multicentre observational study on the wound pain relief properties of ORTODERMINA®**

STUDY ID: SINALGO

PROTOCOL VERSION - DATE: V 2.1 – 23/10/2015

TREATMENT: Lidocaine Hydrocloride (ORTODERMINA®)

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1.0 LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
CRO	Contract Research Organisation
EC	Ethics Committee
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	milligrams
NPRS	Numerical Pain Rating Scale
PP	Per Protocol
QA	Quality Assurance
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
VRS	Visual Rating Scale
WHO-DD	World Health Organization Drug Dictionary

2.0 STUDY SYNOPSIS

Study Title	Multicentre observational study on the wound pain relief properties of ORTODERMINA®
Study Code	SINALGO
Study Sponsor	SOFAR Spa - Via Firenze, 40 - 20060 Trezzano Rosa (MI)
Study Coordinator	Prof.
Study Chairman	Prof.
Participating countries	Italy
Participating centres	4 centres
Background Information and Study Rationale	Anaesthetic treatment is a common clinical problem. Acute pain may occur due to trauma, surgery, infection, disruption of blood circulation or many other conditions in which there is tissue injury. In a medical setting it is usually desirable to alleviate pain when its warning function is no longer needed. Besides improving patient comfort, pain therapy can also reduce harmful physiological consequences of untreated pain. Acute pain can often be managed using analgesics. However, conduction anaesthesia may be preferable because of superior pain control and fewer side effects. The anaesthetic properties of ORTODERMINA® and the ability to maintain the anaesthetic effect are the peculiar characteristic of this lidocaine hydrochloride formulation. Lidocaine hydrochloride is used topically to relieve itching, burning and pain from skin inflammations and it is also injected as a dental anaesthetic or as a local anaesthetic for minor surgery. Overall ORTODERMINA can improve skin tissue lesions leading to a reduction of local pain.
Study Drug	ORTODERMINA® 5%
Study Design	Observational, single-arm, multicentre
Primary Objectives	To observe wound pain relief in patients with painful wounds treated with ORTODERMINA®
Secondary Objectives	To collect safety information on ORTODERMINA® in patients with painful wounds
Primary End-points	- Wound pain relief based on a 5-point Visual Rating Scale (VRS - Appendix 1) - Pain intensity based on a 11-point Numerical Pain Rating Scale (NPRS - Appendix 2)
Secondary End-points	Incidence and severity of AEs and SAEs
Number of patients	78 patients enrolled (70 evaluable)
Inclusion Criteria:	• Age ≥18 years • Patients with painful exuding wounds >1 cm^2 that includes painful exuding ulcers (and pressure ulcers grade II (according to NPUAP classification – appendix 3) • Patients available and able to return to the study site for the scheduled visits • Patients who gave written informed consent to take part into the study

Exclusion Criteria:	• Patients with ulcer infected, discoloured, odorous, pressure ulcer grade I, III, or IV (according to NPUAP classification – Appendix 3) • Diabetic foot ulcer • Patients with contraindication or known allergy to drug's components • Patients with known severe allergies manifested by a history of anaphylaxis, or history or presence of severe multiple allergies • Female patients who are pregnant or lactating. • Patients with vascular disorders (mainly artheriopathies) • Patients known as alcohol or drug abusers. • Patients currently participating in a clinical study
Treatment	Local treatment with ORTODERMINA® over 14 days period (once a day)
Prohibited medication	Other compounds containing Lidocaine
Planned Sample Size and Statistical Methods	A sample size of 70 evaluable patients is needed to test the hypotheses of an improvement in wound pain relief and of a reduction in pain intensity, assuming a standardized effect size equal to 0.35, for a one-tailed test with a 5% significance level and a 90% power. Supposed that a 10% of attrition rate is expected the total number of patients to be enrolled is 78. Differences in wound pain relief from baseline to end of treatment will be analysed with a one-sample t-test, assuming a reference value equal to 0 at baseline; changes in pain intensity with a two-paired samples t-test.
Planned Study Timelines:	FPFV: First quarter 2015 LPLV: First quarter 2016

3.0 STUDY FLOW-CHART

ASSESSMENT/ EVENTS	V1 (Day 1)	V2 (Day 8)	V3 (Day 15)
	Screening, enrollment and start of treatment	Control Visit	End of Study
Informed consent signature	x		
Treatment administration	x (Day 1 – 14)		
Demography	x		
Inclusion/Exclusion criteria	x		
Medical and surgical history and underlying diseases	x		
Previous[1] and concomitant[2] medications	x[1,2]	x[2]	x[2]
Vital signs	x		x
Clinical evaluation	x		
Wound examination	x	x	x
5-point Visual Rating Scale evaluation (recorded by the patient on the Diary)		x (Day 1 -15)	
11-point Numerical Pain Rating Scale evaluation (recorded by the patient on the Diary)		x (Day 1 -15)	
AEs / SAEs	x (from the Informed Consent signature to D15)		
Patient's Diary revised by the Investigator		x	x (collected)

[1] Medications started before the patient's enrolment in the study, including the ongoing treatment.

[2] Medications started during the patient's participation in the study, including the ones related to AE.

4.0 INTRODUCTION AND RATIONALE

In recent years, there has been a better understanding of the acute pain process that may occur due to trauma, surgery, infection, disruption of blood circulation or many other conditions in which there is tissue injury. In a medical setting, it is usually desirable to alleviate pain when its warning function is no longer needed. Besides improving patient comfort, pain therapy can also reduce harmful physiological consequences of untreated pain. Pain represents a major problem for patients with chronic wounds (1–5). Poor management of pain has been shown to affect patients' quality of life (6,7) and potentially influences healing (8). Chronic pain in leg ulcers is often poorly managed (9), with the prevalence of pain reported as being as high as 64% (2).

A participant in one study of painful leg ulcers described his/her situation as being ‘locked in a shell of pain’ (7). Almost 50% of patients in one study investigating the impact of dressings and cleansing agents could not use compression dressings because of the associated pain (8). People with ulcers of venous, arterial, mixed arterial venous, and vasculitis origin are reporting serious problems with wound pain (1,2).

However, there is limited literature on the effect of active treatments in these patients.

Acute pain can often be managed using analgesics. However, conduction anaesthesia may be preferable because of superior pain control and fewer side effects.

In this contest lidocaine play an important role in different pathological conditions (10, 11).

All local anaesthetics are membrane stabilizing drugs; they reversibly decrease the rate of depolarization and repolarization of excitable membranes (like nociceptors). Though many other drugs also have membrane stabilizing properties, not all are used as local anaesthetics (propranolol, for example). Local anaesthetic drugs act mainly by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane, in particular the so-called voltage-gated sodium channels. When the influx of sodium is interrupted an action potential cannot arise and signal conduction is inhibited. The receptor site is thought to be located at the cytoplasmic (inner) portion of the sodium channel. Local anaesthetic drugs bind more readily to sodium channels in an activated state, thus onset of neuronal blockade is faster in neurons that are rapidly firing. This is referred to as state dependent blockade(12)

Local anaesthetics are weak bases and are usually formulated as the hydrochloride salt to render them water-soluble. At a pH equal to the protonated base's pKa, the protonated (ionized) and unprotonated (unionized) forms of the molecule exist in equimolar amounts but only the unprotonated base diffuses readily across cell membranes. Once inside the cell the local anaesthetic will be in equilibrium, with the formation of the protonated (ionized form), which does not readily pass back out of the cell. This is referred to as "ion-trapping". In the protonated form, the molecule binds to the local anaesthetic binding site on the inside of the ion channel near the cytoplasmic end.

Acidosis such as caused by inflammation at a wound partly reduces the action of local anaesthetics. This is partly because most of the anaesthetic is ionized and therefore unable to cross the cell membrane to reach its cytoplasmic-facing site of action on the sodium channel.

All nerve fibres are sensitive to local anaesthetics, but due to a combination of diameter and myelination, fibres have different sensitivities to local anaesthetic blockade, termed "Differential Blockade." Type B fibres (sympathetic tone) are the most sensitive followed by Type C (Pain), Type A delta (temperature), Type A gamma (proprioception), Type A beta (sensory touch and pressure) and Type A alpha (motor). Although Type B fibers are thicker than Type C fibers, they are myelinated, and thus are blocked before the unmyelinated, thin C Fiber. (13)

The properties of ORTODERMINA® and the ability to maintain adequate levels of Lidocaine over the lesions, allow a durable anaesthetic effect. ORTODERMINA® is a drug for topical application in the form of cream.

The drug has a high safety profile and although the incidence of adverse effects with Lidocaine Ointment 5% is quite low, caution should be exercised, particularly when employing large amounts, since the incidence of adverse effects is directly proportional to the total dose of local anaesthetic agent administered.

5.0 STUDY OBJECTIVES

5.1 Primary Objectives

- To observe wound pain relief in patients with painful wounds treated with ORTODERMINA®

5.2 Secondary Objectives

- To collect safety information on ORTODERMINA® in patients with painful wounds.

6.0 STUDY END-POINTS

6.1 Primary End-points

- Wound pain relief based on using a 5-points Visual Rating Scale (14) (Appendix 1)
- Pain intensity based on a 11-point Numerical Pain Rating Scale (15) (Appendix 2)

6.2 Secondary End-points

- AEs occurred over the study period (from the Informed Consent signature to the V3) will be registered.

7.0 STUDY DESIGN

This is an observational, single-arm, multicentre study.

7.1 Duration of Clinical Investigation

After having signed the Informed Consent the patients will undergo a screening visit; patients fulfilling the inclusion/exclusion criteria will be enrolled in the study and treated once a day with ORTODERMINA® throughout a period of 14 days in addition to any therapy the physician will have prescribed for the treatment of the lesion.

8.0 STUDY POPULATION

8.1 Number of patients

A total number of 78 patients will be enrolled (70 patient evaluable) in the study.

8.2 Selection of patients

8.2.1 Inclusion criteria

Subjects must meet all the following inclusion criteria to be eligible for enrolment into the study:

- Age ≥ 18 years

- Patients with painful exuding wounds >1 cm^2 that includes painful exuding ulcers and pressure ulcers grade II (according to NPUAP classification – Appendix 3)
- Patients available and able to return to the study site for the scheduled visits
- Patients who gave written informed consent to take part into the study

8.2.2 Exclusion Criteria

The presence of any following will exclude a subject from study enrolment:

- Patients with ulcer infected, discoloured, odorous, pressure ulcer grade I, III, or IV (according to NPUAP classification – Appendix 3)
- Diabetic foot ulcer
- Patients with contraindication or known allergy to drug's components or to the treatment
- Patients with known severe allergies manifested by a history of anaphylaxis, or history or presence of severe multiple allergies
- Female patients who are pregnant or lactating
- Patients with vascular disorders (mainly artheriopaties)
- Patients known as alcohol or drug abusers
- Patients currently participating in a clinical study

8.3 Screening and Enrolment Procedures

Before any screening procedure the patient must have signed and dated a written informed consent for the study. Then the Investigator assigns the patient study number that is progressive within the centre (preceded by the centre number).

If the patient is eligible for the study the notification of patient registration in the study is submitted to Eudax (fax: +39 0382 1750669) using the "Subject Registration Form".

The following logs must be maintained at each study site and kept in the Investigator File:

✓ "Subject Screening and Enrolment Log" to register all subjects who enter screening and to document chronological enrolment of patients. In case of screening failure the reason(s) for failure will be also documented on the CRF and on the source documents (hospital records).

✓ "Subject Identification Log" for all subjects registered to maintain the correlation with the patient's full identification data (subject study number, name, surname, number of the subject's hospital record - confidential)

8.4 Discontinuation/ Withdrawals of patients from study treatment

Patients will be withdrawn at any time from the study at their own request or at the discretion of the Investigator if considered necessary in the best patient's interest. The reason for withdrawals/drop-outs must be fully documented in the CRFs as well in source documents.

8.5 Replacements

Withdrawals/drop-outs patients will be replaced in order to have a total of 70 evaluable patients.

9.0 STUDY PRODUCT

9.1 Drug Supply

Due to the observational nature of the study, ORTODERMINA® will be prescribed according to clinical practice.

9.2 Drug Administration

ORTODERMINA® is available in 50 g laminate tubes with a child-resistant cap,
A single application of ORTODERMINA® should not exceed 5 g of Lidocaine Ointment 5%. This is roughly equivalent to squeezing a fifteen (15) cm length of ointment from the tube.

9.3 Drug Compliance

The patient will be required to record in the diary the daily ointment application during the study period (Day 1-14). Only the patients compliant with at least the 80% of the applications (at least 11 treatment days) will be included in the efficacy analysis.

9.4 Concomitant Medication

Other compounds containing Lidocaine will not be allowed for the entire study period. Patient using other compound containing Lidocaine during the study will be excluded from the efficacy analysis.
Any additional treatment/medication including any compound prescribed for the routine treatment of the target lesion, taken by the patient during study period, started before the patient's enrolment in the study (ongoing treatment) or started during the patient's participation in the study will be report in the CRF. The patient will be required to record in the diary any new medication used during the study period (Day 1-14).

10.0 STUDY ASSESSMENTS

10.1 Visit 1 (Day 1 - Screening Visit, enrolment and start of treatment)

Before any screening procedure the patients have to sign and date the current version of the Informed Consent Form.

During Visit 1 the following information will be recorded:

- Demography
- Medical and surgical history, and underlying diseases
- Previous medications (not ongoing) in the last 2 weeks
- Concomitant medications (ongoing at the time of the visit, including any compound prescribed for the routine treatment of the target lesion)
- Vital signs
- Clinical evaluation
- Wound examination
- Check of Inclusion/exclusion criteria
- AEs monitoring (AEs will be monitored from the Informed Consent signature to Day 15)
- Treatment prescription/First treatment administration
- Diary distribution

10.2 Visit 2 (Day 8, Control Visit)

During Visit 1, the following information will be recorded:

- Concomitant medications (started before the patient's enrolment in the study and ongoing during the study, or started during the patient's participation in the study and including any compound prescribed for the routine treatment of the target lesion)
- Wound examination
- 5- point VRS evaluation (recorded by the patient on the Diary; Day 1-8)
- 11-point Numerical Pain Rating Scale evaluation (recorded by the patient on the Diary; Day 1-8)
- AEs/SAEs monitoring
- Patient's Diary revised by the Investigator

10.3 Visit 3 (Days 15, End of Study)

During Visit 2 the following information will be recorded:

- Concomitant medications (started before the patient's enrolment in the study and ongoing during the study, or started during the patient's participation in the study and including any compound prescribed for the routine treatment of the target lesion)
- Vital signs
- Wound examination
- 5- point VRS evaluation (recorded by the patient on the Diary; Day 9-15)
- 11-point Numerical Pain Rating Scale evaluation(recorded by the patient on the Diary; Day 9-15)
- AEs/ SAEs monitoring
- Patient's Diary revised by the Investigator for completeness and accuracy and collected

10.4 Details of Individual Assessments

10.4.1 Demography, Medical, Surgical history and Clinical Evaluation

A full demography, medical and surgical history, underlying diseases and clinical evaluation will be collected at the Visit 1.

10.4.2 Vital Signs

Vital signs (heart rate and blood pressure) will be carried out at the Visit 1 and 3.

10.4.3 Wound examination

A wound examination will be carried out at the Visit 1, 2, 3.

10.4.4 5-point Visual Rating Scale (VRS) evaluations

Five-point VRS will be used by the patient to assess the pain relief over the treatment period. The patients mark on the scale their level of pain relief during the past 24 hours. This information is recorded by the investigator at the Visit 1, 2, 3 in the hospital record and by the patient daily in the diary.

10.4.5 11- point Numerical Pain Rating Scale evaluation

Eleven-point NPRS will be used by the patient to assess the pain intensity over the treatment period. This information is recorded by the investigator at the Visit 1, 2, 3 in the hospital record and by the patient daily in the diary.

10.4.6 Safety Evaluations

All AEs will be recorded from informed consent signature up to the end of the study

11.0 REPORTING SAFETY INFORMATION

11.1 Definitions

Adverse Event (AE): as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
In clinical studies, an AE can include an untoward medical occurrence occurring at any time, including run-in or washout periods, even if no study treatment was administered.

Non-serious AE: any untoward change in a patient's medical health that does not meet serious criteria noted below (e.g., is not life-threatening, does not require hospitalization, does not prolong a current hospitalization, is not disabling, etc.).

Serious adverse event (SAE): any adverse experience that meets any of the following criteria:

- Results in death.
- Is life-threatening.

  The patient was at immediate risk of death at the time of the event; it is not referred to cases in which the event might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

  In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting.
- Results in persistent or significant disability/incapacity.

  The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, or accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Is an important medical event.

  An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may

jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

Suspected Unexpected Serious Adverse Event (SUSAR): a serious adverse reaction (AR) which is not consistent with the information about the concerned drug. The reference information is included in the Summary of product characteristics (SmPC).

11.2 Monitoring for Adverse Events

At each visit, after the patient has the opportunity to mention spontaneously any problems, the Investigator or appropriate designee should inquire about AEs by asking the standard questions:

- "Have you had any health problems since your last study visit?"
- "Have there been any changes in the medicines you take since your last study visit?"

AEs should be reported for any clinically relevant change in concomitant medication(s) that is the result of an untoward (unfavourable and unintended) change in a patient's medical health. These clinically relevant changes is reported regardless of causality.

11.3 AEs Recording by the Investigator

All **Adverse Events** (non-serious and serious) which occur during the course of the study will be recorded in the CRF. Any pre-existing medical conditions or signs/symptoms present in a patient prior to the start of the study (i.e., before informed consent is signed) should be entered in medical history section in the CRF. After the informed consent has been signed, all untoward medical occurrences that occur during the course of the study must be documented in the Adverse Event section of the CRF. Whenever possible, signs and symptoms indicating a common underlying pathology should be documented as one comprehensive event.

For each recorded event, the AE documentation must include the onset date, outcome, resolution date (if event is resolved), intensity (for the intensity/severity assessment see below), any action with study treatment taken as a result of the event, and an assessment of the adverse event's relationship to the study treatment (for the causality assessment see below).

11.3.1 AE - Intensity and Causality Assessment

For **every AE**, the Investigator must assess the intensity (severity) and causality (relationship to study treatment) according to the following criteria:

Intensity /Severity

Mild	Grade 1 - Does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Grade 2 - Interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	Grade 3 - Interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable])

Causality:

	UNRELATED/ UNLIKELY RELATED	Temporal relationship to study treatment administration is not plausible	OR	There are no reasonable grounds for suspecting that the product could have caused the event AND other causes (e.g., treatments or underlying diseases) provide plausible explanations
ADVERSE REACTION	**POSSIBLY RELATED**	Temporal relationship to study treatment administration is plausible	BUT	The event can reasonably be explained by other equally or more likely causes
	PROBABLY/ CERTAINLY RELATED	Temporal relationship to study treatment administration is plausible	AND	The event is more likely explained by the treatment than by other causes or there are no other causes that can explain the event

11.4 SAEs Recording and Reporting by the Investigator to SOFAR

The Investigator must record all **Serious Adverse Events** occurred during the study, regardless of presumed causal relationship, in the Serious Adverse Event form and forward it to SOFAR pharmacovigilance by Fax: 02.90967239 or e-mail: farmacovigilanza@sofarfarm.it.

The assessment of seriousness is performed by the Investigator on the basis of criteria provided in the section 11.1.

The Investigator must provide SOFAR with the SAE form within 24 hours from the knowledge of the event. The initial SAE form must include at least the minimal four information to identify the event: patient enrolment number, investigational drug, nature of the adverse event and reporter/Investigator identification.

Depending on the nature and seriousness of the adverse event, SOFAR may request copies of appropriate medical records of the patient (identified by the enrolment number and not by personal identification data) as well as results of laboratory tests performed. If the patient was hospitalized a copy of the discharge summary must be provided to SOFAR as soon as available.

Follow-up SAE information should be provided to SOFAR whenever the investigator becomes aware of new available information regarding the SAE, once the condition is resolved or stabilized and when no more information about the event is expected.

11.5 SAE - Causality and Expectedness Assessment by SOFAR

The sponsor should not downgrade the causality assessment given by the investigator.

An assessment of **expectedness and causality of each SAE** will be performed case by case, when appropriate, by SOFAR within 7 calendar days from the receipt of a serious adverse event, within 1calendar day from the receipt in case of death or life threatening events.

11.6 Follow-Up of Patients with Serious Adverse Events

The Investigator is responsible for adequate and safe medical care of patients during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. A follow-up SAE report will be filled in by the investigator if important follow-up information (i.e. diagnosis, outcome, causality assessment, results of specific investigations) are made available after submission of the initial SAE form. Follow-up SAE forms will be sent to SOFAR as described above for the initial submission.

In any case of an AE that, in the opinion of the Investigator, requires the subject's discontinuation, follow-up information relating to the patients subsequent course must be collected until the event has subsided or the condition stabilised.

11.7 Reporting Procedure to ECs and Competent Authorities

The notification to the ECs and Competent Authorities will be performed by SOFAR according to the post-marketing surveillance regulations.

12.0 STATISTICAL METHODS

12.1 Sample Size Calculation

The sample size calculation takes into account the type of study design, before and after study with two main pain assessments (at baseline and at the end of treatment). Limited to the hypotheses tests that will be run on pain relief and pain intensity, the sample was sized by assuming a standardized effect size equal to 0.35, for a one-tailed test with a 5% significance level and a power equal to 90% (Woodward, 2005). As a consequence 70 evaluable patients are needed for the study. Supposed that a 10% of screening failure is expected the total number of patients to be enrolled is 78.

12.2 Hypothesis Testing

For the first primary endpoint (pain relief) a one-sided test will be carried out, so that the two hypotheses under consideration are:

$$H_0: \mu = \mu_0 = 0 \quad \text{vs.} \quad H_A: \mu > \mu_0$$

where μ is the population parameter representing mean pain relief at the end of treatment.

A similar null and alternative hypothesis will be tested for the second primary endpoint (pain intensity):

$$H_0: \delta = 0 \quad \text{vs.} \quad H_A: \delta > 0$$

where δ is the population parameter representing mean difference in pain intensity before and after treatment.
In order to control the Type I error that results from the multiplicity of endpoints, test of significance for the second primary endpoint will only be made if the primary analysis results in significant treatment effects at $p < 0.05$. In that event, a suitable strategy to deal with multiple endpoints will be adopted (16, 17).

12.3 Study Populations

The primary analyses for efficacy outcome variables will be performed on the Full Analysis Set (FAS) population, defined as all patients enrolled in this study. Descriptive statistics will be provided for demographical or clinically relevant characteristics.
Per-protocol (PP) population will be defined as the subset of the Full Analysis Set population defined by the exclusions of subject with at least one major protocol deviations (e.g. low compliance to treatment, use of prohibited concomitant medications). A per-protocol analysis has been planned only for the primary endpoint.
All patients who applied at least one dose of ORTODERMINA® will be included in the safety population.

12.4 Statistical Analyses

The statistical analyses will be performed by Eudax. No interim analysis has been planned.

Baseline and end of treatment characteristics (Vital signs, and Clinical evaluation, Wound examination) of the patients will be evaluated by descriptive analysis (e.g., median, mean, standard deviation, minimum, maximum for continuous data; frequency tables for categorical data).

12.5 Efficacy Data

The primary analysis of efficacy will be based on the FAS population.

Efficacy will be evaluated according to an improvement in the pain relief (5-point Visual Rating Scale -VRS) and to the reduction of pain intensity (11-point Numerical Pain Rating Scale).

Wound pain relief from baseline (V1, Day 1) to end of treatment (V3, Day 15) will be analysed with a one-sample t-test, assuming a reference value equal to 0 (no relief) at baseline. Improvement in the pain relief will be observed with VRS scores at end of treatment significantly greater than 0.

Differences in pain Intensity from baseline (V1, Day 1) to end of treatment (V3, Day 15) will be analysed with a two-paired samples t-test. Improvement in the pain intensity will be observed with NPRS scores at end of treatment significantly lower than those at baseline.

All assessments coming from patient's pain daily diary concerning both relief and intensity will be reported descriptively and graphically.

Patients who will withdraw their consent before treatment start and who will fail to meet the inclusion criteria will be excluded from efficacy analysis.

12.6 Safety data

The safety analysis population will include all patients who received at least one dose of treatment and had a safety assessment performed at baseline. All safety parameters will be summarized and presented in tables based on this safety population.

Adverse event data will be presented in frequency tables (overall and by intensity) by System Organ Class and Preferred Term (MedDRA dictionary). In tables showing the overall incidence of adverse events, patients who experienced the same event on more than one occasion are counted only once in the calculation of the event frequency.

13.0 Monitoring

Monitoring visits to the study sites will be made by a qualified monitor to verify that the study is conducted according to study protocol, GCP principles and regulatory requirements. The monitor will verify the accurate and complete recording of data on CRFs, source documents and Investigators File.
The investigator/institution guarantees direct access to source documents of the study patients and to any other study related documentation. It is important that the investigator(s) and/or their relevant personnel are available during the monitoring visits.

14.0 DATA HANDLING AND RECORD KEEPING

14.1 Case Report Form (paper CRF)

Paper Case Report Form, provided by the Eudax, will be completed for each screened and enrolled subject. The language used must be English.
The completed original Case Report Forms are the sole property of SOFAR and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from SOFAR.
The Investigator or an authorized staff member (medically qualified) has the responsibility to fill in, review and sign all Case Report Forms. However, the Investigator has final personal responsibility for the accuracy and authenticity of all data entered in the Case Report Form.
Subject source documents are the hospital subject records maintained at the study site. The investigator and Eudax must agree which items will be recorded in the source documents and for which items the patient's diary or the Case Report Form will stand as the source document. This must be stated in the "Data Location List" (to be archived in the Investigator File). One copy of this document should be returned to Eudax for filing into the Trial Master File.

14.2 Patient's diary

The patients will be provided with a diary at the Visit 1 and will be asked to report during the study period (Day 1-15)

information about:

- study drug compliance
- any other medications taken
- AEs
- Wound pain relief assessed using a 5-point Visual Rating Scale
- Pain intensity assessed using a 11-point Numerical Pain Rating Scale

The Investigator will instruct the subject about diary completion at the Visit 1 (Day 1), verify the completeness of the patient's diary at the Visit 2 (Day 8) and collect the completed patient's diary at Visit 3 (Day 15 -End of Study) after having checked the recorded information for completeness and accuracy.

If the information is complete and consistent, the Investigator can report a note in the hospital file referring to the diary and the diary itself will represent the source document for the data. If on the contrary the diary is incomplete or inconsistent, the Investigator should ask the patient for clarification and report in the subject records the correct information without making changes to the diary.

14.3 Data Handling

Data Management will be carried out by Eudax.
Medical terms are coded according to the MedDRA dictionary.
Previous and concomitant medications will be coded using the WHO-Drug Dictionary (WHO-DD).
Actual version of coding dictionaries will be notified in the final report.
The data are checked for completeness, accuracy and consistency by Eudax personnel. The errors detected will be rectified by means of Data Clarification Form/List (DCF/DCL) that will be used by the monitor for resolution of queries.
The original DCF/DCL must be archived together with the patient CRF.
The final data file will be transferred to SOFAR as soon as possible after the clinical investigation is completed.

14.4 Record Retention

To enable evaluation and/or audits and/or regulatory authority inspections, the Investigator agrees to keep the study related documents/records according to local regulations, but at least 7 years, or as specified in the Clinical Trial Agreement with SOFAR.
The documentation includes:

- the identity of all participating subjects ("Subject identification code list")
- all original signed informed consent forms
- copies of all case report forms
- source documents
- Investigator Study File

If the Investigator relocates, retires, or for any reason withdraws from the study, SOFAR should be notified in

advance and appropriate actions will be taken. The investigator must obtain SOFAR written permission before disposing of any records.

15.0 ETHICAL CONSIDERATION

15.1 Ethics Committee (EC)

Before initiating the study a written approval should be obtained by the EC for the study conduction.
Changes to the protocol can be made preparing written amendments to be agreed and signed by the Coordinating Investigator, SOFAR, Eudax and the Study Chairman. Before implementing any Protocol amendment, the EC written approval must be obtained. The only circumstance in which an amendment may be initiated prior to EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the EC must be notified in writing as soon as possible.
It is responsibility of Eudax to provide the Investigator with the EC approval (s). All the correspondence with the EC should be retained in the Investigator Study File.

15.2 Ethical conduct of the trial

The study will be performed in accordance with International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki and applicable local regulatory requirements.

15.3 Informed Consent

It is the responsibility of the investigator or delegate to give each patient (or the patient acceptable representative) full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patient must be informed about his/her right to withdraw from study at any time. The patient should have time and opportunity to enquire about the details of the study and to decide whether or not to participate. Written subject information must be approved by EC and must be obtained from each patient before any trial-related procedure is undertaken.
One copy of the signed and dated Informed Consent Form should be given to the patient. The originally signed document should be archived in the confidential section of the Investigator Study File.
The approved patient information sheet must not be changed without prior approval by SOFAR/Eudax and by the EC.
When new study information arise during the study, the patients still on treatment must be informed and a new Informed Consent form or an addendum to the already signed Informed Consent form must be signed and dated by the patients.

16.0 STUDY DISCONTINUATION CRITERIA

This study may be prematurely terminated or suspended, if in the opinion of SOFAR, Coordinating Investigator and the Study Chairman there is sufficient reasonable cause. Written notification documenting the reason for study

termination will be promptly provided to the investigators. Circumstances that may warrant termination include, but are not limited to:

- ✓ Determination of unexpected, significant, or unacceptable risk to patients
- ✓ Insufficient adherence to protocol requirements
- ✓ Insufficient complete and/or evaluable data

After such a decision, the investigator must promptly contact all participating patients to inform them about the decision taken.

Should the study be closed prematurely or suspended the EC should also be promptly informed and provided with the reason for termination or suspension.

17.0 INSURANCE

Not applicable.

18.0 CONFIDENTIALITY OF INFORMATION AND PUBLICATION OF RESULTs

All information supplied by Sofar/Eudax to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from SOFAR.

The investigator agrees to keep in confidence all the results obtained from the study. Such information shall not be disclosed to third parties without prior written permission from SOFAR/ except to regulatory authority(ies), when requested.

Individual investigators may present results of the study at scientific meetings. However prior to the submission, the SOFAR will have the opportunity to review and comment the abstracts for a period of up to 30 calendar days to allow SOFAR to assess properly that such proposed publication respects and/or is not in conflict with SOFAR's rights.

19.0 CLINICAL INVESTIGATION REPORT

A Clinical Investigation Report of the study will be prepared by the Eudax taking into consideration the ICH topic E3 (CPMP/ICH/137/95).

20.0 REFERENCES

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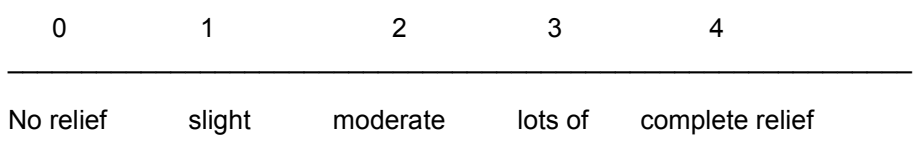
APPENDIX 1 - PAIN RELIEF EVALUATION

5-point Visual Rating Scale (VRS)

A Visual Rating Scale (VRS) is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. For example, the amount of pain relief that a patient feels ranges across a continuum from none to complete. From the patient's perspective this spectrum appears continuous ± their pain relief does not take discrete jumps, as a categorization of none, slight, moderate, lots of, complete would suggest. It was to capture this idea of an underlying continuum that the VRS was devised.
Operationally a VRS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end, as illustrated below. The patient marks on the line the point that they feel represents their perception of their current state.
The VRS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks.

How is your pain relief today? Place a vertical mark on the line below to indicate how you feel your pain relief today



APPENDIX 2 - PAIN INTENSITY EVALUATION

11-point Numerical Pain Rating Scale (NPRS)

Select the number that best describes your pain during the past 24 hours *(circle only one number)*:

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst possible Pain

APPENDIX 3 - NPUAP PRESSURE ULCER STAGES/CATEGORIES

International NPUAP-EPUAP Pressure Ulcer Definition
A pressure ulcer is localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear. A number of contributing or confounding factors are also associated with pressure ulcers; the significance of these factors is yet to be elucidated.

Pressure Ulcer Stages/Categories

Category/Stage I: Non-blanchable erythema
Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area. The area may be painful, firm, soft, warmer or cooler as compared to adjacent tissue. Category I may be difficult to detect in individuals with dark skin tones. May indicate “at risk” persons.

Category/Stage II: Partial thickness
Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled or sero-sanginous filled blister. Presents as a shiny or dry shallow ulcer without slough or bruising*. This category should not be used to describe skin tears, tape burns, incontinence associated dermatitis, maceration or excoriation.
*Bruising indicates deep tissue injury.

Category/Stage III: Full thickness skin loss
Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are *not* exposed. Slough may be present but does not obscure the depth of tissue loss. *May* include undermining and tunneling. The depth of a Category/Stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and Category/Stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep Category/Stage III pressure ulcers. Bone/tendon is not visible or directly palpable.

Category/Stage IV: Full thickness tissue loss
Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present. Often includes undermining and tunneling. The depth of a Category/Stage IV pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and these ulcers can be shallow. Category/Stage IV ulcers can extend into muscle and/or supporting structures (e.g., fascia, tendon or joint capsule) making osteomyelitis or osteitis likely to occur. Exposed bone/muscle is visible or directly palpable.

APPENDIX 4

Please note that this document, translated in English from italian language, has not been validated by the Italian Competent Authority, as the drug Ortodermina is authorized only in Italy.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
ORTODERMINA 5% cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
100 g of cream contain 6.15 g of Lidocaine hydrochloride, equal to 5 g of Lidocaine base.

Excipients with known effects: cetostearyl alcohol, methyl p-hydroxybenzoate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Cream.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Anaesthetic for the accessible mucosae of the oropharyngeal cavity, perianal pruritus. Anaesthetic for use in case of mild skin lesions.

4.2 Posology and method of administration
Apply a suitable amount of cream to the affected area; if the skin is broken, apply the cream using a sterile gauze pad. For dental use, when applying as anaesthetic to the oral mucosae, dry the mucosa using cotton wool and a saliva ejector in order to minimise the dilution of the cream and favour maximum lidocaine absorption. When fitting a new denture, spread the cream over the surface in contact with the mucosa (N.B. for the break-in period).
In the case of perianal pruritus, the applicator tube (provided with the 3 g pack) can be used to facilitate administration.

Daily administration must not exceed 35 g of cream.

4.3 Contraindications
Hypersensitivity to the active substance or to any other excipients listed in section 6.1.

4.4 Special warnings and precautions for use
ORTODERMINA must be used with caution by subjects with a severely traumatised mucosa and infection in the area to which the cream is to be applied.
In any case, the safety of use depends on the dose, a correct application technique and the adoption of precautionary measures. The product should be used at the minimum efficacious dose, appropriately adjusting the dose in relation to age and physical condition in children, the elderly and subjects with acute medical conditions.

4.5 Interactions with other medicinal products and other forms of interaction
There are no known interactions with other substances.

4.6 Fertility, pregnancy and lactation
In pregnant women and very young children, the product should only be used when absolutely necessary and under direct medical supervision.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 Undesirable effects
Lidocaine may cause local and systemic allergic reactions through to anaphylactic reactions. Systemic reactions are rare and are caused by excessive doses, rapid absorption, hypersensitivity or reduced tolerance. In these cases, cardiovascular depression and nervous excitation may occur, followed by sedation with drowsiness or loss of consciousness. In these cases, appropriate emergency measures must be taken.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reaction using the national reporting system via www.agenziafarmaco.gov.it/content/come-segnalare-una-sospetta-reazione-avversa

4.9 Overdose
Excessive dosage, rapid absorption and hypersensitivity or reduced tolerance cause the onset of cardiovascular depression and nervous excitation, followed by sedation with drowsiness or loss of consciousness. In these cases, appropriate emergency measures must be taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anaesthetics for topical use, ATC code: D04AB
Lidocaine stabilises the neuronal membrane and inhibits nerve impulse initiation and conduction (afferent nerve conduction block). It starts to exert its effect 3-5 minutes after application.

5.2 Pharmacokinetic properties
Lidocaine is metabolised primarily by the liver and is excreted via the kidneys: 90% in the form of various metabolites and 10% in unmodified form.

5.3 Preclinical safety data
The oral LD_{50} in mice is 292 mg/Kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Cetostearyl alcohol, Macrogol cetostearyl ether, Vaseline oil, White petroleum jelly, Methyl p-hydroxybenzoate, Purified water.

6.2 Incompatibilities
Not applicable.

6.3 Shelf-life
5 years.

6.4 Special precautions for storage
Not necessary.

6.5 Nature and content of the container
3 g, 10 g and 50 g tube of cream. An applicator tube is included in the 3 g pack.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER(S)
SOFAR S.p.A., Via Firenze 40, Trezzano Rosa (MI)

8. MARKETING AUTHORISATION NUMBER(S)
ORTODERMINA 5% cream - 3 g tube MA no. 005556030
ORTODERMINA 5% cream - 10 g tube MA no. 005556028
ORTODERMINA 5% cream - 50 g tube MA no. 005556016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
May 2010

10. DATE OF REVISION OF THE TEXT

23/02/2019