Assessment of the effect of Gerdoff® administered in combination to a treatments with proton pump inhibitors, compared to proton pump inhibitors as monotherapy, administered for 6 weeks in the treatment of upper symptoms associated with GERD, in patients with first diagnosis of gastro-oesophageal reflux disease

PROTOCOL CODE: PSC-DS GERD AP 16

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Investigational device:	Gerdoff® chewable tablets
Indication:	Symptoms associated with gastro-esophageal reflux disease (GERD)
Investigation Design:	Multicentre, prospective, randomised, open-label, two-parallel groups study
Sponsor:	SOFAR S.p.A. Via Firenze, 40 20060 Trezzano Rosa (MI), Italy
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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
Beta-hCG	Beta Human Chorionic Gonadotropin
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
CIP	Clinical Investigation Protocol
CRO	Contract Research Organisation
CRP	C-reactive Protein
CS	Chondroitin Sulfate
CV	Curriculum Vitae
DBP	Diastolic Blood Pressure
eCRF	Electronic Case Report Form
EEC	European Economic Community
ESR	Erythrosedimentation Rate
EU	European Union
EUDRACT	European Clinical Trials Database
Gamma-GT	Gamma Glutamyl Transpeptidase
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
HA	Hyaluronic Acid
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IMD	Investigational Medical Device
ISO	International Organization for Standardization
ITT	Intention To Treat
MedDRA	Medical Dictionary for Regulatory Activity
PPI	Proton Pump Inhibitor
PT	Preferred Term
RBCs	Red Blood Cells
RSI	Reflux Symptom Index
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class

1 INTRODUCTION

1.1 Background Information

Gastro-oesophageal reflux disease (GERD) is caused by signs and symptoms correlated to the presence of reflux of gastric acids on the oesophageal mucosa (1).

Based on the evidence emerged from the 'Montreal Consensus Conference', the manifestations of GERD have been classified both as oesophageal and extra-oesophageal symptoms, and particularly among the latter, a correlation between the upper reflux, which may reach the pharyngeal-laryngeal level, and GERD, has been established (2). Such reflux may also cause lesions or inflammations directed towards the pharyngeal-laryngeal mucosa, or may indirectly stimulate the existing vagal conductions (3).

It has been estimated that a percentage ranging from 4% to 10% of patients attending the ear, nose and throat (ENT) specialist claim signs and symptoms correlated with GERD (3). A variety of extra-oesophageal symptoms or presentations have been attributed to GERD, which include cough, hoarseness, prolonged loud voice, change of vocal pattern, apparently without a documented cause, which have been erroneously considered as discomforts of little relevance for which the patient generally does not receive adequate attention. Conversely, these disturbances, which are defined as upper symptoms of GERD, have a subtle appearance but may evolve up to impacting on the quality of life of patients (4,5).

An asymptomatic gastro-oesophageal reflux has been demonstrated in a range that varies from 50% to 75% of subjects with chronic cough (6). The link between reflux and cough has been further revealed by the disappearance of episodes of nocturnal cough following an appropriate therapy against the gastro-oesophageal reflux. Furthermore, it has been demonstrated that a proportion of 74.4% of patients with GERD present at least one extra-oesophageal symptom and that laryngeal symptoms are present in a high proportion of patients (19.9-38.7%) (3).

It should be pointed into evidence that, in recent years and particularly from 1990 to 2001, visits performed by ENT specialists due to upper symptoms have increased by 500% (7) and that an upper reflux is present in more than 50% of patients with dysphonia (8). With this respect, an appropriate diagnosis and an adequate therapy against gastro-oesophageal reflux have been proved to be useful in improving the patients' quality of life.

The use of proton pump inhibitors (PPIs) will be proposed as elective therapy for the treatment of upper symptoms related to GERD; however, it has been demonstrated that, in patients with upper symptoms, 50% of patients do not respond to PPIs therapy and 15% of patients exhibit only a partial response (9).

In fact, although the wide use of therapy with PPIs has had a largely positive on the course of GERD, several patients that are refractory to treatment have been observed. Moreover, it is widely accepted that the mucosal lesions caused by GERD may be permanently controlled only with a therapy with PPIs combined with other active substances or devices, which may offer a valuable alternative by potentiating the effects of PPIs (10,11).

1.2 The Investigational Medical Device (IMD)

Gerdoff® is a class 3 CE-marked medical device with mechanical action. The product is based on chondroitin-sulfate (CS), hyaluronic acid (HA) and aluminium hydroxide. It is indicated for the treatment of symptoms associated with GERD and contributes to the protective effect against the irritant action of hydrochloric acid, which is produced in the stomach.

In particular, HA favours the mucosal reparative processes, protects the mucosa by increasing the hydrating and lubricating properties of the saliva through the generation of a mechanical barrier against the aggression of gastric juices. CS is able to protect the epithelium, by inhibiting the mucosal

damage induced by pepsin. Aluminium hydroxide exerts a buffering action and reduces the time of exposure of mucosa to pH values < 4.

The product is indicated for the symptomatic treatment of:

- GERD. It rapidly reduces GERD-related symptoms such as gastric burning (pyrosis), acid regurgitation, epigastric pain, irritative cough and dysphonia;
- Hyperacidity (occasional stomach pain and burning).

The efficacy of HA and CS in the protection of upper digestive mucosa from the chemical irritation of gastric secretions, by inducing a regression of complex symptomatology, which included in increasing frequency also the inflammation or upper airways, has been clinically documented in comparison with placebo, with a highly significant therapeutic result in favour of such combination (HA and CS) (12), with a full disappearance of symptoms in 50% of treated patients compared to 10% of patients treated with placebo.

1.3 Investigation Rationale

The aim of the present study will be to evaluate, in first diagnosed patients presenting with upper symptoms associated with GERD, the effect of a 6-week treatment with a combination based on CS, HA and aluminium hydroxide (Gerdoff®), co-administered with a treatment with PPIs, compared to treatment with PPIs as monotherapy, i.e. to verify, in patients treated with the combination of the two products, the reduction in symptoms frequency by means of a Likert questionnaire and the severity of upper symptoms by means of the Reflux Symptom Index (RSI) questionnaire (13), and to collect safety data. After 6 weeks of treatment, patients included in the two groups will be then classified as responders or non-responders. Responder patients will be defined as those patients that, at the 6th week of treatment, reached a RSI score decreased for at least 50% compared to baseline and an absolute value < 13.

Furthermore, the maintenance of the effect of treatment on the extra-oesophageal symptoms will be evaluated after a period of follow-up lasting 12 weeks, which could be entered only by responder patients randomised in the Gerdoff®-PPI arm. Patients included in the follow-up period will be randomised to receive Gerdoff® or no treatment (control group). Safety data will be also evaluated in the group of patients that continued in the follow-up period.

1.4 Risk/benefit Considerations

It has been estimated that treatment with the IMD should contribute to improve the management of upper symptoms associated with GERD, in patients with first diagnosis of GERD, possibly sparing the use of other drugs or devices available in the market and used in the same indication.

The risk associated with the use of the IMD is estimated to be low, as the protective action on the mucosa exerted by the IMD is produced by a mechanical mechanism of action, and not by pharmacodynamic action. Nonetheless, the investigation protocol will be designed to assess potential risks associated with the use of the device, by deeply investigating the safety of the IMD with the collection of adverse events and incidents occurring at any time during the study, and by evaluating haematology and blood chemistry parameters at baseline, at the end of treatment period and at the end of the follow-up period.

Overall, it will be expected that benefits from participation in this investigation would have outweighed the potential risks.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study will be to evaluate the efficacy of Gerdoff®, a preparation based on CS, HA and aluminium hydroxide, in improving the upper symptoms in combination with a PPI (omeprazole) compared to treatment with PPI monotherapy (omeprazole), during 6 weeks of treatment and during the following 12-week maintenance follow-up period. The evaluation will be performed by means of the Reflux Symptom Index (RSI) questionnaire validated in Italian language.

2.2 Secondary Objectives

The secondary objectives of the study will be to assess:

- The number and percentage of responders/non-responders at visit V4, after 6 weeks of treatment with Gerdoff®-PPI/PPI;
- The number and percentage of patients that maintained the effect of treatment at the follow-up visit V6, compared to the end of study visit V4, after 12 weeks of treatment with Gerdoff® or no treatment (control group);
- The percentage of reduction of symptoms' frequency in the two treatment groups, by means of a Likert questionnaire, at visit V4 after 6 weeks of treatment compared to baseline, and at visit V6 after 18 weeks of treatment compared to Visit V4;
- The overall patient's satisfaction of treatment, by means of a semiquantitative scale;
- The concomitant use of permitted and non-permitted rescue medications, during the first 6 weeks of treatment and the follow-up period;
- The safety of investigational products, evaluated by means of recording of changes in safety haematology and blood chemistry parameters and by collecting possible incidents/adverse events occurred during:
  - The first 6 weeks of treatment, for patients included in Group 2, PPI only, and for non-responder patients included in Group 1 (Gerdoff®-PPI);
  - During the overall 18-week study period for patients that continued with the follow-up period.

3 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The investigation will be conducted in 2 investigational sites in Italy. One more site in Italy will be opened, but no patients will be enrolled in this site.

4 ETHICS

4.1 Ethics Committee

The investigational plan will be submitted to the reference local Ethics Committee of each participating site for the approval, together with the Information Sheet and Informed Consent and all other relevant documents as requested by the local Ethics Committee. An unconditional approval document from the Ethics Committee had to be received with specific reference to this investigational plan before starting the investigation.

Patient selection or any other investigation-related procedures will not commence until approval from the Ethical Committee had been obtained.

Sofar S.p.A. ensured that the IMD will be not dispatched to the sites before the copy of the Ethical Committee approval had been obtained.

4.2 Ethical Conduct of the Study

The investigation protocol will be developed in accordance with the local regulations of the involved country (Italy) relating to the presentation of a protocol for clinical studies on medical devices, and in compliance with the requirements of the ISO 14155 and of the International Conference for Harmonization (ICH) Good Clinical Practices (GCPs).

The investigation will be carried out in accordance with this protocol, the GCPs, the ISO 14155, the EU Directive 93/42/EEC amended by 2007/47/EC, the MEDDEV guidance and the local legislation in force on the conduct of clinical investigations with medical devices.

Application to the National Regulatory Authorities for approval of this investigation will be made according to specific national regulations and based on the 93/42/EEC guideline, ISO 14155, MEDDEV 2. 12-1 rev. 6 and any further amendments. Since the IMD will be certified by CE marking and used under CE marking conditions, the investigation could not need to be notified to the Competent Authorities.

A copy of the Ethical Committee approvals will be included in the investigation master file at Sofar S.p.A. Central Office and in the local investigation file of the Investigator.

4.3 Patient Information and Consent

Before patients could be admitted to the investigation, their written informed consent had to be obtained.

In seeking informed consent, the Investigator informed the patient that participation to the investigation will be voluntary and that refusal would not have led to loss of any benefit or prejudice the relationship with the physician in any way. Furthermore, a statement will be made to the effect that withdrawal from the investigation will be possible at any moment without having to give a specific reason.

Each patient received a full explanation of the nature and purpose of the investigation from the Investigator, together with a description of benefits and risks associated with participation. Insurance coverage will be also mentioned and related procedures in the event of injury will be explained.

A clear Information Sheet covering all important aspects in writing will be given to the patient who read it and had the opportunity to ask any questions whatsoever. The patient will be given adequate time for consideration before he/she will be requested to sign the consent form.

The patient or the patient's legally acceptable representative signed and personally dated the Consent Form prior to participation in the trial. The person who conducted the informed consent discussion (the Investigator or an authorized qualified person) signed and dated the form as well. Prior to participation in the trial, the patient or the subject's legally acceptable representative received a copy

of the signed and dated written informed Consent Form and any other written information provided to the subjects.

All the original signed forms will be kept in the Investigator in the investigation file.

The process of obtaining informed consent will be documented in the patient medical records. The Investigator will not undertake any investigation required for the clinical investigation until informed consent had been obtained.

The patients or the legally acceptable representative received a copy of the signed and dated consent form updates and a copy of the written information provided to the patients.

5 INVESTIGATIONAL DEVICE AND METHODS

5.1 Description of the Medical Device

The investigational medical device (IMD) (Gerdoff®) will be a CE-marked medical device, based on CS, HA and aluminium hydroxide, indicated for the treatment of symptoms associated with GERD, which contributes to the protective effect against the irritant action of hydrochloric acid produced in the stomach.

The investigational product is classified as a class III medical device. The composition is presented in Table 1.

Table 1. Composition of Gerdoff®

Ingredient	Quantity
Chondroitin sulphate sodium salt	400. 0 mg
Saccharose	275.0 mg
Aluminium hydroxide	200. 0 mg
Calcium carbonate	100.0 mg
Anti-binders: fatty acids mono-di-triglycerides, silicon dioxide	35.0 mg
High molecular weight sodium hyaluronate	10.0 mg
Flavour	70.0 mg
Sweetener: ammonium glycyrizate	10.0 mg

Appearance: tablets of uniform ivory colour.

Route of administration: oral (chewable tablets to be dissolved in the mouth).

Dosage regimen: one tablet three times daily, after breakfast, after lunch and in the evening before retiring to bed.

5.2 Intended Use

The IMD device, which has a mechanical action, is indicated for:

- Symptomatic treatment of GERD, by reducing GERD-related symptoms such as gastric burning (pyrosis), acid regurgitation, epigastric pain, irritative cough and dysphonia;
- Symptomatic treatment of hyperacidity (occasional stomach pain and burning).

Copy of instructions for use is attached in Annex 3.

5.3 Previously Intended Use or Indications For Use, if relevant

Not applicable. There will be no previous intended use or indications for use of the IMD in addition to the approved intended purpose, as scheduled in the present investigation.

5.4 Changes to the Investigational Device

Not applicable. There will be no changes to the composition, methods and procedures for use of the IMD with respect to the approved IMD leaflet.

6 CLINICAL INVESTIGATION PLAN

6.1 Overall Study Design

This will be a phase III, multicentre, prospective, randomised, open-label, two-parallel groups study, followed by a follow-up period.

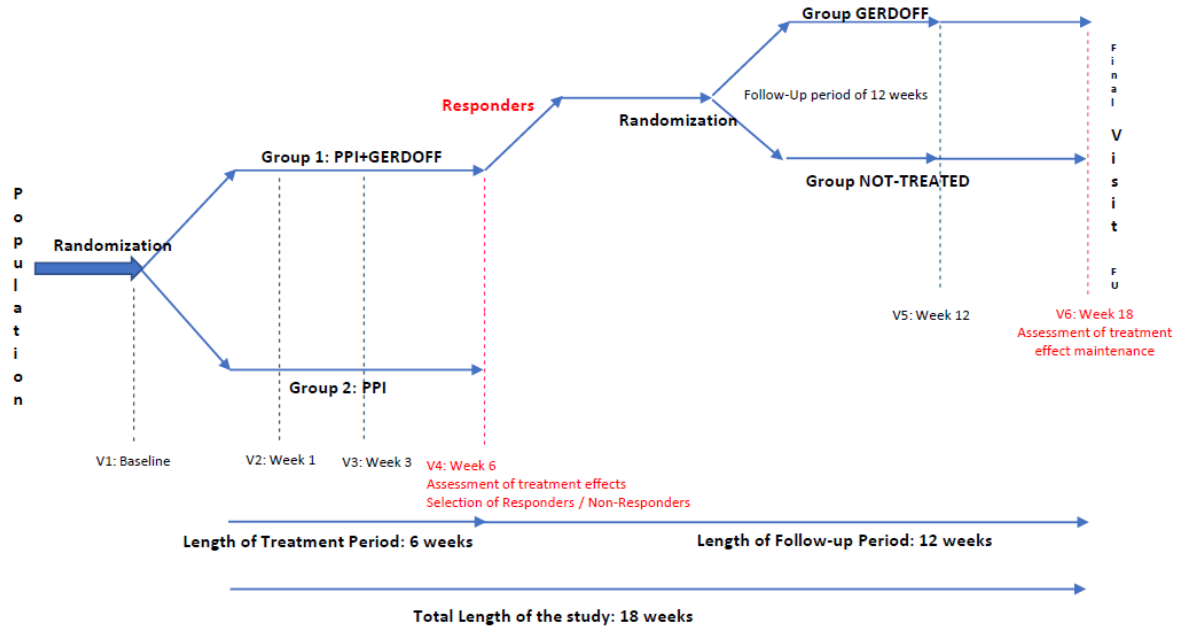
The study plan included a 6-week treatment period, from visit V1 to visit V4, of first-diagnosis patients presenting upper symptoms related to diagnosis of GERD, in the presence/absence of typical symptoms. Patients will be randomised to receive an open-label treatment (in a 1:1 ratio) with Gerdoff®- omeprazole (PPI) (Group 1) or omeprazole (PPI) alone (Group 2). The first administration of investigational products started in the morning of the day following visit V1.

At visit V4, patients in Group 2 who will be treated with omeprazole (PPI) alone, and patients in Group 1 who will be treated with Gerdoff®- omeprazole (PPI) and will be classified as non-responder, completed the study and the most appropriate therapy to treat their symptoms will be prescribed by the investigator.

To assess the maintenance of the effects of treatment, at visit V4 (end of study visit), patients in Group 1 who will be treated with Gerdoff®- omeprazole (PPI) and will be classified as responders could continue with a 12-week follow-up period. During the follow-up period patients could be randomly assigned as open-label (in a 1:1 ratio) to treatment with Gerdoff® or to a control group, which will not receive any treatment. To safeguard the health and well-being of patients, and to keep under control the possible upper symptoms of GERD that could appear, all patients that continued in the follow-up period received omeprazole as rescue medication in a quantity adequate to cover the entire follow-up period. This therapy will be chosen by the study coordinator as it is the treatment commonly used in clinical practice for the treatment of all specific and non-specific symptoms of GERD. The investigator explained to patients that rescue omeprazole could be taken only if necessary and according to the indications given by the Investigator, at constant dosage, and that use will be to be recorded in the daily diary by indicating the reason for administration. The investigator had to report the data in the source documents and in the electronic case report forms (eCRF).

A schematic diagram of the study design follows (Figure 1):

Figure 1. Study diagram



6.2 Discussion of Study Design

A prospective, randomised, open-label, two-parallel groups study divided in two phases, i.e. a treatment period followed by a follow-up period, will be considered as adequate to evaluate the effects of Gerdoff® administered in combination with a treatment with PPIs on the relief of upper symptoms of GERD and the safety of the combination therapy, compared to treatment with PPIs as monotherapy, and the maintenance of the effect of treatment on the extra-oesophageal symptoms after a 12-week period of follow-up, in patients who responded in the 6-week treatment period.

6.3 Selection of Study Population

The study population included outpatients attending the Gastroenterology investigational study site, in which the first diagnosis of upper symptoms of GERD, in the presence/absence of typical symptoms, will be performed and/or confirmed by means of the RSI questionnaire. Patients will be not to be on treatment with PPIs and/or medical devices and/or similar products (e.g. antacid alginates etc..) in the last 4 weeks and had to satisfy all inclusion and exclusion criteria of the study listed below.

6.3.1 Inclusion Criteria

Patients could be enrolled at visit V1 if they met all the following criteria:

1. Male or female subjects aged ≥ 18 years;
2. First diagnosis of GERD with upper symptoms, made on a clinical basis and confirmed by an ENT and/or confirmed by a Gastroenterologist using a RSI questionnaire;
3. Presence of extra-oesophageal symptoms associated with GERD;
4. RSI score ≥ 20;
5. Patients not pre-treated with PPIs, even for problems different from GERD, and/or with medical devices and/or similar products (e.g. antacid alginates etc..) in the last 4 weeks;
6. Cooperative patients, able to understand and adhere to the study procedures;
7. Patient able to freely give their written informed consent to study participation;

8. Patients that freely gave the consent to management of personal data related to the study.

6.3.2 Exclusion Criteria

Patients could not to be enrolled at visit V1 if they met any of the following criteria:

1. Known infective oesophagitis or oesophagitis due to acid or alkaline substances;
2. Acute or chronic rhinosinusitis;
3. Chronic bronchitis;
4. Known Zollinger-Ellison syndrome, hyatal hernia greater than 3 cm and Barrett oesophagus;
5. Ongoing neoplasias;
6. Uncontrolled diabetes;
7. Patients with impaired liver function;
8. Patients with rare hereditary problems of galactose intolerance;
9. Patients that, based on Investigator's opinion, could not take part in the study due to other diseases or concomitant therapies, such as the intake of atazanavir, nelfinavir, clopidogrel, posaconazol and erlotinib (as recommended in the Summary of Product Characteristics of Gerdoff®);
10. Patients with deficiency of Lapp lactase;
11. Patients with syndrome of glu-gal malabsorption;
12. Patients with hypersensitivity to omeprazole, substitute benzymidazolic or any of the excipients;
13. Patients already in treatment with PPIs or similar products;
14. Chronic use of drugs that interfere with the salivary secretion (e.g. anti-histamines or inhaled steroids);
15. Abuse of drug or alcohol;
16. Inability of the subject to adequately express his/her disturbances;
17. Patients with planned or ascertained pregnancy or that will not adopt an accepted contraceptive method;
18. Lactating patients.

6.3.3 Removal of Patients from Therapy or Assessment

Patient withdrawal

Patients had the right to withdraw from the study at any time for any reason including personal reasons (consent withdrawal). The Investigator also had the right to withdraw any patient from the study if he/she deemed this appropriate and in the best interest of the patients.

The following necessitated the discontinuation of a patient from the study:

- Voluntary subject withdrawal for any reason, even if not motivated;
- Appearance of an adverse event that could put at risk the patient's health;
- Sponsor's decision (to be justified);
- Investigator's decision (to be justified), in the patient's best interest;
- Poor patient's compliance to scheduled study visits and/or study procedures,
- Worsening of clinical general conditions requiring the discontinuation of the study;

- Major protocol violations (e.g. intake of any other therapy for GERD, irrespective of dose and frequency of administration);
- Poor adherence to inclusion/exclusion criteria that emerged after the inclusion of a patient and that will not guarantee the patient's safety.

The reasons for the interruption or the exclusion of a patient from the study had to be reported in the eCRF section 'End of study form' or 'End of follow-up period form' and will be to be communicated to the study sponsor.

In the case of early study discontinuation, the patient will be to be considered as a treatment failure. However, the investigator had to make any effort to perform the end of study assessments, scheduled at visit V4, in case a patient interrupted the study during the 6-week treatment period, or scheduled at visit V6, in case a patient interrupted the study during the 12-week follow-up period.

In the discontinuation visit, the patient had to return the investigational product and the daily diary completed up to the time of discontinuation.

The investigator had to record the reasons for the patient's treatment discontinuation and the early study conclusion in the clinical record/worksheet and in the eCRF. The sponsor had to be timely informed.

6.3.4 General and Dietary Restrictions

Not applicable. No specific general or dietary restrictions will be required in the investigation.

6.4 Treatments

6.4.1 Identity of Investigational Device and Reference(s)

Investigational device:

Gerdoff® chewable tablets contain CS 400 mg, high molecular weight HA 10 mg and aluminium hydroxide 200 mg.

Details of the IMD are given in Section 5.1.

PPI (omeprazole)

Omeprazole will be the PPI available on the market and used during the study. Omeprazole will be taken as single agent or associated with Gerdoff® in the first 6 weeks of the study or as rescue medication (only if necessary) in the follow-up period, at constant dose and according to the Investigator's indication.

Route of administration: oral.

Dosage: two 20 mg capsules once daily in the morning before breakfast.

Packaging

The investigational products, Gerdoff® and omeprazole (PPI) will be provided free of change by Sofar S.p.A. by using batches available on the market.

The provided packages contained:

- Study period:
  - Packages of Gerdoff® for study period (Group 1)

At visit V1, each patient in Group 1 received 1 kit containing 14 marketed blisters of Gerdoff®, each containing 10 tablets, to cover a treatment period of 6 weeks.

The patient took 3 tablets/day for 6 weeks (42 days), for a total of 126 tablets, which included 14 reserve tablets.

  - Packages of omeprazole (PPI) for study period (Group 1 and 2)

At visit V1, each patient in Group 1 received 1 kit containing 14 marketed blisters of omeprazole, each containing 7 capsules, to cover a treatment period of 6 weeks.

The patient took 2 capsules/day, in the morning before breakfast, for 6 weeks (42 days), for a total of 84 capsules, which included 14 reserve capsules.

- Follow-up period:
  - Packages of Gerdoff® for follow-up period

At visit V4, each patient included in the follow-up period and randomised in the treatment group received 2 kits of investigational product. Each kit contained 14 marketed blisters of Gerdoff®, each containing 10 tablets, to cover a treatment period of 6 weeks.

The patient took 3 tablets/day for 6 weeks (42 days), for a total of 126 tablets, which included 14 reserve tablets.

  - Packages of omeprazole (PPI) as rescue medication for the follow-up period

At visit V4, each patient included in the follow-up period received 2 kits containing the rescue medication scheduled for the study. Each kit contained 14 marketed blisters of omeprazole, each containing 7 capsules, to cover a treatment period of 6 weeks, including 14 reserve capsules.

Although the patient could take 2 capsules/day, only if necessary and according to the indications of the Investigator, and at constant dose, 14 reserve capsules will be included in any provided kit, which covered a treatment period of 6 weeks (42 days), for a total of 84 capsules.

Labelling

Each blister of Gerdoff® and omeprazole will be labelled with a label that reported the following information:

- Name of the sponsor
- Study code
- Package identification number (Med ID: xxx)
- Batch number

Packages containing blisters of Gerdoff® and omeprazole will be labelled with a tear-off label, and reported the following information on the fixed part:

- Name of the sponsor, address and phone number
- Batch number
- Expiry date
- Study code
- Package identification number (Med ID: xxx)
- Assigned to patient No. xxx
- Only for investigation
- Store at a temperature ≤ 30 °C
- CE-marked Medical Device (only for Gerdoff®)
- Keep out of the reach and the sight of children

The removable part contained the following information:

- Name of the sponsor
- Batch number
- Study code
- Package identification number (Med ID: xxx)
- Assigned to patient No. xxx
- Date of distribution

The marketed blisters of Gerdoff® and omeprazole will be re-packaged by Euromed Clinical Supply Services srl (Eclisse®), via Como 5, 22063 Cantù (CO), Italy.

6.4.2 Treatment Administered

Eligible patients will be randomly assigned to one of the two following treatment groups:

Treatment period

- Group 1
  - Gerdoff®: CS, HA and aluminium hydroxide chewable tablets.

Route of administration: oral

Dosage regimen: one tablet three times daily: 1 tablet after breakfast, 1 tablet after lunch and 1 tablet in the evening before retiring to bed.

Treatment duration: 6 weeks ± 2 days.

- Omeprazole (proton pump inhibitor, PPI)

Route of administration: oral.

Dosage: two 20 mg capsules once daily in the morning before breakfast.

- Group 2
  - Omeprazole (proton pump inhibitor, PPI)

Route of administration: oral.

Dosage: two 20 mg capsules once daily in the morning before breakfast.

Treatment duration: 6 weeks ± 2 days.

Follow-up period

During the 12-week follow-up period, which started from the end of study visit V4, responder patients of Group 1 will be randomly assigned to receive treatment with Gerdoff®, according to the above reported dosage, or will be assigned to the control group and will be therefore not treated. All patients received a packaging of omeprazole, to be taken only if necessary, at constant dose and according to the indications of the Investigator.

The scheduled duration of the follow-up period will be 12 weeks ± 3 days for both treatment groups.

Administration of investigational products

- Study period

Patients will be instructed to take, starting from the morning of the day following Visit V1, the investigational products every day for the next 6 weeks.

- Follow-up period

Patients will be instructed to take, starting from the morning of the day following Visit V4, the investigational products every day for the next 12 weeks.

6.4.3 Selection of Doses of the Investigational Device

The dose regimen of Gerdoff® used in the present study (i.e. one tablet three times daily: 1 tablet after breakfast, 1 tablet after lunch and 1 tablet in the evening before retiring to bed) is that scheduled in the marketed package insert of the product for adults and children over 12 years.

6.4.4 Selection of Timing and Dose for Each Patient

Refer to Section 6.4.3.

6.4.5 Compliance and Device Accountability

Patients will be instructed to record in the daily diary the amount of investigational products taken during the entire study period, highlighting that the administered quantity will be not to be lower than that scheduled for the study to not invalidate the efficacy of treatment.

At the end of the study, the Investigator counted the amount of tablets and of capsules returned by the patient and compared this amount with the quantities reported in the patient daily diary. In case of discrepancies, clarifications will be asked to the patient and will be reported in the clinical records/worksheet and in the eCRF.

The study monitor counted the returned investigational products and compared the returned quantity with the use reported in the patient diary to assess the patient's adherence to the scheduled dosage.

Patients with values of compliance ≥ 95% of the overall dosage scheduled in the 6-week treatment period , evaluated on the basis of minimal taken daily dose, will be considered as adherent to treatment.

6.4.6 Prior and Concomitant Medications

At the baseline visit, the Investigator instructed the patients on the use of rescue medication, and on the list of permitted and non-permitted concomitant medications.

Permitted concomitant medications

With the exception of those drugs listed among non-permitted medications, participants will be allowed to use any concomitant medication necessary for the treatment of pre-existing concomitant pathologies or for intercurrent diseases, provided that they will not interfere with study evaluation parameters and that it will be not taken for the treatment of GERD.

Rescue medication

During the first 6 weeks of treatment, the use of any type of rescue medication, i.e. the intake of any other therapy for GERD irrespective from the dose and frequency of administration, will be to be considered as a protocol violation. In the event of intake of non-permitted medications, the Investigator had to decide whether it will be the case for maintaining the patient into the study, even if it will be considered as a protocol violator. The administered treatment will be to be recorded in the source documentation and in the eCRF.

During the follow-up period, (V4-V6), in case of worsening of symptoms, the use of omeprazole (PPI) will be permitted as rescue medication at constant dose, both in patients included in the control group and in those included in the Gerdoff® group. The administration of omeprazole will be to be recorded in the source documentation and in the eCRF.

In the case of use of any other product taken as rescue medication for the control of GERD, patients will be to be considered as protocol violators and will be to be discontinued from the study. The possible intake of any other PPI different from omeprazole, the change in dosage or the intake of other rescue medications will be to be recorded in the source documentation and in the eCRF.

Non-permitted concomitant medications

The following medications will be not permitted during the whole study period:

- Chronic use of drugs that interfere with the salivary secretion (e.g. anti-histamines of inhaled steroids) and previous use of PPIs and/or medical devices and/or similar products (e.g. alginates, antacids etc..) in the 4 weeks preceding the inclusion in the study;
- During the first 6-week treatment period, the use of any type of rescue medication will be not permitted, as well as the use of any other therapy for GERD, irrespective of dosage and frequency of administration. In case of intake of any type of rescue medication, patients will be to be considered as protocol violators;
- During the follow-up period only the use of omeprazole will be permitted as rescue medication at constant dose, to be taken only if necessary and according to the indications of the Investigator. The administration of any other therapy for GERD will be not permitted.

6.4.7 Treatment Allocation and Randomisation

All patients that accepted to take part in the study and freely signed the informed consent received an individual progressive screening number. Following the verification of all inclusion and exclusion criteria, a progressive randomisation number will be assigned to patients, which identified the patient for the entire study duration.

The randomization list will be in balanced-block design and will be prepared using a validated system that automates the random assignment of treatment groups to randomization numbers. Randomisation will be performed as a function of lists produced for the study, which provided the correct sequence

for the assignment of patients to the study groups and for the dispensation to patients of the treatment scheduled for the assigned group and as a function of the phase of the study.

In case of screening failure or study discontinuation, the screening and randomisation number could not be re-assigned to another patient and the patient will be not allowed to re-enter the study. Similarly, in case that a patient interrupted the participation in the study after the randomisation but before the start of use of the kit of the investigational product, this kit could not be assigned to another patient.

6.4.8 Blinding and Labelling

Not applicable, as this will be an open-label investigation.

6.5 Study Procedures and Study Schedule

6.5.1 Overview of Data Collection

The study plan and scheduled examination and procedures are summarised in the following flow-chart (Figure 2).

Figure 2. Flow-chart of the study

Visit	**V1 Baseline**	**V2 (intermediate visit)**	**V3 (intermediate visit)**	**V4 [a] End of study/ Early interruption[c]**	**V5 [b] Follow-up (control visit) [d]**	**V6[b] End of follow-up/Early interruption[c]**
Period	**T0**	**T 1 1 week ± 1 day**	**T 3 3 weeks ± 2 days**	**T6 6 weeks ± 2 days**	**T12 12 weeks ± 3 days**	**T18 18 weeks ± 3 days**
Informed consent	X					
Inclusion/exclusion criteria	X					
Demographic data	X					
Vital signs	X			X		X
First GERD diagnosis or diagnosis confirmation	X					
Anamnesis	X					
Reference. ENT specialist	X					
Objective examination and concomitant diseases	X			X		X
Assessment of symptoms	X	X	X	X	X	X
Haematology and blood chemistry	X			X		X
Beta-hCG [1]	X			X		X
Treatment dispensing Gerdoff® + PPI or PPI	X					
Treatment dispensing Gerdoff®/no treatment and rescue [2]				X		
Concomitant therapies	X	X	X	X	X	X
Likert scale	X	X	X	X	X	X
RSI questionnaire	X	X	X	X	X	X
Diary dispensing/returning	X	X	X	X	X	X
Questionnaire of treatment likelihood		X	X	X		
Assessment of responder/ non-responder patients				X		
Assessment of maintenance of the effect						X
Incidents/adverse events		X	X	X	X	X

Visit	V1 Baseline	V2 (intermediate visit)	V3 (intermediate visit)	V4 [a] End of study/ Early interruption[c]	V5 [b] Follow-up (control visit) [d]	V6[b] End of follow-up/Early interruption[c]
Period	**T0**	**T 1 1 week ± 1 day**	**T 3 3 weeks ± 2 days**	**T6 6 weeks ± 2 days**	**T12 12 weeks ± 3 days**	**T18 18 weeks ± 3 days**
Assessment of compliance to Gerdoff® and PPI, and product accountability				X		
Assessment of compliance to Gerdoff® and product accountability						X
Use of rescue medication [3]		X	X	X	X	X
End of study visit				X		
End of follow-up visit						X

(a) End of study visit for all patients included in the study. Responder patients included in Group 1 (Gerdoff®+PPI) immediately continued the study with the follow-up phase.

(b) Only responder patients included in Group 1 (Gerdoff®+PPI) will be included in the follow-up phase.

(1) Only in childbearing potential women.

(2) Only in responder patients in Group 1 that took part in the follow-up study.

(3) During the first 6 weeks of treatment the use of any type of rescue medication will be not permitted in both treatment groups. The possible intake of rescue medication during the first 6 weeks of the study will be to be considered as a protocol violation. During the follow-up phase only the use of omeprazole as rescue will be permitted as rescue medication, at constant dose and only if necessary, in both the group of untreated patients (control group) and the group of treated patients, whereas the use of other products for the treatment of GERD will be not permitted. In case of intake patients will be to be considered as protocol violators and will be to be discontinued from the study. The possible rescue medications used during the overall study period will be to be recorded in the source documentation and in the eCRF.

(c) In case of early study discontinuation the patient will be to be considered as a treatment failure and the investigator had to do all the possible to perform:

- End of study assessments, scheduled at visit V4, in case the patient interrupted the study during the 6-week treatment period;
- End of follow-up period assessments, scheduled at visit V6, in case the patient interrupted the study during the 12-week follow-up period.

(d) Visit V5 could be also performed as phone visit, only if agreed with the patient at Visit V4, during which the Likert scale and the RSI questionnaire for the visit V5 and the daily diaries for the visits V5 and V6 will be to be handed to the patient. At visit V6, the patient had to return them to the Investigator.

Study periods

The study plan included two consecutive study periods:

- Treatment period

From Visit V1 to Visit V4, in which randomised patients took Gerdoff® + PPI (omeprazole) or PPI (omeprazole) for a period of 6 weeks. During the treatment period patients attended 4 scheduled visits: Visit V1 will be the baseline visit for patients' inclusion in the study, Visits V2 and V3 will be intermediate visits for the evaluation of the effects of treatment, and Visit V4 will be the end of study visit in which patients will be classified as responders or non-responders.

- Follow-up period

From visit V4 to visit V6, in which patients classified as responders and belonging to Group 1 (Gerdoff® + PPI) will be randomised to treatment with Gerdoff® or to the control group (untreated group). All patients included in the follow-up period received a packaging of omeprazole as rescue medication, to be taken only if necessary at constant dose and according to the indications of the Investigator. The follow-up period lasted 12 weeks. During the follow-up period, patients performed, in addition to visit V4, other two scheduled visits. Visit V5 will be an intermediate visit for the evaluation of the effects of treatment (which could be performed by phone), and visit V6 will be the end of treatment visit, in which the effects of the maintenance of treatment will be evaluated.

6.5.2 Study Procedures

Treatment period

Visit 1 (T0): baseline/inclusion

A first specialist visit could be performed by an ENT as per common clinical practice based on patient's symptoms. In the case that the ENT performed a first diagnosis of typical upper symptoms due to GERD, the diagnosis could be confirmed according to the diagnostic process scheduled by the usual clinical practice in use at the investigational site prior to attending the Gastroenterologist or the investigator could directly send the patient to the Gastroenterologist for the confirmation of the diagnosis and for assigning an appropriate therapy. Patients sent by the ENT should not have been pre-treated with PPIs and/or medical devices and/or similar products (e.g. alginates, antacids etc...). The Gastroenterologist Investigator that recruited patients in the study collected the consent, performed and/or confirmed the first diagnosis of upper symptoms of GERD in case the patient will be sent by the ENT, and included the patients in the study provided that they had not yet received treatments for GERD. At the baseline/inclusion visit (V1, T0), patients will be instructed on the nature of the study and received any information on the risks and benefits related to study participation.

After the time to freely decide and after giving their written informed consent to study participation and to the management of personal data related to the study, patients underwent the clinical and instrumental investigations needed to assess their eligibility.

Recruited patients will be visited by a Gastroenterology specialist, who performed and/or confirmed the diagnosis of upper symptoms of GERD and recorded all the following information and results performed during the visit on a clinical record/worksheet (source document) and on the eCRF:

- Verification of inclusion/exclusion criteria, with special attention to upper symptoms of GERD;
- Demographic data (birth date, gender, race);
- Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, weight and height with calculation of body mass index [BMI]);
- Clinical diagnosis of GERD: first diagnosis nor confirmation of first diagnosis;
- Clinical assessment of extra-oesophageal symptoms, upper symptoms associated with the diagnosis of GERD;
- Identification of the reference ENT and of his/her affiliation;
- Patient's anamnesis, with brief details of medical history and particular attention to medical history of upper symptoms (i.e. date of onset, symptoms' description, frequency and intensity of symptoms);
- Anamnesis of concomitant therapies, treatments taken in the last 4 weeks and ongoing treatments, with particular attention to remote and recent therapies, intake of PPIs and/or medical devices and/or similar products (e.g. alginates, antacids, etc..), chronic use of drugs that interfere with the salivary secretion (e.g. anti-histamines or inhaled steroids) and thus represented an exclusion criterion and other non-permitted therapies;
- Objective examination and concomitant diseases;
- Haematology and blood chemistry: haemochrome, erythrosedimentation rate (ESR), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transpeptidase (gamma-GT), total and direct bilirubin, glycaemia, creatininemia, blood urea nitrogen (BUN) (tests performed in the last 3 months will be kept as valid);

- The evaluation of beta-human chorionic gonadotropin (beta-hCG) levels will be performed only in women of childbearing potential;
- RSI questionnaire, completed by patients following the Investigator's explanation;
- Likert scale, completed by patients following the Investigator's explanation.

Furthermore, the Investigator:

- Explained to patients which other products could or not could be taken for the entire study duration;
- Dispensed a diary to patients, to be completed daily, explaining to patients the procedures for completion and the importance of a correct filling, recommending them to daily report the presence and intensity of upper symptoms, the amount of taken investigational product, the possible use of other products taken on-demand for the treatment of GERD and of all other products, the possible changes of dose of taken treatments and all possible adverse events or incidents occurred during the study.

Patients satisfying inclusion/exclusion criteria and that, by signing the informed consent provided at the beginning of the study, accepted to adhere to the study procedures and to complete the daily diary, will be included in the study and will be randomly allocated to the investigational product to be taken for the following 6 weeks of treatment. Thus the Investigator proceeded to:

- Patient's randomisation and assignment of a randomisation number;
- Dispensing of treatment, Gerdoff® and/or PPI (omeprazole), for the following 6 weeks of treatment;
- Recommendation to take the first dose of investigational products in the morning of the day following Visit V1;
- Registration in the source document and in the eCRF of the screening and the randomisation number assigned to patient and of the number of product kit dispensed to the patient;
- Planning with the patient of the date for the following visit V2.

Visit 2 (T1 after 1 week ± 1 day from the baseline visit): intermediate assessment

Patients will be visited by a Gastroenterology specialist, who recorded all the following data collected during this visit in the source document and in the eCRF:

- Concomitant therapies, maintenance of the ongoing therapies, new therapies or changes in frequency or dosage of ongoing therapies, with particular attention to possible intake of non-permitted medications;
- Assessment of upper symptoms associated with the diagnosis of GERD, by pointing into evidence possible changes from baseline;
- RSI questionnaire, completed by patients during the visit;
- Likert scale, completed by patients during the visit;
- Questionnaire on patient's likelihood of treatment, completed by patients during the visit;
- Review of diaries and Investigator's assessment of diary entries, dispensing of new diaries and adequate recommendations for completion;
- Compliance to treatment, based on verification of diaries, In case of necessity, the patient will be re-trained;
- Use of rescue medication: used products, frequency, dosage and reasons for intake;

- Possible incidents and/or adverse events: treatments/procedures taken to treat the event/incident, duration of the event/incident and correlation with the investigational product;
- Planning with the patient of the date for the following visit V3.

Visit 3 (T3 after 3 weeks ± 2 days from the baseline visit): end of treatment visit

Patients will be visited by a Gastroenterology specialist, who recorded all the following data collected during this visit in the source document and in the eCRF:

- Concomitant therapies, maintenance of the ongoing therapies, new therapies or changes in frequency or dosage of ongoing therapies, with particular attention to possible intake of non-permitted medications;
- Assessment of upper symptoms associated with the diagnosis of GERD, by pointing into evidence possible changes from baseline;
- RSI questionnaire, completed by patients during the visit;
- Likert scale, completed by patients during the visit;
- Questionnaire on patient's likelihood of treatment, completed by patients during the visit;
- Review of diaries and Investigator's assessment of diary entries, dispensing of new diaries and adequate recommendations for completion;
- Compliance to treatment, based on verification of diaries. In case of necessity, the patient will be re-trained;
- Use of rescue medication: used products, frequency, dosage and reasons for intake;
- Possible incidents and/or adverse events: treatments/procedures taken to treat the event/incident, duration of the event/incident and correlation with the investigational product;
- Planning with the patient of the date for the following visit V4.

Visit 4 (T6 after 6 weeks ± 2 days from the baseline visit): intermediate assessment

Patients will be visited by a Gastroenterology specialist, who recorded all the following data collected during this visit in the source document and in the eCRF:

- Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, weight and height with calculation of BMI);
- Concomitant therapies, maintenance of the ongoing therapies, new therapies or changes in frequency or dosage of ongoing therapies, with particular attention to possible intake of non-permitted medications;
- Objective examination, by pointing into evidence possible changes from baseline;
- Assessment of upper symptoms associated with the diagnosis of GERD, by pointing into evidence possible changes from baseline;
- Haematology and blood chemistry: haemochrome, ESR, CRP, AST, ALT, alkaline phosphatase, gamma-GT, total and direct bilirubin, glycaemia, creatininemia, BUN, and changes from baseline;
- Evaluation of beta-hCG levels, only in women of childbearing potential;
- RSI questionnaire, completed by patients during the visit;
- Likert scale, completed by patients during the visit;
- Questionnaire on patient's likelihood of treatment, completed by patients during the visit;

- Review of diaries and Investigator's assessment of diary entries;
- Compliance to treatment, collection of investigational products accountability of the product returned by patient during this visit;
- Use of rescue medication: used products, frequency, dosage and reasons for intake;
- Possible incidents and/or adverse events: treatments/procedures taken to treat the event/incident, duration of the event/incident and correlation with the investigational product;
- Assessment of patients responder/non-responder to investigational products;
- End of study assessments.

Furthermore, the Investigator:

- Selected responder patients in Group 1 and treated with Gerdoff®+PPI;
- In case the patient will be willing to continue in the study, dispensed a new diary to the patient, to be completed daily for the 12-week follow-up period, further explaining the procedures of completion and the importance of a correct completion to patient, and recommending him/her to report daily the presence and intensity of upper symptoms, the amount of administered investigational product, the possible use of other products taken on-demand for the treatment of GERD, and all the other products taken, and all the possible adverse events or incidents occurred during the study.

Responder patients Group 1 (Gerdoff®+PPI) that, by signing the informed consent at the beginning of the study, accepted to attain the procedures scheduled for the follow-up period and to continue to complete the daily diary will be then included in the follow-up period (starting from visit V4) and will be randomly assigned to dispensing of product adequate for the next 12 weeks or to control group (i.e. no treatment). All patients included in the follow-up period received a dispensing of omeprazole adequate for the next 12 weeks, to be taken as rescue medication only if necessary and according to the Investigator's indications. The investigator explained to patients when and why omeprazole could be taken and that the intake and the reason will be to be reported in the daily diary. Then the investigator proceeded to:

- Patient's randomisation to Gerdoff® group or control group;
- Dispensing of the kit of Gerdoff® for the following 12 weeks of treatment to patients randomised in this group;
- Dispensing of the kit of omeprazole for the following 12 weeks of treatment to patients that continued in the follow-up period;
- Registration in the source document and in the eCRF of the number of product kit dispensed to responder patients in Group 1 that continued in the follow-up period;
- Registration in the source document and in the eCRF of the number of kit of omeprazole as rescue medication dispensed to all patients that continued in the follow-up period;
- Recommendation to take the first dose of investigational products in the morning of the day following Visit V4;
- Planning with the patient of the date for the following visit V5, which could be performed by phone. In this case, the Investigator dispensed to patients all required documents, i.e. the Likert scale, the RSI questionnaire and the diaries for visits V5 and V6, to be completed to perform visit V5 by phone;
- In case that visit V5 will be performed by phone, patients will be to be reminded that they had to return to the Investigator all documents received for the study.

Follow-up period

Visit 5 (T12 after 12 weeks ± 3 days from the baseline visit): control visit

Patients will be visited by a Gastroenterology specialist, who recorded all the following data collected during this visit (that could be performed by phone) in the source document and in the eCRF:

- Concomitant therapies, maintenance of the ongoing therapies, new therapies or changes in frequency or dosage of ongoing therapies, with particular attention to possible intake of non-permitted medications;
- Assessment of upper symptoms associated with the diagnosis of GERD, by pointing into evidence possible changes from baseline and from end of study visit V4;
- RSI questionnaire, completed by patients during the visit. In case the visit will be conducted by phone, the patient will be reminded to return the diary to the investigational site in the following visit V6;
- Likert scale, completed by patients during the visit. In case the visit will be conducted by phone, the patient will be reminded to return the diary to the investigational site in the following visit V6;
- Compliance to treatment, based on verification of diaries. In case of necessity, the patient will be re-trained;
- Use of rescue medication: used products, frequency, dosage and reasons for intake;
- Possible incidents and/or adverse events: treatments/procedures taken to treat the event/incident, duration of the event/incident and correlation with the investigational product;
- Planning with the patient of the date for the following visit V6, and patient's remind to return all materials received for the study.

Visit 6 (T18 after 18 weeks ± 3 days from the baseline visit): end of follow-up visit

Patients will be visited by a Gastroenterology specialist, who recorded all the following data collected during this visit in the source document and in the eCRF:

- Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, weight and height with calculation of BMI);
- Concomitant therapies, maintenance of the ongoing therapies, new therapies or changes in frequency or dosage of ongoing therapies, with particular attention to possible intake of non-permitted medications;
- Objective examination, by pointing into evidence possible changes from baseline;
- Assessment of upper symptoms associated with the diagnosis of GERD, by pointing into evidence possible changes from baseline and from visit V4;
- Haematology and blood chemistry: haemochrome, ESR, CRP, AST, ALT, alkaline phosphatase, gamma-GT, total and direct bilirubin, glycaemia, creatininemia, BUN, and changes from baseline;
- Evaluation of beta-hCG levels, only in women of childbearing potential;
- RSI questionnaire, completed by patients during the visit;
- Likert scale, completed by patients during the visit;
- Review of diaries and Investigator's assessment of diary entries;
- In case that visit V5 will be performed by phone, collection of the Likert scale, the RSI questionnaire and the diaries for visits V5;

- Compliance to treatment, collection of investigational products accountability of the product returned by patient during this visit;
- Use of rescue medication: used products, frequency, dosage and reasons for intake;
- Possible incidents and/or adverse events: treatments/procedures taken to treat the event/incident, duration of the event/incident and correlation with the investigational product;
- Assessment of maintenance of the effects based on data obtained from the RSI questionnaire and the Likert scale;
- End of follow-up assessments.

6.5.3 Study Endpoints

Primary performance variable

The primary performance variable of the study will be the change from baseline to visit V4 of the total score of RSI questionnaire, used to assess the effect of treatment on upper symptoms. The RSI questionnaire examines 9 items, to be scored from 0 to 5, with a higher score indication a higher severity of the symptom (range of total score: 0-45).

Secondary performance variables

The secondary performance variables of the study will be:

- Change of the total score of RSI questionnaire from baseline to the other time points;
- Change of the score of single items of the RSI questionnaire from baseline at any time point;
- Number and percentage of responder/non-responder patients at end of treatment (visit V4);
- Change from baseline to end of treatment (visit V4) and end of follow-up (visit V6) of upper symptoms, assessed using the Likert scale. The Likert scale scored symptoms from 0 to 4, with a higher score indication a higher frequency of the symptom;
- Presence of upper symptoms at baseline, end of treatment (visit V4) and end of follow-up (visit V6), assessed using the RSI questionnaire and the Likert scale;
- Use of rescue medication during the follow-up period: administered therapy, frequency of administration, timing of administration and administered dose;
- Patient's opinion of satisfaction with treatment, requested at intermediate Visits V2 and V3, and at the end of treatment visit V4, by means of a semiquantitative ordinal scale, where: 0 = low, 1 = discrete, 2 = good, 3 = excellent.

Safety variables

The safety variables of the study will be:

- Frequency of adverse events and incidents occurring at any time, during the study;
- Changes from baseline of haematology and blood chemistry parameters;
- Changes from baseline of vital signs (weight, BMI, blood pressure, heart rate and respiratory rate).

Incidents and adverse events

Incidents

According to MEDDEV 2.12.1, Rev. 8, a medical device incident is defined as 'any malfunction or deterioration in the characteristics and/or clinical performance of a device, as well as any inadequacy in the labelling or the instructions for use, which, directly or indirectly, might lead to or might have

led to the death of a patient, or a user or of other persons or to a serious deterioration in their state of health'.

A medical device incident that required reporting included:

a) Serious public health threat: any event type which resulted in imminent risk of death, serious deterioration in state of health, or serious illness that required prompt remedial action (MEDDEV 2.12.1 rev.8).

b) Death or unanticipated serious deterioration in state of health of a subject that resulted in:
    1) A life-threatening illness or injury, or
    2) A permanent impairment of a body structure or a body function, or
    3) In-patient or prolonged hospitalization, or
    4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

c) Other events: events that had an established link between the device and the event.

Adverse events and serious adverse events

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

An adverse event could therefore be any unfavourable and unintended sign (including laboratory abnormal finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered as related to the investigational medicinal product.

A Serious Adverse Event (SAE)/Serious Adverse Drug Reaction will be defined as any untoward medical occurrence or effect that at any dose fell in one or more of the following categories:

- Resulted in death;
- Will be life-threatening;
- Required patient hospitalisation or prolongation of existing inpatients' hospitalisation;
- Resulted in persistent or significant disability or incapacity;
- Will be judged as clinically significant and/or as requiring a treatment and/or an intervention to prevent the above outcomes;
- Caused a congenital anomaly or birth defect;
- Caused the presumed transmission of an infective agent through the product.

Expectedness

An expected adverse event will be an adverse event, the nature or severity or consequence of which will be consistent with the applicable product reference safety information (Investigator's Brochure for an unapproved investigational product or Patient Information sheet for an authorised product). Expected adverse events that appears in a different mode of with a frequency higher than expected will be to be considered unexpected as well.

Intensity

Each adverse event will be rated on a 3-points scale of increasing intensity:

- Mild: the event presented with signs and symptoms that will be evident, but will be well tolerated;
- Moderate: the event caused discomforted that interfered with the usual activity of the patient ;

- Severe: the event determined that the subject will be unable to work or to perform the usual daily activities.

Causality assessment

The relationship with the investigational product will be classified as follows:

- Related: following a careful evaluation, a certain relation with the use of the investigational product will be ascertained;
- Possibly related: following a careful evaluation, a possible relation with the use of the investigational product will be ascertained, but it will be not fully certain;
- Not related: the event will be not due to causes not related with the investigational product.

6.6 Changes in the Conduct of the Clinical Investigation

Not applicable. No protocol amendments will be generated at any time during the investigation.

7 DATA QUALITY ASSURANCE

7.1 Study Conduct

Before implementation of the study, a meeting with all Investigators involved in the study will be arranged in order to ensure the comprehension of study protocol and procedures.

During the site initiation visit all study procedures will be detailed to the Study Staff. A science graduate monitor of High Research s.r.l. periodically visited the Investigators to ensure that the study will be conducted according to the protocol and to perform source data verification on all eCRFs filled in until the visit day.

7.2 Study Monitoring

At regular intervals during the clinical investigation, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team of High Research s.r.l. to review investigation progress, Investigator and patient compliance with clinical investigation protocol requirements and any emergent problems. These monitoring visits included but will be not limited to review patient informed consent, patient recruitment and follow-up, AE and SAE documentation and reporting, medical device administration, medical device accountability, concomitant therapy use and quality of safety and performance data.

7.3 Site Audits

Not applicable. Site audits will be performed at any time during the investigation.

7.4 Case Report Forms (CRFs) and patient diaries

Electronic case report form (eCRF)

The data generated in this trial will be recorded at the study site by the appointed study personnel on a study-specific, validated (as per 21 CFR Part 11) eCRF.

eCRFs will be designed in order to act as a reminder both as far as the timing and the nature of the data to be collected are concerned. The initial (entry) page specified how to fill them in, in agreement with satisfactory regulatory standards.

eCRFs will be designed by an appointed eCRF Designer, using a validated clinical data management system. Access by User ID and password to the eCRFs will be provided to the Investigators together with a User Manual with careful instructions on how to fill them in, in agreement with satisfactory regulatory standards. Training on the use of the eCRF will be performed.

Data entered in the eCRF will be captured by a fully validated system and stored in a dedicated Excel electronic database, which will be used to produce all planned statistical analyses.

In agreement with satisfactory regulatory standards, the investigators, study coordinators, and study monitors will be instructed on the proper use of the electronic eCRF system and will be provided with a user manual with appropriate instructions on software usage, together with individual, private User ID and Password to have access to the eCRF.

The name of personnel authorized to complete an eCRF will be to be given to the assigned study monitor before trial initiation.

The eCRF should have been filled-in during or immediately after the conclusion of each visit, preferably within 24 hours but no later than five working days after the visit.

Copy of the eCFR is attached in Annex 2.

Patient diaries

Specific paper patient diaries for the collection of the data pertaining to this clinical trial will be provided to the patients. They will be designed in order to act as a reminder both as far as the timing and the nature of the data to be collected are concerned. The initial page specified how to fill them in, in agreement with satisfactory regulatory standards.

During the study period, patients will be requested to complete a daily diary for the registration of the presence and intensity of upper symptoms, in line with the questions listed in the RSI questionnaire, of the use of rescue medication on an as-needed basis, during the first 6 weeks of treatment and the follow-up phase, and of all possible adverse events or incidents occurred during the study period. At each visit, the Investigator evaluated the data entered in the daily diary and reported them in the eCRF.

7.5 Data Management

As said above, computer systems used for remote data collection and the system for data storing and processing will be validated. Verification and cross-verification of the data entered by the study personnel at each visit will be automatically performed by the system, according to predefined nature/type of the data, value ranges and rules. All rules applied by the system to check specific items will be detailed in a document issued by the Data Management service of the CRO. Queries will be automatically generated by the system for all data found to be inconsistent, incorrect or missing. Queries to be solved/unclear data to be corrected (or confirmed) will be highlighted by the system, to be easily identified by the study personnel when accessing the eCRF website. All changes performed by the Investigator will be tracked by the system.

Once all data will be entered in the eCRF and all outstanding queries will be solved, the Monitor of the study authorized the Investigator to “freeze” the data of the subject’s eCRF. No change will be accepted by the system after freezing. Nonetheless, it could have been still necessary to edit additional queries following general quality control checks performed by the Data Manager of the study on the frozen database: in case, queries will be to be edited in paper form and referred to the appropriate hospital/study site personnel, to be resolved with assistance of the study Monitors.

When all data will be received, all data problems will be resolved, all data checks and quality control checks will be performed, and a data review meeting will be held, the trial database will be considered clean and could be locked. After database lock, the appointed statistician performed the statistical analysis as planned. Any further modification of recorded data will be to be documented in a database log form.

The data of all patients, recorded on the eCRFs and on the patient diaries, will be stored in a suitable, properly designed database.

8 STATISTICAL METHODS

The statistical methods will be planned in the protocol and will be then updated, agreed and approved in the final Statistical Analysis Plan (SAP), version 1.1, dated 19 February 2019 (Annex 10).

Statistical analysis will be performed by the statistical department of High Research S.r.l., Viale Abruzzi, 13/A, 20131 Milan, Italy.

8.1 Sample Size Justification

Although a search in literature has not identified any published article for trials that used the same investigation design as that used in the present study, some recently published articles (9, 13-15) allowed to formulate a sample size calculation for the present investigation.

The calculation of the sample size will be based on the primary objective of the investigation, i.e. to assess the change of RSI questionnaire from baseline to 6 weeks of treatment in the two treatment arms, Gerdoff®- PPI and PPI alone, based on an hypothesis that the addition of Gerdoff® to PPI could improve the effect of disappearance and of rapidity of control of upper symptoms of GERD. Such effect will be evaluated as the mean change in RSI compared to baseline, taking into consideration the variable age, standard deviation (SD) and expected value after treatment with omeprazole.

The following assumptions will be made for the sample size calculation:

Difference between the two arms (delta): 3.6; SD of the difference: 5.

Based on these assumptions, for a comparison based on unpaired Student t test, at a power of 80% and a level of probability of 5% for a two-tailed test, 62 patients (31 in each treatment arm) will be to be included in the study. Estimating a drop-out rate of 20%, 78 patients (39 in each treatment arm) will be to be included in the study.

The software PS Power and Sample Size Calculations Version 3.0, January 2009, will be used for the sample size calculation.

8.2 Populations for Analysis

All efficacy and safety analyses will be conducted on the Intent-to-Treat population (ITT), defined as all randomized patients in the first period of study (first 6 weeks) who took at least one study treatment dose.

In addition to the primary analysis carried out on the ITT population, some secondary sensitivity analyses will be carried-out in accordance with the criteria mentioned above. The sensitivity analyses will be implemented according to the following criteria:

- Considering that a minimum intake of study treatment will be required for the assessment of the efficacy of therapy on the primary objective, it will be considered that evaluable patients on the primary end-point had taken at least 95% of the total dosage in the 6-week treatment period, as foreseen in the study protocol. Patients who will not reach this target will be excluded from the primary analysis, but entered in the sensitivity analysis to confirm the efficacy of treatment with Gerdoff® in the improvement of the high symptoms.
- Patients who took not allowed rescue medication will be excluded from the sensitivity analysis on the primary end-point.
- Patients who took drugs that interfere with salivary secretion remained included in the sensitivity analyses by derogation from the study protocol, since during the data review meeting the clinicians considered as not significant the interference of these drugs on the response of the primary variable.
- Patients who had a worsening of the upper symptoms and required an additional therapy or a modification of the dosage of omeprazole taken compared to the protocol during the 6-week

treatment period, according to the Investigator's opinion, will be considered major violators but remained in the study until visit V4 and entered into the ITT efficacy analysis. Such patients will be considered as non-responders in the analysis of the follow-up phase.

8.3 Statistical Analyses

The statistical testing will be conducted at the two-sided $\alpha = 0.05$ and 95% confidence interval (CI) will be computed, unless otherwise specified.

All p-values will be rounded to four decimal places. Statistical significance will be to be declared if the rounded p-value will be less than 0.05. Two-sided 95% CIs will be calculated.

Descriptive Statistics:

Descriptive statistics will be provided in summary tables according to the type of variable.

Continuous variables will be summarized by descriptive statistics (number of cases, mean, and standard deviation, median, minimum, and maximum). Categorical variables will be summarized using counts of patients and percentages.

Demographics and other baseline characteristics:

Demographic and baseline characteristics data will be summarized by means of descriptive statistics.

Demographic data, inclusion/exclusion criteria, general clinical data (medical history, vital signs and diagnosis, objective examination, and blood-chemical examinations) will be listed and presented in tables using only descriptive statistics. Inferential statistics will be applied only in case of evident discrepancies between the two treatment groups. A listing with the study treatment received by the patients will be made.

Since this study had two different time period, theses data could be listed by time period: period V1-V4 and V5-V6.

Concomitant treatments and rescue medication

Data of concomitant treatments and rescue medication will be coded and listed by treatment and study visit. Summary tables will be also produced on the frequencies of the reported treatments.

8.3.1 Primary Performance Analysis

In the analysis of primary performance variable, i.e. the mean difference from the baseline (delta) of the RSI score measured after 6 weeks of treatment, the two treatment groups will be compared using a Student's t-test for independent data.

The test results will be tabulated with the appropriate descriptive statistics and with the calculation of the 95% CI of the difference relative to the delta between the two study treatments.

The primary objective of the study will be achieved only if the statistically significant difference between the two study treatments with the current delta value will be coincident with that planned in the calculation of the numerosity, i.e. 3.6.

Sensitivity analyses will be conducted on the primary performance variable. The study of the temporal profile of the RSI questionnaire will be performed using the analysis of variance for repeated measures (ANOVA). In addition to the treatment effect, the time effect and the treatment by time interaction will be included in the model.

8.3.2 Secondary Performance Analyses

All secondary variables will be listed and presented with the most appropriate descriptive statistics.

Number and percentage of responder/non-responder patients at end of treatment (visit V4)
Patients who at the 6^{th} week of treatment showed a reduction of at least 50% vs. the baseline and an

absolute value < 13 will be considered as responders. The Chi-square test with the correction of Yates or, if more appropriate, the Exact Fisher's test will be used to compare the distribution of the proportions of responders and non-responders in the two treatment groups. The patients responders in the group treated with Gerdoff® + PPI entered the follow-up period and continued in the observation according to the procedures provided by the study protocol;

Change of frequency of symptoms from baseline to end of treatment (visit V4) of frequency of symptoms , assessed using the Likert scale

The same analyses foreseen for the RSI questionnaire will be performed.

Use of rescue medication

In the first 6 weeks of treatment, the intake in each treatment group of the rescue medication, allowed or not allowed, will be calculated as the frequency of intake of the specific drug and the comparison between groups will be performed using the Fisher's exact test.

In the first 6 weeks of treatment, the comparison of the median dose of rescue medication in the two study groups will be performed by means of the non-parametric (distribution-free) test of the median. If a mean value of intake could also be calculated, the comparison between the two treatment groups will be performed using the Mann-Whitney U test.

Patient satisfaction of treatment

This evaluation will be expressed with a semi-quantitative ordinal scale: 0 = low, 1 = discrete, 2 = good, 3 = excellent). The frequencies of judgments will be compared between groups using the Chi-square Mantel-Haenszel test.

In the follow-up period, the efficacy data collected will be presented by treatment group using only the most appropriate descriptive statistics and consistent with the current numerosity of the sample.

8.3.3 Safety Analyses

All safety data will be listed and tabulated by study treatment and visit.

Adverse events

Adverse events reported will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to the MedDRA thesaurus. Adverse events will be presented in a listing by treatment group. Summary tables will be also produced on the frequencies of recorded events.

Changes in vital signs

Changes in vital signs will be presented both in an individual line listing and in summary tables by treatment group.

Changes in hematology and blood chemistry parameters

Changes clinically significant will be presented both in an individual line listing and in summary tables according to the study treatment.

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