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A Pre-Market, Two-Stages Interventional Clinical Investigation To Evaluate The Safety and The Performance of Fibroin Syrup In Reducing The Gastroesophageal Reflux Symptomatology In Non-Erosive Reflux Disease (NERD) Patients

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Abbreviations: AE: Adverse Events**;** EOS: End Of Study**;** FS: Fibroin Syrup**;** GERD: Gastroesophageal Reflux Disease**;** HA: Hyaluronic Acid**;** NERD: Non Erosive Reflux Disease**;** PPI: Proton Pump Inhibitor**;** PP: Per Protocol**;** RDQ: Reflux Disease questionnaire**;** SAS: Safety Analysis Plan; SF: Silk Fibroin; CP: Centipoise

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1. Abstract

1.1. Background/Objectives

Non-erosive reflux disease (NERD) is the most common phenotype of gastroesophageal reflux disease (GERD) and is frequently characterized by persistent symptoms despite standard acid-suppressive therapy. Concerns regarding long-term proton pump inhibitor (PPI) use have increased interest in non-pharmacological approaches capable of providing mechanical protection against refluxate while supporting mucosal repair. A novel oral medical device combining hyaluronic acid (HA) and silk fibroin (SF) has been developed for this purpose. The product shows interesting bioadhesive properties and forms a solid gel when exposed at pH below 3.

1.2. Methods

This pre-market, adaptive, two-stage interventional clinical investigation evaluated the safety and performance of an HA- and fibroin-based medical device (Fibroin Syrup) in adult subjects with symptomatic NERD. Following an initial pilot safety phase, the pivotal stage enrolled 47 adults with typical reflux symptoms lasting ≥8 weeks and absence of erosive esophagitis at upper endoscopy. Subjects received the investigational device for 6 weeks and were followed for 12 weeks. Gastroesophageal symptoms were assessed using the Reflux Disease Questionnaire (RDQ). The primary endpoint was the change in RDQ total score from baseline to the end of treatment. Safety was assessed through adverse event (AE) monitoring, physical examination, and vital signs.

1.3. Results

All enrolled subjects completed the study and were included in safety and efficacy analyses. A significant reduction in GERD symptoms was observed after 6 weeks of treatment, with a 65.2% median decrease in RDQ total score compared with baseline ($p < 0.0001$). Symptom improvement was maintained at follow-up ($p < 0.001$). RDQ frequency and severity sub-scores also showed statistically significant reductions at all post-baseline visits ($p < 0.001$). Treatment satisfaction was high, with 95.7% of subjects reporting moderate-to-high satisfaction. The device demonstrated a favorable safety profile with only mild, non-serious AEs and no treatment discontinuations.

1.4. Conclusions

Fibroin Syrup was safe and effective in reducing NERD-related symptoms, supporting its role as a non-pharmacological therapeutic option in reflux disease management.

2. Introduction

Nonerosive reflux disease (NERD) comprises subjects who have typical symptoms of gastroesophageal reflux disease (GERD) without any mucosal breaks at endoscopy [1]. The estimated prevalence of NERD in the general population is at least 11–12% [2]. For decades, NERD has been considered a mild form of GERD, and thus has been treated conservatively with lifestyle modifications, H_2-blockers, or standard-dose proton pump inhibitors. However, most studies have shown that subjects with NERD are less likely to respond to anti-reflux therapy compared with those with erosive oesophagitis by approximately 20–30% after 4 weeks of treatment [3]. In subjects with failure to respond to PPI treatment, it has been suggested that pain modulators like tricyclics and selective serotonin reuptake inhibitors are an alternative treatment option for controlling refractory symptoms such as heartburn and chest pain. However, there is no sufficient evidence to support their routinely use [3].

Consequently, a significant number of NERD subjects continue to experience heartburn, suggesting a heterogeneous group of subjects with uncontrolled symptoms [4].

Independent of the relevance of each mechanism involved in the pathophysiology of reflux, the ultimate phenomenon is that mucosal epithelium is exposed for a longer time to agents such as acid and pepsin or is in contact to luminal agents not commonly present in gastric refluxate such as trypsin or bile acids. This leads to visible damage of the epithelium (e.g., erosive esophagitis) or impairing mucosal integrity without any sign of macroscopic alteration as occurs in non-erosive reflux disease [5]. Luminal factors are not the only responsible for such impairment; more recent data indicate that endogenous factors may also play a role [6]. For these reasons, topical protection of functionally vulnerable mucosa may be an attractive therapeutic strategy [7,8]. An ideal therapy for NERD subjects, in addition to mitigating acid secretion, should provide a barrier to the residual aggressive components of the refluxate (i.e. weakly acidic and non-acidic gastric juice contents) while also stimulating mucosal repair.

In the last years new medical devices containing hyaluronic acid and chondroitin have been developed in order to improve esophageal mucosal defenses [9]. Hyaluronic acid (HA) is a widespread, biologically active substance which regulates cellular function through interaction with specific receptors [10]. While fibroin has wide applications in textiles and in biomedical applications owing to its biocompatible, nontoxic, biodegradable, less immunogenic, and noncarcinogenic nature. Silk fibroin has also been known to induce wound healing by increasing cell proliferation and growth and migrating various types of cells that are involved in different stages of the wound healing process [11].

Fibroin Syrup (FS) is a new medical device with a mechanical action, indicated for the treatment of the symptoms of Gastro-Esophageal Reflux Disease (GERD), and contains both hyaluronic acid and fibroin as key ingredients. This device is intended for oral administration to reduce symptoms such as heartburn, epigastric pain, irritative and nocturnal cough, dysphagia and dysphonia, which may occur especially after meals or during the night due to position.

Fibroion syrup (FS) is able to adhere to the esophagus epithelium, forming layers over the mucosa. In particular, FS adheres to the epithelial cell layers, including the cells of the esophagus mucosa. Further, in an experimental session, FS was tested against a placebo product containing hyaluronic acid without fibroin hydrolysate, in the adhesion model of the inclined plane, which consists of a plexiglass support that was previously coated with a biological substrate and can be inclined at different angles, in a close chamber to maintain the set temperature. Underneath, an electronic balance capable of registering weight at pre-set time points is placed. The test was performed as described in Materiel and methods below, and resulted in an increased adhesion of the fibroin /hyaluronic composition, compared to the placebo solution (Figure 1).

Another preclinical experimental assay was made to compare the behavior of a representative composition of FS with respect to a composition containing only sodium hyaluronate and a composition containing sodium hyaluronate and chondroitin sulfate (in lieu of water-soluble hydrolyzed fibroin) at acidic pH, i.e. at a pH of the stomach and of the esophagus in the presence of gastroesophageal reflux (Figure 2). As shown, the composition of the invention at acidic pH forms a cohesive gel, while no gel is formed with the composition comprising only sodium hyaluronate and a just a weak increase in viscosity was shown by the composition containing sodium hyaluronate and chondroitin sulfate. The formation of a cohesive gel showed by the composition of the product is completely unexpected and particularly advantageous, as it helps the composition to adhere to the esophagus and stomach epithelium.

Therefore, the aim of this pre-market, two-stages (pilot stage + pivotal stage), interventional clinical investigation was to evaluate the safety and the performance of Fibroin Syrup, a HA- and fibroin-based medical device, in subjects with symptomatic NERD.

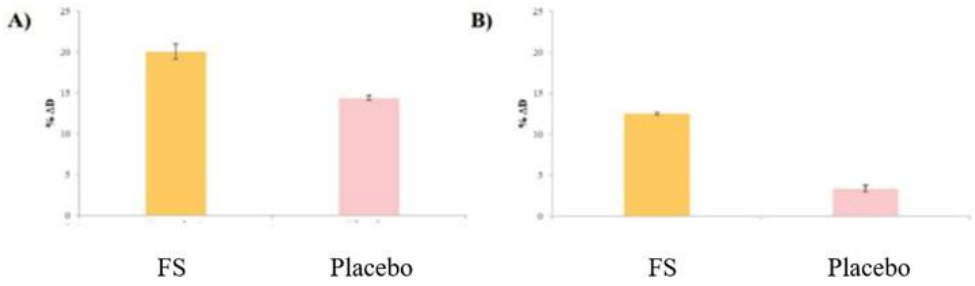

Figure l: The mucoadhesive parameter % ΔD calculated for FS and placebo.

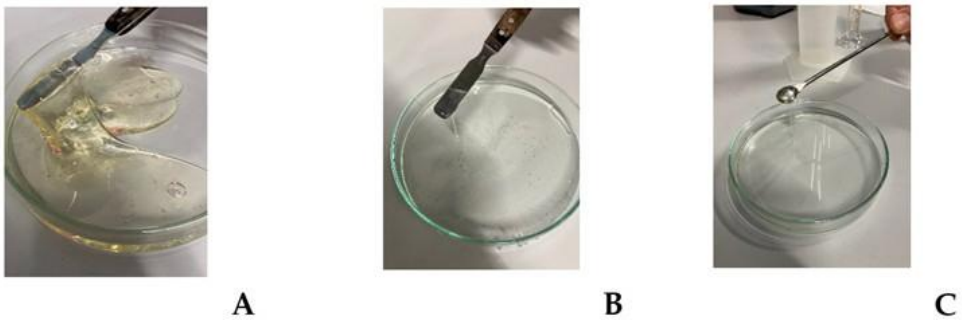

Figure 2: Formation of a solid gel.

3. Materials and Methods

3.1. Preclinical Study

3.1.1. Adhesion and Solid Gel Formation Tests

In this session, two tests have been described. In the adhesion test, FS was prepared according to the patent application WO 2024/246701 and compared to placebo solutions freshly made containing only hyaluronic acid at the same concentration of FS and no water-soluble hydrolyzed fibroin, while in the solid gel formation test also a solution of hyaluronic acid at the same concentration of FS in association with chondroitin sulphate (2 %) was compared.

In the adhesion test method, an inert surface is coated with a layer of mucus. Each test item is then applied on top and the plane is inclined to a certain angle, usually between 15 and 45 degrees. This mimics the contact of the test item and the mucus in vivo. The adhesion strength of the test item to the mucus prevents the solution from sliding off due to the force of gravity. A gastric mucin suspension was used as a biological substrate. Mucoadhesion is a function of pH, ionic strength, and mucin concentration; therefore, given the intended use of the medical device, mucoadhesive properties were evaluated both at pH 7 and pH 3. This analysis was performed at a controlled temperature, specifically at 37°C which is the expected temperature of the site of application of the test item.

3.1.2. Preparation of Buffer Solutions

Citrate and phosphate buffer solutions, characterized by pH values equal to 3 and 7 respectively, were prepared according to the European Pharmacopoeia. For pH 3 citrate buffer, sodium citrate dihydrate and citric acid were dissolved in MilliQ water, while for pH 7 phosphate buffer, monobasic potassium phosphate and sodium hydroxide were solubilized in MilliQ water.

3.1.3. Preparation of Mucin Suspensions

Two different mucin suspensions were prepared by dispersing porcine gastric mucin in 25 citrate buffer solution (MUC pH 3) or phosphate buffer solution (MUC pH 7) under magnetic stirring at room temperature. The final mucin concentration was 8 % w/w.

3.1.4. Inclined Plane Method

The inclined plane apparatus consists of a plexiglass support coated with a biological substrate and can be inclined at different angles in a close chamber to maintain the set temperature. Underneath an electronic balance capable of registering weight at pre-set time points is placed to maintain a constant pre-set temperature.

The biological substrate consisted of a mucin film, which was prepared by casting 2.5 ml of an 8% w/w mucin suspension in pH 3 citrate buffer and pH 7 buffer, at 45^0 C for 45 minutes. The test items described above were analyzed as such, and all the measurements were carried out at 37°C. An amount of each sample equal to 2 mL was placed onto the mucin film at the top of the support, still held in horizontal position; subsequently, the plane was inclined at 45° and the amount of formulation dropped on the microbalance was recorded after 3 minutes of time. Blank measurements were performed in the absence of the biological substrate. Differential dropped percentage parameter (% ΔD) was considered as an index of sample mucoadhesive properties, and it was calculated according to the following equation:

10 % ΔD = % DROPPED without mucin film - % DROPPED with mucin film wherein:

% DROPPED without mucin film = % amount of formulation dropped on the microbalance in the absence of the biological substrate
% DROPPED with mucin film = % amount of formulation dropped on the microbalance in the presence of artificial mucus. Three Replicates Were Considered for Each Sample.

3.1.5. Solid gel Formation Test

FS (Testing sample) was compared with a composition containing no water-soluble hydrolyzed fibroin (only sodium hyaluronate) (Reference 1), and with a composition containing chondroitin sulphate in place of water-soluble hydrolyzed fibroin (Reference 2) as described above. The three samples had a final pH of 4.8-5.2 and a dynamic viscosity of 1,000-2,000 cP. The three solutions have been brought to pH <3 with 2 M hydrochloric acid.

3.2. Clinical Study Design and Setting

This was a pre-market, interventional, non-comparative, single-center clinical investigation conducted at IRCCS Azienda Ospedaliero-Universitaria di Bologna between July 2024 and August 2025. The study was conducted in two sequential stages addressing distinct objectives.

In Stage 1, the primary objective was to assess the safety and tolerability of FS through physical examination, monitoring of vital signs, and evaluation of adverse events (AEs), including assessment of the relationship of each AE to FS at each scheduled visit.

In Stage 2, the primary objective was to evaluate the performance of FS in reducing gastroesophageal symptoms in patients with NERD, as assessed by the change in total Reflux Disease Questionnaire (RDQ) score between baseline and end of treatment (EOT). Secondary objectives included further assessment of safety and tolerability and evaluation of patient satisfaction using a 5-point Likert scale administered at the end-of-study (EOS) visit.

3.3. Study Population

Eligible participants were required to meet all of the following inclusion criteria: provision of written informed consent; male or female subjects aged ≥18 years at the time of informed consent; symptomatic NERD (heartburn and/or regurgitation) for at least 8 weeks; baseline RDQ total score ≥12.

Exclusion criteria included: evidence of erosive esophagitis according to the Los Angeles classification (grades A–D); diagnosis of Helicobacter pylori infection; use of proton pump inhibitors or histamine-2 receptor antagonists within 4 weeks prior to enrollment; uncontrolled cardiac, renal, hepatic, or pulmonary disease; diabetes mellitus; active malignancy; pregnancy or breastfeeding; known hypersensitivity to any component of the investigational device; concurrent participation in another interventional clinical study or participation within 1 month prior to study inclusion; known drug and/or alcohol abuse; and mental incapacity precluding adequate understanding of the study or cooperation with study procedures. Informed consent was obtained from all subjects involved in the study.

3.4. Investigational Device and Treatment Regimen

Fibroin Syrup is a medical device intended for use by lay people. Its composition includes water, sorbitol, fibroin hydrolysate (250 mg), polyvinylpyrrolidone, hyaluronic acid (80 mg), kiwi flavor, hydroxyethyl cellulose, potassium sorbate, and sodium benzoate. The investigational sample under evaluation was provided by Rose Pharma SA (batch LP04).

Participants were instructed to administer FS in accordance with the instructions for use: one 10-mL stick after each main meal (breakfast, lunch, and dinner), for a total of three sticks per day, over a treatment period of 6 weeks.

3.5. Study Visits and Assessments

Each participant underwent a total of four planned study visits: screening (Visit −1), conducted within 7 days prior to baseline; baseline (Visit 0, Day 0); end of treatment (Visit 1, EOT), scheduled at 6 weeks ± 3 days from baseline; and end of study (Visit 2, EOS), scheduled at 12 weeks ± 5 days from baseline. When feasible, screening and baseline assessments could be combined into a single visit. At the initial visit (V-1), any previous or ongoing pathologies or conditions experienced by the subjects were documented as part of their medical history. An endoscopy was also performed to confirm the diagnosis of NERD and to exclude the presence of Esophagitis according to the Los Angeles classification.

3.6. Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and applicable international and European regulatory standards for clinical investigations of medical devices, including ISO 14155:2020, MDCG 2020-10 (Guidance on Safety Reporting in Clinical Investigations), Regulation (EU) 2017/745 (Medical Device Regulation), and MEDDEV 2.12-1 rev. 8 (Guidelines on a Medical Devices Vigilance System), as well as national laws, regulations, and insurance requirements. The study was approved by the ethical committee (Comitato Etico Territoriale Della Regione Siciliana, Palazzo Orleans, Piazza Indipendenza 21, 90129 Palermo on the 02/04/2025.

3.7. Statistical Analysis

Sample size calculations were performed using SAS® software, version 9.4. During Stage 1, a total of 10 subjects were planned for enrollment to assess safety and tolerability. The sample size for Stage 2 was estimated based on a two-sided paired t-test, assuming a normal distribution of RDQ score changes. A minimum expected reduction of 30% in RDQ total score (corresponding to 9.3 points) between baseline and EOT, a standard deviation of 17, a Pearson correlation coefficient of 0.25 between time points, and a two-sided type I error of 5% were assumed. Under these conditions, 42 subjects were required to achieve statistical power greater than 80%. Allowing for an anticipated dropout rate of approximately 10%, a total of 47 subjects were planned for enrollment. Considering the 10 subjects enrolled during Stage 1, an additional 37 subjects were required for Stage 2.

For Stage 1, the primary endpoint was the assessment of the safety and tolerability of Fibroin Syrup. Safety evaluations were conducted at each scheduled visit and included physical examination, monitoring of vital signs, and assessment of adverse events (AEs), with specific evaluation of the relationship of each AE to the investigational device (ID). An interim analysis was performed at the completion of Stage 1 to assess if Fibroin Syrup was well-tolerated, with no safety concerns identified in the target population.

For Stage 2, the primary endpoint was analyzed using descriptive statistics. Changes in the Reflux Disease Questionnaire (RDQ) score between baseline and end of treatment (EOT) were evaluated using a paired t-test or, where appropriate, the Wilcoxon signed-rank test for paired data. A minimum expected improvement of 30% between the two time points was predefined. The primary endpoint was considered achieved if a statistically significant reduction of at least 30% in RDQ score was observed between baseline and EOT. A two-sided p-value < 0.05 was considered statistically significant.

All statistical analyses were pre-specified in the Statistical Analysis Plan (SAP), which was finalized (Version 1.0) prior to database lock (DBL).

4. Discussion

In recent years, increasing attention has been directed toward visceral hypersensitivity and impaired mucosal resistance as key contributors to GERD pathophysiology, particularly in the context of proton pump inhibitor (PPI) failure, which is more frequently observed in patients with NERD [12]. Experimental and clinical evidence suggests that noxious components of the refluxate interact with the oesophageal epithelium, triggering symptom generation [13]. Pathophysiological hallmarks of impaired mucosal integrity in GERD include microscopic esophagitis with increased epithelial permeability, closer proximity of sensory afferent nerve fibers to the luminal surface, and activation of inflammatory pathways that sensitize nociceptive endings. Collectively, these mechanisms support the existence of an unmet medical need in GERD/NERD management and provide the rationale for therapeutic strategies aimed at enhancing oesophageal mucosal defences through topical protection [14].

Several placebo-controlled clinical trials have demonstrated that topical agents such as alginates, hyaluronic acid, chondroitin sulphate, and polysaccharide-based formulations, administered either alone or as adjunctive therapy for short treatment periods, can reduce symptoms and improve quality of life in patients with GERD [15]. However, to date, no clinical studies have evaluated the oral administration of fibroin-based products, although extensive toxicological data support the safety of fibroin hydrolysate [15,16].

At present, no marketed products combining hyaluronic acid and fibroin are available, precluding direct comparisons of safety and performance data. Nevertheless, the findings of the present study are consistent with published evidence on formulations containing these compounds separately [15-19]. In particular, in a previously published study investigating two different oral formulations in patients with NERD, significant reductions in symptom severity and frequency were reported, as assessed by the RDQ at 3 and 6 months, with no adverse events observed [8].

Similarly, in a study involving patients with laryngopharyngeal reflux treated with an oral combination of hyaluronic acid and chondroitin sulphate on a bioadhesive carrier, significant symptom improvement was reported after 2 weeks of treatment, with a marked reduction in Reflux Symptom Index scores compared with baseline [17]. Palmieri et al. further demonstrated, in a double-blind crossover study of patients with NERD and poor response to PPIs, that a bioadhesive formulation containing hyaluronic acid and chondroitin sulphate resulted in significantly greater symptom improvement than placebo, with acceptable tolerability and high compliance [18]. Notably, the adverse events reported were mainly gastrointestinal in nature and similar to those observed in the present investigation.

Consistent findings were also reported with a hyaluronic acid–chondroitin sulphate–based bioadhesive formulation, which proved superior to placebo in reducing NERD symptoms when administered in combination with PPIs, without an increased risk of serious adverse events [18-19]. Across these studies, the safety profile was favourable, and the most frequently reported adverse events were mild gastrointestinal or respiratory symptoms, comparable to those observed with FS.

Unlike PPIs, which primarily target gastric acid secretion, FS acts through a mechanical barrier effect, potentially providing protection against both acidic and weakly acidic reflux components. This complementary mechanism suggests a possible role for FS either as an alternative option in PPI-refractory patients or as an adjunctive therapy.

The mechanism of action of FS can be described as an adhesion of the gel to the oesophageal epithelium. This composition is liquid when administered with a medium viscosity (> 200 cp) that provides a slow migration to the stomach and produce a protective layer on the oesophageal epithelium. Moreover, the peculiar characteristic of the FS combination to generate a solid gel below pH 3 enhances the protective effect by absorbing the protons and providing a stronger structure to the protective layer.

Of particular interest, the safety profile of FS observed in our study was comparable to that reported for other topical mucosal protectants, despite the longer treatment duration. Moreover, our results indicate that the beneficial effects of FS were maintained up to 6 weeks after the end of treatment, suggesting a potential sustained protective effect on oesophageal mucosal integrity.

Despite this clinical investigation showed encouraging results in terms of safety and performance of FS, we acknowledge the lack of a control group as the major limitation of the study design. Furthermore, although the present study demonstrated a favourable safety profile over a 6-week treatment period with sustained symptom improvement at follow-up, the implications of long-term use remain to be established. Comparative trials of adequate size, with different control arms, would allow a more thorough evaluation of the product's performance in different patient populations.

5. Results

5.1. Preclinical Tests

5.1.1. Adhesion Test

In all cases, with mucin or without mucin, at pH 7 and especially at pH 3, the % drop is lower for the Fibroin Syrup solution (Table 1).

In Figure l, the mucoadhesive parameter % ΔD calculated for FS and placebo, in the presence of MUC pH 3 (Figure 1-A) and MUC pH 7 (Figure 1-B) are reported. ΔD% parameter higher than 0, in both conditions considered, indicates a mucoadhesive potential for the two samples. In both the experimental conditions when the normalization operated calculating the mucoadhesive parameter % ΔD, Fibroin Syrup showed a higher mucoadhesive potential than placebo. Both the samples were characterized by higher values in presence of MUC pH 3.

Inclined plane method measurements indicate that for both pH values considered, stronger interactions are established between the composition of Fibroin Syrup and mucins, even stronger at lower pH values, i.e. at pH similar to the one of the stomach and of the esophagus in the presence of gastroesophageal reflux.

The formation of a solid gel was tested as described in material and method. In these conditions the Testing sample (containing fibroin) formed a cohesive solid gel as reported in Figure 2-A below, while Reference 1 did not show a gel formation at all (Figure 2 B) and Reference 2 just showed an increase in viscosity (Figure 2-C). Thus, the presence of water-soluble hydrolyzed fibroin, but not chondroitin sulfate, induces the formation of a cohesive gel at low pH.

Table 1: Percentage of dropped values for placebo and FS with mucin at two pHs and without mucin.

	placebo - % dropped	Fibroin syrup - % dropped
with mucin pH 3	61.30 ± 0.95	51.77 ± 0.29
with mucin pH 7	68.85 ± 0.19	62.78 ± 0.43
without mucin	81.36 ± 1.15	66.15 ± 1 52

5.2. Clinical Test

A total of 47 screened subjects were enrolled and included during the study period. Since no participant withdrew consent before receiving the Investigational Product (IP) and all received at least one dose of IP, all 47 subjects were included both in the Safety Analysis Set (SAS) and the Full Analysis Set (FAS). Since no major protocol deviations liable to affect efficacy were reported, all subjects were also included in the Per Protocol analysis (PP). Table 2 shows demographic and baseline characteristics for all the subjects included in SAS at baseline.

The IP was dispensed to all subjects at the baseline visit (V0) and was retrieved by all subjects at V1. Compliance was assessed overall, and the median value was 100%, with values ranging from 89.8% to 100% and Q1-Q3 spanning from 98.4% to 100.0%.

The primary endpoint of the second stage of the study was to evaluate the performance of the Fibroin Syrup in reducing the gastroesophageal symptomatology in NERD patients, through the evaluation of the difference in the Reflux disease questionnaire (RDQ) total score between baseline and EOT visit (V1).

In the FAS, at V0, the median value of RDQ total score was 26.0 (Q1-Q3: 19.0- 31.0), while, at V1, the median value decreased to 9.0 (Q1-Q3: 6.0- 12.0) showing a statistically significative median change from baseline of -17 points (Q1-Q3: -19.0- -13.0), and a median -65.2% reduction from baseline ($p<0.0001$). Since FAS and PP coincided, the results obtained in the PP were the same.

The first secondary endpoint was the evaluation of the capability of the Fibroin Syrup in reducing the gastroesophageal symptomatology in NERD patients, evaluated at all visits for both the total score and each intensity/frequency sub-scores.

Regarding the RDQ total score, as mentioned above, at V0 the median value was 26.0 (Q1-Q3: 19.0- 31.0); the median RDQ total score decreased to 9.0 (Q1-Q3: 6.0- 12.0) at V1 and to 8.0 (Q1-Q3: 5.0-11.0) at V2. The median difference between V0 and V1 was −17 (Q1–Q3: −19.0- −13.0), and between V0 and V2 was − (Q1–Q3: −21.0-−13.0); both differences were statistically significant ($p < 0.0001$).

Regarding RDQ frequency sub-score, the median value was 14.0 (Q1-Q2: 10.0- 16.0) at V0; the median sub-score decreased to 5.0 (Q1-Q3: 3.0- 7.0) at V1 and again to 4.0 (Q1-Q3: 2.0- 6.0) at V2. Also in this case, the differences between V0 and the following visits were statistically significant ($p< 0.0001$ at both visits).

In terms of RDQ severity sub-score, similar conclusions can be made; in particular, the median value was 12.0 (Q1-Q3: 9.0- 15.0) at V0, decreased to 4.0 at V1 (Q1-Q3: 3.0- 6.0) and at V2 (Q1-Q3: 2.0- 6.0). Also in this case, the differences between V0 and the following visits were statistically significant, $p<0.0001$ at both time points.

As second secondary endpoint, the evaluation of the subject's satisfaction was obtained using a 5-Likert Scale at EOS (V2). All (100%) subjects completed the 5-Likert Scale; 17 (36.2%) subjects recorded a score equal to 5 (highest satisfaction), 25 (53.2%) subjects recorded a score of 4, 3 (6.4%) subjects a score equal to 3 and only 2 (4.3%) subjects recorded a lower satisfaction score.

Table 3 shows adverse events in terms of type and intensity. A total of 23 AEs occurred, of these AEs, only 8 were considered as possibly related to the IP: 4 cases of flatulence, 2 cases of abdominal distension, 1 case of constipation and 1 case of gastrointestinal disorder. All the AEs were judged as mild, not serious and resolved without any action taken, except for a case of flatulence, possibly related to the IP, which was stable but ongoing. No AE was serious or severe or led to study discontinuation. This research was funded by ROSE PHARMA S.A. Via S. Gottardo 10, 6900 Lugano-Switzerland.

Table 2: Characteristics of the study population at baseline.

		All subjects (N = 47)
Age (years)	Median	58
	Q1-Q3[1]	46-68
Gender		
Male	N(%)	17(36.2)
Female	N(%)	30(63.8)
Ethnic group		
Caucasian	N(%)	43(91.5)
Asian	N(%)	2(4.3)
Black	N(%)	2(4.3)
Weight (Kg)	Median	66
	Q1-Q3	60-75
Height (Cm)	Median	165
	Q1-Q3	160-170
Alcohol intake		
Yes	N(%)	0(0.0)
No	N(%)	47(100.0
Smoking habits		
Former smoker	N(%)	0(0.0)
Non-smoker	N(%)	46(97.9)
Smoker	N(%)	1(2.1)

[1]Q1-Q3 interquartile range.

Table 3: Demographic and baseline characteristics of the study population at baseline.

		All subjects (N=47)
Number of subjects with at least one AE*	N(%)	10(21.3)
Number of subjects with at least one related AE*	N(%)	5(10.61)
Number of subjects with at least one serious AE*	N(%)	0(0.0)
Number of subjects with at least one severe AE*	N(%)	0(0.0)
Number of subjects who prematurely terminated the study due to an AE	N(%)	0(0.0)
Number of deaths	N(%)	0(0.0)
Number of AEs	N	23
Number of SAEs	N	0
Number of related AEs	N	8
Number of severe AEs	N	0
Number of deaths	N	0

The same subject may have had more than one adverse event or more than once the same AE. AE: Adverse Event; SAE: Serious Adverse Event.

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