

# Randomized clinical trial: Randomized, controlled, single-blind, three-way crossover study to evaluate the efficacy and safety of a new preparation for post-prandial heartburn

Gordana Bothe<sup>1\*</sup>, Miquel Sans<sup>2</sup>, Udo Bongartz<sup>1</sup> and Ralf Uebelhack<sup>3</sup>

<sup>1</sup>analyze & realize GmbH, Waldseeweg 6, 13467 Berlin, Germany.

<sup>2</sup>Centro Médico Teknon, Department of Digestive Diseases, 12 Vilana St, 08022 Barcelona, Spain.

<sup>3</sup>Charité – Universitätsmedizin Berlin, Clinic for Psychiatry and Psychotherapy, Campus Charité Mitte, Charitéplatz 1, 10117 Berlin, Germany.

Accepted 10 July, 2015

---

## ABSTRACT

Heartburn is a prevalent symptom related to gastro-oesophageal reflux. Its treatment includes, amongst others, the use of alginates, which combine a rapid onset of action with a longer duration of symptom relief than antacids. The aim of this study was to investigate the time to onset of action of two alginate preparations, Reduflux® liquid sachets (RL) and Reduflux® chewable tablets (RT). This was a randomized, placebo-controlled, single-blind, three-way crossover clinical investigation with subjects prone to suffer from post-prandial heartburn. Heartburn was triggered by a refluxogenic meal and subjects were randomized to receive RL, RT or placebo. Subjects identified the onset of perception of soothing and cooling effects in the throat and oesophagus, by using a previously described dual-stopwatch method. 48 subjects were screened, 42 were randomized and 41 completed the study. Mean time to onset of soothing was 1.71, 1.92, and 29.43 min, for RL, RT and placebo, respectively ( $p < 0.001$ ). Mean time to onset of cooling was 0.76, 0.78, and 28.83 min, for RL, RT and placebo, respectively ( $p < 0.001$ ). Only 1 out of 41 subjects experienced reappearance of heartburn in the 4 h after symptoms relief in each of the RL and RT groups. RL and RT were considered highly efficacious and safe by both the investigator and subjects. In conclusion, Reduflux® chewable tablet and liquid sachet were efficacious in the treatment of post-prandial heartburn, providing a quick onset and a long duration of action, with sustained symptoms relief in 97% of the subjects.

**Keywords:** Gastro-oesophageal reflux, heartburn treatment, alginates, Reduflux®.

\*Corresponding author. E-mail: GBothe@a-r.com. Tel: +49 30 4000 8105. Fax: +49 30 4000 8405.

**Abbreviations:** RT, Reduflux® chewable tablets; RL, Reduflux® liquid sachet.

---

## INTRODUCTION

Heartburn is a very frequent symptom, mostly related to a certain degree of gastro-oesophageal acid reflux. While it can occur irrespective of food intake, in most cases it appears or it is exacerbated after meals. In addition to anatomic defects at the oesophageal-gastric junction level, such as hiatal hernia, it is well known that certain

diet components, including fat, chocolate, tea or coffee can trigger post-prandial heartburn, so can a very spicy or abundant meal, or lying down immediately after a meal (Robinson, 2004; Yuan and Hunt, 2009). Further, it is known that pregnancy as well as intake of NSAID are associated with increased occurrence of heartburn

(Bannwarth, 2004; Richter, 2005).

Heartburn can be treated with a variety of drugs, including antacids, aimed at bulk neutralization of the gastric acid, alginate compounds that promote raft formation to prevent gastro-oesophageal reflux, H<sub>2</sub>-receptor antagonists and proton-pump inhibitors (Hershovici and Fass, 2011; Piche and Galmiche, 2005; Wang et al., 2013). Antacids have a rapid onset of action, but a short duration of their effect. Both H<sub>2</sub>-receptor antagonists and proton-pump inhibitors have the advantage of inducing a marked and sustained increase in gastric pH that results in a longer duration of action, but are usually unable to provide immediate symptomatic relief. The success of alginate compounds in the treatment of heartburn is due to the combination of a quick onset of action with sustained benefit over time, clearly longer than that provided by antacids (Chiu et al., 2013; Leake, 2013; Savarino et al., 2012; Sweis et al., 2013).

Something to be taken into account is the fact that most subjects suffering from post-prandial heartburn usually do not consult their doctors, but purchase and treat themselves with over-the-counter medications including the ones mentioned above (Haag et al., 2009; Holtmann et al., 2011; Kushner, 2010; McRorie et al., 2014; Sheikh et al., 2014; Tran et al., 2007). This behaviour is based in the chronic nature of reflux symptoms, their relationship with the subject's lifestyle and specially diet content and the perception that these symptoms are not serious.

In that setting a quick onset of symptom relief becomes the key success factor for any product aimed at treating post-prandial heartburn. Recent studies have demonstrated that certain alginate compounds can provide soothing and cooling effects in the range of few minutes after their administration, when treating post-prandial heartburn (Strugala et al., 2010).

The aim of the present study was to investigate the time to onset of subject-perceived soothing and cooling effects in the throat and oesophagus after taking two formulations of Reduflux<sup>®</sup>, an alginate product, compared to an oral placebo to treat post-prandial heartburn. To accomplish this aim a prospective, randomized, placebo-controlled, three-way crossover study was performed using a dual stopwatch technique.

## MATERIALS AND METHODS

### Study design and subjects

This study was a randomized, placebo-controlled, single-blind, three-way crossover clinical investigation conducted in a single centre in Berlin, Germany. The sponsor was InQpharm Europe Ltd (Hertfordshire, UK) and the study was performed between November 2012 and March 2013 according to the EN ISO 14155:2011, based on the principles of the World Medical Association (Declaration of Helsinki) and the Guideline for Good

Clinical Practice (GCP) ICH E6 (R1). The clinical investigation was approved by the ethics commission of Charité-Universitätsmedizin, Berlin.

All subjects provided written informed consent before initiation of any study-related procedures.

### Eligibility

Eligible subjects were males and females of 18 to 65 years of age who had experienced post-prandial heartburn at least two times a week in at least 2 months prior to study inclusion. Participants were not allowed to receive prescribed treatment for heartburn, gastro-oesophageal reflux or upper gastrointestinal disorders.

The main exclusion criteria were any serious organic or systemic diseases of the heart, metabolic system, or the gastrointestinal tract, as well as hypersensitivity to any of the constituents of the investigational product or the standardized refluxogenic meal. A detailed list of all inclusion and exclusion criteria is given in Table 1.

### Screening, randomization and blinding

Subjects who satisfied the inclusion and exclusion criteria at visit 1 were invited to attend visit 2 (2 to 7 days after visit 1) in which, after at least 4 h fasting, the subjects received a standard refluxogenic meal comprising 60% fat (relative to calorie content) and were asked to lie in a supine position after the meal. Subjects were instructed to change to a sitting position once they experienced heartburn of at least moderate severity on a self-rating 5-point Likert scale (no, mild, moderate, severe, very severe). The time point when experiencing at least moderate heartburn was recorded. Subjects experiencing heartburn of at least moderate severity within 60 min of the meal were considered eligible to continue in the study, randomized to receive one of the three possible treatments (Reduflux<sup>®</sup> liquid sachet, Reduflux<sup>®</sup> chewable tablets or placebo taken with water) in a 1:1:1 ratio, and treated with the randomly allocated investigation product. Subjects failing to experience heartburn of at least moderate severity within 60 min of the meal were not randomized and had their study participation terminated.

Randomization was performed using random permuted blocks with a length of four. The randomization code was provided by an independent statistician of Medizin & Service GmbH, using the randomization scheme BiAS V 9.2 (2009). The label of the issued device contained the consecutive random number. The assignment of the random numbers to verum tablet, verum liquid and placebo device was performed externally (by the manufacturer) and prior to study start. The subjects were not aware as to which of the dosage forms are the actives. The necessary emergency envelopes were prepared by the responsible department of biostatistics (Medizin & Service GmbH).

### Study products

Reduflux<sup>®</sup> is a non-sterile medical device intended for intermittent, short-term use, classified as medical device, class IIa, according to MDD 93/42/ECC. Reduflux<sup>®</sup> contains Phycodol, a natural sodium alginate derived from brown algae, Phaeophyceae. Phycodol provides the main structural component for raft formation together with sodium bicarbonate and calcium carbonate as excipients. The study products were provided by InQpharm Europe Ltd (Hertfordshire, UK). Reduflux<sup>®</sup> liquid sachet (RL) contains 500 mg sodium alginate per 10 ml dose while Reduflux<sup>®</sup> chewable tablets (RT) contains 250 mg sodium alginate per tablet. The placebo tablet was made of microcrystalline cellulose.

**Table 1.** Inclusion and exclusion criteria.**Inclusion criteria**

- Age between 18 and 65 years
- Post-prandial heartburn (e.g. after a high-fat meal) in at least 2 months prior to the study (at least 2 times a week)
- Females of child-bearing potential: agreement to use appropriate contraceptive methods during the active study period
- Not receiving prescribed treatment for heartburn, reflux or upper gastrointestinal disorders
- Written informed consent is a prerequisite for subject enrolment.

**Exclusion criteria**

- Weight loss of  $\geq 6$  kg in the last 6 months prior to the study
- Gastrointestinal bleeding within 12 months prior to the study
- Difficulty swallowing (dysphagia)
- History of or symptoms suggestive of Zollinger–Ellison syndrome, oesophageal or gastric malignancy, gastric or duodenal ulcer, pernicious anaemia, Barrett's oesophagus or systemic sclerosis
- History of coronary disease (e.g. myocardial infarction)
- History of apoplectic stroke
- Angina pectoris symptoms
- Anorexia
- Inflammatory bowel syndrome
- Previous surgery of the oesophagus, stomach or small intestine
- Oesophageal varices
- Hypophosphataemia
- Severe constipation
- Colonic stenosis
- Impaired renal function
- Diabetes mellitus
- Subjects on highly restricted sodium diet
- Subjects with a coronary stent
- Serious organ or systemic diseases
- Any other acute or chronic disease that could interfere with the evaluation of study device
- Clinically relevant excursions of laboratory parameters
- Hypersensitivity to any of the constituents of the investigational product or the standardized refluxogenic meal
- Use of antacids, histamine type-2 receptor antagonists, motility stimulants, prokinetics or other treatment for the relief of reflux within 2 days or proton-pump inhibitors within 4 days prior to entry and/or during the study
- Use of anticoagulants, diazepam, digoxin, propranolol, anticholinergics, anti-inflammatory drugs, aspirin during the study
- Use of treatment for *Helicobacter pylori* eradication or bismuth compounds within 3 months prior to entry or during the study
- Females of child-bearing potential: pregnancy or nursing
- Abuse of drugs, alcohol or medication within 6 months prior to entry and/or during the study
- Inability to comply
- Participation in other studies within the last 30 days prior to entry or during the study

**Study protocol**

All randomized subjects were provided with two distinctly labelled stopwatches, which were started by the study staff at the time of the allocated treatment administration: one to record the time to first perception of a soothing effect in the throat/oesophagus and the other to record the time to first perception of a cooling effect in the throat/oesophagus. The robustness of using this stopwatch technique in heartburn sufferers to assess the time to onset of soothing and cooling effects in response to heartburn treatments

has been demonstrated in previous studies (Strugala et al., 2009a; Strugala et al., 2009b; Strugala et al., 2010).

Subjects were instructed to stop the respective stopwatch when they perceived a relevant effect. In case the subject did not perceive a soothing or cooling effect within 30 min after treatment administration, the result was censored at 30 min. After having perceived an effect, subjects were then observed for 4 h and were instructed to inform the study staff at first perception of recurring heartburn symptoms. Time to perception of recurring heartburn symptoms was recorded by the study staff.

The same procedures were carried out at visits 3 and 4. Treatment crossover was performed at each one of these two visits to ensure that all randomized subjects received only once each of the 3 possible study treatments (RT, RL and placebo). There was a washout period of 2 to 7 days between the visits. Test for carry over effect has been performed.

Subjects were asked to report about possible adverse events at each study visit. At the end of each subject's visit 2, 3, and 4 both subjects and study staff were asked to evaluate the treatment efficacy and safety, using a 4-degree qualitative scale (very good, good, moderate, and poor).

### Primary and secondary end points

Two primary efficacy end points were pre-specified: 1) Difference in the time to onset of perception of a soothing effect after intake of the investigational product between the three study arms, and 2) Difference in the time to onset of perception of a cooling effect after intake of the investigational product between the three study arms.

Additional pre-specified secondary efficacy outcomes were number of subjects experiencing soothing within 3 min after treatment, number of subjects experiencing cooling within 3 min after treatment, time until recurring heartburn symptoms after treatment, number of subjects not experiencing recurring heartburn, global evaluation of efficacy and use of rescue medication.

The pre-specified safety end points included global evaluation of safety and number of adverse events.

### Sample size calculation

The primary endpoints are the basis of sample size calculation. Based on the study results from a comparable study design (Strugala et al., 2010), the onset of the soothing and the cooling effect, respectively, can be expected to average within 5 min after taking the verum product, while under placebo it can take more than 20 min. Due to the wash-out phase no interactions are expected (correlation coefficient 0.0). Thus, for the three-way crossover design, the sample size calculation can be performed using the methods applicable for the parallel-group design.

Assuming that the Mann-Whitney estimator between verum and the placebo group in each case is at least 0.75 (that is,  $P(TV < TP) > 0.75$ ), and that there is no statistical difference between the two verum groups ( $P(TV_{tablet} < TV_{liquid}) = 0.50$ ), a total of 30 cases are recommended to be able to detect differences between the three groups at the significance level of 2.5% and power 90%, using the (non-parametric) Kruskal-Wallis test. Taking into account a drop-out rate of approximately 20%, 40 cases should be included.

### Statistical analysis

The primary endpoints were the basis of the sample size calculation and performed with a power of 90%, to detect differences between the three groups at the significance level of 2.5% (two-tailed). As there was at least a two-day washout period phase, no carry over interactions were expected.

In the case of metrically and ordinally scaled variables, number, mean, standard deviation, median, quartiles and range were calculated. For ordinally scaled and qualitative variables, the frequencies were calculated.

Because of the small sample size and possible outliers and / or non-normally distributed values, all endpoints were analysed using

non-parametric statistical tests: for qualitative data Fisher's exact test, for quantitative data Mann-Whitney-U test for two independent groups, Kruskal-Wallis test for more than two independent groups, and Wilcoxon test for paired observations.

For the analysis of the co-primary endpoints, as the first step, the measured values of the three groups were tested by a Kruskal-Wallis test regarding any differences in the distribution. If the null hypothesis were rejected with statistical significance the pairwise multiple comparisons with Bonferroni correction were performed. Both co-primary endpoints were analysed independently.

The null hypotheses to be tested were that no differences between the study arms exist, either with regard to the observed time of onset of the soothing effect, or with regard to the observed time of onset of the cooling effect. These null hypothesis were independently tested (multiple testing) against the respective alternative hypotheses (that differences exist) using non-parametric Kruskal-Wallis test. Taking into account the multiple testing each of these tests were performed at the significance level of 2.5% (two-tailed) to meet the global significance level of 5% (Bonferroni correction).

If the null hypotheses could be rejected, the pairwise comparisons of the study groups could be performed: RL vs. RT, RL vs. placebo and RT vs. placebo.

All tests except for the primary end points were conducted with a type I error,  $\alpha = 5\%$ , two-tailed. In the analysis of the co-primary endpoints the multiple testing aspect was considered. Temporal changes in the parameters with repeated measurements were evaluated by analysis of variance.

The valid case analysis set population (subjects completing all the study) was used in the efficacy analysis, since subjects need to have completed all 3 interventions for the treatment comparisons.

## RESULTS

### Study population

48 subjects were screened, but only 42 subjects demonstrated heartburn in response to a refluxogenic meal, fulfilling the criteria for randomization and were randomized in the study (full analysis set). Baseline characteristics are summarized in Table 2. 41 out of 42 subjects completed the study, including the 3 treatment interventions, and constitute the valid case analysis set. 1 subject did not display heartburn symptoms in response to refluxogenic meal and therefore was excluded from VCAS population. Subject allocation and flow chart is represented in Figure 1.

### Time to onset of soothing

The efficacy of the three treatment arms in inducing perception of a soothing effect is summarized in Table 3. While most subjects treated with placebo failed to achieve soothing (only 1 subject reported soothing within 30 min), all subjects treated with RL and RT perceived a soothing effect within 30 min, the maximum time being 7.70 and 4.17 min, for the RL and RT groups, respectively (Figure 2). Mean time to onset of soothing

**Table 2.** Baseline characteristics of participants.

Parameter	RL (n = 14)	RT (n = 14)	Placebo (n = 14)	P-value
Age (years ± SD)	48.6 ± 13.3	49.3 ± 11.4	44.5 ± 10.7	>0.05
Gender				
Male	5	6	4	>0.05
Female	9	8	10	>0.05
Height (cm ± SD)	171.3 ± 9.1	169.6 ± 10.1	170.0 ± 7.2	>0.05
Weight (kg ± SD)	81.3 ± 16.6	70.1 ± 11.7	81.9 ± 20.8	>0.05

RL: Reduflux® liquid sachet; RT: Reduflux® chewable tablets.

was significantly lower in the RL than in the RT group ( $p = 0.04$ ).

Significantly more subjects experienced an onset of soothing effect within 3 min after product intake in the RL group (95.1%) and the RT group (90.2%), compared to the placebo group (0%);  $p < 0.001$ . The difference was not significant between the RL and RT groups ( $p = 0.309$ ).

#### Time to onset of cooling

The efficacy of the three treatment arms in inducing perception of a cooling effect is summarized in Table 3. While most subjects treated with placebo failed to achieve cooling (only 2 subjects reported cooling within 30 min), all subjects treated with RL and RT perceived a cooling effect within 30 min, the maximum time being 5.30 and 2.60 min, for the RL and RT groups, respectively (Figure 3). There were no statistically significant differences in mean time to onset of cooling between the RL and the RT groups ( $p = 0.51$ ).

Significantly more subjects experienced an onset of cooling effect within 3 min after product intake in the RL group (97.5%) and the RT group (100%), compared to the placebo group (0%);  $p < 0.001$ . The difference was not significant between the RL and RT groups ( $p = 0.105$ ).

#### Time to recurrence of heartburn symptoms

Only 2 subjects, one in the RL group and one in the RT group, who experienced soothing and cooling effects after product intake, reported recurrence of heartburn symptoms within the 4 h of observation. None of the subjects of the placebo group, who reported soothing or cooling within 30 min (only 3 in total), had recurrent symptoms. Time to recurring heartburn was 2 h and 14 min in the subject receiving RT and 3 h and 2 min in the subject receiving RL. For all other subjects in both the RL and the RT groups (97.6% of participants in each of both groups) the soothing and cooling effects lasted at least 4

hours (time period of assessment).

#### Use of rescue medication

No subject from the RL and RT groups required rescue medication.

On the contrary, most subjects allocated to the placebo group required the administration of rescue medication during the observation period. This includes 10 out of 14 subjects at visit 2 (71.4%), 8 out of 14 at visit 3 (57.1%) and 8 out of 14 at visit 4 (57.1%).

#### Global evaluation of efficacy

The global evaluation of the efficacy of the 3 treatment options, as reported by the investigator and participating subjects is summarized in Tables 4 and 5, respectively.

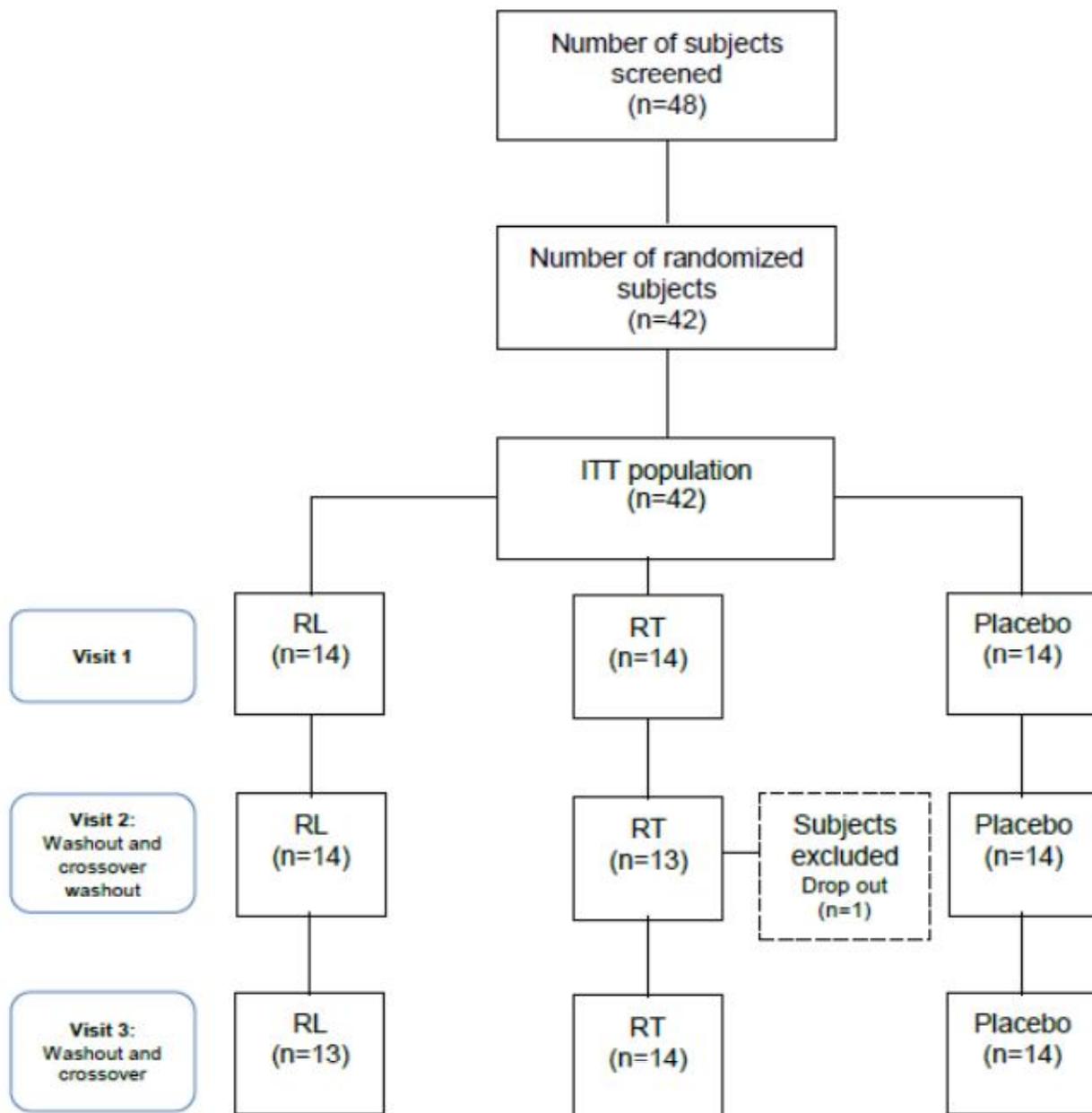
There was a statistically significant difference in global evaluation of efficacy by the investigator between the 3 treatment groups ( $p < 0.001$ ), but not between the RL and RT groups ( $p = 0.455$ ) (Table 4). Similarly, there was a statistically significant difference in global evaluation of efficacy by the participating subjects between the 3 treatment groups ( $p < 0.001$ ), but not between the RL and RT groups ( $p = 0.467$ ) (Table 5).

#### Adverse events and global evaluation of safety

There were no product-related adverse events reported during the study.

The global evaluation of the safety of the 3 treatment options, as reported by the investigator and participating subjects is summarized in Tables 6 and 7, respectively.

There was a statistically significant difference in global evaluation of safety by the investigator between the 3 treatment groups ( $p < 0.001$ ), but not between the RL and RT groups ( $p = 0.312$ ) (Table 6). Similarly, there was a statistically significant difference in global evaluation of safety by the participating subjects between the 3 treatment groups ( $p < 0.001$ ), but not between the RL and

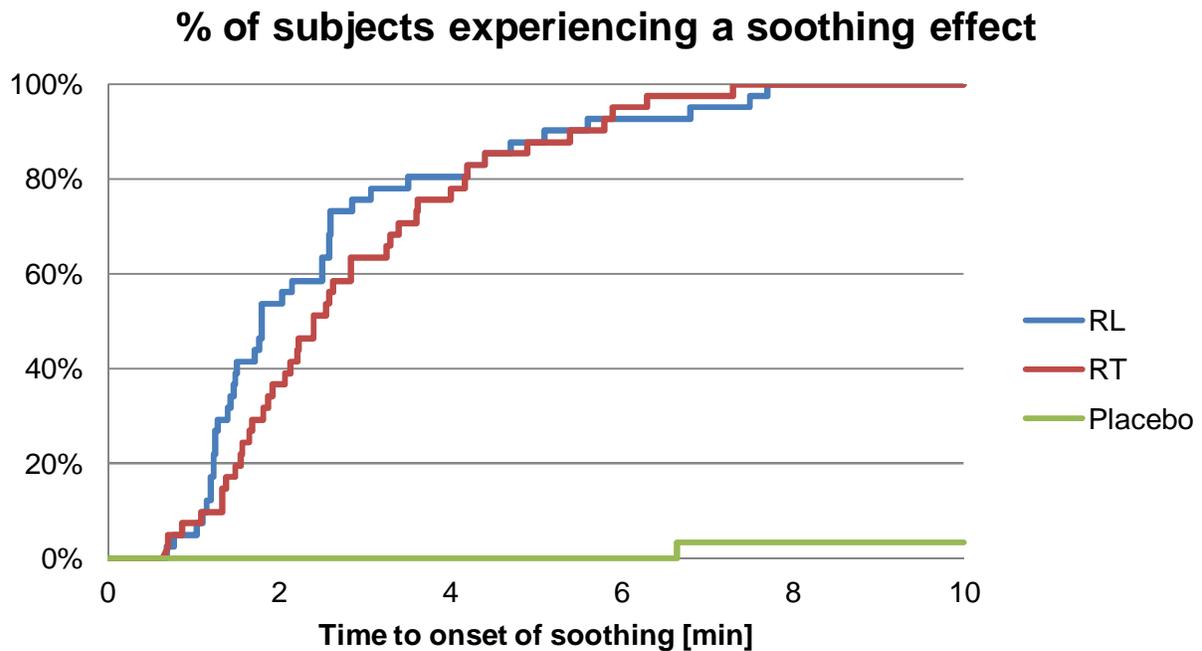


**Figure 1.** Consort diagram for study flow. Forty-eight subjects were screened. Of them 42 subjects demonstrated heartburn in response to a refluxogenic meal, and were randomized in the study (full analysis set = ITT). At visit 2 subjects were randomized to receive Reduflux® chewable tablets (RT), Reduflux® liquid sachets (RL) or control treatment (14 subjects each). According to the 3-way crossover design of this study, subjects changed treatment at visits 3 and 4. Forty-one out of 42 subjects completed the study, including the 3 treatment interventions, and constitute the valid case analysis set.

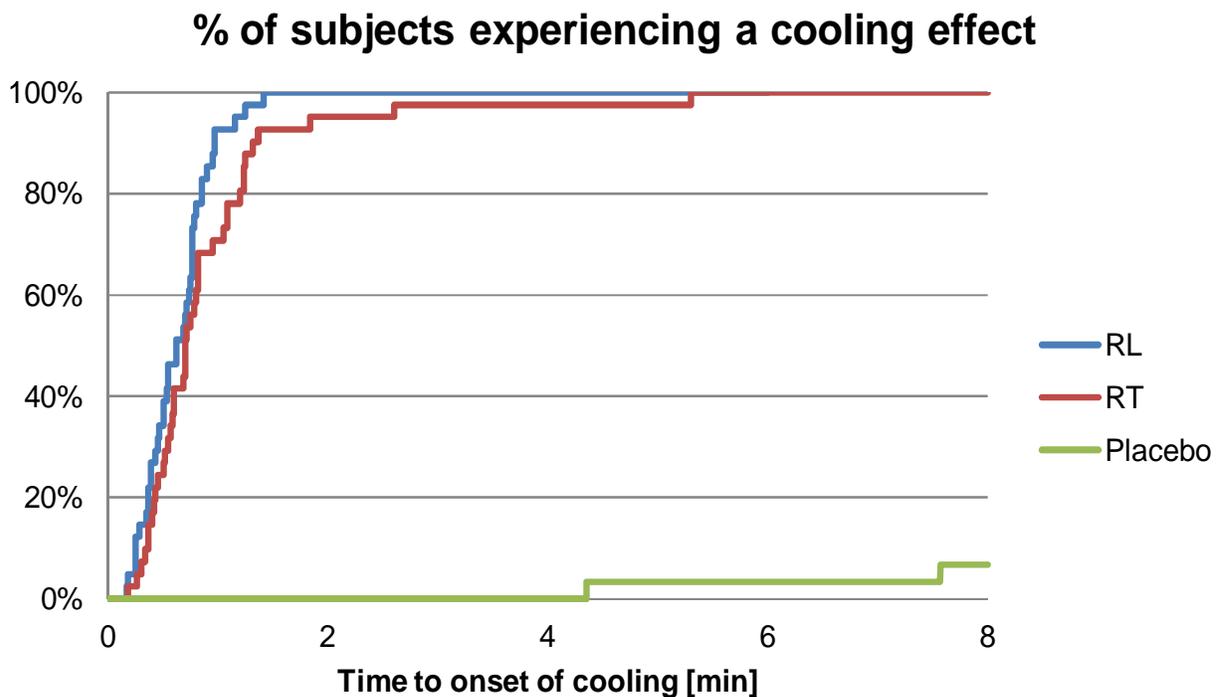
**Table 3.** Summary of primary analyses results (data presented as mean  $\pm$  SD).

Time to onset (min)	RL (n = 41)	RT (n = 41)	Placebo (n = 41)	P <sub>anova</sub> -value
Soothing	1.71 $\pm$ 1.15	1.92 $\pm$ 0.83	29.43 $\pm$ 3.65	<0.001
Cooling	0.76 $\pm$ 0.78	0.78 $\pm$ 0.47	28.83 $\pm$ 5.26	<0.001

RL: Reduflux® liquid sachet; RT: Reduflux® chewable tablets.



**Figure 2.** Kaplan-Meier curves of time to onset of perception of a soothing effect. Kaplan-Meier curves display the time (in minutes) elapsed until first perception of a soothing effect in the throat and oesophagus of subjects treated with Reduflux® chewable tablets (RT), Reduflux® liquid sachets (RL) and placebo,  $n = 41$  for each treatment group, after triggering of heartburn by a refluxogenic meal.  $P < 0.0001$  for RT vs. control and RL vs. control each.



**Figure 3.** Kaplan-Meier curves of time to onset of perception of a cooling effect. Kaplan-Meier curves display the time (in minutes) elapsed until first perception of a cooling effect in the throat and oesophagus of subjects treated with Reduflux® chewable tablets (RT), Reduflux® liquid sachets (RL) and placebo,  $n = 41$  for each treatment group, after triggering of heartburn by a refluxogenic meal.  $P < 0.0001$  for RT vs. control and RL vs. control each.

**Table 4.** Global evaluation of efficacy as assessed by investigator.

Parameter	RL (n = 41)		RT (n = 41)		Placebo (n = 41)	
	No.	%	No.	%	No.	%
Very good	31	75.6	28	68.3	0	0
Good	9	22.0	13	31.7	0	0
Moderate	1	2.4	0	0	1	2.4
Poor	0	0	0	0	40	97.6

RL: Reduflux® liquid sachet; RT: Reduflux® chewable tablets.

**Table 5.** Global assessment of efficacy as assessed by participating subjects.

Parameter	RL (n = 41)		RT (n = 41)		Placebo (n = 41)	
	No.	%	No.	%	No.	%
Very good	30	73.2	27	65.9	0	0
Good	10	24.4	14	34.1	0	0
Moderate	1	2.4	0	0	1	0
Poor	0	0	0	0	41	100

RL: Reduflux® liquid sachet; RT: Reduflux® chewable tablets.

**Table 6.** Global assessment of safety by investigator.

Parameter	RL (n = 41)		RT (n = 41)		Placebo (n = 41)	
	No.	%	No.	%	No.	%
Very good	33	80.5	28	68.3	4	9.8
Good	8	19.5	13	31.7	35	85.4
Moderate	0	0	0	0	2	4.9
Poor	0	0	0	0	0	0

RL: Reduflux® liquid sachet; RT: Reduflux® chewable tablets.

**Table 7.** Global assessment of safety by participating subjects.

Parameter	RL (n = 41)		RT (n = 41)		Placebo (n = 41)	
	No.	%	No.	%	No.	%
Very good	33	80.5	27	65.9	4	9.5
Good	8	19.5	13	31.7	34	82.9
Moderate	0	0	1	2.4	2	4.9
Poor	0	0	0	0	1	2.4

RL: Reduflux® liquid sachet; RT: Reduflux® chewable tablets.

RT groups ( $p = 0.212$ ) (Table 7).

## DISCUSSION

The present investigation demonstrates that the two Reduflux® formulations studied are highly efficacious in

the treatment of post-prandial heartburn with a mean time to provide a soothing effect of 1.71 to 1.92 min and a mean time to provide a cooling effect of 0.76 to 0.78 min after treatment administration in a population prone to suffer from these symptoms.

This is a sensorial study, meaning that its co-primary efficacy outcomes are the subject's perception of

soothing and cooling effects after study treatment administration, once heartburn had been triggered by a refluxogenic meal. However, the subjective nature of this study does not minimize the robustness of its findings. On one hand, there are no objective methods available to quantify heartburn relief in response to medications. Some of the more objective techniques used to quantify the degree of gastro-oesophageal reflux, such as the 24-h pH-metry or the impedance-metry, would indeed provide information on pH and degree of reflux, but not specifically on the patient's symptoms. On the other hand, our study clearly demonstrates that the study subjects were able to distinguish the onset of soothing and cooling effects, as shown by the marked differences found in these parameters due to intake of the different products. Moreover, previous studies, also using the dual-stopwatch method, had demonstrated the validity of this approach to determine the efficacy of different treatments for post-prandial heartburn (Strugala et al., 2009a; Strugala et al., 2009b; Strugala et al., 2010).

Interestingly, the present investigation found that the two Reduflux® formulations were between 2 and 14 times faster in achieving a soothing or a cooling effect after triggering of heartburn by a refluxogenic meal than the different Gaviscon® preparations evaluated in a recently published study (Strugala et al., 2010). In spite of the absence of a "head-to-head" study directly comparing the usefulness of Reduflux® and Gaviscon® in the same study population, the fact that the previously published Gaviscon® study and the present one share almost identical inclusion and exclusion criteria, experimental design, methods to evaluate soothing and cooling effects, and sample size, enables the comparison to be made and is highly relevant from a clinical practice standpoint.

The quick onset of Reduflux®-induced relief of heartburn symptoms suggests that, in addition to the well-known, main mechanism of action of this alginate product, which is the raft formation within the stomach, other additional mechanism such as demulcent effect must play a role at the throat and oesophagus level, leading to the observed soothing and cooling effects of Reduflux®. This additional mechanism of action has been discussed for Gaviscon® (Strugala et al., 2010).

Another strength of the present study is the information provided about duration of the heartburn relief. Of note, in most subjects (40 out of 41, 97.6% of each of the 2 Reduflux® formulation groups) the soothing and cooling effects remained during at least the 4 h of observation after product intake. This finding confirms the relatively long duration of action of alginate products, one of their key advantages over antacids in the treatment of gastro-oesophageal reflux symptoms (Giannini et al., 2006; Mandel et al., 2000). Generally, in the event that symptoms of heartburn persist, further diagnostics assessments are recommended, especially if recurrent symptoms occur post-treatment.

The main limitation of this study is that, due to formulation constraints, a double-blind design was not possible and, therefore, a placebo tablet, swallowed with water was used as control treatment. Although the placebo tablet was not ideal, clear and significant improvement in heartburn symptoms in Reduflux treated group compared with non-responders in the placebo group suggest that improvement of symptoms was not due to a placebo effect.

## CONCLUSION

In conclusion, this randomized, controlled, three-way crossover trial demonstrates that Reduflux® chewable tablets and Reduflux® liquid sachets were highly efficacious in the treatment of post-prandial heartburn, providing not only a very quick onset of action with a mean time to the onset of soothing of less than 2 min and to the onset of cooling of less than 1 min, but also a long duration of action with sustained symptoms relief that lasted over 4 h in 97% of the subjects.

## ACKNOWLEDGEMENT

The study was sponsored by InQpharm. Gordana Bothe and Udo Bongartz are employed by analyze & realize GmbH, a contract research organization. The authors declare no other competing interests regarding this study.

## REFERENCES

- Bannwarth B, 2004.** Gastrointestinal safety of Paracetamol: is there any cause for concern? *Expert Opin Drug Safety*, 3(4):269-72.
- Chiu CT, Hsu CM, Wang CC, Chang JJ, Sung CM, Lin CJ, Chen LW, Su MY, Chen TH, 2013.** Randomised clinical trial: sodium alginate oral suspension is non-inferior to omeprazole in the treatment of patients with non-erosive gastroesophageal disease. *Aliment Pharmacol Ther*, 38(9):1054-1064.
- Giannini EG, Zentilin P, Dulbecco P, Iiritano E, Bilardi C, Savarino E, Mansi C, Savarino V, 2006.** A comparison between sodium alginate and magaldrate anhydrous in the treatment of patients with gastroesophageal reflux symptoms. *Dig Dis Sci*. 51(11):1904-1909.
- Haag S, Andrews JM, Katelaris PH, Gapasin J, Galmiche JP, Hunt R, Lamer P, Malfertheiner P, Holtmann G, 2009.** Management of reflux symptoms with over-the-counter proton pump inhibitors: issues and proposed guidelines. *Digestion*, 80(4):226-234.
- Hershcovici T, Fass R, 2011.** Pharmacological management of GERD: where does it stand now? *Trends Pharmacol Sci*, 32(4):258-264.
- Holtmann G, Bigard MA, Malfertheiner P, Pounder R, 2011.** Guidance on the use of over-the-counter proton pump inhibitors for the treatment of GERD. *Int J Clin Pharm*, 33(3):493-500.
- Kushner PR, 2010.** Role of the primary care provider in the diagnosis and management of heartburn. *Curr Med Res Opin*, 26(4):759-65.
- Leake I, 2013.** GERD: Alginate rafts localize to the acid pocket and reduce acid reflux in GERD. *Nat Rev Gastroenterol Hepatol*, 10(7):386.
- Mandel KG, Daggy BP, Brodie DA, Jacoby HI, 2000.** Review article: Alginate-raft formulations in the treatment of heartburn and acid

- reflux. *Aliment Pharmacol Ther*, 14(6):669-690.
- McRorie JW Jr., Gibb RD, Miner PB Jr., 2014.** Evidence-based treatment of frequent heartburn: the benefits and limitations of over-the-counter medications. *J Am Assoc Nurse Pract*, 26(6):330-339.
- Piche T, Galmiche JP, 2005.** Pharmacological targets in gastro-oesophageal reflux disease. *Basic Clin Pharmacol Toxicol*, 97(6):333-41.
- Richter JE, 2005.** The management of heartburn in pregnancy. *Alimentary Pharmacol Therapeut*, 22(9):749-757.
- Robinson M, 2004.** Review article: pH, healing and symptom relief with rabeprazole treatment in acid-related disorders. *Aliment Pharmacol Ther*, 20 Suppl 6:30-37.
- Savarino E, de Bortoli N, Zentilin P, Martinucci I, Bruzzzone L, Furnari M, Marchi S, Savarino V, 2012.** Alginate controls heartburn in patients with erosive and nonerosive reflux disease. *World J Gastroenterol*, 18(32):4371-4378.
- Sheikh I, Waghay A, Waghay N, Dong C, Wolfe MM, 2014.** Consumer use of over-the-counter proton pump inhibitors in patients with gastroesophageal reflux disease. *Am J Gastroenterol*. 109(6):789-794.
- Strugala V, Dettmar P, Dewland P, Sarratt K, Sykes J, Thomas E, Berry P, 2009a.** Pilot evaluation of a stopwatch method to assess time to onset of the soothing and cooling effect of heartburn treatments. In: *Gut*. Vol. 58, ed. BMJ Publishing Group British Med Assoc House, Tavistock Square, London WC1H 9JR, England, pp. A146-A146.
- Strugala V, Dettmar PW, Sarratt K, Sykes J, Berry P, Thomas E, 2010.** A randomized, controlled, crossover trial to investigate times to onset of the perception of soothing and cooling by over-the-counter heartburn treatments. *J Int Med Res*, 38(2):449-457.
- Strugala V, Dettmar, PW, Dewland, PM, Sarratt, K, Sykes, J, Thomas, EC, Berry, PJ, 2009b.** M1899 new method for determining the speed of onset of consumer-perceived symptom relief from heartburn. *Gastroenterology*, 136(5):A-441-A-442.
- Sweis R, Kaufman E, Anggiansah A, Wong T, Dettmar P, Fried M, Schwizer W, Avvari RK, Pal A, Fox M, 2013.** Post-prandial reflux suppression by a raft-forming alginate (Gaviscon Advance) compared to a simple antacid documented by magnetic resonance imaging and pH-impedance monitoring: mechanistic assessment in healthy volunteers and randomised, controlled, double-blind study in reflux patients. *Aliment Pharmacol Ther*, 37(11):1093-1102.
- Tran T, Lowry AM, El-Serag HB, 2007.** Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies. *Aliment Pharmacol Ther*, 25(2):143-153.
- Wang YK, Hsu WH, Wang SS, Lu CY, Kuo FC, Su YC, Yang SF, Chen CY, Wu DC, Kuo CH, 2013.** Current pharmacological management of gastroesophageal reflux disease. *Gastroenterol Res Pract*. 2013:983653.
- Yuan Y, Hunt RH, 2009.** Evolving issues in the management of reflux disease? *Curr Opin Gastroenterol*, 25(4):342-351.

---

**Citation:** Bothe G, Sans M, Bongartz U, Uebelhack R, 2015. Randomized clinical trial: Randomized, controlled, single-blind, three-way crossover study to evaluate the efficacy and safety of a new preparation for post-prandial heartburn. *Int Res J Med Med Sci*, 3(3): 78-87.

---