

A Novel, Duodenal-Release Formulation of a Combination of Caraway Oil and L-Menthol for the Treatment of Functional Dyspepsia: A Randomized Controlled Trial

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OBJECTIVES: We conducted a randomized, placebo-controlled trial, which evaluated a novel formulation of caraway oil and L-menthol using microsphere-based site-specific targeting (COLM-SST) vs placebo in patients with functional dyspepsia (FD).

METHODS: Adult men and women with FD defined by Rome III criteria were recruited. Patients were randomized to COLM-SST (25 mg of caraway oil and 20.75 mg of L-menthol per capsule, at 2 capsules per dose, twice per day) or placebo. Efficacy was measured at 24 hours, 2 weeks, and 4 weeks. Patients were allowed to take concomitant medications for their FD throughout the trial, and rescue medicines were allowed, 48 hours after start of dosing.

RESULTS: Ninety-five patients were enrolled (mean age = 43.4 years; 75.8% women). At 24 hours, the active arm reported a statistically significant reduction in postprandial distress syndrome symptoms ($P = 0.039$), and a nonsignificant trend toward benefit of epigastric pain syndrome symptoms ($P = 0.074$). In patients with more severe symptoms, approximately 3 quarters of patients showed substantial global improvement (i.e., clinical global impressions), after 4 weeks of treatment, vs half in the control arm. These differences were statistically significant for patients with epigastric pain syndrome ($P = 0.046$), and trending toward significance for patients with postprandial distress syndrome ($P = 0.091$). There was no statistically significant difference between groups for Global Overall Symptom scores for the overall population at 2 and 4 weeks. Treatment emergent adverse events were mild to moderate, and no serious adverse events were reported.

DISCUSSION: In patients taking their usual medications for FD, COLM-SST provided rapid relief (within 24 hours) and relief of severe FD symptoms. It was safe and well tolerated.

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INTRODUCTION

Functional dyspepsia (FD) is defined by the Rome IV criteria as bothersome postprandial fullness, early satiation, epigastric pain, and/or epigastric burning experienced for the previous 3 months with symptom onset at least 6 months prior to the diagnosis in the absence of structural disease (1). Clinically, patients may also present with upper abdominal bloating. Most patients with FD report intermittent symptoms, experiencing asymptomatic periods followed by episodes of symptom relapse (2). According to the Rome IV criteria, FD is divided into 2 subgroups: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS) (1).

No medication is currently approved by the FDA for the treatment of FD, although proton pump inhibitors, histamine type-2 receptor antagonists, antidepressants, and prokinetics are commonly used “off-label” to treat affected patients (3,4). Unfortunately, these medications offer only a modest therapeutic gain over placebo, often require continuous dosing, and may be associated with adverse events. The high prevalence of FD, coupled with the lack of effective medications, indicates that there is a substantial unmet medical need for patients suffering from this condition.

Previous studies have shown that peppermint oil and caraway oil (primarily composed of approximately equal parts D-carvone

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and L-limonene), either alone or in combination, may possess gastroprotective (5–8), analgesic (9), prokinetic (10,11), and anti-inflammatory (12,13) properties, all of which might benefit patients with FD. Peppermint oil and caraway oil have demonstrated synergistic peripheral analgesic activity in preclinical studies (14). Several clinical trials, which assessed a combination of peppermint oil and caraway oil in patients with FD, exhibited significant efficacy vs placebo (10,15–18). However, no studies have evaluated the efficacy of these agents in patients categorized using Rome III criteria. Furthermore, no studies have tested a multiparticulate system, such as microspheres, designed for duodenal release for FD.

We sought to test a novel combination of Caraway Oil and L-Menthol, the key active ingredient of peppermint oil, with microsphere-based Site-Specific Targeting (FDgard) to the duodenum. This site was targeted primarily due to the mounting evidence that gastroduodenal mucosal integrity and low-grade inflammation play a role in FD (19). Furthermore, studies have shown that caraway oil and peppermint oil act on the duodenum to induce smooth muscle relaxation (11), and that L-menthol has anti-inflammatory effects (12). Since the combination of caraway oil and L-menthol is an oil, it has not been possible to deliver this combination reliably and quickly to the duodenum, with the historical oil in enteric-coated capsule formulations. Pharmacodynamic studies done with enteric-coated capsules containing peppermint oil and caraway oil showed that “The activity of the enteric-coated capsules is strongly influenced by the gastric emptying of these preparations. Particles larger than 1 mm in diameter pass the pylorus during the interdigestive phase III activity of the MMC” (10). The caraway oil and L-menthol using microsphere-based Site-Specific Targeting (COLM-SST) microsphere delivery system, with an average particle size of approximately 1 mm, is anticipated to have their effect during the first migrating motor complex after administration for rapid onset of action. We developed a novel method of converting this oil-based combination into a solid state by the use of microcrystalline cellulose. This solid state was then converted into microspheres with extrusion and then spheronization, and triple-coated in fluid beds.

The aims of this study were to evaluate the efficacy of COLM-SST in reducing Global Overall Symptom (GOS) scores compared with placebo in patients with EPS and PDS, to assess the efficacy of COLM-SST in reducing key individual FD symptoms, and to assess the safety and tolerability of COLM-SST in patients with FD in a real-world setting where they were allowed to take concomitant medications for their FD symptoms.

METHODS

Study subjects

In order to be eligible for the Functional Dyspepsia Reduction Evaluation and Safety Trial (FDREST), subjects had to meet Rome III criteria for FD, which includes one or more of the following: bothersome postprandial fullness, early satiation, epigastric pain, and/or epigastric burning (20). In addition, subjects were required to have no evidence of structural disease that was likely to explain symptoms as verified by a normal upper endoscopy performed within the past 36 months. If upper endoscopy screening was not done within 36 months, it was required prior to study enrollment. Subjects who tested positive for *Helicobacter pylori* by blood antibody test during the screening period or the previous 12 months were excluded from the study. Subjects aged 18–65 years who

reported at least moderate symptoms (≥ 4 points on either EPS or PDS question of the 7-point GOS scale) on at least 4 days during the 14-day screening period were eligible. This validated (21) GOS scale is as follows: (i) no problem; (ii) minimal problem (can be easily ignored without effort); (iii) mild problem (can be ignored with effort); (iv) moderate problem (cannot be ignored but does not influence my daily activities); moderately severe problem (cannot be ignored and occasionally limits my daily activities); (v) severe problem (cannot be ignored and often limits my concentration on daily activities); (vi) very severe problem (cannot be ignored and markedly limits my daily activities and often requires rest) (21).

Experimental design

The protocol was approved by the Chesapeake Institutional Review Board. The Palm Beach Clinical Research Organization (West Palm Beach, FL) was responsible for conducting the study. Subjects were enrolled by gastroenterologists, family practitioners, internists, and general medicine practitioners, all of whom had been qualified as investigators by the Clinical Research Organization. For a consort chart (Figure 1).

The study agent consisted of capsules containing 25 mg of caraway oil and 20.75 mg of L-menthol (equivalent to 50 mg of peppermint oil) or placebo. The COLM-SST and the placebo capsules contained microspheres of the same size (≈ 1.2 mm in diameter) and density. Active microspheres in the COLM-SST capsules contained 60% fiber while the placebo contained 100% fiber. The microspheres of the active and matching placebo were encapsulated and blister packaged to prevent patients from distinguishing active therapy from placebo by detecting the odor of L-menthol or caraway oil.

During a 14-day screening period, subjects were asked to complete a washout of prohibited medications but were allowed to keep taking their off-label drugs prescribed for FD (such as antibiotics, proton pump inhibitors, histamine type-2 receptor antagonists, tricyclic antidepressants, selective serotonin reuptake inhibitors/serotonin norepinephrine reuptake inhibitors, antinociceptives such as gabapentin and pregabalin) if they remained on a stable dose. Subjects were asked to score the severity of their FD symptoms in a daily diary.

On day 1, subjects completed baseline assessments prior to beginning treatment. Subjects then began treatment with COLM-SST or placebo immediately and continued to take the study agent twice daily (2 capsules in the morning and 2 capsules at dinner time, 30–60 minutes before a meal) for 4 weeks. Subjects were randomized 1:1 to either COLM-SST or placebo using concealed allocation (day 1). Forty-eight hours after completing the wash out and after initiating dosing, prohibited medicines were allowed after approval by the clinical monitor (visit 3 day 3). These medications included antiemetics, prokinetics, anticholinergics, antidiarrheals, sedative hypnotics, nonsteroidal anti-inflammatory drugs, narcotic analgesics, oral heartburn and gas relief agents, probiotics, and antispasmodics on an as needed basis (p.r.n.).

Compliance was assessed by capsule count during research visits. In a daily diary, subjects reported the severity of their FD symptoms during the previous 24 hours. On days 1, 3, 14, and 28 of the treatment period, subjects returned to the clinic to be monitored for adverse events. Also, on days 14 and 28, the investigators completed their own assessment of the subjects' improvement using a 7-point scale from “very much improved” to “very much worse.” Subjects were free to withdraw from participation in the study at any time.

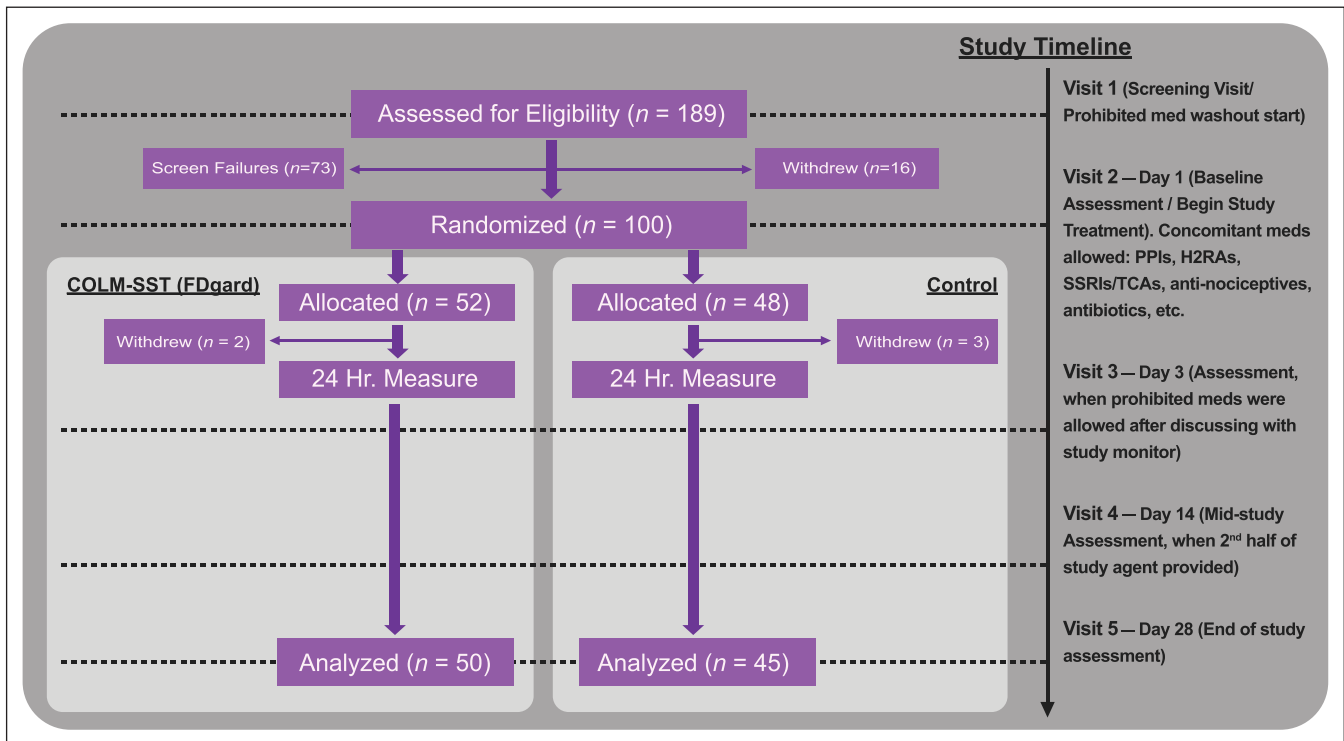


Figure 1. FDREST consort chart. COLM-SST, caraway oil and L-menthol using microsphere-based Site-Specific Targeting; FDREST, Functional Dyspepsia Reduction Evaluation and Safety Trial; H2RA, histamine type-2 receptor antagonist; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Statistical analysis

One hundred subjects were enrolled at 7 clinical sites. The sample size was modeled after a previous clinical trial (15). With 100 subjects (50 subjects per product group), differences of 0.6 points in the GOS score between product groups would be detectable at 2-sided $\alpha = 0.05$ with greater than 84% power, assuming a s.d. of 1 point.

All statistical testing was performed at a 2-sided $\alpha = 0.05$ level of significance. No adjustment was made to the alpha level for any analyses. A detailed statistical analysis plan was finalized prior to unblinding the study. On the basis of previous study outcomes with similar active components, a power analysis was performed by a third-party (Statistics & Data Corporation) to determine the number of participants needed for the trial.

The study endpoints utilized in this trial were as follows:

- Mean percent change in epigastric pain or discomfort score (per the EPS question on the GOS scale) between baseline and
 - Day 2
 - Average of days 2–14
 - Average of days 15–28
- Mean percent change in sensation of pressure, heaviness, and fullness (per the PDS question on the GOS scale) between baseline and
 - Day 2
 - Average of days 2–14
 - Average of days 15–28
- Proportion of subjects with physician-reported symptom improvement per clinical global impression (CGI) (CGI item 2) at day 28

- Incidence and severity of treatment-emergent adverse events (TEAEs) during the 28-day treatment period.

All subjects who were randomized, received at least one dose of study product, and had at least one postbaseline diary assessment were included in the intent to treat (ITT) population. Patients were further categorized into high symptom burden of PDS or EPS subcategories. High-symptom-burden PDS patients had to report an elevated GOS score (≥ 5) for a sensation of pressure, heaviness, or fullness, while higher EPS patients had to report an elevated GOS score (≥ 4.5) for epigastric pain or discomfort. The 2 GOS scores were chosen on the basis of having a similar number of subjects (18 or 19) in the active arm.

RESULTS

Patients

A total of 95 subjects who satisfied the inclusion criteria were randomized and had at least one postbaseline diary assessment were considered to be in the ITT population. There were no statistically significant differences between cohorts in age, gender, height, or body mass index (Table 1). Primary reasons for screen failures were positive test for *H. pylori*, positive test for celiac disease, and failure to attend the scheduled endoscopy session.

Response to treatment

At 24 hours, the COLM-SST-treated group demonstrated a statistically significant ($P = 0.039$) reduction in PDS symptoms (sensations of pressure, heaviness, and fullness) with a trend toward improving EPS symptoms ($P = 0.074$) in the overall ITT population (Figure 2a). After 2–14 days and 15–28 days, patients

Table 1. Subject demographics

n	COLM-SST n (%) 50	Control n (%) 45	All subjects n (%) 95
Age (yr)			
Mean (s.d.)	43.7 (11.33)	43.1 (12.90)	43.4 (12.04)
Median	44.5	44	44
Min, max	18, 60	22, 65	18, 65
<i>P</i> value, 1-sample <i>t</i> -test	0.8063		
Gender			
Male	11 (22.0%)	12 (26.7%)	23 (24.2%)
Female	39 (78.0%)	33 (73.3%)	72 (75.8%)
<i>P</i> value, Pearson χ^2 test	0.5960		
Race			
Asian	3 (6.0%)	1 (2.2%)	4 (4.2%)
Black or African-American	11 (22.0%)	9 (20.0%)	20 (21.1%)
White	36 (72.0%)	35 (77.8%)	71 (74.7%)
Rome III criteria—<i>n</i> (%)			
Bothersome postprandial fullness	46 (92.0%)	36 (80.0%)	82 (86.3%)
Early satiation	44 (88.0%)	36 (80.0%)	80 (84.2%)
Epigastric pain	48 (96.0%)	44 (97.8%)	92 (96.8%)
Epigastric burning	25 (50.0%)	20 (44.4%)	45 (47.4%)

COLM-SST, caraway oil and L-menthol using microsphere-based Site-Specific Targeting.

in the ITT population receiving COLM-SST experienced a greater reduction in symptoms from sensations of pressure, heaviness, and fullness compared with the placebo group, although these changes did not reach statistical significance (for GOS scores, percent changes, and *P*-values, Table 2). Patients in the ITT population receiving COLM-SST also experienced a reduction in epigastric pain scores after 2–14 days and 15–28 days compared with the placebo group, although these reductions did not reach statistical significance. After 4 weeks, there was an absolute increase in the proportion of participants in the ITT population taking COLM-SST who reported much or very much improved symptoms, as measured by CGI, although this did not reach statistical significance ($P = 0.230$; Figure 2b).

In the PDS subcategory, the COLM-SST-treated group demonstrated statistically significant reduction in PDS symptoms ($P = 0.023$) and EPS symptoms ($P = 0.012$) at 24 hours (Figure 3a). In addition, patients in the PDS subgroup of the ITT population showed a nonsignificant reduction in PDS symptoms compared with the control group between 2 and 14 days and 15–28 days. A similar favorable trend was also observed for the PDS subgroup when measuring CGI ($P = 0.091$; Figure 3b).

In the EPS subcategory, the COLM-SST-treated group demonstrated a statistically significant reduction in both EPS ($P = 0.003$) and PDS symptoms ($P = 0.019$) at 24 hours (Figure 4a). Patients in the EPS subgroup also demonstrated a reduction in EPS symptoms vs the control group at 2–14 days and 15–28 days, although these differences did not reach statistical significance. As measured by CGI, there was a statistically significant difference observed in the EPS subgroup compared with the control group ($P = 0.046$; Figure 4b).

Safety and tolerability

An overall summary of TEAEs by treatment group is shown in Table 3. The main gastrointestinal adverse events observed

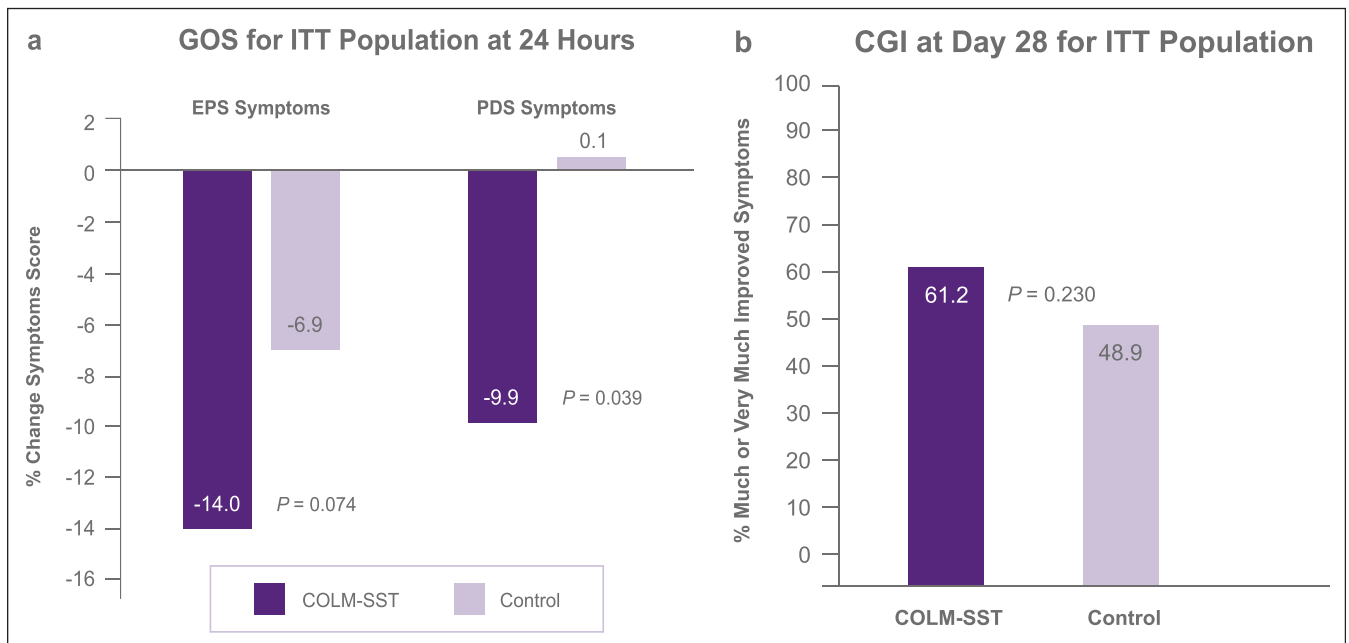


Figure 2. Response to COLM-SST in the intent to treat (ITT) population—change in GOS scores at the 24-hour time point (a) CGI at day 28 (b). COLM-SST, caraway oil and L-menthol using microsphere-based Site-Specific Targeting; CGI, clinical global impression; EPS, epigastric pain syndrome; GOS, Global Overall Symptom; PDS, postprandial distress syndrome.

Table 2. Global overall symptom scores

Population	Symptom		COLM-SST				Control			
			Baseline score	Day 2 score	Day 14 score	Day 28 score	Baseline score	Day 2 score	Day 14 score	Day 28 score
ITT	Epigastric pain or discomfort	GOS score	4.4	3.8	3.4	3.0	4.4	4.2	3.6	3.1
		Percent change		-14.0%	-21.0%	-32.1%		-6.9%	-18.1%	-28.2%
		<i>P</i> -value vs control		0.074	0.449	0.530				
	Sensations of pressure, heaviness, & fullness	GOS score	4.5	4.0	3.6	3.1	4.4	4.4	3.6	2.9
		Percent change		-9.9%	-19.5%	-30.5%		+0.1%	-16.7%	-30.2%
		<i>P</i> -value vs control		0.039	0.760	0.989				
Higher epigastric pain group	Epigastric pain or discomfort	GOS score	5.3	4.2	3.8	3.2	5.5	5.5	4.5	3.7
		Percent change		-20.7%	-26.6%	-38.7%		+1.5%	-16.6%	-29.1%
		<i>P</i> -value vs control		0.003	0.183	0.344				
	Sensations of pressure, heaviness, & fullness	GOS score	5.5	4.7	4.2	3.5	5.3	5.4	4.2	3.5
		Percent change		-13.2%	-22.2%	-34.8%		+6.9%	-17.8%	-29.5%
		<i>P</i> -value vs control		0.019	0.579	0.627				
Higher sensations of pressure, heaviness, & fullness group	Epigastric pain or discomfort	GOS score	5.3	4.2	3.8	3.1	5.6	5.6	4.5	3.7
		Percent change		-19.5%	-26.8%	-40.1%		+1.8%	-18.4%	-30.5%
		<i>P</i> -value vs control		0.012	0.336	0.502				
	Sensations of pressure, heaviness, & fullness	GOS score	5.6	4.7	4.2	3.4	5.7	5.6	4.4	3.6
		Percent change		-15.8%	-24.7%	-38.5%		-0.9%	-23.5%	-34.0%
		<i>P</i> -value vs control		0.023	0.837	0.720				

COLM-SST, caraway oil and L-menthol using microsphere-based Site-Specific Targeting; GOS, Global Overall Symptom; ITT, intent to treat.

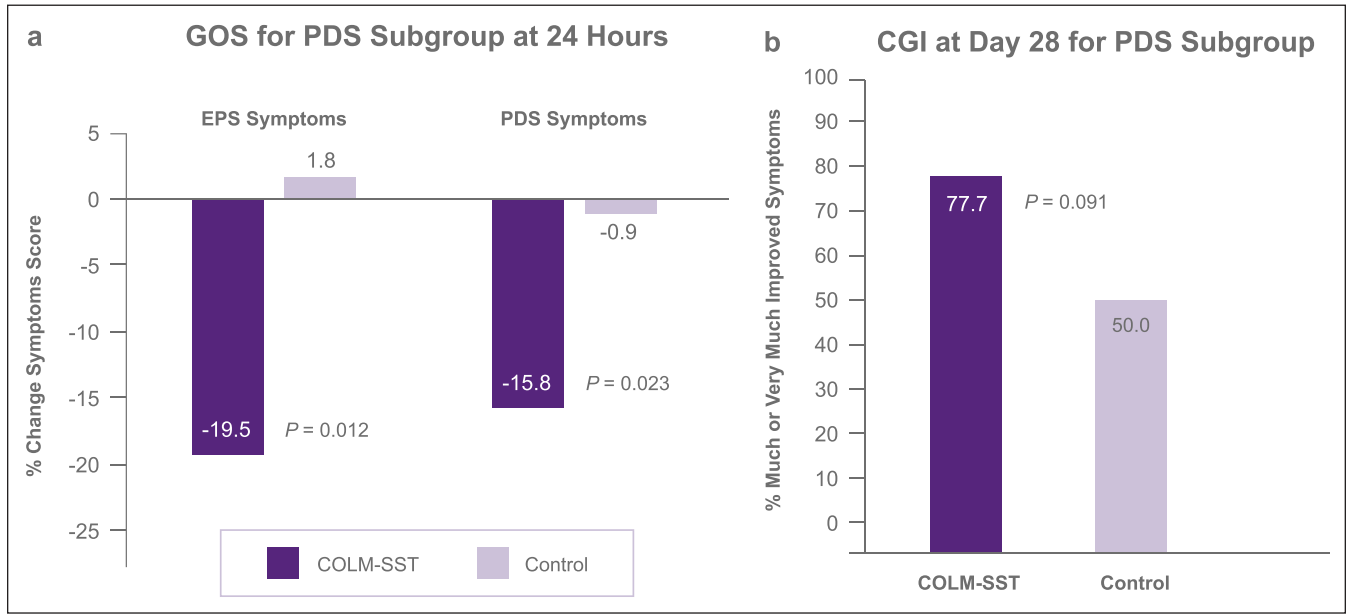


Figure 3. Response to COLM-SST in the PDS subgroup of ITT population (COLM-SST n = 18, control n = 16)—change in GOS scores at the 24-hour time point (a) change in CGI at day 28 (b). COLM-SST, caraway oil and L-menthol using microsphere-based Site-Specific Targeting; CGI, clinical global impression; EPS, epigastric pain syndrome; GOS, Global Overall Symptom; PDS, postprandial distress syndrome.

were abdominal pain, nausea, and dyspepsia and were felt to be related to the condition being studied. There were 17 gastrointestinal disorder adverse events in the control group (17.8% of subjects) vs 9 in the COLM-SST group (12% of subjects). All TEAEs were mild to moderate in intensity. There were no serious adverse events or deaths. No subjects were withdrawn due to TEAEs.

DISCUSSION

One of our main findings was that COLM-SST resulted in a statistically significant reduction in FD symptoms within 24 hours of administration. These benefits held true for the overall FD study population as well as for the EPS and PDS subgroups. This finding is clinically important because patients with FD typically report intermittent symptoms that are often triggered

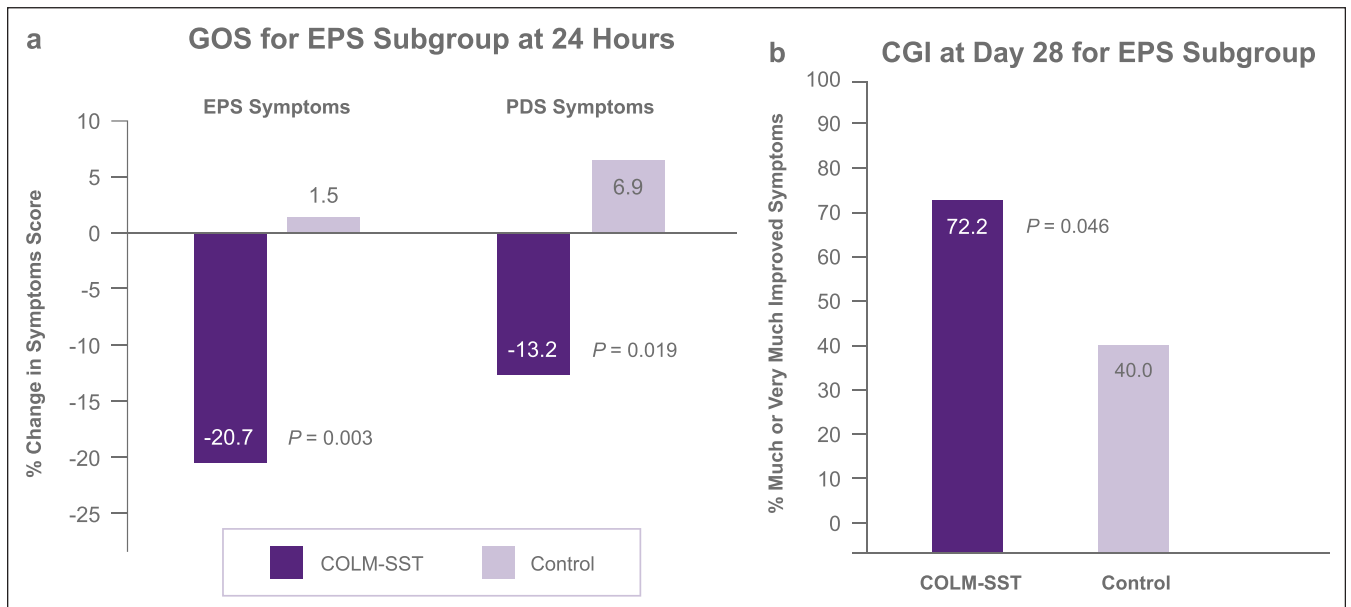


Figure 4. Response to COLM-SST in the EPS subgroup of ITT population (COLM-SST n = 19, control n = 20)—change in GOS scores at the 24-hour time point (a) change in CGI at day 28 (b). COLM-SST, caraway oil and L-menthol using microsphere-based Site-Specific Targeting; CGI, clinical global impression; EPS, epigastric pain syndrome; GOS, Global Overall Symptom; PDS, postprandial distress syndrome.

Table 3. Treatment-emergent adverse events

	COLM-SST (N = 50) n (%)	Control (N = 45) n (%)	All subjects (N = 95) n (%)
No. of TEAEs	24	29	53
No. of subjects with any TEAE	16 (32.0%)	15 (33.3%)	31 (32.6%)
No. of treatment-related TEAEs	8	9	17
No. of subjects with any treatment-related TEAE	6 (12.0%)	7 (15.6%)	13 (13.7%)
No. of TEAEs > grade 1	12	10	22
No. of subjects with any TEAEs > grade 1	7 (14.0%)	7 (15.6%)	14 (14.7%)
No. of serious TEAEs	0	0	0
No. of subjects with any serious TEAE	0	0	0
No. of deaths on study	0	0	0
No. of subjects with TEAE(s) that led to discontinuation	0	0	0
No. of subjects with gastrointestinal disorders	6 (12.0%)	8 (17.8%)	14 (14.7%)
Abdominal pain	1 (2.0%)	3 (6.7%)	4 (4.2%)
Nausea	2 (4.0%)	2 (4.4%)	4 (4.2%)
Dyspepsia	1 (2.0%)	2 (4.4%)	3 (3.2%)

COLM-SST, caraway oil and L-menthol using microsphere-based Site-Specific Targeting; TEAE, treatment-emergent adverse event.

by meals (22). As well, patients desire rapid relief from their FD symptoms, rather than waiting days or weeks for some therapeutic options to take effect (e.g., tricyclic antidepressants, buspirone). The technology used in COLM-SST is anticipated to deliver the active ingredients to the duodenum within 1 hour. This study was not designed to measure symptoms at less than 24 hours. However, a separate postmarketing survey study found that the vast majority of patients with FD who used COLM-SST experienced relief within 1–2 hours of administration (23).

A scientific rationale exists for the use of peppermint oil or its major constituent, L-menthol, in combination with caraway oil to treat patients with FD (15,17). The findings of impaired duodenal mucosal integrity and localized low-grade inflammation in FD (19,24,25) and the stronger anti-inflammatory effects of L-menthol compared with peppermint oil (12) guided us to use L-menthol (the primary active component in peppermint oil) at the same levels as used in previous studies that utilized peppermint oil (15,17).

L-menthol, the key active ingredient in peppermint oil, plus carvone and limonene, the major active ingredients in caraway oil, has been shown to be clinically effective against symptoms of FD (15,26,27). The COLM-SST capsules utilized in this study contain individually enteric-coated microspheres of L-menthol with caraway oil, in a specially developed solid-state fiber matrix. Each microsphere is enteric-coated to

prevent release of L-menthol or caraway oil in the stomach. Such release from oil-filled capsules has been shown to cause side effects, including heartburn (28). With an average diameter of less than 2 mm, these microspheres pass through the pylorus and disperse throughout the small intestine. Unlike currently available liquid-filled, enteric-coated single-unit, non-disintegrating dosage forms (29) of peppermint oil plus caraway oil, the solid-state microspheres in COLM-SST are designed to rapidly release L-menthol and caraway oil in the duodenum (30).

While COLM-SST achieved statistically significant benefits vs placebo at the earliest time point (24 hours), longer durations of treatment (2 and 4 weeks) did not lead to statistically significant benefits for FD symptoms. This differs from previous studies, which have found more durable benefits for peppermint and caraway oil (15,17). For example, May et al. (15) showed a reduction in epigastric pain by 40% compared with placebo, and a 43% reduction in pressure, heaviness, and fullness compared with placebo at the end of 4 weeks.

The current study differs significantly from the previously published literature. Firstly, patients in previous studies received PCC (Enteroplant, Dr Willmar Schwabe Pharmaceuticals), a fixed dose combination of 90 mg of peppermint oil and 50 mg of caraway oil 3 times per day (17), twice per day (15), or once per day (16). In contrast, the formulation used in FDREST contained L-menthol, as opposed to peppermint oil. L-menthol was selected since it has been shown to induce a greater anti-inflammatory effect than peppermint oil (12), acting through the TRPM8 pathway to reduce pain and inflammation (9). Secondly, in contrast to single-unit enteric-coated capsules, this study used SST technology, incorporating solid-state microspheres that embedded the active ingredients. Finally, unlike previous studies which were more traditional parallel group randomized, controlled treatment trials, patients in the current study were randomized to receive COLM-SST or placebo along with other over the counter (OTC) and/or prescription medication for FD to reflect real-world practice where it is common to treat patients with a wide range of OTC and prescription medications. Patients with FD also may take rescue medications to combat severe symptoms. While one could argue that this design more closely reflected real-world practice, it also meant the final results, after the 24-hour time point, were obfuscated by multiple variables. By introducing treatment heterogeneity, we may have increased the likelihood of a type II error.

An important subgroup analysis found that COLM-SST led to statistically significantly greater benefits than placebo in patients suffering from more severe PDS and EPS symptoms at each of the time points (24 hours, 2 weeks, and 4 weeks). It is also important to note that symptom reduction for all measures was greater with longer duration of COLM-SST use in both subgroups. For the EPS subgroup, the CGI score showed a statistically significant difference at 4 weeks. By examining the effects of COLM-SST on these subgroups, we can more closely compare the results from this study to those reported previously in the literature. Similar studies have typically only allowed patients with FD to be included in the trial if they were experiencing a current episode (i.e., daily symptoms) lasting for at least 1 week (18) or 2 weeks (15). The frequency and intensity of symptoms in these studies more closely matches the patients categorized into high-symptom-burden PDS and EPS subgroups of the ITT

population of FDREST. By analyzing these subgroups, we demonstrated that COLM-SST provides relief not only to those who experience minor symptoms but also to those with more severe symptoms.

The precise mechanism(s), which underlies the clinical benefits of COLM-SST for FD, remains to be fully elucidated. L-menthol and caraway oil have both been shown to possess gastro-protective properties (5–8,31). This, perhaps combined with the anti-inflammatory effects of L-menthol (12), establishes a model through which a combination of caraway oil and L-menthol might prevent or reduce duodenal mucosal barrier disruption. The prokinetic effects of L-menthol and caraway oil, as shown by Micklefield et al. (10,11), could also underlie the benefit observed in some patients in the current trial.

COLM-SST was generally well tolerated. Treatment emergent adverse events were similar between the COLM-SST and control groups. Acknowledging that this study was not powered to address safety endpoints, this differs from adverse event data in association with a different formulation, where issues such as eructation, substernal burning, nausea, and vomiting were observed (15,17,18). This could be expected, given the enteric-coated capsule preparations of peppermint oil and caraway oil used in these earlier studies were dissolved in tea seed oil. These types of single-unit enteric-coated capsules have been shown to stay in the stomach for up to 10 hours and can be exposed to the grinding action in the stomach. The COLM-SST formulation in FDREST allows rapid transit through the pylorus from the stomach into the duodenum. There were no serious adverse events or deaths reported in either treatment group.

In summary, COLM-SST, a novel and innovative formulation of caraway oil and L-menthol, taken daily and proactively 30–60 minutes before meals, was effective and well tolerated as a short-term treatment for patients with FD suffering from EPS or PDS. We also found that patients with more severe FD symptoms achieved greater and more durable benefits with the addition of COLM-SST to their typical medical regimen. These results suggest that COLM-SST may provide an effective treatment candidate for patients with meal and nonmeal-related FD symptoms.

CONFLICTS OF INTEREST

Guarantor of the article: Syed M. Shah, PhD.

Specific author contributions: W.D.C.: planned the study, interpreted the data, drafted the manuscript, approved the final draft submitted. B.E.L.: planned the study, conducted the study, collected the data, drafted the manuscript, approved the final draft submitted. B.D.C.: conducted the study, collected the data, drafted the manuscript, approved the final draft submitted. M.E.: planned the study, interpreted the data, drafted the manuscript, approved the final draft submitted. P.E.C.: interpreted the data, drafted the manuscript, approved the final draft submitted. S.M.S.: planned and conducted the study, interpreted the data, drafted the manuscript, approved the final draft submitted.

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Study Highlights

WHAT IS KNOWN

- ✓ FD is a common disorder for which there is no FDA-approved product.
- ✓ The older technology for delivering a combination of caraway oil and peppermint oil has shown effectiveness in managing FD after at least 2 weeks of treatment.
- ✓ In preclinical studies, L-menthol (the principal component of peppermint oil) has been shown to have better anti-inflammatory activity than peppermint oil.

WHAT IS NEW HERE

- ✓ The novel combination of caraway oil and L-menthol, in conjunction with the unique delivery system is shown to relieve symptoms of FD within 24 hours.
- ✓ COLM-SST is effective in providing relief for more severely affected patients with FD.
- ✓ This new combination of actives and their special delivery system was found to be safe and well tolerated.

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