World Journal of Gastrointestinal Pharmacology and Therapeutics

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World J Gastrointest Pharmacol Ther 2024 May 28; 15(3): 90757

DOI: 10.4292/wjgpt.v15.i3.90757

ISSN 2150-5349 (online)

ORIGINAL ARTICLE

Prospective Study

Efficacy and tolerability of chitin-glucan combined with simethicone (GASTRAP® DIRECT) in irritable bowel syndrome: A prospective, open-label, multicenter study

Nathalie Talbodec, Pauline Le Roy, Peggy Fournier, Benoit Lesage, Elodie Lepoutre, François Castex, Jean Michel Godchaux, Lionel Vandeville, Benjamin Bismuth, Xavier Lesage, Pauline Bayart, Michael Genin, Christel Rousseaux, Veronique Maquet, Salvatore Modica, Pierre Desreumaux, Caroline Valibouze

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade D, Grade D

Novelty: Grade B, Grade C, Grade C

Creativity or Innovation: Grade B, Grade C, Grade C

Scientific Significance: Grade B, Grade C, Grade C

P-Reviewer: Bortolotti M, Italy; Zheng H, China

Received: January 25, 2024

Revised: March 19, 2024

Accepted: May 8, 2024

Published online: May 28, 2024

Nathalie Talbodec, Peggy Fournier, Benoit Lesage, Elodie Lepoutre, Lionel Vandeville, Benjamin Bismuth, Xavier Lesage, Pauline Bayart, Department of Gastroenterology, Hôpital privé Le Bois, Lille 59000, France

Pauline Le Roy, François Castex, Jean Michel Godchaux, Department of Gastroenterology, Hôpital privé de Villeneuve d'Ascq, Villeneuve d'Ascq 59650, France

Michael Genin, Univ. Lille, CHU Lille, ULR 2694–METRICS, Évaluation des Technologies de Santé et des Pratiques Médicales, Lille 59000, France

Christel Rousseaux, Development of Intestinal Biotech, 1 Avenue Oscar Lambret, Lille 59045, France

Veronique Maquet, KitoZyme SA, Parc Industriel des hauts Sarts Zone 2, Rue de Milmort, Herstal 4040, Belgium

Salvatore Modica, BiOkuris A, Parc Industriel des hauts Sarts Zone 2, Rue de Milmort, Herstal 4040, Belgium

Pierre Desreumaux, Department of Hepato-Gastroenterology, Lille University Hospital, Lille 59000, France

Pierre Desreumaux, Caroline Valibouze, U1286-INFINITE, Institute for Translational Research in Inflammation, Univ. Lille, Inserm, CHU Lille, Lille 59000, France

Caroline Valibouze, Department of Digestive Surgery and Transplantation, Lille University Hospital, Lille 59037, France

Corresponding author: Caroline Valibouze, MD, PhD, Department of Digestive Surgery and Transplantation, Lille University Hospital, Rue Michel Polonowski, Lille 59037, France. caroline.valibouze@chu-lille.fr

Abstract

BACKGROUND

Irritable bowel syndrome (IBS), defined according to the Rome IV diagnostic criteria, is a chronic functional gastrointestinal disorder characterized by recurrent abdominal pain related to altered bowel habits. First-line recommended treatments are limited to combining drugs targeting predominant symptoms, particularly pain (antispasmodics), constipation (laxatives), and diarrhea (loperamide), yielding only a limited therapeutic gain. GASTRAP® DIRECT is a class IIa medical formulation composed of a combination of chitin-glucan and simethicone indicated for the symptomatic treatment of gas-related gastrointestinal disorders by combining different mechanisms of action.

AIM
To evaluate the efficacy, tolerability, and safety of 4-week GASTRAP® DIRECT treatment in patients with IBS.

METHODS
In this prospective, multicenter, open-label trial, 120 patients with IBS received three sticks of GASTRAP® DIRECT (1.5 g/d of chitin-glucan and 0.75 mg/d of simethicone) per day for 4 weeks. The primary endpoint was the responder rate, defined as the number of patients whose abdominal pain score decreased by ≥ 30% from baseline to week (W) 4. The analysis was performed using the per-protocol set. Cardinal symptoms, impact of global symptoms on daily life, change in stool consistency, and improvement in defecatory disorders were evaluated.

RESULTS
Overall, 100 patients were evaluated. At W4, 67% (95%CI: 57-75) showed improvement in abdominal pain (score: 5.8 ± 2.4 *vs* 2.9 ± 2.0, $P < 0.0001$). Similar improvements were observed for bloating [8.0 ± 1.7 *vs* 4.7 ± 2.9, $P < 0.0001$; 60% (95%CI: 50-70) responders], abdominal distension [7.2 ± 2.1 *vs* 4.4 ± 3.1, $P < 0.0001$; 53% (95%CI: 43-63) responders], and impact of global symptoms on daily life [7.1 ± 2.0 *vs* 4.6 ± 2.9, $P < 0.0001$; 54% (95%CI: 44-64) responders]. Stool consistency improved in most patients (90% and 57% for patients with liquid and hard stools, respectively). Overall, 42% of patients with defecatory disorders reported very much/considerable improvements by W2. No severe adverse event occurred, and tolerability was rated "good" or "very good" by 93% of patients.

CONCLUSION
GASTRAP® DIRECT is safe and well tolerated, alleviating IBS symptoms rapidly in 2 weeks. This open-label study suggests that the combination of chitin-glucan and simethicone could be beneficial in patients with IBS.

Key Words: Chitin-glucan; Irritable bowel syndrome; Abdominal pain; Flatulence; Defecatory disorders; Stool consistency; Natural non-pharmacological treatment

Core Tip: Irritable bowel syndrome is a common functional gastrointestinal disorder characterized by recurrent abdominal pain associated with altered bowel habits. Treatment options are limited and often inadequate, which leads to dissatisfaction among patients receiving standard medical care. Our study showed that 4 weeks of daily treatment with GASTRAP® DIRECT, a class IIa medical formulation containing a combination of chitin-glucan and simethicone, is well tolerated and rapidly effective in reducing abdominal pain, bloating, abdominal distension, and flatulence with an improvement of stool consistency and defecatory disorders.

Citation: Talbodec N, Le Roy P, Fournier P, Lesage B, Lepoutre E, Castex F, Godchaux JM, Vandeville L, Bismuth B, Lesage X, Bayart P, Genin M, Rousseaux C, Maquet V, Modica S, Desreumaux P, Valibouze C. Efficacy and tolerability of chitin-glucan combined with simethicone (GASTRAP® DIRECT) in irritable bowel syndrome: A prospective, open-label, multicenter study. *World J Gastrointest Pharmacol Ther* 2024; 15(3): 90757
URL: https://www.wjgnet.com/2150-5349/full/v15/i3/90757.htm
DOI: https://dx.doi.org/10.4292/wjgpt.v15.i3.90757

INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder that is prevalent in 5%-10% of the global population. IBS accounts for 3% of visits to general practitioners and approximately 40% of all gastroenterology outpatient consultations[1]. The high prevalence is associated with annual direct and indirect costs of more than $20 billion per year in the United States (US), corresponding to 3.5 million physician visits annually. IBS is also one of the leading causes of work absenteeism[2,3]. This chronic condition is defined according to Rome IV criteria for symptoms and is characterized by recurrent abdominal pain related to altered bowel habits[4]. Although abdominal pain and gas-related bloating are the two dominant and most troublesome symptoms[5], patients with IBS also have frequent

defecation disorders, for which straining, sensation of incomplete evacuation, and manual maneuvers to facilitate defecation are highly suggested to improve their quality of life[4,6]. Although IBS represents a major burden, the recommended therapeutic strategies (*e.g.*, those from European, American, Canadian, Japanese, and British societies)[7-13] are often inadequate, leading to dissatisfaction for many patients with standard medical care[14,15].

Chitin-glucan is a novel non-digestible dietary compound that is considered a safe food ingredient by the European Food Safety Authority (EFSA)[16]. It is the major component of the cell walls of the mycelium of *Aspergillus niger* fungi and is mainly composed of a branched β-1, 3/1, 6 glucan that is linked to chitin *via* a β-1, 4 linkage. Previous preclinical studies in rodent models[14,15], functional in vitro evaluation using the Simulator of the Human Intestinal Microbial Ecosystem model, and clinical exploration in healthy volunteers[17] showed that oral administration of chitin-glucan at the EFSA-recommended dosage induces a microbial signature of a prebiotic[13]. These studies found that chitin-glucan is slowly fermented in all colon segments without enhancement of gas production or fecal calprotectin concentration[18,19]. Gut microbiota analysis using Illumina sequencing also revealed an increased relative abundance of the butyrate-producing genera *Roseburia spp*. and *Faecalibacterium prausnitzii*, a genus with strong anti-inflammatory properties[18,19].

We recently performed preclinical molecular, cellular, and animal studies to evaluate the roles of chitin-glucan in the main pathophysiological mechanisms responsible for symptom generation in IBS (*e.g.*, visceral analgesia, intestinal inflammation, and barrier function) and developed a computational molecular model of the molecule[20]. The results showed that chitin-glucan rapidly and significantly decreases visceral perception and intestinal inflammation through regulation of master genes for pain, inflammation, and intestinal barrier function. Further, it neutralizes harmful substances in the intestinal lumen, such as microbial pathogenic lipids, auguring the use of chitin-glucan treatment in patients with IBS[20].

Simethicone (dimethylpolysiloxane, $[(CH^3)_2[Si(CH^3)_2O]n]$) is a chemically inert compound in silica gel that is not absorbed by the gastrointestinal tract. It is physiologically inactive and non-toxic when administered orally. An *in vitro* study investigating its antifoaming action suggested that simethicone decreases the surface tension of liquids[21]. In rats, oral administration of simethicone reduced stress-induced colonic permeability and hypersensitivity[22]. In humans, simethicone has been used since the 1960s as a well tolerated medication to improve the quality of gastric and colonic mucosal visualization during endoscopy by preventing bubble formation and gas retention[23,24]. In IBS, simethicone in combination with spasmolytics has shown efficacy in reducing abdominal pain and bloating[25,26]. These results suggest that the combination of simethicone and chitin-glucan may be beneficial in patients with IBS by targeting the mechanisms responsible for symptom generation[27,28], including visceral hypersensitivity, intestinal gas retention, dysbiosis, barrier dysfunction, and inflammation. Further, it may help address the low fiber intake observed in European and US populations[29,30]. GASTRAP® DIRECT is a class IIa medical formulation containing 250 mg of simethicone combined with 500 mg of chitin-glucan per sachet. This study aimed to evaluate the efficacy, tolerability, and safety of 4-week GASTRAP® DIRECT treatment in patients with IBS. Toward this goal, GASTRAP® DIRECT was administered for 4 wk in patients with IBS symptoms.

MATERIALS AND METHODS

This prospective, open-label, multicenter study was conducted between September 2021 and June 2022 in France. The study was approved by the Ethics Committee Sud-Est VI of Clermont-Ferrand (France) (Ref. ID-RCB: 2019-A03202-55) and performed in accordance with the International Conference on Harmonization Good Clinical Practice and the ethical principles of the Declaration of Helsinki. A patient information form and a request by the gastroenterologist for non-opposition to the study were obtained from all participants.

Study population

Patients with IBS were recruited by a trial board of 12 French gastroenterologists organized in one tertiary care setting (P. Desreumaux, Coordinator of the study) corresponding to the Department of Gastroenterology of the University Hospital of Lille (Center 1: Principal investigational center) and four secondary care settings located in northern France (Center 2: P Fournier, B Lesage, and B Bismuth; Center 3: N Talbodec and E Lepoutre; Center 4: P Bayart, X Lesage, and L Vandeville; and Center 5: P Le Roy, F Castex, and JM Godchaux). Female and male patients, aged 18–75 years, were eligible for inclusion if they were diagnosed with IBS according to the Rome IV criteria[4]: The presence of bloating or abdominal pain score of ≥ 2 on a visual analog scale (VAS). Patients were excluded on the basis of the following exclusion criteria: (1) Chronic gastrointestinal conditions other than IBS (*e.g.*, lactose intolerance, celiac disease, inflammatory bowel diseases, and diverticulitis); (2) metabolic disorders affecting intestinal transit function or nutrient absorption (*e.g.*, diabetes or unbalanced thyroid dysfunction); (3) pregnant status; (4) chronic alcoholism; and (5) allergy to GASTRAP® DIRECT components or to fructose. Patients with high risk of secondary bile acid malabsorption were excluded (patients with terminal ileal disease or resection, pelvic radiotherapy, diarrhea occurring after cholecystectomy). Concerning primary bile acid malabsorption, since the accurate diagnosis remains challenging, methods of testing were not performed leading to the possibility that this condition may co-exist in about 30% of our patients with diarrhea-predominant IBS.

All patients agreed to maintain their lifestyle behaviors during the study period. Symptomatic drug treatments acting on intestinal functions, including laxatives, anti-bloating agents, probiotics, prebiotics, symbiotics, antispasmodics, anxiolytics, antidepressants, analgesics, and antibiotics, were authorized if consumed for longer than 1 month before inclusion without dose modification and maintained at a stable dosage for the entire study duration.

Study design

This was a 4-wk multicenter, prospective, observational, open-label study. Three medical visits [visit (V) 1–3] were scheduled at day 0 (V1), day 15 (V2), and at the end of the study on day 28 (V3) (Figure 1). At V1, eligibility according to the inclusion/exclusion criteria was assessed, and study instructions concerning the administration of GASTRAP® DIRECT were provided to eligible patients. Altered bowel habits [abnormal stool frequency and stool consistency as evaluated according to the Bristol stool scale (BSS)], symptoms of defecatory disorders including straining at stool and/or sensation of incomplete evacuation, intensity of IBS cardinal symptoms (abdominal pain, bloating, abdominal distension, and flatulence), and impact of global symptoms on daily life were evaluated at V2 and/or V3. The outcomes of individual IBS cardinal symptoms were evaluated using a three-point questionnaire (0, unchanged; 1, very much relieved; and 2, considerably relieved). Treatment tolerability was evaluated at the end of the study (V3) using the following categories: Bad, good, or very good (Figure 1).

Study product (GASTRAP® DIRECT) and compliance evaluation

The class IIa medical formulation GASTRAP® DIRECT is an oral gluten-free and lactose-free powder with vanilla flavor. Each sachet contains 500 mg of chitin-glucan and 250 mg of simethicone, sorbitol, silicon dioxide, acacia gum, xanthan gum, sucralose, and acesulfame K. GASTRAP® DIRECT is prepared in a 12-stick secondary packaging and is administered orally after meals. The recommended daily dose is up to three sticks per day. Patients initially started with one stick per day in the morning during the first 3 d; then increased to two sticks per day at one in the morning and one in the evening for the following 3 d; and finally to three sticks per day at one in the morning, one at noon, and one in the evening until the end of the 4-wk study (Figure 1). Compliance was determined through the assessment of returned packaging and interviews with the patients during V3.

Endpoints

The primary endpoint was the percentage of responders at V3, defined as patients whose abdominal pain score using the 10-point VAS score was reduced by at least 30% from baseline.

The secondary endpoints were the change in abdominal pain, abdominal bloating, abdominal distension. And impact of global symptoms on daily life evaluated by the 10-point VAS score and a three-point satisfaction questionnaire (0: Unchanged; 1: Very much relief; and 3: Considerable relief). Flatulence, constipation, diarrhea, and defecatory disorders were evaluated by the three-point satisfaction questionnaire. Improvement of stool consistency was evaluated according to the percentage of patients having hard (BSS score, ≤ 2) or liquid (BSS score, ≥ 6) stools at V0 and normal stool consistency (BSS score, ≥ 3 to ≤ 5) at V3. Treatment tolerability was analyzed at V3 using a three-point satisfaction score (0: Bad tolerability; 1: Good tolerability; and 2: Very good tolerability).

Safety variables

Adverse events were recorded by the patients and immediately communicated to the investigator for assessment of severity and causality. Severe and non-severe adverse events were recorded using two different forms.

Statistical analyses

Quantitative variables are described as mean ± standard error of the mean. Categorical variables are expressed as percentage and frequency. Responder rates for IBS symptoms (abdominal pain, bloating, abdominal distension, and impact of global symptoms on daily life) are expressed when appropriate using the standard method (normal distribution) with their 95% two-sided confidence intervals (95%CI) of means. Efficacy analyses were performed for the per-protocol population (intention-to-treat population who completed the study and presented no major protocol deviations). For all score outcomes, intragroup analyses were conducted using the two-tailed paired *t*-test or Wilcoxon signed-rank test (non–parametric test comparing ranks) depending on the distribution of the variable of interest for continuous variables to compare baseline values with the values recorded at V2 or V3. Comparisons between groups were performed using the Student t-test or Mann–Whitney–Wilcoxon test (non-parametric test comparing ranks) depending on the distribution of the variable of interest. All statistical analyses were conducted using StatXact 9 software (Cytel Studio 9, Cambridge, MA, United States). All statistical tests were two-sided at the 5% overall alpha risk level. All CIs were two-sided and presented at the 95% confidence level.

RESULTS

Baseline patient characteristics

Among the 145 screened patients, 120 patients were enrolled at V1. Among them, five patients were further excluded owing to voluntary withdrawal and 15 patients discontinued the trial owing to noncompliance (less than 70% intake of expected treatment administration), no follow-up (n = 14), or constipation (n = 1). A total of 100 patients with IBS (76 females and 34 males) who met the Rome IV criteria were included and homogeneously distributed across all care settings (center 1: n = 15, center 2: n = 23, center 3: n = 23, center 4: n = 14, center 5: n = 25). The participant selection flowchart is shown in Figure 2. Overall, 38% of patients had constipation-predominant IBS, 32% had diarrhea-predominant IBS, and 20% had mixed IBS. Most patients (67%) had normal stool consistency at V1 (liquid stools, 18%; hard stools, 15%). Good compliance was recorded during the 1-month treatment (88% ± 5%). The baseline characteristics of the participants are presented in Table 1.

Table 1 Baseline patient characteristics, *n* (%)

	V1 (*n* = 100)
Female sex	76 (76)
Age (yr), mean ± SD	47 ± 13
IBS type	
Constipation-predominant	37/98 (38)
Diarrhea-predominant	31/98 (32)
Mixed	20/98 (20)
Undefined	10/98 (10)
Stool consistency (BSS score), mean ± SD	4.1 ± 1.1
Hard stool (1–2)	14/93 (15)
Normal stool (3–5)	62/93 (67)
Liquid stool (6–7)	17/93 (18)
Excessive flatulence	91/98 (93)
Defecatory disorders	26/100 (26)

V: Visit; BSS: British stool scale.

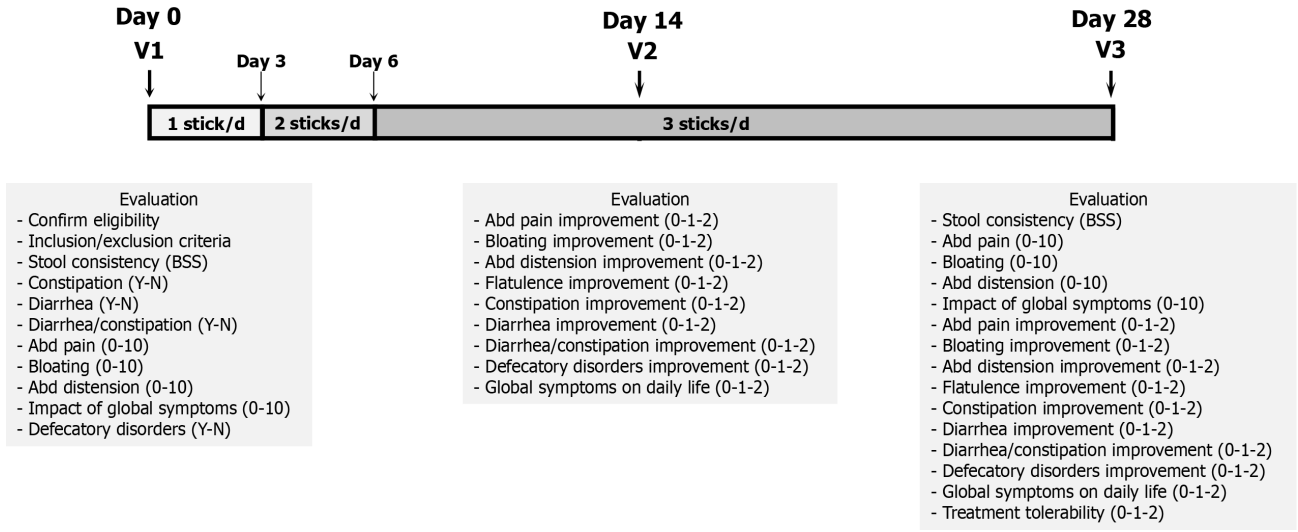

Figure 1 Study design. D: Day; BSS: British stool scale; d: day; V: Visit; Y: Yes; N: No; abd: Abdominal; SGA: Subjective global assessment.

Primary endpoint: Abdominal pain

The responder rate was 67% (64/96, 95%CI: 57-75) (Table 2 and Figure 3). The abdominal pain score was significantly decreased throughout the 4-wk treatment period (5.8 ± 2.4 at V0 *vs* 2.9 ± 2.0 at V3), with a mean reduction of pain intensity of 50% corresponding to a 2.9-point decrease ($P < 0.0001$) (Table 2 and Figure 3). Overall, 66% of the patients reported very much/considerable improvement in abdominal pain score at V3 with a rapid relief of abdominal pain observed from the second week of treatment in 58% of the patients (Table 3).

Secondary endpoints: Bloating, abdominal distension, global symptoms, and flatulence

A significant reduction of bloating (8.0 ± 1.7 at V0 *vs* 4.7 ± 2.9 at V3) and abdominal distension (7.2 ± 2.1 at V0 *vs* 4.4 ± 3.1 at V3) scores were observed after 4 wk of treatment, with a 40% reduction of symptom intensity ($P < 0.0001$) (Table 2, Figures 4A, 4B, 5A and 5B). The responder rates with respect to bloating and abdominal distension were 60% and 53%, respectively (Table 2, Figures 4C and 5C). In total, 67% and 57% of the patients reported very much/considerable improvements in scores on bloating and abdominal distention, respectively, at V3. More than 45% of the patients reported rapid relief for these symptoms starting from the second week of treatment (Table 3). The improvements of cardinal symptoms of IBS were seen with a similar degree of beneficial changes in patients with IBS patients with prevalent constipation (IBS-C), IBS patients with prevalent diarrhea (IBS-D), and IBS patients with mixed symptoms

Table 2 Change in paired scores of irritable bowel syndrome symptoms after week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3)

IBS symptoms	V1, mean ± SEM	V3, mean ± SEM	Responders, Δ > 30%, *n* [% (95%CI)]	Paired decrease, mean ± SE (%)
Abdominal pain (0–10)	5.8 ± 2.4	2.9 ± 2.0[c]	64/96 [67 (57; 75)]	-2.9 ± 0.3 (50)
Bloating (0–10)	8.0 ± 1.7	4.7 ± 2.9[c]	58/96 [60 (50; 70)]	-3.2 ± 0.3 (40)
Abdominal distension (0–10)	7.2 ± 2.1	4.4 ± 3.1[c]	51/96 [53 (43; 63)]	-2.8 ± 0.4 (39)
Impact of global symptoms on daily life	7.1 ± 2.0	4.6 ± 2.9[c]	51/94 [54 (44; 64)]	-2.5 ± 0.3 (35)

[c]$P < 0.001$.

95%CI: Confidence interval of the responder rate (Wilson method); IBS: Irritable bowel syndrome; V: Visit.

Table 3 Symptom relief at weeks 2 and 4 of GASTRAP® DIRECT treatment

Symptom relief	W2 (%)	W4 (%)
Abdominal pain		
Unchanged	42	34
Relief (very much, considerable)	58 (53, 5)	66 (48, 18)
Bloating		
Unchanged	48	33
Relief (very much, considerable)	52 (45, 7)	67 (49, 18)
Abdominal distension		
Unchanged	55	43
Relief (very much, considerable)	45 (33, 12)	57 (40, 17)
Impact of global symptoms on daily life		
Unchanged	37	23
Relief (very much, considerable)	63 (42, 21)	77 (53, 24)
Flatulence		
Unchanged	46	44
Relief (very much, considerable)	54 (44, 10)	56 (41, 15)

W: Week.

(Table 4).

The impact of global symptoms on daily life was significantly decreased by 35% at V3 (4.6 ± 2.9 *vs* 7.1 ± 2.0, $P < 0.0001$) (Table 3 and Figure 6). A total of 63% and 77% of the patients reported very much/considerable relief after 2 and 4 wk of treatment, respectively (Table 3).

Overall, 93% of the patients had excess flatulence at baseline (Table 1). After 4 wk of treatment, 56% reported very much/considerable symptom relief, with improvements starting from V2 in 54% of the patients (Table 3).

Altered bowel habits and symptoms of defecatory disorder

Among the patients with liquid stools at baseline, approximately 90% had normal stool consistency after 4 wk of treatment, with very much/considerable relief of diarrhea observed in 58% of the patients (Table 5 and Figure 7). For patients with hard stools at baseline, 57% had normal stool consistency at V3, and 46% observed a very much/considerable improvement in constipation (Table 5 and Figure 7).

Among the 26% of patients with defecatory disorders (*e.g.*, straining at the stool and/or sensation of incomplete evacuation), 42% showed very much/considerable improvement starting from the second week of treatment (Table 5 and Figure 7).

Safety and tolerability

No serious adverse events were observed. The most frequent symptoms, which accounted for more than 70% of all adverse events, were abdominal pain ($n = 2$), bloating ($n = 2$), constipation ($n = 5$), diarrhea ($n = 1$), and pruritus ($n = 2$).

Table 4 Symptom relief at week 4 of GASTRAP® DIRECT treatment in patients with IBS having prevalent constipation, diarrhea, and mixed irritable bowel syndrome

Symptom relief at W4	IBS-C (%)	IBS-D (%)	IBS-M (%)
Abdominal pain			
Unchanged	42	27	34
Relief (very much, considerable)	58 (50, 8)	73 (46, 27)	66 (48, 18)
Bloating			
Unchanged	42	32	31
Relief (very much, considerable)	58 (46, 12)	68 (41, 27)	69 (53, 16)
Abdominal distension			
Unchanged	46	50	39
Relief (very much, considerable)	54 (39, 15)	50 (36, 14)	61 (39, 21)

W: Weeks; IBS: Irritable bowel syndrome; IBS-C: IBS patients with prevalent constipation; IBS-D: IBS patients with prevalent diarrhea; IBS-M: IBS patients with mixed symptoms.

Table 5 Relief of altered stool pattern at weeks 2 and 4 of GASTRAP® DIRECT treatment

Symptom relief (% *vs* W0)	W2 (%)	W4 (%)
Constipation		
Unchanged	58	54
Relief (very much, considerable)	42 (27, 15)	46 (37, 9)
Diarrhea		
Unchanged	44	42
Relief (very much, considerable)	46 (42, 14)	58 (39, 19)
Defecatory disorders		
Unchanged	56	58
Relief (very much, considerable)	44 (36, 8)	42 (31, 11)

W: Week.

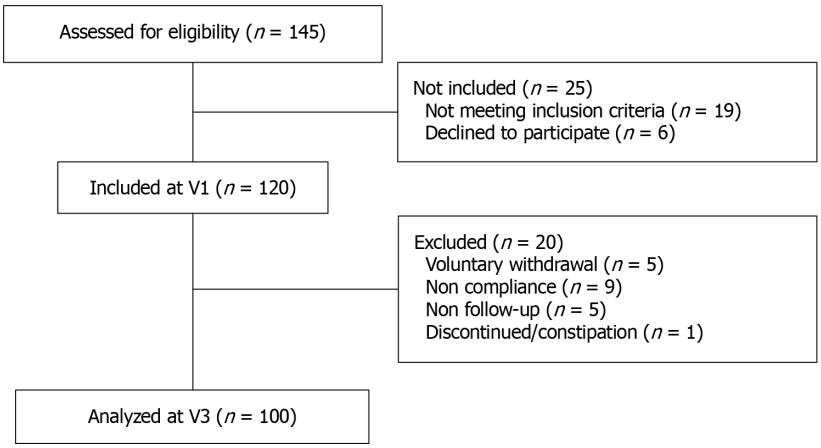

Figure 2 Patient selection flow chart. N: Number; V: Visit.

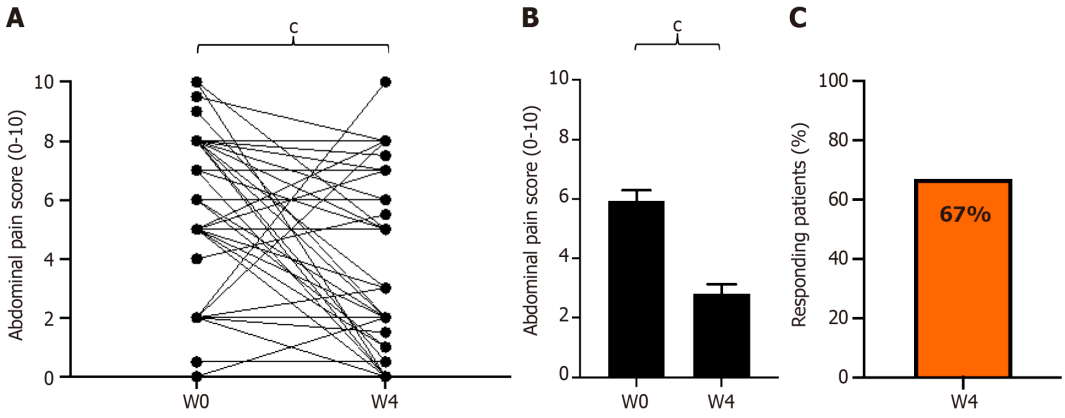

Figure 3 Change in paired abdominal pain scores from baseline to week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3). A: Paired abdominal pain scores; B: Abdominal pain scores (0–10); C: Patient responders (delta > 30%) with respect to abdominal pain. °*P* < 0.001. W: Weeks.

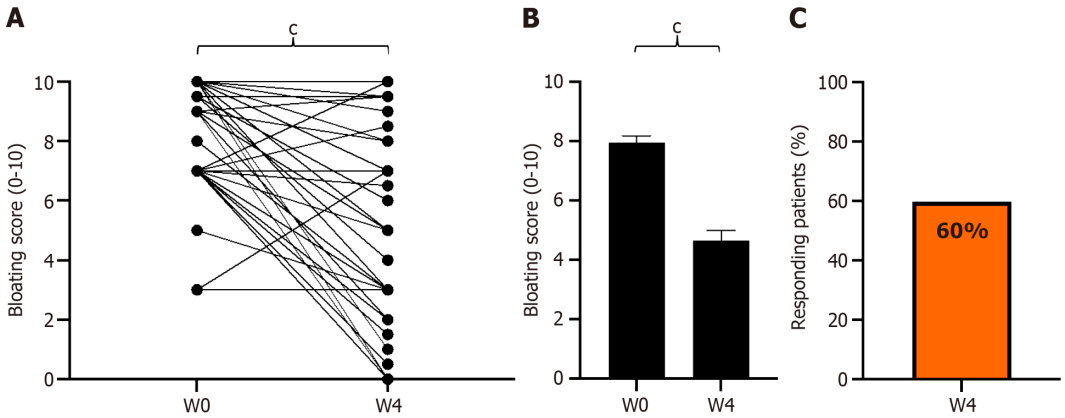

Figure 4 Change in paired bloating scores from baseline to week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3). A: Change in paired bloating scores; B: Abdominal bloating scores (0–10); C: Patient responders (delta > 30%) with respect to bloating. °*P* < 0.001. W: Weeks.

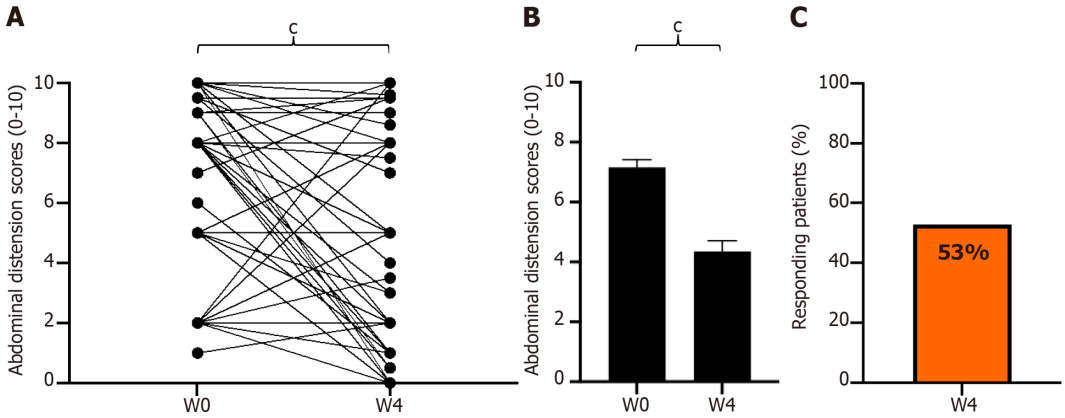

Figure 5 Change in abdominal distension scores from baseline to week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3). A: Change in paired abdominal distension scores; B: Abdominal distension scores (0–10); C: Patient responders (delta > 30%) with respect to abdominal distension. °*P* < 0.001. W: Weeks.

The relationship with the study product was considered "not excluded" for one patient with constipation who discontinued the treatment. Overall, 93% of the patients at V3 considered that the tolerability of GASTRAP® DIRECT was "good" or "very good" (Figure 8).

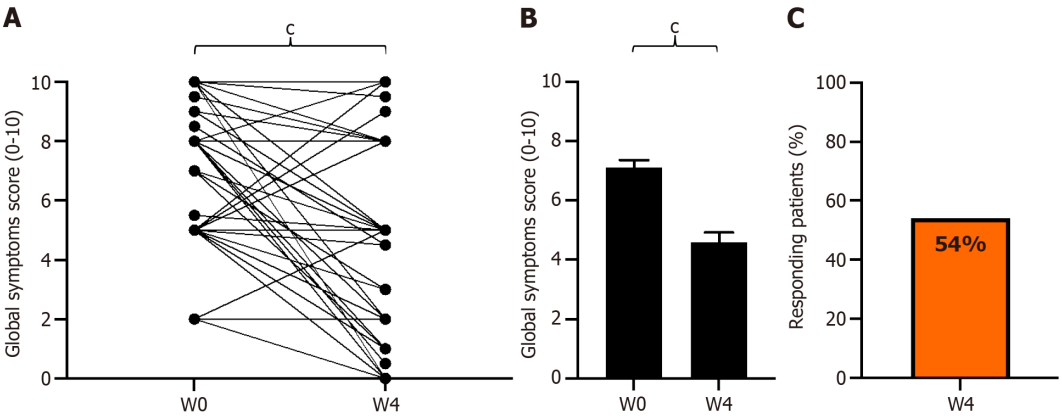

Figure 6 Change in impact of global symptoms on daily life scores from baseline to week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3). A: Paired global symptom scores; B: Global symptom scores (0–10); C: Patient responders (delta > 30%) with respect to global symptoms. $^{c}P < 0.001$. W: Weeks.

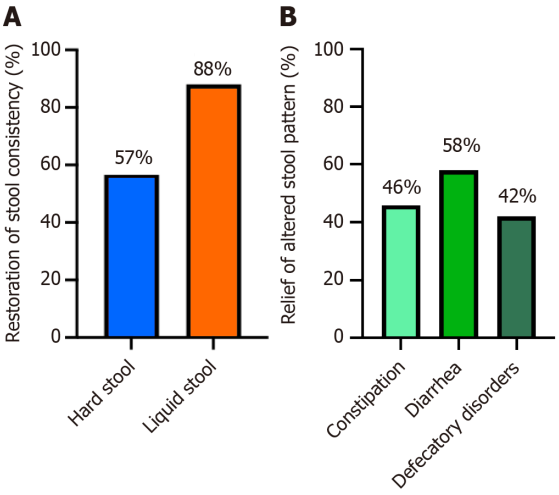

Figure 7 Changes in stool from baseline to week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3). A: Restoration of stool consistency {hard stool [Bristol stool scale (BSS) score 1–2] to normal; liquid stool (BSS 6–7) to normal}; B: Relief of altered stool pattern.

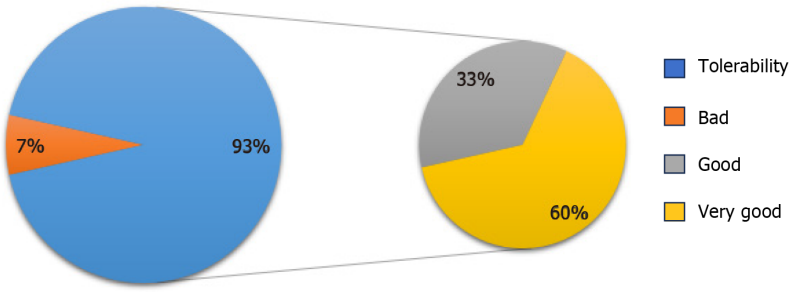

Figure 8 Tolerability of GASTRAP® DIRECT evaluated at week 4.

DISCUSSION

IBS is a heterogeneous disorder with multiple physiopathological mechanisms[27,28]. Exposure to pathogenic organisms, changes in host-microbiota interactions, and disruption of the intestinal barrier can affect the gut–brain axis, triggering locally persistent low inflammation and altering visceral sensitivity[27]. Studies focusing on the basic molecular mechanisms are crucial for improving IBS management and promoting the development of new, specific targeted treatments[27]. In our previous study, we demonstrated that the prebiotic chitin-glucan can rapidly and significantly decrease visceral perception and intestinal inflammation by regulating master genes and binding harmful substances (*e.g.*,

microbial cell walls) in the intestinal lumen[20].

To our best knowledge, the present study is the largest prospective, multicenter open-label trial using chitin-glucan and simethicone in patients with IBS and the first study to be entirely conducted in secondary and tertiary care settings. In a population of IBS patients without benefit from classic first-line therapies, GASTRAP® DIRECT three times a day met the primary outcome with a 50% decreased of abdominal pain score at 1 month compared with baseline resulting in 67% of responders corresponding to patients with a 30% or greater improvement in abdominal pain intensity. GASTRAP® DIRECT also improved the secondary outcomes, showing effectiveness in significantly reducing bloating, abdominal distension, flatulence, and symptoms of defecatory disorders, with an improvement of global symptom-reporting scores considered as important by 77% of patients. No significant adverse events occurred, and 93% of the participants judged the tolerability of the treatment as good or very good.

Our chosen primary outcome of clinically relevant abdominal pain response, defined as ≥ 30% improvement from baseline, follows the Food and Drug Administration (FDA) and European Medicine Agency recommended endpoints[31,32]. Although FDA guidance does not include bloating and abdominal distension as potential exploratory endpoints in clinical trials of IBS, these symptoms are recognized to be troublesome to patients. The 4-week GASTRAP® DIRECT treatment decreased bloating and abdominal distension scores by 40%, with responder rates of 60% and 53% for these symptoms, respectively. Similarly, a comparable improvement in flatulence and the impact of global symptoms on daily life was observed in most patients starting from the second week of treatment. Constipation, diarrhea, and defecatory disorders (*e.g.*, straining of the stool and/or sensation of incomplete evacuation) were also improved. These results are of great clinical interest as they meet the clinically relevance threshold previously proposed[31,32], and they suggest that GASTRAP® DIRECT may be a rapid and effective modality for the management of IBS, regardless of the constipated or diarrheal predominant subtypes.

This study had a number of strengths and some limitations. This prospective, multicenter, observational, open-label study recruited a large number of participants who were objectively diagnosed according to the Rome IV criteria. The patients were recruited from secondary and tertiary care centers, and the population was representative of adults of all ages, with equally represented IBS subtypes. Given that a low baseline symptom score is significantly associated with a higher placebo response rate[33], we included patients with significant abdominal pain (mean VAS pain score: 5.8) and excluded patients with low symptom severity at baseline. Notably, the treatment duration of 4 wk was relatively short, although it is reasonable based on the pharmacology of the compound. Early exploratory studies showed that chitin-glucan is a new-generation prebiotics, which induces rapid antinociception and immediate chelation of harmful microbial products present in the intestinal lumen[20]. Another clinical study aiming to evaluate the efficacy of a 12-wk chitin-glucan treatment for IBS (BK-IBS-2301/NCT number: NCT05780749) is currently ongoing. The placebo effect is an important consideration in clinical trials for IBS treatment, which made it impossible to determine the precise impact of the combination of chitin-glucan and simethicone on IBS symptoms in the present study. The pooled placebo response rate in IBS trials was as high as 37.5%, particularly for clinical studies performed in Europe with a treatment duration of 1–4 wk[34]. Recently, pooled placebo response rates of 34.6% and 40.2% according to the abdominal pain responder definition (≥ 30% improvement) have been reported in patients with IBS-C and IBS-D, respectively[35]. However, the responder rate to abdominal pain was 67% in the current study, exceeding the estimated 35%–40% placebo effect by approximately 30%. In addition, although no formal sample size calculation was performed, using a placebo responder rate of 37.5%, we calculated that a sample size of 100 participants would allow us to show that an observed responder rate of 52% is significantly higher than the reference value (37.5%), considering a power of 80% and a two-sided one-sample proportion test at 0.05 significance level. Thus, the results of this clinical trial are encouraging and could be meaningful in daily practice.

GASTRAP® DIRECT is a class IIa medical with different mechanisms of action involved in its clinical effects as observed in our study. Simethicone is a silicone compound that functions locally as a surfactant and decreases the surface tension of gas bubbles[36]. It acts on the coalescence and dispersion of gas bubbles, facilitating their elimination from the gastrointestinal tract, thus reducing the occurrence and intensity of flatulence and bloating[37]. In contrast, chitin-glucan acts differently, targeting most of the pathophysiological mechanisms associated with IBS. In addition to its prebiotic effect of selectively promoting the growth and activity of beneficial gut bacteria (*e.g.*, *Roseburia spp*. and the *Faecalibacterium prausnitzii*)[18,19], oral administration of chitin-glucan induces visceral analgesic effect, which leads to a rapid and significant inhibition of pain perception. This action is possibly mediated by an increased expression of μ-opioid receptor and cannabinoid receptor 2 on epithelial cells[20]. In mice with colitis, chitin-glucan decreased the intensity of inflammation by 50%, with complete regeneration of the colonic mucosa and restoration of stool consistency through the regulation of major key players driving intestinal inflammation [interleukin (IL)-1, IL-8, and IL-10] and epithelial barrier integrity (mucin-5AC, claudin-2, and zonula occludens-2)[20]. In silico studies have revealed that chitin-glucan exhibits antimicrobial activities by chelating the most active components of Gram-negative and Gram-positive bacteria, as well as the phospholipomannan of yeasts[20].

Rapid action, safety, and tolerability are essential for the development of new IBS therapeutic strategies. The present study observed a significant and rapid improvement of all quantitative and subjective clinical endpoints after 2 wk of GASTRAP® DIRECT administration. GASTRAP® DIRECT showed a high safety profile as evidenced by the absence of serious adverse events and a low number of adverse events. Only one patient developed constipation. The relationship with the study product was considered "not excluded." These data, which should be confirmed in a double-blinded controlled study, may have important implications, particularly for the long-term treatment of IBS with GASTRAP® DIRECT. In addition, the outcomes reflect the results of 10 years of post-market surveillance for this treatment in Europe, with more than 90% of patients reporting that GASTRAP® DIRECT has good or very good tolerability.

CONCLUSION

GASTRAP® DIRECT is a safe and well tolerated non-pharmacological treatment for IBS, providing in this open-label study rapid and significant improvement of cardinal symptoms, including abdominal pain, bloating, flatulence, constipation, diarrhea, and dyschezia, within 2 weeks. Hence, GASTRAP® DIRECT could be a promising natural non-chemotherapeutic solution in the management of patients with IBS. Further double blind randomized controlled study with longer follow-up should be performed in patients with IBS or those with IBS-like symptoms to confirm and extend the use of GASTRAP® DIRECT in patients with intestinal functional disorders.

ACKNOWLEDGMENTS

We thank the Charity European Foundation Digest Science and Catherine Cunisse for their help with study supervision.

FOOTNOTES

Author contributions: Desreumaux P and Valibouze C designed the study; Talbodec N, Le Roy P, Fournier P, Lesage B, Lepoutre E, Castex F, Godchaux JM, Vandeville L, Bismuth B, Lesage X, Bayart P, and Desreumaux P included patients with irritable bowel syndrome; Genin M supervised the statistical analysis; all authors interpreted the data; Valibouze C and Desreumaux P drafted the article; All authors critically reviewed the manuscript and approved the final version for submission. Intestinal Biotech Development supervised study coordination, data collection, and analysis.

Institutional review board statement: This study was approved by the Ethics Committee Sud-Est VI of Clermont-Ferrand (France) (Ref. ID-RCB: 2019-A03202-55) and was performed in accordance with the International Conference on Harmonization of Good Clinical Practice and the ethical principles of the Declaration of Helsinki.

Conflict-of-interest statement: Desreumaux P reports receiving personal fees from Abbvie, Abbott, Amgen, Biocodex, Biofortis, Biogen, Biokuris, Ferring, Fresenius, Janssen, Kitozyme, Lesaffre, MSD, Norgine, Pfizer, Sandoz, Shire, Takeda, Tillotts, and UCB outside the submitted work. Dr. Desreumaux has a patent (WO2009103884) issued. Veronique Maquet is a product development manager at Kitozyme. Salvatore Modica is chief operating officer at Biokuris, a spin-off company of Kitozyme. Christel Rousseaux reports other from Biotech Companies, outside the submitted work. The other authors declare no conflicts of interest.

Country/Territory of origin: France

ORCID number: Nathalie Talbodec 0009-0008-9956-459X; Pauline Le Roy 0009-0002-8141-4880; Peggy Fournier 0009-0002-7986-2588; Benoit Lesage 0009-0009-3746-6940; Elodie Lepoutre 0009-0000-9240-3349; François Castex 0009-0009-5419-3390; Jean Michel Godchaux 0009-0001-9503-6625; Lionel Vandeville 0009-0005-3020-5220; Benjamin Bismuth 0009-0000-6478-2329; Xavier Lesage 0009-0008-2121-6894; Pauline Bayart 0009-0006-3613-0116; Michael Genin 0000-0002-9098-7528; Christel Rousseaux 0009-0003-3618-5895; Veronique Maquet 0009-0009-3714-989X; Salvatore Modica 0009-0001-8386-0975; Pierre Desreumaux 0000-0002-6127-5281; Caroline Valibouze 0000-0002-2198-1392.

S-Editor: Liu JH
L-Editor: A
P-Editor: Wang WB

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