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Alimentary Tract

A randomized clinical trial of *Saccharomyces cerevisiae* versus placebo in the irritable bowel syndrome

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ABSTRACT

Background: We aimed to evaluate clinical symptoms in subjects with irritable bowel syndrome receiving *Saccharomyces cerevisiae* in a randomized double-blind placebo-controlled clinical trial.
Methods: Overall, 179 adults with irritable bowel syndrome (Rome III criteria) were randomized to receive once daily 500 mg of *Saccharomyces cerevisiae*, delivered by one capsule ($n = 86$, F: 84%, age: 42.5 ± 12.5), or placebo ($n = 93$, F: 88%, age: 45.4 ± 14) for 8 weeks followed by a 3-week washout period. After a 2-week run-in period, cardinal symptoms (abdominal pain/discomfort, bloating/distension, bowel movement difficulty) and changes in stool frequency and consistency were recorded daily and assessed each week. A safety assessment was carried out throughout the study.
Results: The proportion of responders, defined by an improvement of abdominal pain/discomfort, was significantly higher ($p = 0.04$) in the treated group than the placebo group (63% vs 47%, OR = 1.88, 95%, CI: 0.99–3.57) in the last 4 weeks of treatment. A non-significant trend of improvement was observed with *Saccharomyces cerevisiae* for the other symptoms. *Saccharomyces cerevisiae* was well tolerated and did not affect stool frequency and consistency.
Conclusion: Saccharomyces cerevisiae is well tolerated and reduces abdominal pain/discomfort scores without stool modification. Thus, *Saccharomyces cerevisiae* may be a new promising candidate for improving abdominal pain in subjects with irritable bowel syndrome.

1. Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder with a worldwide prevalence of 5–15%, accounting for 3% of the visits to general practitioners and about 40% of all gastroenterology outpatient consultations [1]. This high prevalence is associated with annual direct and indirect costs of more than 20 billion USD/year in the USA, corresponding to 3.5 million physician visits annually, and is one of the leading causes of work absenteeism [2,3]. Despite the prevalence and impact of IBS in the community, its pathogenesis remains unclear, and the efficacy of treatments using pharmacological and probiotic approaches is modest, focusing mainly on abdominal pain and bloating, considered as the two dominant and most troublesome symptoms of IBS [4].

IBS pathogenesis is multifactorial and involving at least visceral hypersensitivity, gastrointestinal motor dysfunction, dysregulation of the brain–gut axis, psychosocial, genetic, and environmental factors, as well as low grade intestinal inflammation [5]. The possibility that gut microbiota may have a role in IBS is supported by descriptive culture- and molecular-based studies in patients showing the following characteristics: a temporal instability and a reduction of the diversity of the enteric microbial populations, excessive bacteria in the small bowel, decreased levels of colonic lactobacilli and bifidobacteria, increased numbers of strict and facultative anaerobic organisms, and increased ratios of luminal dominant Firmicutes compared to Bacteroidetes phylas [6]. In addition, evidences of

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metabolic activity alteration of the intestinal flora [7], together with observations that post-acute enteric infection leading to IBS-like syndrome accounts for 25% of the overall IBS population [8], reinforce a potential role for the gut microbiota in some patients with IBS. Based on these data, the benefits of microbiota-directed therapies have been evaluated in IBS using antibiotics, diets containing low fermentable saccharides and polyols, prebiotics, and probiotics [9]. Probiotics are live microorganisms that, when given in sufficient amount, confer a health benefit to the host [10]. Probiotics can be bacteria, virus, parasites, or yeasts. The main clinical feature of IBS is abdominal discomfort and/or abdominal pain. In these IBS patients, a recent systematic review of randomized controlled trials indicates that probiotics, mainly belonging to the genus *Lactobacillus* and/or *Bifidobacterium*, have a trend for being efficacious; however, the magnitude of benefit and the mechanisms of actions of these strains are still unknown [11].

In a previous study, it has been shown that a specific strain of *Lactobacillus acidophilus*, NCFM, was able to decrease the visceral pain perception in rats via induction of the Mu opioid receptor and cannabinoid receptor expression by colonic epithelial cells [12]. More recently, we reported that a new strain of *Saccharomyces cerevisiae*, CNCM I-3856, selected from the Lesaffre baker's yeast strain collection, had analgesic effects in the gut through a local activation of the peroxisome proliferator-activated receptor alpha [12]. In this preclinical study, oral administration of CNCM I-3856 improved pain similarly to the standard dosage of morphine in a model of colorectal distension in rats. This analgesic effect was dose-dependent with a maximal effect at 10^{10} CFU/day, corresponding to the classical active dose of probiotics used in most human clinical trials [11]; the effect appeared 15 days after the beginning of probiotic administration and was transitory, disappearing 3 days after the last CNCM I-3856 administration.

Given this preclinical evidence of the analgesic effect of CNCM I-3856 in the gut, the aim of this study was to investigate whether oral administration of CNCM I-3856 is effective in alleviating IBS symptoms in a randomized double-blind placebo-controlled clinical trial.

2. Materials and methods

2.1. Patients

Patients were recruited in one investigative site at Biofortis, in Nantes, France. Patients included were males and females between 18 and 75 years of age with a diagnosis of IBS according to the Rome III criteria [14] and a pain/discomfort score strictly above 1 and strictly below 6, as determined on a pain/discomfort scale using arbitrary grading from 0 to 7 in the 7 days preceding the inclusion visit (Fig. 1). Subjects had normal blood counts, within reference values, for serum creatinine, urea, alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (γGT), liver transaminases (ALT, ALP), and thyroid-stimulating hormone (TSH), and had C-reactive protein (CRP) levels below twice the upper limit of the normal value of the laboratory. Treatments for diarrhoea, laxatives, and antispasmodic drugs were not exclusion criteria under the condition that they had been started more than 1 month before inclusion without dose modification until the end of the study. Hormone treatment in menopausal women, or contraception in non-menopausal women must have been started at least 3 months beforehand at stable doses and without modification for the entire duration of the study.

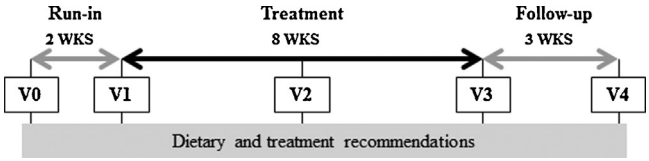

Fig. 1. Study design. A 13-week study including a run-in, treatment and follow-up periods with five medical visits.

Subjects were excluded if they had organic intestinal diseases, underwent treatments likely to influence IBS, in particular by modifying intestinal sensitivity or motility (antidepressants, opioids, and narcotic analgesics), had antibiotic therapy in progress or prescribed in the 8 weeks before inclusion in the study, or had long-term treatment with analgesics or non-steroidal anti-inflammatory drugs. Subjects not willing to stop taking probiotics, prebiotics, or synbiotics in the form of dietary supplements or convenience goods were not eligible. Pregnancy in progress, chronic alcoholism, vegetarian or vegan regimens, eating disorders such as anorexia or bulimia, and documented food allergies were all exclusion criteria.

2.2. Study design

This was a 13-week single-centre double-blind placebo-controlled clinical study randomizing 2 parallel groups of 100 IBS patients. During a 2-week run-in period, scores for abdominal pain/discomfort (defined as an uncomfortable sensation corresponding to a continuum between discomfort and pain), bloating and flatulence, difficulty with defecation, stool frequency, and consistency were recorded (Fig. 1). Dietary recommendations were explained to each patient in particular concerning the consumption of fermented dairy products and certain cheeses. After verification of the inclusion/exclusion criteria, eligible IBS patients were randomized to consume daily, for 8 weeks, either 1 capsule of *S. cerevisiae* CNCM I-3856 (500 mg, 8×10^9 CFU/g) or a placebo (calcium phosphate). A total of five medical visits were regularly scheduled during the 13-week study, including the 3 weeks of follow-up (Fig. 1). The study was conducted in accordance with the Declaration of Helsinki and its protocol was approved by the Ethics Committee of Amiens, France. All subjects provided written informed consent before inclusion in the study.

2.3. Study products and compliance evaluation

The products studied were presented in capsule form and packaged in blister packs of 15. All capsules of active product and placebo were without flavour and had the same size, colour, and vegetal hydroxypropylmethylcellulose composition. They were to be taken orally, one capsule a day, in the morning at breakfast time with a glass of water. The probiotic preparation specifically contained 500 mg per capsule of *S. cerevisiae* CNCM I-3856 (8×10^9 CFU/g). The placebo consisted of a 500 mg dibasic calcium phosphate.

The CNCM I-3856 strain is a proprietary, well-characterized strain of Lesaffre. The *S. cerevisiae* species were characterized by using both phenotypic (API® ID32C, Biomerieux SAS) and genotypic referenced methods (genetic amplification and sequencing of 26S DNA) [15,16]. Moreover, the strain CNCM I-3856 was identified by PCR Interdelta typing technique and complete genome sequencing [17].

Patients had to return all their treatment units, whether consumed or not, to calculate compliance, which was evaluated during the treatment period at visits V2 and V3.

2.4. Assessment of symptoms and study endpoints

The primary endpoint specified in the protocol was the evolution of abdominal pain/discomfort evaluated daily and assessed each week during the 13-week study according to a 7-point Likert

scale [18]. Abdominal pain/discomfort scores were first analyzed using the area under the curve (AUC) in placebo and treatment groups, where the score at week 0 (W0), defined as a baseline value, was added to the model to improve adjustment. A second analysis comparing the percentage of subjects who experienced an improvement in their abdominal pain/discomfort in the last 4 weeks of the treatment period was carried out using the Cochran-Mantel-Haenszel test. Improvement was defined as a reduction in the abdominal pain/discomfort score of 1 arbitrary unit (au) for at least 50% of the time, i.e. for at least 2 weeks out of 4 [19].

Secondary outcome measures were the weekly scores of bloating/distension and bowel movement difficulty, recorded daily in the same condition using the 7-point Likert scales [18]. Changes in stool frequency and consistency were followed daily using the Bristol Stool Scale (ranging from 1, corresponding to separate hard lumps, to 7 for entirely liquid stools) [20].

2.5. Safety variables

Adverse events were recorded by patients and immediately transmitted to the investigator to estimate their severity. Severe and non-severe adverse events were recorded on two different forms. The list of severe adverse events was transmitted to the authorities every six months throughout the study.

2.6. Sample size

On the basis of preclinical data obtained in a model of rectal distension in rats receiving *S. cerevisiae* CNCM I-3856 [13], a reduction of 20% or 25% in the abdominal pain/discomfort score was assumed. With a power of 80% and a significance level of 0.05, the difference between the treatment versus placebo groups would be statistically significant with 106 and 66 patients, respectively. In the present study, inclusion of 100 patients per group was considered realistic.

2.7. Randomization and statistical methods

Randomization and statistical analyses were conducted using SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, USA). Each subject included at the visit (V1) received in a random manner one of the two products (placebo or active). Block randomization was performed by type of subject (with predominant constipation (IBS-C), with predominant diarrhoea (IBS-D), or mixed symptoms (IBS-M)) with dynamic allocation software using the block permutation technique. Product allocation remained blind throughout the study.

The AUCs (W1-W8) of the abdominal pain/discomfort scores, bloating/distension scores, and bowel movement difficulty scores was calculated and analyzed using an ANCOVA model including terms of treatment, type of bowel habit (diarrhoea, constipation, or mixed), treatment/type interaction, and baseline value of the score at W0 as a covariate in the statistical model. Analysis of these scores was performed at each week of the treatment period using the same ANCOVA model. For all score outcomes, intra-group analyses were conducted using the paired Student's *t*-test to compare baseline values to each week of the treatment period.

The number of adverse events and their severity were compared between the treatment and placebo groups (with Fisher's exact test and chi-square test).

The analysis of efficacy was performed on the per-protocol (PP) population as well as on the Intention-To-Treat (ITT) population. This study presents the PP and ITT analysis results taking into account the included subjects finishing the study without any major protocol violation.

3. Results

3.1. Patients

Baseline characteristics of the patients in the placebo and treatment groups showed no significant differences (Table 1). The flow of subjects through the protocol is presented in Fig. 2. From the 262 screened subjects, 200 were randomized and equally distributed between the placebo ($n = 100$) and treatment ($n = 100$) groups. Six subjects were rapidly excluded (1 with systemic disease, 5 voluntary withdrawals) and 15 discontinued the intervention (antibiotic treatment ($n = 12$), bladder tumour ($n = 1$), antidepressant treatment ($n = 1$), colorectal cancer ($n = 1$) leaving 86 and 93 subjects assigned to the treatment and placebo groups, respectively, and giving an ITT population of 179. A majority of patients (46.9%) were IBS-C subjects (46.2% and 47.7% in the placebo and product groups, respectively). Good compliances were recorded in both the probiotic and placebo groups for the first and the second month of administration (respectively for V2 + V3 99% ± 2.7 and 99% ± 3.2: Table 1).

3.2. Primary outcome measures

Abdominal pain/discomfort scores, expressed in au on a scale from 0 (no symptoms) to 7 (severe symptoms), showed homogeneity at baseline for both the placebo (3.16 ± 1.1) and product (3.22 ± 1.12) groups ($p = 0.76$). Intragroup analysis revealed a significant reduction of the score both in the probiotic and placebo groups throughout the 8 weeks of treatment period (W0–8); this led to a mean score reduction of 26.9% and 37.2% compared with baseline, respectively in the placebo and product group ($p < 0.001$ in both treated groups; Fig. 3, Table 2). This intergroup difference for abdominal pain/discomfort AUC during the 8 weeks of treatment was not significant ($p = 0.13$). The reduction of abdominal pain/discomfort scores was higher during the first month than the second month of placebo administration (2.42 ± 1.5 vs 0.11 ± 1.49). During the period of follow-up without product administration (W8–11), the abdominal pain/discomfort score did not vary significantly in the placebo group ($p = 0.89$) but continued to decrease (−0.02 ± 0.07). In contrast, this score showed a significant increase between W8 and W11 in the product group (+0.31 ± 0.02, $p = 0.012$: Fig. 3, Table 2). The effect of the product on abdominal pain/discomfort scores was similar whatever the type of subjects (IBS-C, IBS-D, or IBS-M) and in the ITT population, with

Table 1
Baseline characteristics of the 179 subjects: comparison between groups.

	Placebo group *n* (%)	Product group *n* (%)	*P* value
n	93	86	
Female	82 (88%)	72 (84%)	0.51
Age	45.4 ± 14	42.5 ± 12.5	0.85
Smoker	18 (20%)	26 (30%)	0.12
IBS-C	43 (46%)	41 (48%)	0.88
IBS-D	27 (29%)	24 (28%)	0.88
IBS-M	23 (25%)	21 (24%)	1
Pain/discomfort[a,b]	3.16 ± 1.1	3.22 ± 1.12	0.76
Bloating score[a,b]	3.26 ± 1.31	3.46 ± 1.23	0.39
Bowel movement difficulty[a,b]	2.56 ± 1.6	2.61 ± 1.72	0.94
Stool frequency[a,c]	1.2 ± 0.65	1.21 ± 0.67	0.78
Stool consistency[a,c]	3.39 ± 1.19	3.52 ± 1.24	0.24
Compliance[a]	99± 2.7%	99± 3.2%	>0.9

IBS-C, constipation predominant IBS; IBS-D, diarrhoea predominant IBS; IBS-M, mixed IBS.

[a] Mean ± SD.

[b] Assessed with a 7-point Likert scale.

[c] assessed using the Bristol Stool scale.

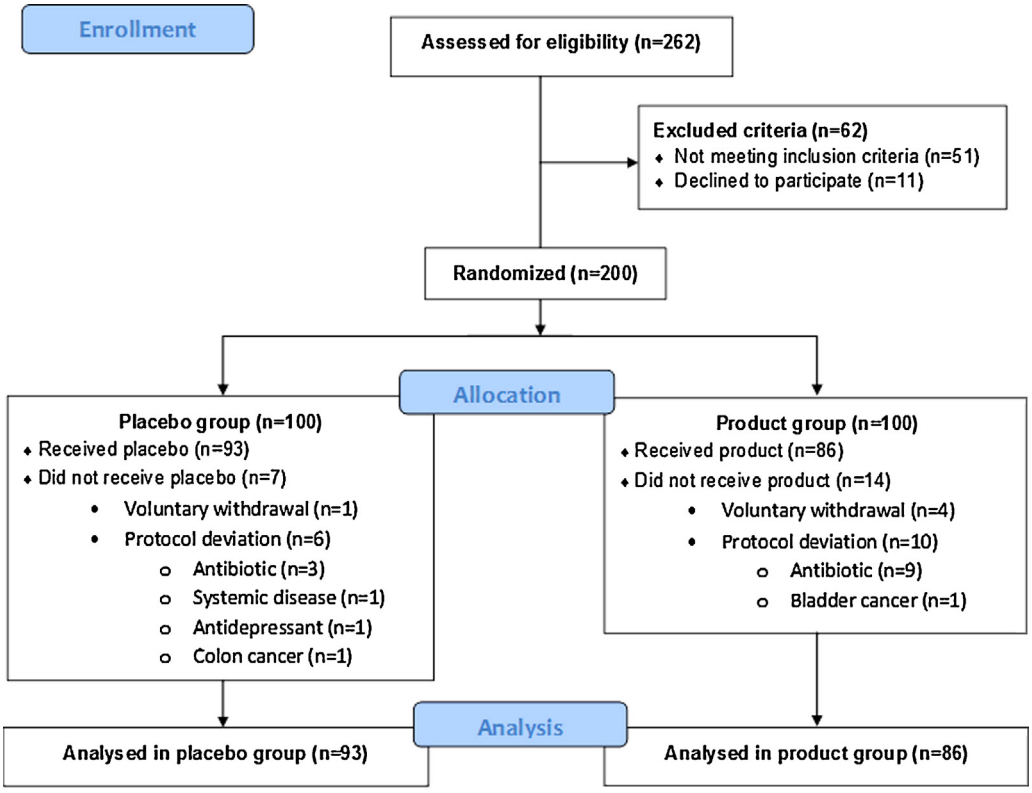

Fig. 2. Flowchart of the patients through the study.

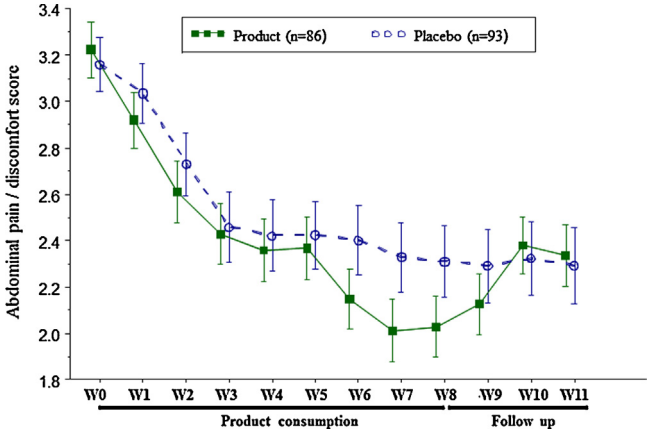

Fig. 3. Evolution of abdominal pain/discomfort scores (7-point Likert scale, mean ± SEM) in placebo and product groups through the study.

regard to the non-significant treatment/type interaction in the statistical models (data not shown).

Analysis of improvement in abdominal pain/discomfort demonstrated a significantly higher percentage of subjects experiencing improvement in the product group than the placebo group during the second month of *S. cerevisiae* administration (respectively 62.8% vs 47.3%, $p = 0.04$).

3.3. Secondary outcome measures

Scores evaluating bloating/distension, bowel movement difficulty, stool frequency, and stool consistency showed homogeneity at baseline for both the placebo and product groups (Table 1). Intragroup analysis revealed a significant reduction of bloating/distension and bowel movement difficulty scores compared with baseline both in the product and placebo groups throughout the 8-week treatment period (W0–W8) ($p < 0.001$ in both treated groups), but without intergroup differences. Stool frequency and stool consistency scores remained similar during the 8 weeks of treatment without intragroup and intergroup differences. The

Table 2
Evolution of abdominal pain/discomfort scores (7-point Likert Scale) during the study in placebo and product groups.

	Placebo group >Mean ± SD	*P* value intragroup	Product groupMean ± SD	*P* value intragroup	*P* value intergroup
Week 0	3.16 ± 1.1		3.22 ± 1.12		0.76
Week 8	2.31 ± 1.49		2.03 ± 1.122		0.13
Week 11	2.29 ± 1.56		2.34 ± 1.24		0.98
Change between baseline versus end of treatment period	−0.85 ± 1.44 (−27%)	<0.0001	−1.2 ± 1.31 (−37%)	<0.0001	0.09
Change between end of treatment period versus follow up period	−0.02 ± 0.07	0.89	+0.31 ± 0.02	0.012	0.98

SD, standard deviation.

effect of the product was similar whatever the type of subjects (IBS-C, IBS-D, or IBS-M) and in the ITT population, with regard to the non-significant treatment/type interaction in the statistical models (data not shown).

3.4. Adverse events

No significant adverse event was recorded during the study in either the placebo or product group. The frequency of subjects with at least one adverse event was similar in the two groups throughout the study (50.35% vs 49.65%, $p = 0.88$). Sixty-five adverse events considered to have a potential connection with the study were reported. The most frequent symptoms, representing more than 70% of these adverse events, were abdominal pain/bloating ($n = 15$), diarrhoea ($n = 14$), constipation ($n = 13$), and headache ($n = 6$). Their frequencies were similar in the placebo ($n = 31$) and product ($n = 34$) groups ($p = 0.94$).

Two subjects reported a serious adverse event: a bladder neoplasm in the product group and a colorectal cancer in the placebo group. Fourteen significant adverse events were recorded in the placebo ($n = 9$) and product ($n = 5$) groups: abdominal pain/bloating ($n = 5$), dorsal pain ($n = 2$), gastroesophageal reflux ($n = 2$), diarrhoea ($n = 1$), headache ($n = 1$), urinary infection ($n = 1$), flu-like syndrome ($n = 1$), and haemorrhoidal crisis ($n = 1$). There was no difference in severity between the events in the active product group and the placebo group ($p = 0.28$). Finally, no change in blood parameters was detected throughout the study in the placebo and product groups.

4. Discussion

The present randomized double-blind placebo-controlled study demonstrates, in a French population, that *S. cerevisiae* CNCM I-3856 is a safe yeast strain able to relieve abdominal pain/discomfort in IBS patients fulfilling the Rome III criteria. This 13-week clinical trial was performed according to the recommended designs of treatment trials for functional gastrointestinal disorders [4], in order to demonstrate statistical superiority of a treatment with *S. cerevisiae* for the most invalidating symptom characterizing IBS patients.

This is the first clinical trial reporting a statistical efficacy of yeast treatment on abdominal pain/discomfort in IBS patients. Abdominal pain/discomfort was chosen as the primary end point since the selected strain of *S. cerevisiae* CNCM I-3856 was able to induce a strong visceral analgesic effect allowing a 50% increased colorectal distension threshold in treated versus untreated rats [13]. Based on these data, and expecting a 20% therapeutic gain over placebo for the score assessing abdominal pain/discomfort, 200 IBS patients were randomized and treated for 8 weeks with either *S. cerevisiae* CNCM I-3856 at a daily dose of 500 mg, or placebo. The 2-week prospective baseline observation period ensured that patients were currently symptomatic, with a comparable moderate abdominal pain score of 3.2 on the seven-point Likert scale, in both the active and placebo groups [20]. Even if the optimal dose remains to be clearly established, the daily intake of 500 mg corresponding to 8×10^9 CFU of *S. cerevisiae* CNCM I-3856 was chosen. This choice was based both on the known classical range of active probiotic concentrations used in human clinical trials [11] and on preclinical studies performed in rats showing that escalating doses of this strain of yeast gave a linear analgesic dose-dependent effect beginning at 10^5 CFU/d and reaching a plateau at 10^9 CFU/d [13].

After 4 weeks of treatment, the improvement of abdominal pain/discomfort, defined by a reduction in the abdominal pain/discomfort score of 1 for at least 50% of the time, was significantly higher in patients receiving *S. cerevisiae* CNCM I-3856 than in the placebo group. This decrease in score activity in the active group represented a mean 37.5% reduction in the initial visual analogue Likert scale rating of abdominal pain severity. During the first month of treatment, changes in the intensity of abdominal pain/discomfort were similar in the groups of patients receiving the treatment or the placebo, suggesting a potential delayed action of *S. cerevisiae* to induce analgesia. This hypothesis is consistent with previous findings obtained in rodents where the analgesic effect of *S. cerevisiae* CNCM I-3856 appeared two weeks after the beginning of treatment [13]. This delayed action of *S. cerevisiae* may explain, at least in part, why the difference for the weekly scores evaluating abdominal pain/discomfort during the 8-week period of treatment was in favour of *S. cerevisiae* CNCM I-3856 therapy but without significant intergroup differences. The present clinical trial included a 3-week follow-up to determine treatment durability [19]. The different profiles of abdominal pain/discomfort scores in the placebo and product groups during this period showed a significant increase of abdominal pain only in the product group at one week after the last administration of *S. cerevisiae* CNCM I-3856. These data suggest that, similarly to our preclinical study performed in rats [13], the analgesic effect induced by oral administration of *S. cerevisiae* CNCM I-3856 in IBS patients is transitory and limited to the time of product administration.

Evidence from the review literature outlines that a significant proportion of IBS patients receiving a placebo respond to therapy [21,22]. The magnitude of this placebo response rate in randomized clinical trials conducted in Europe may vary from 0% to 91.7%, with a mean value of 43% [21]. In our study, the improvement of abdominal pain in 47% of IBS subjects receiving a placebo is consistent with the placebo response rate observed in most European single-centre trials [21,23]. Nevertheless, the statistically significant reduction in the abdominal pain/discomfort score of 1 au for at least 50% of the time in 63% versus 47% of subjects receiving the product versus placebo raises the question of the clinical benefit in IBS patients derived from taking *S. cerevisiae* CNCM I-3856. There is no consensus defining what would constitute a clinically meaningful improvement for IBS patients [11]. Some studies accept a 10% reduction in a visual analogue scale rating of symptom severity [24] or a 1-point reduction on a 7-step ordinal scale [25]. In the present clinical trial, the decrease of 1.2 points on the 7-point Likert scale measuring abdominal pain, and the 63% improvement of abdominal pain for at least 50% of the time in subjects receiving the product, suggest that this improvement could be clinically relevant with a therapeutic benefit from taking *S. cerevisiae* CNCM I-3856 versus placebo.

Probiotics are living bacteria, viruses, parasites, or yeasts having demonstrated functional or health benefits for the consumer. Probiotic administration is considered as a promising, safe, and acceptable strategy in IBS [11]. Most studies evaluating the effects of probiotics in IBS patients have been performed with bacterial strains of lactobacilli and/or bifidobacteria [11]. Despite the numerous advantages offered by yeast compared to bacteria, including antibiotic and phage resistances, as well as higher natural robustness against gastric acid and bile salts, and stronger capacity to regulate the innate immune response [26], only two clinical trials assessed the effect of yeast in patients with IBS [27,28]. These two randomized double-blind placebo-controlled clinical trials showed no superiority of *Saccharomyces boulardii*, given daily at 500 mg during 1 month, compared to placebo for individual symptoms and, particularly, abdominal pain/discomfort in patients with IBS-D and/or IBS-M. Given the significant differences in the enrolled populations in our study, i.e. mainly IBS-C rather than IBS-D patients, and the longer duration of treatment (2 vs 1 month), the comparison between these previously published studies and our present clinical trial remains difficult. The different biochemical characteristics and the genomic and functional properties, particularly regarding their ability to activate the peroxisome

proliferator-activated receptor alpha versus gamma [13,15,29], between *S. cerevisiae* and *boulardii* may also explain the different activity of these yeasts on the regulation of abdominal pain.

In conclusion, *S. cerevisiae* CNCM I-3856 at 500 mg/day, conveniently delivered once daily by one capsule, is well tolerated and reduces abdominal pain/discomfort scores without altering stool frequency and consistency. Further clinical studies are warranted to confirm that *S. cerevisiae* could be a new promising candidate to improve abdominal pain/digestive discomfort in subjects with IBS.

Conflict of interest

Guillaume Pineton de Chambrun and Amélie Chau have no conflict of interest. Christel Neut has received a research grant from Lesaffre International. Murielle Cazaubiel has received consulting fees from Lesaffre. Fanny Pelerin and Peter Justen are employees of Lesaffre International. Pierre Desreumaux has received consulting fees, paid advisory boards and research grants from Lesaffre International.

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