META-ANALYSIS

Saccharomyces cerevisiae CNCM I-3856 in irritable bowel syndrome: An individual subject meta-analysis

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Author contributions: All authors have made substantial contributions to conception and design of the study, acquisition of data, analysis and interpretation of data; Cayzeele-Decherf A, Leuillet S and Housez B have drafted the article and other authors have made critical revisions related to important intellectual content of the manuscript; All authors have been involved for final approval of the version of the article to be published.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

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Abstract

AIM

To confirm previous conclusions on *Saccharomyces cerevisiae* (*S. cerevisiae*) CNCM I-3856 for irritable bowel syndrome (IBS) management.

METHODS

An individual patient data meta-analysis was performed on two randomized clinical trials studying the effect of *S. cerevisiae* CNCM I-3856 supplementation on gastrointestinal (GI) symptoms in IBS subjects. A total of 579 IBS subjects were included. Outcomes were the daily Likert scale scores of abdominal pain/discomfort and bloating [area under the curve (AUC) and weekly means], responder status, and bowel movements (stool frequency and consistency). Statistical analyses were conducted in Intent to Treat (ITT) population, IBS-C subjects and IBS-C subjects with an abdominal pain/discomfort score higher than or equal to 2 at baseline ("IBS-C ⩾ 2 subpopulation").

RESULTS

S. cerevisiae CNCM I-3856 significantly improved abdominal pain/discomfort and bloating during the second month of supplementation [AUC (W5-W8)]

with improvement up to the minimal clinically relevant threshold of 10%: a 12.3% reduction of abdominal pain/discomfort in the ITT population compared to the Placebo group (P = 0.0134) has been observed. In the IBS-C $\geqslant$ 2 subpopulation, there were a 13.1% reduction of abdominal pain/discomfort and a 14.9% reduction of bloating compared to the Placebo group (P = 0.0194 and P = 0.0145, respectively). GI symptoms significantly decreased during supplementation but no statistical differences were reported between groups at the end of the supplementation period. Responder status was defined as a subject who experienced a decrease of 1 arbitrary unit (a.u.) or 50% of the abdominal discomfort score from baseline for at least 2 wk out of the last 4 wk of the study. A significant difference between groups was reported in the ITT population, when considering the first definition: subjects in the Active group had 1.510 higher odds to be a responder (reduction of 1 a.u. of abdominal pain/discomfort) compared with subjects in the Placebo group (P = 0.0240). At the end of supplementation period, stool consistency in the Active group of the ITT population was significantly improved and classified as "normal" compared to Placebo (respectively 3.13 ± 1.197 a.u. *vs* 2.58 ± 1.020 a.u., P = 0.0003). Similar results were seen in the IBS-C $\geqslant$ 2 subpopulation (Active group: 3.14 ± 1.219 a.u. *vs* Placebo group: 2.59 ± 1.017 a.u., P = 0.0009).

CONCLUSION
This meta-analysis supports previous data linking *S. cerevisiae* I-3856 and improvement of GI symptoms, in IBS overall population and in the IBS-C and IBS-C $\geqslant$ 2 subpopulations.

Key words: Irritable bowel syndrome; *Saccharomyces cerevisiae*; Constipation; Abdominal pain; Probiotics

Core tip: Since the gut microbiota is considered to play a role in the pathophysiology of Irritable Bowel Syndrome, the use of probiotics has gained interest for the management of gastrointestinal symptoms of irritable bowel syndrome (IBS). However, the properties of probiotics are strain-dependent. We performed an individual patient data meta-analysis to assess the effectiveness of *Saccharomyces cerevisiae* CNCM I-3856 on the management of IBS symptoms.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder with high prevalence, affecting up to 20% of the population in some geographical areas[1]. Diverse GI symptoms occur in IBS, mainly abdominal pain, bloating and altered bowel habits. Subjects also report some extra-GI symptoms and an impaired quality of life[2]. According to Rome Ⅲ criteria, IBS diagnosis is based on the presence of abdominal pain and/or discomfort, associated with at least two of the following: improvement with defecation, onset associated with a change in frequency of stool, onset associated with a change in form of stool[3]. The diagnosis is confirmed by the absence of any organic disorder. Some IBS subtypes are distinguished depending on the predominant stool pattern: constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), mixed IBS (IBS-M) alternating constipation and diarrhea, and an un-subtyped IBS. To date, the pathogenesis of IBS is still not clear. Different mechanisms may be implicated, such as altered GI motility, visceral hypersensitivity, intestinal barrier disorder, dysfunction of the brain-gut axis, intestinal inflammation and disruption of the intestinal flora[2,4]. When investigating IBS, the gut microbiota is of great interest. First, some IBS cases begin after an acute episode of a GI infection, which can alter the gut microbiota's diversity[5,6]. Secondly, the intestinal microbiota is thought to be involved in most of the mechanisms of IBS[7]. Due to a lack of satisfactory pharmacological treatments suitable for long-term administration[8], both patients and caregivers turn to alternative methods for the management of IBS. In such an approach, probiotics prove to be an interesting and promising option. Their supplementation may help to counterbalance mechanisms involved in IBS[5,9] and to alleviate associated symptoms. Today the challenge is to identify which probiotic strains are relevant for IBS management and the conditions for their use (preparations, doses, duration).

Saccharomyces cerevisiae (*S. cerevisiae*) CNCM I-3856, a proprietary yeast strain from Lesaffre, has been studied for its beneficial properties in alleviating GI symptoms in IBS subjects. Two randomized clinical trials (RCTs) have been conducted and published[10,11] involving a total of 579 IBS subjects. We decided to perform an individual patient data (IPD) meta-analysis to confirm the previous findings and strengthen conclusions on this particular yeast strain.

MATERIALS AND METHODS

Design and study selection
Methods for statistical analyses were pre-specified in a Statistical Analysis Plan. We evaluated manuscripts that studied the effect of *S. cerevisiae* CNCM I-3856 supplementation on GI symptoms in IBS subjects.

Only the two aforementioned clinical trials were identified and included in this meta-analysis.

Study product

The I-3856 strain of *Sacharomyces cerevisiae* is a proprietary, well-characterized strain of Lesaffre, registered in the French National Collection of Cultures of Microorganisms (CNCM). The *S. cerevisiae* species has been characterized by using phenotypic (API® ID32C, Biomerieux SAS) and genotypic referenced methods (genetic amplification and sequencing of 26S DNA)[12,13]. Moreover, the strain I-3856 is identified thanks to the Polymerase Chain Reaction (PCR) Interdelta typing technique[14], and other genetic methods (*e.g.*, complete genome sequencing).

Data collection

All data were provided by the sponsor of the trials. Uniform collection methods were employed in the two trials.

Definition of outcomes

Outcomes were defined as the daily Likert scale scores of abdominal pain/discomfort and bloating (calculated on a weekly basis) over the common study period of both studies (8 wk) and also expressed as total Area Under the Curve (AUC) [total AUC (W0-W8) and total AUC (W5-W8)]. According to the abdominal score at baseline, responder status was considered. A subject was defined as responder if he/she experienced a decrease of 1 arbitrary unit (a.u.) or 50% of the abdominal discomfort score from baseline for at least 2 wk out of the last 4 wk of the study. Bowel movements, *i.e.*, stool frequency and consistency, were also studied.

Statistical analysis

Statistical analyses were conducted, in first instance, on the Intent to Treat (ITT) population. Two subpopulations of interest where then derived from this population: IBS-C subjects (IBS subjects with hard or lumpy stools $\geq$ 25% and loose (mushy) or watery stools < 25% of bowel movements[3]) and IBS-C subjects with an abdominal pain/discomfort score higher than or equal to 2 at baseline (referred as "IBS-C $\geq$ 2 subpopulation" in this paper). In both RCTs of this meta-analysis, subjects were included if they reported a score of abdominal pain/discomfort ranging between 1 and 6 (on a 7-point Likert scale) at baseline. Nevertheless, only subjects presenting a score $\geq$ 2 and < 6 at baseline have been considered in the IBS-C $\geq$ 2 subpopulation. IBS typology can vary a lot from one individual to another, inducing great variability in symptoms scores intensity. The supplementation with *S. cerevisiae* CNCM I-3856 aims to be administered to healthy subjects with a medium level of abdominal pain/discomfort. IBS patients who need a follow-up at hospital because of high-level of pain ($\geq$ 6) are out of the scope of the present supplementation. Inversely, subjects with low level of symptoms intensity (strictly below 2) can't be considered as being improvable. In the ITT population, outcomes throughout the study period were analyzed using a fixed-effect repeated measure model including the factors Product, Week, IBS Type, Study and interactions Product*Week, Product*Study and Product*Week*Study[15,16]. An Analysis of Covariance (ANCOVA), including factors Product, IBS Type, Study, Product*Study and the baseline value as a covariate, was conducted to analyze total AUCs. Finally, a Generalized Linear Model (GLM, binomial distribution) including factors Product, Study, IBS Type and interaction Product*Study was conducted to assess the responder status. In the subpopulations, the same statistical models, without the IBS Type effect, were run. Statistical analyses were performed using SAS® software version 9.3 (SAS Institute Inc., Cary, NC, United States).

RESULTS

The two clinical trials were published in 2015 and 2016 in two different peer-reviewed journals. Characteristics of the trials are shown in Table 1.

Subjects

Data were obtained from 579 subjects, diagnosed with IBS according to Rome Ⅲ criteria[3]. All IBS subtypes were represented in the two trials. Patient characteristics for the 2 trials are listed in Table 2. There are no significant differences at baseline between the Placebo and Active groups on the total population, nor on the IBS-C subpopulation and the IBS-C $\geq$ 2 subpopulation.

Gastrointestinal symptoms - Total area under the curve

Any change in GI symptoms throughout the supplementation period was analyzed using AUC. Data are presented in Figure 1 (abdominal pain/discomfort) and Figure 2 (bloating).

Over the 2 mo of supplementation, no differences were determined by AUC (W0-W8) analysis of abdominal pain/discomfort and bloating between Active and Placebo groups of the ITT population and the IBS-C subpopulation.

A significant difference between the Active and Placebo groups was observed in the IBS-C $\geq$ 2 subpopulation on abdominal pain/discomfort (P = 0.0417, diff[95%CI] = -2.096 [-4.112;-0.080]) for AUC (W0-W8); and a trend was reported on bloating (P = 0.0540) in favor of the Active group.

Considering the second month of supplementation [AUC (W5-W8)], *S. cerevisiae* CNCM I-3856 improved GI symptoms in all analyzed populations. Abdominal pain/discomfort was significantly reduced in the Active group compared to the Placebo group in

Table 1 Characteristics of the trials

Trial	Type of IBS	Criteria	Sample size	Probiotic	Probiotic dosage[1]	Control	Duration of treatment	Follow-up
Pineton de Chambrun *et al*[10] 2015	All types	Rome Ⅲ	200	*Saccharomyces cerevisiae* CNCM I-3856	1 capsule (500 mg) of *S. cerevisiae*/d 8 × 10⁹ CFU/g	Placebo	8 wk	3 wk
Spiller *et al*[11] 2015	All types	Rome Ⅲ	379	*Saccharomyces cerevisiae* CNCM I-3856	2 capsules of 500 mg of *S. cerevisiae*/d 8 × 10⁹ CFU/g	Placebo	12 wk	-

[1]The capsules contained viable yeast cells only, no excipient has been added. Probiotic products should contain the adequate amount of living cells to be efficient. Then, it is needed to maintain a suitable level of viable cells during the product's shelf life. This living yeast cells count is expressed most of time as a minimum of colony forming unit per gram. This count of the yeast strain CNCM I-3856 cells after manufacturing was around 8×10^9 CFU/g. It could slightly vary within the specification limits at release depending on the batch even if the manufacturing process and the microbiological methods are validated. This variation is due to the type of products (microbiological products obtained by fermentation) and due to the method variability of viable cell counts ($\pm$ 0.5 log). Moreover, it has to be considered that viable cell count slightly decreases with time (sensitivity to humidity and temperature), which has already been confirmed by a stability test program performed according international conference on harmonisation guidelines. That is why, an overdose is commonly adopted for probiotics. Based on these considerations, efficacy of probiotics is considered by the scientific community as similar when dosage remains within the same log. CFU: Colony forming unit; IBS: Irritable bowel syndrome.

Table 2 Patient characteristics for the 2 trials *n* (%)

	Placebo group	Active group
Subjects, *n*	287	292
Age (yr), mean ± SD	45.3 ± 14.03	44.4 ± 14.79
Subject weight (kg), mean ± SD	64.6 ± 12.37	65.8 ± 13.75
Subject height (cm), mean ± SD	164.3 ± 7.75	164.9 ± 8.19
Subject BMI (kg/m²), mean ± SD	23.9 ± 3.93	24.1 ± 4.53
Heart rate (bpm), mean ± SD	70.2 ± 9.10	70.6 ± 9.08
Female	244 (85.0)	245 (83.9)
Smoker	65 (22.6)	75 (25.7)
IBS-C	134 (46.7)	130 (44.5)
IBS-C with an abdominal pain/discomfort score ⩾ 2 at baseline	111 (38.7)	111 (38.0)
IBS-D	55 (19.2)	56 (19.2)
IBS-M	96 (33.4)	103 (35.3)

BMI: Body mass index; IBS: Irritable bowel syndrome.

the ITT population (-12.3%, P = 0.0134, diff[95%CI] = -0.728 [-1.305;-0.152]) and in the IBS-C ⩾ 2 subpopulation (-13.1%, P = 0.0194, diff[95%CI] = -1.144 [-2.100;-0.187]). A trend was reported in the IBS-C subpopulation (-10.4%, P = 0.0544). Bloating was significantly decreased during the second month of supplementation in the ITT population (-9.2%, P = 0.0105, diff[95%CI] = -0.743 [-1.311;-0.175]); in the IBS-C population (-12.3%, P = 0.0463, diff[95%CI] = -0.864 [-1.714;-0.014]); and in the IBS-C ⩾ 2 subpopulation (-14.9%, P = 0.0145, diff[95%CI] = -1.192 [-2.143;-0.240]).

Gastrointestinal symptoms - Scores over the study period

In a complementary approach, daily Likert scale scores of abdominal pain/discomfort and bloating were analyzed on a weekly basis. At baseline, in the ITT population, the two groups were not different regarding the abdominal pain/discomfort scores (3.15 ± 1.163 a.u. in the Active group *vs* 3.16 ± 1.110 a.u. in the Placebo group, P = 0.9714). Abdominal pain/discomfort was significantly reduced throughout the study in the two study groups (between W0 and W8, P < 0.0001 in both groups). At W8, lower abdominal pain/discomfort scores were reported in the Active group compared to Placebo but the difference did not achieve statistical significance (Active group: 2.14 ± 1.292 a.u., Placebo group: 2.31 ± 1.355 a.u., P = 0.1052). In the IBS-C subpopulation, abdominal pain/discomfort significantly decreased between W0 and W8 in both groups (Active group: 3.25 ± 1.177 a.u *vs* 2.23 ± 1.231 a.u.; Placebo group: 3.22 ± 1.159 a.u. *vs* 2.40 ± 1.420 a.u., P < 0.0001 in both groups). Similar evolution was observed for bloating over the supplementation period (Active group: 3.31 ± 1.272 a.u. at W0 *vs* 2.25 ± 1.257 a.u. at W8; Placebo group: 3.36 ± 1.179 a.u. at W0 *vs* 2.54 ± 1.390 a.u. at W8, P < 0.0001 in both groups).

In the IBS-C ⩾ 2 subpopulation, slightly higher abdominal pain/discomfort was expressed at baseline (3.54 ± 1.005 a.u. in the Active group; 3.54 ± 0.918 a.u. in the Placebo group) as compared to the IBS-C subpopulation. Abdominal pain/discomfort scores significantly decreased from W0 to W8 in both groups

A

B
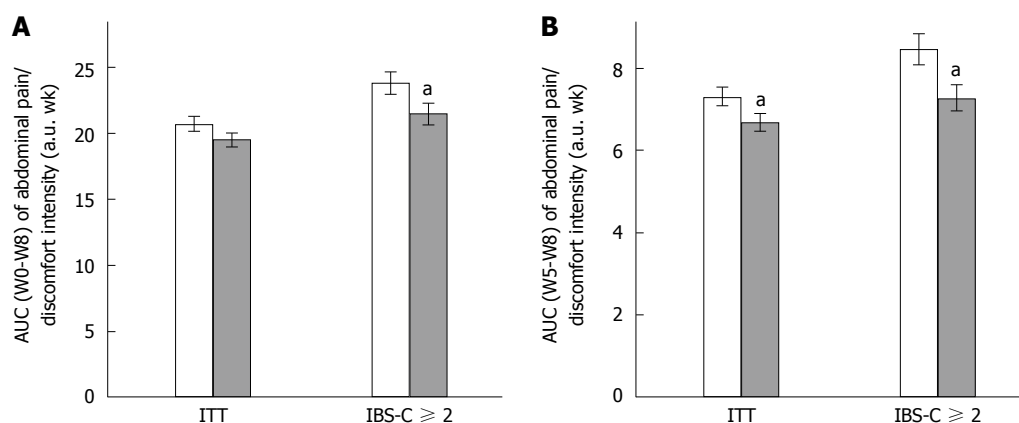
Figure 1 Area under the curve (W0-W8) (A) and area under the curve (W5-W8) (B) of abdominal pain/discomfort in intent to treat population (all irritable bowel syndrome subtypes) and in irritable bowel syndrome-C subjects with an abdominal pain/discomfort score higher than or equal to 2 at baseline (irritable bowel syndrome-C ≥ 2) under placebo (white) or *Saccharomyces cerevisiae* CNCM I-3856 (grey) supplementation. Significant differences compared to placebo are symbolized by [a]*P* < 0.05. IBS-C: Irritable bowel syndrome-C; a.u.: Arbitrary unit; ITT: Intent to treat; AUC: Area under the curve.

A

B
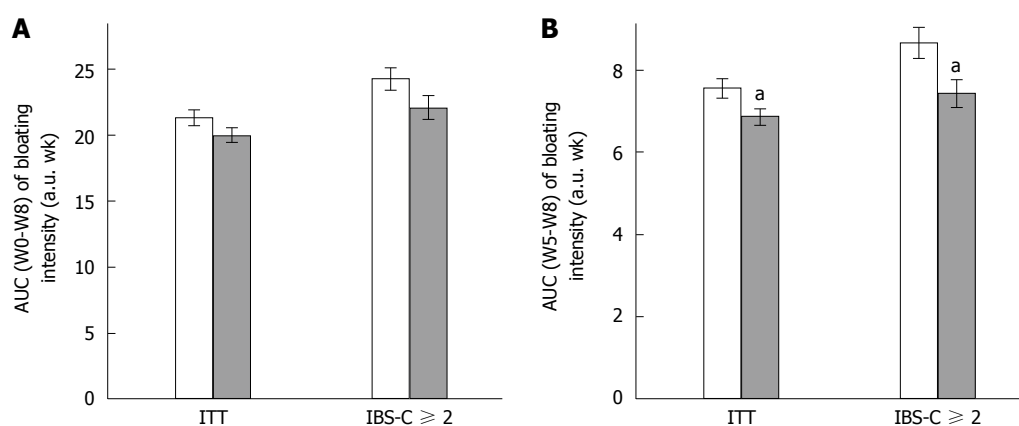
Figure 2 Area under the curve (W0-W8) (A) and area under the curve (W5-W8) (B) of bloating in intent to treat population (all irritable bowel syndrome subtypes) and in irritable bowel syndrome-C subjects with an abdominal pain/discomfort score higher than or equal to 2 at baseline (irritable bowel syndrome-C ≥ 2) under placebo (white) or *Saccharomyces cerevisiae* CNCM I-3856 (grey) supplementation. [a]*P* < 0.05, Significant differences, *vs* placebo are symbolized. IBS-C: Irritable bowel syndrome-C; a.u.: Arbitrary unit; ITT: Intent to treat; AUC: Area under the curve.

(Active group: -1.21 ± 1.249 a.u.; Placebo group: -0.91 ± 1.340 a.u., *P* < 0.0001 in both groups). Bloating significantly improved throughout the supplementation period in both study groups (between W0 and W8, *P* < 0.0001 in both groups).

Abdominal pain/discomfort - Responder status

Two definitions of responder status were applied in this meta-analysis. In the ITT population, subjects in the Active group had 1.510 higher odds to be a responder compared to subjects in the Placebo group (*P* = 0.0240, OR[95%CI] = 1.510 [1.056;2.161]) when responders were defined by a reduction of 1 a.u. of abdominal pain/discomfort score from W0 for at least 2 wk between W5 and W8. This difference was not significant anymore when responders were defined by a reduction of 50% of abdominal pain/discomfort score.

No significant differences were reported between the Active and Placebo groups in both IBS-C and IBS-C

≥ 2 subpopulations.

Bowel movements

Bowel movements are not reported in the ITT population because of the variety of stool patterns in regard to the different IBS subtypes present in the study population.

Stool consistency statistically improved in the Active and Placebo groups of the IBS-C subpopulation during the supplementation period. There was a statistically significant increase in the Bristol Stool Scale (BSS) score between W0 and W8 in the Active group (2.41 ± 0.817 a.u. *vs* 3.13 ± 1.197 a.u., *P* < 0.0001, diff[95%CI] = 0.752 [0.391;1.114]) and in the Placebo group (2.24 ± 0.714 a.u. *vs* 2.58 ± 1.020 a.u., *P* = 0.0266, diff[95%CI] = 0.402 [0.032;0.771]) (Figure 3). Over the 8 wk of supplementation, a significant product effect was reported in the IBS-C subpopulation in favor of *S. cerevisiae* CNCM I-3856 (*P* < 0.0001) and stool consistency was significantly different from Placebo from W2
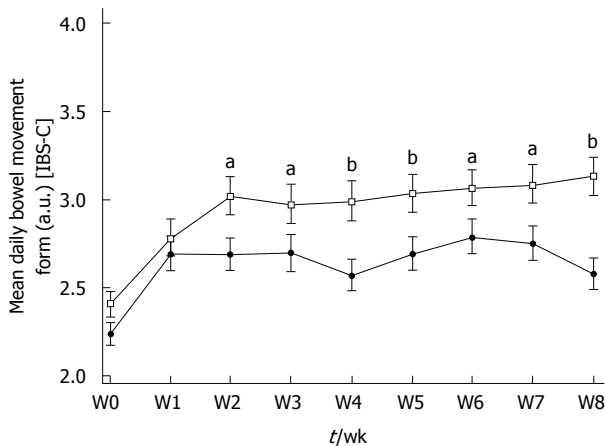
Figure 3 Evolution of stool consistency in irritable bowel syndrome-C subjects during the 8-wk supplementation with active product (*Saccharomyces cerevisiae* CNCM I-3856, white squares) or placebo product (black circles). Values are estimated means, with standard error represented by vertical bars. [a]$P < 0.05$, [b]$P < 0.01$, Significant differences, *vs* placebo are symbolized. IBS-C: Irritable bowel syndrome-C; a.u.: Arbitrary unit.
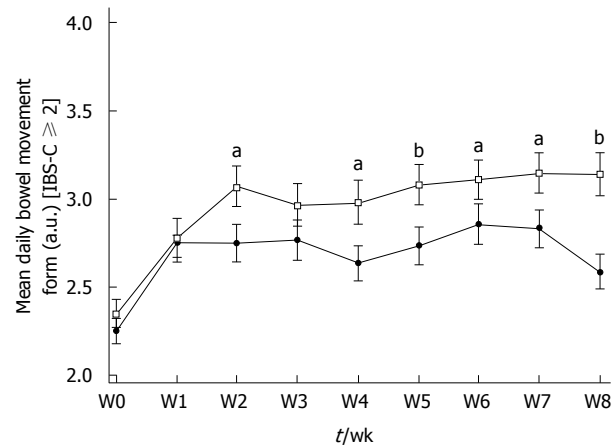
Figure 4 Evolution of stool consistency in irritable bowel syndrome-C subjects with an abdominal pain/discomfort score higher than or equal to 2 at baseline (irritable bowel syndrome-C $\geqslant$ 2) during the 8-wk supplementation with active product (*Saccharomyces cerevisiae* CNCM I-3856, white squares) or placebo product (black circles). Values are estimated means, with standard error represented by vertical bars. [a]$P < 0.05$, [b]$P < 0.01$, Significant differences, *vs* placebo are symbolized. IBS-C: Irritable bowel syndrome-C; a.u.: Arbitrary unit.

to W8. At the end of the supplementation period, stool consistency in the Active group was significantly higher and classified as "normal" compared to the Placebo group (respectively 3.13 ± 1.197 a.u. *vs* 2.58 ± 1.020 a.u., $P = 0.0003$, diff[95%CI]: 0.510 [0.231-0.788]).

In the IBS-C $\geqslant$ 2 subpopulation, stool consistency improved in the same way. BSS scores increased in Active and Placebo groups between W0 and W8. A statistically significant difference was reported in the Active group (W0: 2.35 ± 0.832 a.u. *vs* W8: 3.14 ± 1.219 a.u., $P < 0.0001$, diff[95%CI]: 0.808 [0.411-1.204]) but not in the Placebo group (2.25 ± 0.728 a.u. *vs* 2.59 ± 1.017 a.u., $P = 0.0865$) (Figure 4). A significant product effect in favor of *S. cerevisiae* CNCM I-3856 was apparent in the IBS-C $\geqslant$ 2 subpopulation over the supplementation period ($P = 0.0017$) and stool consistency was significantly different from Placebo during the second part of the supplementation ($P < 0.05$ from W4 to W8).

Statistically significant product effects were irregularly observed on stool frequency in the IBS-C subpopulation and the IBS-C $\geqslant$ 2 subpopulation in favor of the Active group. However the non-persistence of the effect and the absence of clinical relevance between Active *vs* Placebo did not demonstrate any benefits from *S. cerevisiae* CNCM I-3856 supplementation on this outcome.

DISCUSSION

Based on the data of two RCTs investigating the benefits of *S. cerevisiae* CNCM I-3856 on IBS symptoms management, this IPD meta-analysis confirmed some promising qualities of this yeast strain to alleviate GI symptoms.

Analysis of GI symptoms (abdominal pain/discomfort and bloating) on a week-by-week basis demonstrated a great variability in patient complaints over the supple-

mentation period which has already been discussed by different authors[17,18]. No significant benefits of *S. cerevisiae* CNCM I-3856 supplementation were observed during the first month of supplementation compared to placebo. This point has been previously reported by Pineton de Chambrun *et al*[10] who mentioned a potential delay of action of *S. cerevisiae*. The yeast may positively impact abdominal pain/discomfort due to an analgesic effect, with a delay before significant effectiveness as reported in animal studies[19]. In rats, some significant product effects were noted over the second month of study but the analgesic effect was transitory and limited to the time of product administration.

From a clinical point of view, AUC data provide relevant information in regard to overall subjective feelings. First, the AUC presents an overview of GI symptom intensity during the study period. This provides an indication of symptom alleviation over the supplementation period. The present analysis hardly succeeded in demonstrating a beneficial effect of *S. cerevisiae* CNCM I-3856 on the global AUC [AUC (W0-W8)] for abdominal pain/discomfort and bloating. Statistically positive effects were reported in the IBS-C $\geqslant$ 2 subpopulation, but not in the ITT population and IBS-C subpopulation. An AUC was also calculated over the second month of supplementation. This period was chosen in order to account for the aforementioned delay for significant action of the probiotic. Analysis on this specific period [AUC (W5-W8)] confirmed the product effect associated with yeast supplementation, in comparison to placebo, in all analyzed populations. Additionally, every statistically significant difference or trend was related to an improvement in the Active group from 9.2% and up to 14.9% compared to Placebo. This observation is of great interest from a clinical point of view: the 10% difference is considered as a minimal clinically relevant

threshold[20]. This means that *S. cerevisiae* CNCM I-3856 improves IBS symptoms in a significant and relevant manner in IBS patients, in a global IBS population and in the IBS-C subtype during the second month of consumption. Another approach in validating the clinical benefits of therapy consists of analyzing the percentage of patients who positively respond to the treatment. Various definitions of responder status are suggested by the literature[21]. In addition, food and drug authorities have since established some complete definitions for responder status[22,23]. Two different definitions of responder status were applied in the two RCTs[10,11]. They were re-used in the present meta-analysis for consistency. Conclusions on responder status were limited to the ITT population who experienced an improvement of 1 a.u. of abdominal pain/discomfort for at least 50% of the second month of supplementation.

One point limiting the positive conclusions on *S. cerevisiae* CNCM I-3856 relates to the placebo response commonly reported in GI disorders. A meta-analysis of placebo-controlled RCTs conducted in IBS patients reported a mean placebo response rate of 37.5%[24]. This is consistent with previous meta-analysis from Patel *et al*[25] who observed that 40.2% of patients respond to placebo. The placebo effect is one factor influencing the placebo response rate, but it does not affect it alone. The authors of this meta-analysis tried to determine the confounding factors which may influence the placebo response rate (duration of therapy, run-in phase, single or multi-centre study, *etc.*); but, inconsistent data were reported[24,25].

Today, probiotics are an alternative approach being extensively researched for the management of symptoms in IBS patients. While the effects of probiotics on IBS physiopathology are still under scrutiny[9], many clinical trials investigating the benefits of one or more bacterial strains in IBS have been published. Increased resources are now available to examine probiotic benefits in IBS management. It remains difficult to clearly conclude efficacy and set up recommendations for probiotics supplementation because of the poor repeatability of the data and the difficulty in comparing studies. Indeed, great heterogeneity is observed between trials in terms of variety of strains used, probiotic dosage, treatment duration, outcome definitions, and statistical analyses. This point is highlighted in literature reviews and meta-analyses[26-28]. In the absence of comparable studies, meta-analyses are performed to integrate qualitative clinical trials irrespective of the probiotic strains studied[26-31]. All authors globally agree as to the benefits of probiotics supplementation in IBS patients. Neither individual probiotic nor combination of strains was, however, identified as effective by itself and conclusions were drawn for probiotics in general. Some authors directed their meta-analyses specifically to *Lactobacillus* strains[32] or to *Lactobacillus rhamnosus* GG in children[33]. Only a few trials were included in these meta-analyses (six trials investigating *Lactobacillus* strains and three trials investigating

Lactobacillus rhamnosus GG in children), but their conclusions can be considered relevant in light of the studies selected. Both authors concluded on beneficial effect of *Lactobacillus* spp on IBS symptoms, namely on frequency and intensity of abdominal pain. However, no recommendations for dose and treatment duration were proposed.

In regards to these meta-analyses, the present IPD meta-analysis demonstrates two advantages. First, the two RCTs were designed to evaluate the same probiotic strain, *i.e.*, *S. cerevisiae* CNCM I-3856, and the methodologies were very similar. Study designs were double-blind, randomized, placebo-controlled to achieve high quality studies, and recommendations for treatment trial design were applied[21]. These points strengthen the integration of data and their analyses as a whole. Second, individual data on all subjects were compiled to perform new statistical analyses, which provide a more robust result than meta-analyses based on aggregate data. The pooling of the two original individual trials[10,11] for meta-analysis increased the sample size and thus the power of the statistical analyses, in particular in the context of the analysis in the IBS-C subpopulation. In addition, this meta-analysis allowed answering and confirming questions not initially raised by both studies and consolidated previous results reported on *S. cerevisiae* CNCM I-3856.

In conclusion, this IPD meta-analysis confirms previous data linking *S. cerevisiae* CNCM I-3856 supplementation and improvement of GI symptoms in IBS overall population and in the IBS-C and IBS-C $\geq$ 2 subpopulations. Despite great similarities in study designs, the two RCTs considered in the meta-analysis differ in terms of endpoints. The present observations would gain in being validated by a new RCT designed according to these meta-analysis conclusions.

COMMENTS

Background
Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder with high prevalence. Its diagnosis is based on the presence of abdominal pain and/or discomfort associated with at least two of the following: improvement with defecation; onset associated with a change in frequency of stool; onset associated with a change in form of stool. With the lack of satisfactory pharmacological treatments suitable for long-term administration, an alternative approach such as probiotic use may be of interest for IBS management.

Research frontiers
The intestinal microbiota appears to play a key role in IBS, even if its implication is not clearly identified. Probiotics are live microorganisms that confer a health benefit to the host. The present meta-analysis focuses on yeast strain *Saccharomyces cerevisiae* (*S. cerevisiae*) CNCM I-3856.

Innovations and breakthroughs
Two randomized clinical trials have been included in this individual patient data meta-analysis. Data on 579 subjects were compiled and analyzed to increase the power of the initial statistical analyses. Results confirm the efficacy of *S. cerevisiae* CNCM I-3856 supplementation in subjects suffering from IBS for

the improvement of GI symptoms. Interesting results were reported in subjects characterized by IBS-C or by IBS-C with score of abdominal pain/discomfort ≥ 2 at baseline.

Applications

The results suggest that *S. cerevisiae* CNCM I-3856 may be an alternative approach to deal with GI symptoms associated with IBS.

Terminology

IBS is defined as recurrent abdominal pain or discomfort at least 3 d per month in the last 3 mo associated with 2 or more of the following: 1. Improvement with defecation, 2. Onset associated with a change in frequency of stool, 3. Onset associated with a change in form (appearance) of stool.

Peer-review

The study contents are interesting, being focused on the efficacy of *S. cerevisiae* CNCM I-3856 supplementation in subjects suffering from IBS for the improvement of GI symptoms. The title and abstract accurately convey the study contents. The objectives of the study are clear. The methods are appropriate and well described, the data are sound and controlled. The discussion and conclusions are well balanced and adequately supported by the data.

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