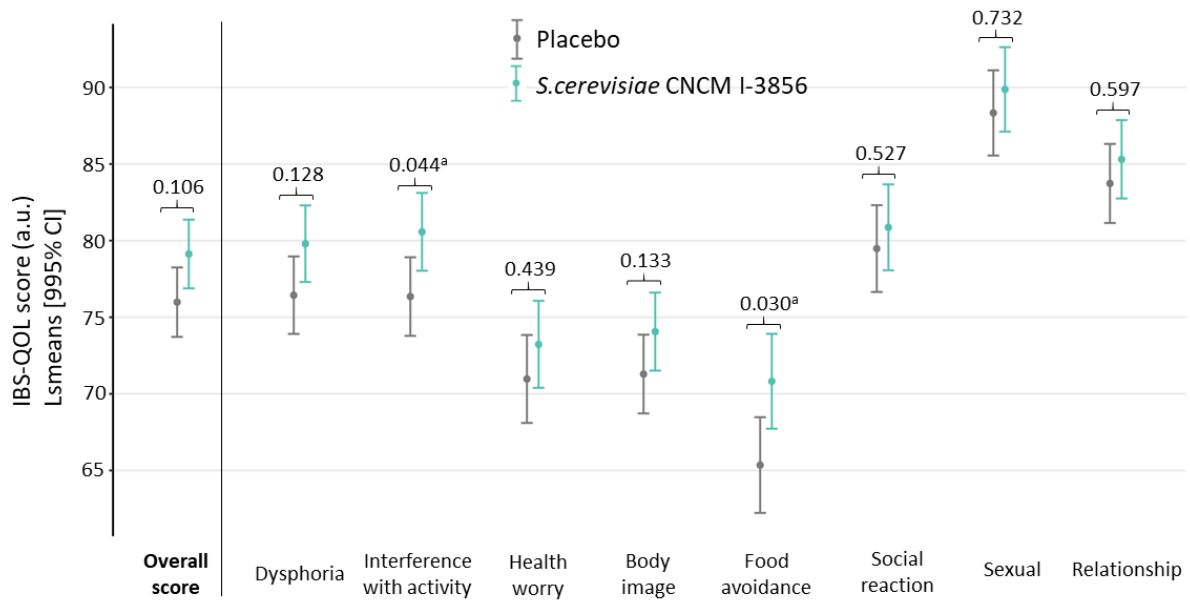
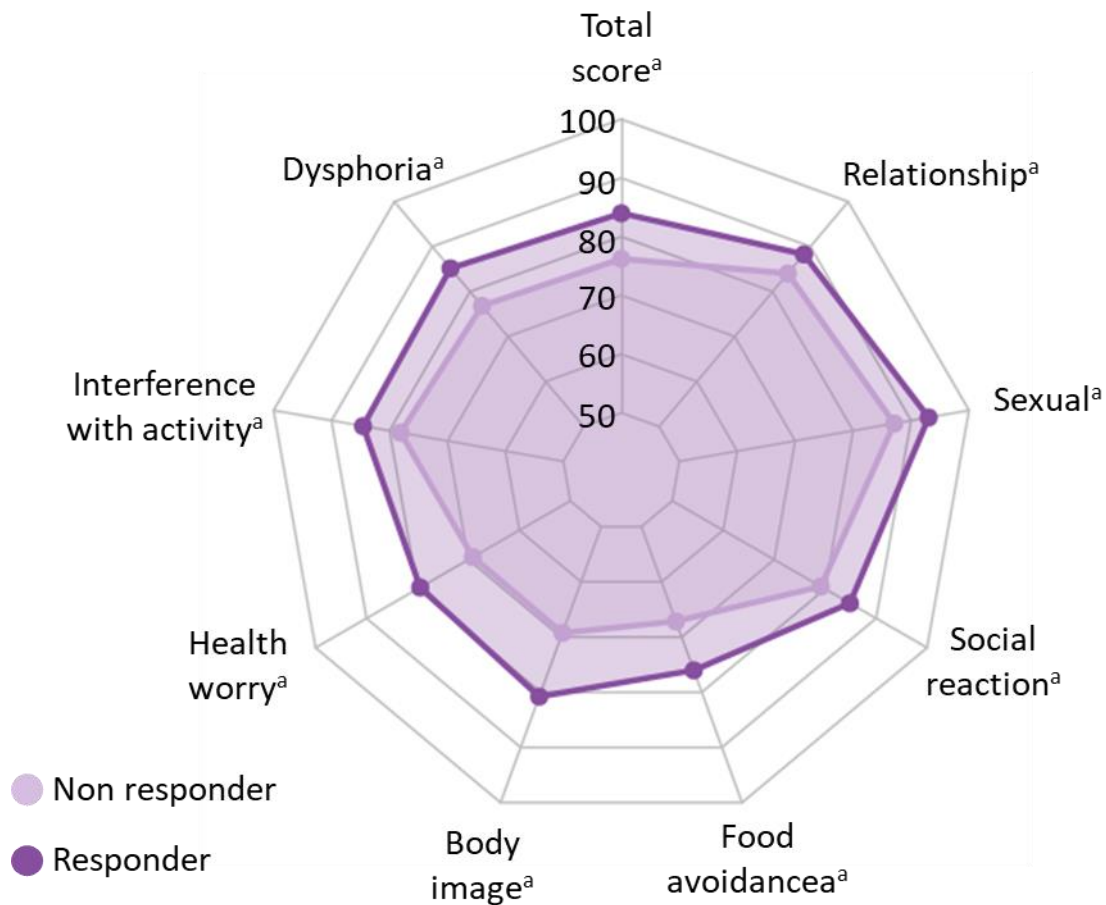


Supplementary Figure 1 Abdominal pain. A: Abdominal pain score evolution; B: Area Under the Curve (W5-W8) of abdominal pain ($P = 0.10$); C: Percentage of abdominal pain responders ($P = 0.018$) in PP population. Significant result ($^aP < 0.05$. Chi2 test).



Supplementary Figure 2 Irritable bowel syndrome-specific quality of life questionnaire scores at the end of the intervention (V3) in ITT population. Significant result (^a $P < 0.05$. ANOVA model).



Supplementary Figure 3 IBS-QoL scores at the end of the intervention (V3) adjusted on baseline (V1) in PP abdominal pain responders supplemented with *S.cerevisiae* CNCM I-3856. Significant result (^a $P < 0.05$. ANCOVA for repeated measures). Between-group difference are showed in Supplementary Table 2. IBS-QoL scores between-group differences from ANOVA models at the end of the intervention (V3). ^aHochberg adjustment for multiple comparisons.

Supplementary Table 1 IBS-QOL scores between-group differences from ANOVA models at the end of the intervention (V3)

IBS-QOL scores	ITT population				PP population			
	CNCM 3856 Placebo difference Estimate (95%CI)	I- vs 1	Adjust ed pvalue 1	SM D ²	CNCM vs I-3856 Placebo difference Estimate (95%CI)	Adjuste d P value ¹	SM D ²	
Overall score	3.14 (-0.04; 6.33)		0.106	0.14	3.86 (0.52; 7.20)	0.047	0.18	
Dysphoria	3.36 (-0.19; 6.92)		0.128	0.14	4.21 (0.51; 7.92)	0.052	0.18	
Interference with activity	4.22 (0.62; 7.83)		0.044	0.16	4.30 (0.54; 8.05)	0.050	0.18	
Body image	2.77 (-0.85; 6.39)		0.133	0.07	3.96 (0.17; 7.75)	0.040	0.17	
Health worry	2.26 (-1.78; 6.30)		0.439	0.09	2.71 (-1.49; 6.91)	0.315	0.11	
Food avoidance	5.47 (1.07; 9.87)		0.030	0.21	5.69 (1.10; 10.28)	0.030	0.22	
Social reaction	1.38 (-2.60; 5.37)		0.527	0.05	2.87 (-1.30; 7.04)	0.311	0.11	
Sexual	1.54 (-2.38; 5.45)		0.732	0.05	1.73 (-2.43; 5.90)	0.728	0.07	
Relationship	1.58 (-2.06; 5.21)		0.597	0.06	2.18 (-1.64; 5.99)	0.263	0.09	

¹ Hochberg adjustment for multiple comparisons. ² Standardized Mean Difference.

Supplementary Table 2 IBS-QoL scores between-group differences from ANCOVA models at the end of the intervention (V3) adjusted on baseline (V1) in abdominal pain responders supplemented with *S. cerevisiae* CNCM I-3856

IBS-QoL scores	ITT population			PP population		
	Responders vs Non-responders difference Estimate (95% CI)	Adjusted pvalue ¹	Standardized Mean Difference (SMD)	Responders vs Non-responders difference Estimate (95% CI)	Adjusted pvalue ¹	Standardized Mean Difference (SMD)
Overall score	8.30 (5.50; 11.10)	< 0.001	0.49	7.76 (4.87; 10.65)	< 0.001	0.43
Dysphoria	8.86 (5.79; 11.92)	< 0.001	0.42	8.34 (5.18; 11.50)	< 0.001	0.40
Interference with activity	6.95 (3.70; 10.20)	< 0.001	0.44	6.46 (3.06; 9.86)	< 0.001	0.38
Body image	11.94 (8.53; 15.35)	< 0.001	0.56	11.54 (7.98; 15.09)	< 0.001	0.52
Health worry	10.91 (7.16; 14.66)	< 0.001	0.43	10.33 (6.55; 14.12)	< 0.001	0.37
Food avoidance	9.90 (5.14; 14.66)	< 0.001	0.38	8.85 (3.90; 13.80)	0.001	0.32
Social reaction	6.42 (2.92; 9.92)	< 0.001	0.37	5.70 (2.13; 9.28)	0.004	0.31
Sexual	5.85 (2.21; 9.50)	0.003	0.32	5.94 (2.05; 9.83)	0.006	0.31
Relationship	4.75 (1.07; 8.42)	0.012	0.34	4.24 (0.47; 8.02)	0.028	0.30

¹ Hochberg adjustment for multiple comparisons. ² Standardized Mean Difference.

Supplementary Table 3 Descriptive statistics of adverse events by body system

Adverse events		Placebo (<i>n</i> = 226)		<i>S.cerevisiae</i> CNCM I-3856 (<i>n</i> = 230)	
		Subjects	Events	Subjects	Events
		n (%)	n	n (%)	n
All the adverse events		87 (38.5%)	173	109 (47.4%)	194
System	Allergy	2 (0.9%)	2	1 (0.4%)	1
	Cardiovascular	3 (1.3%)	3	1 (0.4%)	2
	Dermatological	5 (2.2%)	5	4 (1.7%)	4
	Endocrine/Hematologic	1 (0.4%)	1	0 (0.0%)	0
	Otolaryngology/Ophthalmology	31 (13.7%)	36	27 (11.7%)	30
	Gastrointestinal	26 (11.5%)	34	34 (14.8%)	41
	Gynaecological	10 (4.4%)	13	7 (3.0%)	8
	Immunological	1 (0.4%)	1	3 (1.3%)	3
	Rheumatologic	14 (6.2%)	14	22 (9.6%)	28
	Metabolic	0 (0.0%)	0	0 (0.0%)	0
	Nephro-urological	1 (0.4%)	1	5 (2.2%)	6
	Neurologic/Psychiatric	36 (15.9%)	60	49 (21.3%)	67
	Respiratory	1 (0.4%)	1	1 (0.4%)	1
	Other	2 (0.9%)	2	3 (1.3%)	3