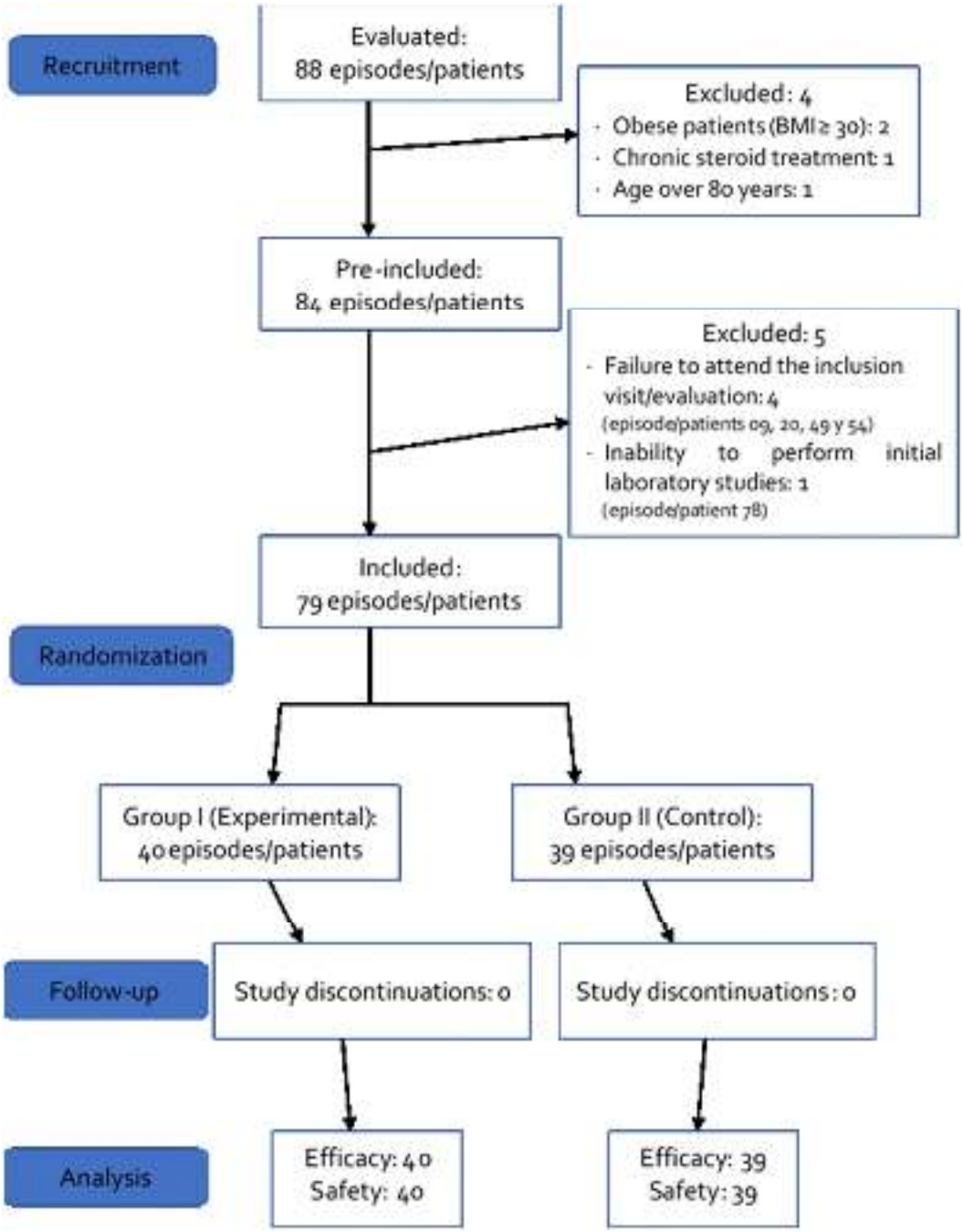
GENERAL INFORMATION OF THE CLINICAL TRIAL

RPCEC code	RPCEC00000294
Public title	Colilen IBS- Irritable Bowel Syndrome- adults-Phase III
Scientific title	Phase III clinical trial, prospective randomized, of superiority, to evaluate the efficacy and safety of Colilen IBS vs. placebo in Irritable Bowel Syndrome.
Intervention description	Group I (Experimental) - Colilen IBS (Batch A): 2 capsules of 587 mg by oral route, three times a day, between 30 minutes and 2 hours before meals, for 12 weeks. Group II (Control)- Placebo: 2 capsules by oral route, three times a day, between 30 minutes and 2 hours before meals, for 12 weeks.

PARTICIPANT FLOW



BASELINE CHARACTERISTICS

Baseline characteristics are reported for the 79 episodes included in the study, with a similar distribution across the treatment groups. In both groups, there was a predominance of women, cases of diarrhea-predominant IBS (IBS-D), and severe IBS at baseline.
The mean age of the patients at the time of evaluation for the included episodes was 53 years in the group randomized to Colilen IBS and 52.7 years in the placebo group. The mean duration since diagnosis was 5.1 years and 4.2 years, respectively.
Furthermore, the study population was characterized by a high prevalence of non-adherence to dietary recommendations, a history of chronic medical conditions, and the absence of chronic use of antidepressants and/or steroids, as well as the absence of rescue therapy at the time of enrollment.
Based on the initial physical examination of the patients experiencing the included episodes, the subjects were, in general, of normal weight.

Characteristics of IBS episodes evaluated by treatment group.

		Colilen IBS N=40		Placebo N=39	
		n	%	n	%
Sex	Male	3	7,5	5	12,8
	Female	37	92,5	34	87,2
Age	Mean (SD)	53 (15.4)		52.7 (11.9)	
	Median(P25; 75)	57 (43 -66)		54 (45 -63)	
	min; máx.	(23 -71)		(27 -71)	
Time to diagnosis (years)	Mean (SD)	5.1 (7)		4.2 (5.5)	
	Median(P25; 75)	3 (1 -5)		3 (1 -4)	
	min; máx.	(0; 34)		(0; 32)	
IBS subtype	IBS_C	6	15,0	7	17,9
	IBS_D	23	57,5	22	56,4
	IBS_M	6	15,0	6	15,4
	IBS_U	5	12,5	4	10,3

		Colilen IBS N=40		Placebo N=39	
		n	%	n	%
Initial severity	Moderate	7	17,5	8	20,5
	Severe	33	82,5	31	79,5
Total IBS-SSS score at baseline	Mean (SD)	395 (83)		385 (82)	
	Median(P25; 75)	408 (325 -463)		385 (310 -450)	
	min; máx.	(210; 499)		(190; 500)	
Treatment with antidepressants	Yes	3	7,5	2	5,1
	No	37	92,5	37	94,9
Meets dietary recommendations at the start	Yes	6	15,0	6	15,4
	No	34	85,0	33	84,6
Consumes probiotic yogurt at the start	Yes	15	37,5	14	35,9
	No	25	62,5	25	64,1
Chronic steroid treatment at the time of inclusion	Yes	2	5,0	0	0,0
	No	38	95,0	39	100,0
Use of rescue therapy	Yes	0	0, 0	2	5, 1
	No	40	100, 0	37	94, 9
History of chronic illness	Yes	38	95,0	33	84,6
	No	2	5,0	6	15,4

OUTCOME MEASURES

a) Primary outcomes

Percentage reduction in the IBS-SS (Francis) questionnaire score: The percentage reduction in the Irritable Bowel Syndrome Severity Score (IBS-SS) (Francis) questionnaire score from baseline to the end of treatment was evaluated. Measurement time points: baseline, weeks 2, 4, 12, and week 14 (follow-up).

Based on the total score from the questionnaire, a patient was considered a "responder" if they showed a reduction of 30% or more in the overall score after 12 weeks of treatment (V3) compared to the baseline value (V0). A "non-responder" was defined as a patient who, after 12 weeks of treatment (V3), showed a reduction of less than 30% in the overall IBS-SS (Francis) questionnaire score compared to the baseline value (V0).

The analysis of the 79 randomized episodes showed that, after 12 weeks of treatment, response rates were higher in the Colilen IBS group, with a response rate of 75% (30/40 episodes), compared to 48.7% (19/39 episodes) in the placebo group.

Descriptive and analytical summary of the frequency of episodes according to the response criterion: a reduction of ≥ 30% in the IBS-SSS score relative to the baseline value, broken down by group and by study week.

Study Week/Response Criteria		Colilen IBS N =40		Placebo N=39		Difference $\hat{\pi}_1 - \hat{\pi}_2$ (IC95%) [&] P*
		n	%	n	%	
Weeks 0-2	Yes	24	60,0%	17	43,6%	16.4% (-5.6; 37.8)
	No	16	40,0%	22	56,4%	
Weeks 0-4	Yes	33	82,5%	21	53,8%	28.7% (8.3; 47,7)
	No	7	17,5%	18	46,2%	
Weeks 0-12	Yes	30	75,0%	19	48,7%	26.3% (2.4; 43.9) p=0.016
	No	10	25,0%	20	51,3%	
Weeks 0-14	Yes	30	75,0%	19	48,7%	26.3% 2.4; 43.9
	No	10	25,0%	20	51,3%	

b) Secondary outcomes

➢ **Reduction in the IBS-SSS (Francis) questionnaire score:** The difference in the total score on the IBS-SSS (Francis) questionnaire—assessed at the end of the 12-week treatment period compared to the baseline—was evaluated. Measurement time points: baseline, weeks 2, 4, 12, and week 14 (follow-up).

A reduction of at least 50 points in the total score was the threshold used to evaluate this secondary efficacy endpoint.

In the group treated with Colilen IBS, the frequency of episodes meeting this criterion was high. At week 2, this was observed in 85% of the episodes randomized to this treatment (34/40), and it remained above 80% at all subsequent assessment points. Specifically, after 12 weeks of treatment, 82.5% of the episodes treated with Colilen IBS showed a reduction of at least 50 points in the total IBS-SSS score compared to baseline. In the placebo group, the response frequency was 64.1% (25/39) at week 2, reached a peak of 79.5% at week 4, and subsequently decreased to 71.8% at 12 weeks. The difference between the groups at 12 weeks was 10.7% (95% CI: -8.1, 29.0; p=0.257).

Descriptive and analytical summary of the frequency of episodes according to the response criterion—an absolute difference of ≥ 50 points on the IBS-SSS compared to baseline—by group and by study week.

Study Week/Response Criteria		Colilen IBS N =40		Placebo N=39		Difference $\hat{\pi}_1 - \hat{\pi}_2$ (IC95%) & P*
		n	%	n	%	
Weeks 0-2	Yes	34	85,0%	25	64,1%	20.9% 1.5; 39.3
	No	6	15,0%	14	35,9%	
Weeks 0-4	Yes	33	82,5%	31	79,5%	3.0% -14.6; 20.5
	No	7	17,5%	8	20,5%	
Weeks 0-12	Yes	33	82,5%	28	71,8%	10.7% (-8.1; 29.0) p=0.257
	No	7	17,5%	11	28,2%	
Weeks 0-14	Yes	32	80,0%	25	64,1%	15.9% -4.1; 35.2
	No	8	20,0%	14	35,9%	

- **Improvement in Irritable Bowel Syndrome (IBS) severity:** IBS severity was assessed using an IBS severity classification system, based on the total score on the scale:

- normal: 0 to < 75
- mild: ≥ 75 to < 175
- moderate: ≥ 175 to ≤ 300
- severe: > 300

An improvement in severity was defined as a decrease of at least one severity level by week 12 compared to the baseline classification.

At the start of the study, a high prevalence of episodes classified as "severe" was observed in both groups. From the second week of treatment onward, an improvement in severity was noted in both groups, with the emergence of episodes falling into the "normal" and "mild" categories. In the group treated with Colilen IBS, the percentage of episodes in these categories was higher than that observed in the placebo-treated group.

By week 12, in the group treated with Colilen IBS, the percentages of episodes classified as normal, mild, moderate, and severe (> 300 points) were 45%, 20%, 20%, and 15%, respectively; in the placebo-treated group, the corresponding percentages were 25.6%, 12.8%, 25.6%, and 35.9%.

In the Colilen IBS group, a higher proportion of episodes fell into the lower-severity categories (normal and mild). Conversely, the placebo group showed a higher proportion of episodes in the higher-severity categories (moderate and severe). Statistical analysis of this variable indicated that Colilen IBS was more effective than the placebo in improving IBS severity.

In both treatment groups, a progressive improvement was observed over time.

Frequency of episodes according to IBS severity categories, by group and time point assessed.

IBS severity (IBS-SSS categories)		Colilen IBS N=40		Placebo N=39		*p value
		n	%	n	%	
Inicio	Moderate	7	17,5%	8	20,5%	0,733
	Severe	33	82,5%	31	79,5%	
Week 2	Normal	4	10,0%	4	10,3%	0.249
	Mild	14	35,0%	9	23,1%	
	Moderate	10	25,0%	6	15,4%	
	Severe	12	30,0%	20	51,3%	
Week 4	Normal	12	30,0%	10	25,6%	0.162
	Mild	12	30,0%	6	15,4%	
	Moderate	9	22,5%	8	20,5%	
	Severe	7	17,5%	15	38,5%	
Week 12	Normal	18	45,0%	10	25,6%	0.094
	Mild	8	20,0%	5	12,8%	
	Moderate	8	20,0%	10	25,6%	
	Severe	6	15,0%	14	35,9%	
Week 14	Normal	12	30,0%	9	23,1%	0.153
	Mild	11	27,5%	8	20,5%	
	Moderate	9	22,5%	5	12,8%	
	Severe	8	20,0%	17	43,6%	

Regarding the distribution of episodes based on individual variation from the baseline value—classified as improvement, stability, or worsening according to a change of at least one severity category at each assessment point—greater improvement was observed throughout the study in the Colilen IBS group compared to the placebo group. Improvement was defined as a reduction of at least one category relative to the baseline classification of IBS severity. The differences between the groups were statistically significant at all three assessment points: weeks 2, 4, and 12 (p-values = 0.037, 0.025, and 0.044, respectively). During the follow-up period after the end of treatment, at week 14, the percentage of episodes showing improvement was higher among those treated with Colilen IBS than among those treated with placebo, although the difference between the groups did not reach statistical significance.

Frequency of response—defined by a change in severity categories relative to baseline—by group, and an assessment of the difference in this response between groups at various time points during the study.

Improvement in Severity		Colilen IBS N=40		Placebo N=39		Comparison between groups p*
		n	%	n	%	
Week 2 vs basal	Improvemen	26	65,0%	16	41,0%	p=0.037
	Equal	13	32,5%	23	59,0%	
	It gets worse	1	2,5%	0	0,0%	
Week 4 vs basal	Improvemen	33	82,5%	23	59,0%	p=0.025
	Equal	5	12,5%	15	38,5%	
	It gets worse	2	5,0%	1	2,6%	
Week 12 vs basal	Improvemen	32	82,1%	24	61,5%	p=0.044
	Equal	7	17,9%	15	38,5%	
Week 14 vs basal	Improvemen	30	75,0%	22	56,4%	p=0.082
	Equal	10	25,0%	17	43,6%	

The percentage of IBS episodes showing improvement at 12 weeks of treatment—comparing improvement against a lack of improvement (stability or worsening)—was 82.1% in the Colilen IBS group (32 out of 40 episodes) and 61.5% in the placebo group (24 out of 39 episodes).

- **Pain intensity:** The difference between the values assigned to this variable at each assessment of the IBS-SSS questionnaire and the baseline value was determined. Measurement time points: baseline, weeks 2, 4, 12, and week 14 (follow-up).

At the start of the study, the mean pain intensity scores were similar in both groups. Within-group variation relative to the baseline value showed a greater reduction in pain in the Colilen IBS group than in the placebo group at all assessment time points, with a statistically significant difference between the groups starting from week 4 ($p = 0.021$).

At week 12, the mean reduction was −51.1 points (95% CI: −64.4; −37.8) in the Colilen IBS group and −27.4 points (95% CI: −41.7; −13.2) in the placebo group. The mean difference between the groups was −23.7 points, which was statistically significant (95% CI: −42.9; −4.5; $p = 0.016$).

Description and assessment of the change in pain intensity score by group and time point.

Variable pain intensity at the time points evaluated		Colilen IBS N=40	Placebo N=39	Dif μ1-μ2 (IC 95%), p*
Basal	n	40	39	
	Mean (SD)	75 (20.1)	73.5 (24.3)	
	Median (p25; p75)	80 (57.5 -90)	80 (50 -98)	
	(Min; Max)	(30; 100)	(10; 100)	
2 weeks	n	40	39	
	Mean (SD)	40.3 (35.1)	50.5 (35.9)	
	Median (p25; p75)	40 (0 -70)	60 (10 -80)	
	(Min; Max)	(0; 100)	(0; 100)	
$^{\$}$*Dif* μ2-μ0 (IC 95%)		-34.7 (-46.7; -22.7)	-23 (-35.2; -10.8)	-11.7 (-28.5; 5.1)
4 weeks	n	40	39	
	Mean (SD)	23.1 (32.8)	42.6 (36.8)	
	Median (p25; p75)	0 (0 -45)	50 (0 -70)	
	(Min; Max)	(0; 100)	(0; 100)	
$^{\$}$*Dif* μ4-μ0 (IC 95%)		-51.8 (-64.8; -38.9)	-30.9 (-43.3; -	-20.9 (-38.6; -3.3)
12 weeks	n	39	39	
	Mean (SD)	24 (33.5)	46.1 (41.1)	
	Median (p25; p75)	0 (0 -50)	50 (0 -90)	
	(Min; Max)	(0; 100)	(0; 100)	
$^{\$}$*Dif* μ12-μ0 (IC 95%)		-51.1 (-64.4; -37.8)	-27.4 (-41.7; -13.2)	-23.7 (-42.9; -4.5)
14 weeks	n	40	39	
	Mean (SD)	30.4 (36.1)	45 (41.8)	
	Median (p25;p75)	20 (0 -55)	40 (0 -90)	
	(Min; Max)	(0; 100)	(0; 100)	
$^{\$}$*Dif* μ14-μ0 (IC 95%)		-44.6 (-57.9; -31.3)	-28.5 (-41.7; -15.3)	-16 (-34.5;2.4)

➢ **Intensity of abdominal distension:** The difference between the values assigned to this variable at each assessment of the IBS-SSS questionnaire and the baseline value was determined. Measurement time points: baseline, weeks 2, 4, 12, and week 14 (follow-up).

At the start of the study, mean scores differed between the treatment groups. The group treated with Colilen IBS showed higher mean values than the placebo group: mean (SD) of 77.0 (29.2) and 56.3 (33.9), respectively. Regarding within-group variation relative to the baseline value, the reduction in abdominal distension was greater in the Colilen IBS group than in the placebo group at all assessment time points, with a statistically significant difference between the groups starting from

week 2. At week 12, the mean reduction was −54.8 points (95% CI: −67.1; −42.5) in the Colilen IBS group and −12.3 points (95% CI: −24.0; −0.6) in the placebo group. The mean difference between the groups was −42.5 points, which was statistically significant (95% CI: −59.2; −25.8; $p < 0.001$).

Description and assessment of the change in the abdominal distension score, by group and time point.

Variable abdominal distension at the time points evaluated		Colilen IBS N=40	Placebo N=39	Dif µ1-µ2 (IC 95%), p*
Basal	n	40	39	
	*Mean (SD)	77.0 (29.2)	56.3 (33.9)	
	Median (p25; p75)	90 (65 -100)	50 (30 -80)	
	(Min; Max)	(0; 100)	(0; 100)	
2 weeks	n	40	39	
	Mean (SD)	44 (34.9)	44.2 (38.8)	
	Mediana (p25; p75)	45 (5 -75)	50 (0 -80)	
	(Min; Max)	(0; 100)	(0; 100)	
$Dif µ2-µ0 (IC 95%)		-33 (-42.9; -23.1)	-12.1 (-24.5; 0.4)	-20.9 (-36.6; -5.3) 0.009
4 weeks	n	40	39	
	Mean (SD)	36.6 (34.7)	41 (36.3)	
	Median (p25; p75)	30 (0 -65)	50 (0 -70)	
	(Min; Max)	(0; 100)	(0; 100)	
$Dif µ4-µ0 (IC 95%)		-40.3 (-52.6; -28.0)	-15.3 (-27.7; -2.9)	-25 (-42.2; -7.8) 0.005
12 weeks	n	39	39	
	Mean (SD)	24.1 (34.3)	44 (43)	
	Median (p25; p75)	10 (0 -40)	40 (0 -90)	
	(Min; Max)	(0; 100)	(0; 100)	
$Dif µ12-µ0 (IC 95%)		-54.8 (-67.1; -42.5)	-12.3 (-24; -0.6)	-42.5 (-59.2; -25.8) 0.000
14 weeks	n	40	39	
	Mean (SD)	28 (37)	43.5 (44)	
	Median (p25;p75)	10 (0 -60)	50 (0 -100)	
	(Min; Max)	(0; 100)	(0; 100)	
$Dif µ14-µ0 (IC 95%)		-49.0 (-61.2; -36.7)	-12.8 (-25.2; -0.4)	-36.1 (-53.2; -19) 0.000

➢ **Changes in bowel habits:** The degree of patient dissatisfaction regarding bowel habits was determined by calculating the difference between the values assigned to this variable at each assessment point in the IBS-SSS questionnaire and the baseline value. Additionally, during the final week of the study treatment, data were collected on the number and consistency of bowel movements; these values were then compared with those recorded during the final week of the pre-inclusion (run-in) period. Stool consistency was assessed using the Bristol Stool Form Scale.
At baseline, mean scores were similar across both treatment groups. Regarding within-group changes from baseline, the reduction in dissatisfaction with bowel habits was greater in the Colilen IBS group than in the placebo group at all assessment time points. At week 12, the mean reduction was −54.4 points (95% CI:

−66.2; −42.5) in the Colilen IBS group and −28.7 points (95% CI: −40.1; −17.2) in the placebo group. The mean difference between the groups was −25.7 points, which was statistically significant (95% CI: −42.0; −9.5; p = 0.002).

Description and assessment of the change in the score for dissatisfaction with bowel function, by group and time point.

Dissatisfaction at the moments evaluated		Colilen IBS N=40	Placebo N=39	Dif µ1-µ2 (IC 95%), p*
Basal	n	40	39	
	Mean (SD)	90.25 (16.1)	89.7 (18.1)	
	Median (p25; p75)	100 (80 -100)	100 (80 -100)	
	(Min; Max)	(50; 100)	(30; 100)	
2 weeks	n	40	39	
	Mean (SD)	55.6 (31.1)	66.8 (31.6)	
	Median (p25; p75)	55 (30 -80)	80 (50 -90)	
	(Min; Max)	(0; 100)	(0; 100)	
$^{\$}$*Dif* µ2-µ0 (IC 95%)		-34.6 (-44.5; -24.7)	-22.9 (-33.2; -12.7)	-11.7 (-25.7;
4 weeks	n	40	39	
	Mean (SD)	49.5 (34.5)	55.8 (37.9)	
	Median (p25; p75)	50 (15 -80)	65 (10 -90)	
	(Min; Max)	(0; 100)	(0; 100)	
$^{\$}$*Dif* µ4-µ0 (IC 95%)		-40.8 (-51.4; -30.1)	-33.9 (-45.6; -22.3)	-6.8 (-22.3; 8.8)
12 weeks	n	39	39	
	Mean (SD)	35.6 (35.3)	61.1 (36.5)	
	Median (p25; p75)	30 (0 -50)	60 (40 -100)	
	(Min; Max)	(0; 100)	(0; 100)	
$^{\$}$*Dif* µ12-µ0 (IC 95%)		-54.4 (-66.2; -42.5)	-28.7 (-40.1; -17.2)	-25.7 (-42; -9.5)
14 weeks	n	40	39	
	Mean (SD)	43.0 (36.7)	59.9 (38.7)	
	Median (p25;p75)	50 (2.5 -80)	60 (30 -100)	
	(Min; Max)	(0; 100)	(0; 100)	
$^{\$}$*Dif* µ14-µ0 (IC 95%)		-47.3 (-58.9; -35.6)	-29.8 (-41.2; -18.3)	-17.5 (-33.5; -1.4)

Improvement in bowel habits was defined as a shift toward stool consistency types 3, 4, or 5 on the Bristol Stool Form Scale, starting from a baseline of diarrheal (types 6 or 7) or constipated (types 1 or 2) bowel habits.

After 12 weeks of treatment, 37.5% of episodes in the Colilen IBS group showed an improvement in stool consistency compared to baseline, versus 12.8% of episodes in the placebo group. The difference between the groups was 24.7% and was statistically significant (95% CI: 5.5, 42.6; p = 0.012).

Frequency of episodes according to type of bowel habit, by group and assessment. Analysis of change at 12 weeks of the study, based on bowel habit at enrollment.

Bowel habit (Stool consistency)		Colilen IBS		Placebo		Comparison between groups
		n	%	n	%	
Bristol classification by assessment (general)						
Basal	**Bristol_Type 1-2 (C)**	15	37,5%	15	38,5%	
	Bristol_Type 3-4-5 (N)	18	45,0%	31	79,5%	
	Bristol_Type 6-7 (D)	30	75,0%	29	74,4%	
Week 12	**Bristol_Type 1-2 (C)**	7	17,5%	13	33,3%	
	Bristol_Type 3-4-5 (N)	33	82,5%	28	71,8%	
	Bristol_Type 6-7 (D)	22	55,0%	22	56,4%	
• **Improvement in bowel habits (stool consistency)**						
Improvement Bristol Type (C) o Type (D) change to Type (Normal)		15	37,5%	5	12,8%	Dif 24.7% IC 95%*** (5.5; 42.6) p*=0.012
Another change		25	62,5%	34	87,2%	
• **Change in bowel habit E and in bowel habit D**						
Initial Bristol Type 1-2 (C)		6	40.0%	3	20.0%	
Initial Bristol Type 6-7 (D)		11	36.7%	3	10.3%	

The analysis of stool consistency, taking into account the predominant bowel habit type, showed a greater effect—though not statistically significant—with Colilen IBS treatment (19.3%; 95% CI: -2.2, 39.8; p=0.077). In the final assessment, after 12 weeks of treatment, the response rate for episodes treated with Colilen IBS was 47.5%, whereas for episodes treated with a placebo, it was 28.2%.

Frequency of episodes according to stool consistency or the predominant type of bowel habit at the start of the study, by group, and assessment of improvement in stool consistency.

Bowel habit according to the Bristol scale (Stool consistency)		Colilen IBS		Placebo		Comparison between groups
		n	%	n	%	
Bristol classification by assessment						
Basal	**Bristol_Type 1-2 (C)**	8	20,0%	7	17,9%	0,263
	Bristol_Type 3-4-5 (N)	7	17,5%	13	33,3%	
	Bristol_Type 6-7 (D)	25	62,5%	19	48,7%	
Week 12	**Bristol_Type 1-2 (C)**	1	2,5%	7	17,9%	0.056**
	Bristol_Type 3-4-5 (N)	25	62,5%	21	53,8%	
	Bristol_Type 6-7 (D)	14	35,0%	11	28,2%	
• **Improvement in bowel habits (change in Bristol Stool Scale classification, at 12 weeks)**						
Improvement Bristol Type (C) o Type (D) change to Type (Normal)		19	47.5%	11	28.2%	Dif=19.3% IC 95%*** (-2.2; 39.8) *p=0.077*
Another change		21	52,5%	28	71.8%	
• **Change in Bristol scale score at 12 weeks of treatment**						
Change from Type (E) or (D) to Normal Type (N)		19	47.5	11	28.2	
Remains normal		6	15.0	10	25.6	
Remain in Type (E) or Type (D)		12	30.0	13	33.3	
Change from Type (N) to Type (C) or (D)		1	2.5	3	7.7	
Change from Type (D) to (C) or Change from Type (C) to (D)		2	5.0	2	5.1	

In episodes characterized by a predominance of constipation at the start of the study, an average increase of 2 bowel movements was observed after 12 weeks of treatment in the Colilen IBS group, whereas in the placebo group, the number of bowel movements remained unchanged from baseline. In episodes characterized by a predominance of diarrhea, the mean number of bowel movements at the end of the treatment was similar to that recorded at the start of the study. This pattern was observed in both treatment groups.

Number of bowel movements according to stool consistency or the type of predominant bowel habit at the start of the study, by group.

Bowel habit initial predominant		Colilen IBS N=40	Placebo N=39	***Difference μ_1- μ_2 (IC95%)*
Stool type (constipation): Bristol Type 1–2				
Basal	**n**	8	7	0.1 (-3.8;4.0)
	Mean (SD)	6.4 (4.3)	6.3 (2.2)	
	Median (p25; p75)	5 (3.5 -15)	7 (5 -8)	
	(Min; Máx.)	(2; 15)	(2; 8)	
12 weeks	**n**	8	7	1.7 (-0.8;4.1)
	Mean (SD)	8.3 (2.9)	6.6 (0.8)	
	Median (p25; p75)	7.5 (6.5 -13)	7 (6 -7)	
	(Min; Máx.)	(4; 13)	(5; 7)	
Difference: week 12 vs. baseline				
Mean (SD)		1.9 (4.9)	0.3 (2.6)	1.6 (-2.9;6.01) *p=0.179
Median (p25-75) min; máx		2 (0 -7) -8; 7	-1 (-1 -5) -3; 5	
p		*0.343*	*0.931*	

Typical bowel habit (diarrhea), Bristol type 6–7				
Basal	**n**	25	19	-0.8 (-4.8;3.3)
	Mean (SD)	11.7 (6)	12.5 (7.3)	
	Median (p25; p75)	11 (7 -21)	10 (7 -30)	
	(Min; Máx.)	(3; 29)	(4; 30)	
12 weeks	**n**	25	19	1.2 (-4;6.4)
	Mean (SD)	12.6 (8.4)	11.4 (8.5)	
	Median (p25; p75)	9 (7 -31)	9 (7 -41)	
	(Min; Máx.)	(4; 33)	(4; 41)	
Difference: week 12 vs. baseline				
Mean (SD)		0.9 (8.2)	-1.1 (11)	1.9 (-3.9;7.8)
Median (p25-75)		0 (-4 -14)	0 (-4 -34)	**p=0.585*
****p**		*0.920*	*0.433*	
Hábito tipo Bristol (Normal); Tipo 3-4- 5				
Basal	**n**	7	13	-4.6 (-13.5;4.2)
	Mean (SD)	9.1 (7.8)	13.8 (9.5)	
	Median (p25; p75)	7 (4 -25)	13 (8 -38)	
	(Min; Máx.)	(3; 25)	(2; 38)	
12 weeks	**n**	7	13	-2.3 (-7.1;2.4)
	Mean (SD)	8.3 (4.3)	10.6 (5)	
	Median (p25; p75)	7 (5 -15)	9 (8 -22)	
	(Min; Máx.)	(5; 15)	(5; 22)	
Difference: week 12 vs. baseline				
Mean (SD)		-0.9 (8.1)	-3.2 (9.0)	2.3 (-6.3;10.9)
Median (p25-75)		1 (-1 -8)	0 (-6 -6)	**p=0.661*
****p**		*0.439*	*0.373*	

➢ **Quality of Life:** This was assessed using the IBS-QOL questionnaire, which patients completed during the consultations/evaluations at the beginning (baseline; V0) and at the end of the treatment period (V3).

An increase in the IBS-QOL questionnaire score indicates an improvement. The total IBS-QOL score increased similarly in both groups. The mean increase in the total score was 12.9 points in the Colilen IBS group (95% CI: 7.8; 18.0) and 11.9 points in the placebo group (95% CI: 5.9; 17.9). However, no statistically significant differences were observed between the groups, either in the total IBS-QOL score or in the IBS-QOL subscales.

Notably, although the subscales related to social relationships (IBS-RL) and sexual relationships (IBS-SX) showed a statistically significant improvement within the

group treated with Colilen IBS—compared to a smaller, non-statistically significant mean change in the placebo group—the comparison between the groups did not reveal any statistically significant differences (IBS-RL: difference μ1−μ2 = 4.2; 95% CI: −5.4; 13.9; p = 0.470; IBS-SX: difference μ1−μ2 = 5.9; 95% CI: −4.7; 16.5; p = 0.486).

Description and evaluation of the total score and the 8 subscales of the IBS-QOL questionnaire, by group and at the initial time point and at 12 weeks.

IBS-QOL	Colilen IBS (N =40)		Placebo (N=39)		Colilen IBS $^{\&}\mu_{12s}$- μ_0 (IC95%)	Placebo $^{\&}\mu_{12s}$- μ_0 (IC95%)	**Dif μ1-μ2 (IC 95%) p*
	Inicio	Fin	Inicio	Fin			
Total score							
Mean (SD)	56.9 (22.6)	69.7 (17.0)	48.7 (20.4)	60.6 (22.5)	12.9 (7.8; 18.0)	11.9 (5.9; 17.9)	0.9 (-6.8;8.7) 0.829*
Median	54.4	71.3	47.8	58.1			
Pct 25-75	39.7 -73.9	60.7 -84.2	31.6 -66.2	44.9 -77.2			
Min, Max	4.4; 96.3	25; 94.9	13.2; 86.8	11.8; 96.3			
Subscales							
Emotional state (IBS-DY)							
Mean (SD)	57.5 (28.3)	74.8 (19.6)	46.1 (25.1)	65.5 (24.6)	17.3 (10.4;24.3)	19.4 (12.6;26.2)	-2 (-11.6;7.5) 0.569*
Median	57.8	78.1	43.8	65.6			
Pct 25-75	34.4 -79.7	70.3 -87.5	25 -68.8	50 -84.4			
Min, Max	3.1; 100	15.6; 100	0; 93.8	9.4; 100			
Routine activities (IBS-IN)							
Mean (SD)	48.8 (27.3)	61.1 (21.6)	39.4 (21.8)	51.6 (27.1)	12.3 (5.3;19.3)	12.3 (4.5;20)	0.1 (-10.2;10.3) 0.810*
Median	48.2	64.3	35.7	57.1			
Pct 25-75	28.6 -71.4	50 -75	21.4 -57.1	28.6 -75			
Min, Max	0; 96.4	0; 92.9	3.6; 82.1	7.1; 96.4			
Body image (IBS- BI)							
Mean (SD)	65.5 (25.2)	81.3 (18.8)	63.9 (25.6)	75.3 (23.6)	15.8 (10.3;21.3)	11.4 (4.4;18.4)	4.4 (-4.3;13.1) 0.393*
Median	71.9	87.5	62.5	81.3			
Pct 25-75	43.8 -87.5	68.8 -96.9	43.8 -87.5	68.8 -93.8			
Min, Max	6.3; 100	37.5; 100	6.3; 100	6.3; 100			
Concern about health (IBS –HW)							
Mean (SD)	46.9 (24.9)	63.3 (21.0)	38.2 (25.5)	51.9 (27.7)	16.5 (10.6;22.3)	13.7 (6.3;21.1)	2.8 (-6.5;12.1) 0.260*
Median	50	66.7	33.3	41.7			
Pct 25-75	33.3 -66.7	45.8 -83.3	16.7 -58.3	33.3 -83.3			
Min, Max	0; 91.7	16.7; 100	0; 91.7	0; 91.7			
Dietary limitations (IBS –FA)							
Mean (SD)	30.6 (27.1)	35.4 (23.6)	27.4 (25.6)	33.5 (29.8)	4.8 (-3.0;12.6)	6.2 (-3.2;15.6)	-1.4 (-13.4;10.6) 0.820*
Median	25	29.2	25	33.3			
Pct 25-75	8.3 -50	16.7 -50	0 -41.7	8.3 -58.3			
Min, Max	0; 91.7	0; 83.3	0; 83.3	0; 91.7			
Social reactions (IBS –SR)							
Mean (SD)	70.2 (23.4)	80.5 (18.3)	58.8 (26.7)	68.8 (23.2)	10.3 (3.8;16.9)	9.9 (2.9;17.0)	0.4 (-9.1;9.8) 0.937 0.992*
Median	75	87.5	62.5	68.8			
Pct 25-75	56.3 -87.5	75 -93.8	43.8 -81.3	56.3 -87.5			
Min, Max	0; 100	37.5; 100	0; 100	12.5; 100			

IBS-QOL	Colilen IBS (N =40)		Placebo (N=39)		Colilen IBS $^{\&}\mu_{12s}$- μ_0 (IC95%)	Placebo $^{\&}\mu_{12s}$- μ_0 (IC95%)	**Dif μ1-μ2 (IC 95%) p*
	Inicio	Fin	Inicio	Fin			
Sexual relations (IBS- SX)							
Mean (SD)	75 (31.0)	82.5 (25.4)	70.2 (30.7)	71.8 (32.5)	7.5 (1.2;13.8)	1.6 (-7.3;10.5)	5.9 (-4.7;16.5) 0.486*
Median Pct 25-75	87.5 62.5 -100	93.8 75 -100	75 62.5 -100	75 50 -100			
Min, Max	0; 100	0; 100	0; 100	0; 100			
Social relationships (IBS- RL)							
Mean (SD)	69 (25.7)	78.8 (19.1)	60.9 (23.9)	66.5 (29.8)	9.8 (3.6;16.0)	5.6 (-2.1;13.2)	4.2 (-5.4;13.9) 0.470*
Median Pct 25-75	70.8 45.8 -91.7	83.3 66.7 -91.7	66.7 41.7 -75	75.0 50 -91.7			
Min, Max	8.3; 100	33.3; 100	8.3; 100	0; 100			

The analysis of the correlation between the variables "quality of life" (QoL) and "IBS severity" (IBS-SSS) revealed a positive—or direct—relationship. At the time of inclusion in the study, the correlation between scores on the IBS-QOL and IBS-SSS questionnaires showed—in both treatment groups (Colilen IBS and placebo)—a higher concentration of cases within the categories representing greater IBS severity and poorer quality of life.

After 12 weeks, a general shift in the distribution of cases was observed toward categories representing lower IBS severity and better quality of life. In the placebo group, this distribution was more dispersed compared to the Colilen IBS group, where a greater concentration of cases was evident within the categories corresponding to the best outcomes.

ADVERSE EVENTS

At least one adverse event was reported in 21 episodes (11 in the Colilen IBS group and 10 in the placebo group); no serious adverse events were recorded. Only 5 adverse events were considered related to the study treatment: 1 in the Colilen IBS group and 4 in the placebo group. These 5 adverse events were reported across 1 episode in the Colilen IBS group and 3 episodes in the placebo group.

Características generales de los eventos adversos.

General characteristics		Colilen IBS		Placebo	
		n	%	n	%
... of the adverse event (AE) by Episode					
Episodes involving an AE		11	25%	10	25.6%
Episodes with an associated EA		1	2.5%	3	7.7%
Episodes involving a serious adverse event		0	0	0	0
Episodes involving an adverse event (AE) of		5	12.5%	6	15.4%
... of the AEs recorded in the study					
Total AEs reported		42	100,0%	28	100,0%
Severity	Not serious/not serious	42	100,0%	28	100,0%
Intensity	Mild	11	26,2%	5	17,9%
	Moderate	16	38,1%	14	50,0%
	Severe	15	35,7%	9	32,1%
Causal relationship	Very likely/certain	1	2,4%	1	3,6%
	Possible	0	0,0%	3	10,7%
	Unrelated	40	95,2%	24	85,7%
	Not assessable	1	2,4%	0	0,0%
Treatment under study	No changes	38	90,5%	27	96,4%
	Dose modification	0	0,0%	1	3,6%
	Temporary interruption	4	9,5%	0	0,0%
AE result	Recovered	30	71,4%	20	71,4%
	Improved	3	7,1%	2	7,1%
	Persists	9	21,4%	6	21,4%
It required treatment	No	14	33,3%	18	64,3%
	Yes	28	66,7%	10	35,7%
Symptom of IBS	Yes	0	0,0%	3	10,7%
	No	42	100,0%	25	89,3%
Duration of AEs (Days)		N válidos= 31		N válidos= 20	
	Mean (SD)	2.9 (4)		4.7 (11.1)	
	Median	2 (0 -6)		0 (0 -4.5)	
	Min; máx.	(0; 20)		(0; 49)	