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Clinical trial: the efficacy of alverine citrate/simeticone combination on abdominal pain/discomfort in irritable bowel syndrome– a randomized, double-blind, placebo-controlled study

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SUMMARY

Background
Alverine citrate and simeticone combination has been used for almost 20 years in irritable bowel syndrome (IBS), but supportive scientific evidence of efficacy was limited.

Aim
To evaluate the efficacy of alverine citrate and simeticone combination in patients with IBS-related abdominal pain/discomfort.

Methods
A total of 412 IBS patients meeting ROME III criteria were included in this double-blind randomized placebo-controlled study if their abdominal pain/discomfort intensity was at least 60 mm on a 0–100 mm visual analogue scale (VAS) during a 2-week run-in treatment-free period. Patients were randomly assigned through the use of Interactive Voice Response System to receive either alverine citrate 60 mg with simeticone 300 mg three times daily or matching placebo for 4 weeks.

Results
The full analysis set included 409 patients (71.4% female: mean age: 46.2 ± 13.9 years). At week 4, alverine citrate and simeticone group had lower VAS scores of abdominal pain/discomfort (median: 40 mm vs. 50 mm, $P = 0.047$) and higher responder rate (46.8% vs. 34.3%, OR = 1.3; $P = 0.01$) as compared with placebo group. Patient receiving alverine citrate and simeticone reported greater global symptom improvement compared with those receiving placebo ($P = 0.0001$). Reported adverse events were similar in both groups.

Conclusion
Alverine citrate/simeticone combination was significantly more effective than placebo in relieving abdominal pain/discomfort in patients with IBS.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common, nonlife-threatening condition characterized by abdominal pain and/or discomfort associated with altered bowel habits (constipation, diarrhoea or both) and very often bloating, which are not explained by bowel anatomical anomalies or biochemical abnormalities. Depending on the criteria, the prevalence of IBS is estimated to range between 8% and 15% in North America and Europe.[1–3] When using Rome III criteria,[4] a homogeneous IBS population may be obtained. Symptoms tend to recur at highly variable intervals, worsen during flares and significantly impact on quality of life in a large subset of patients.[5, 6]

IBS has been linked to several pathophysiological mechanisms: visceral hypersensitivity, digestive motor disturbances, brain-gut axis dysfunction, intestinal dysbiosis and micro-inflammatory changes in the gut wall.[7–10] Moreover, a subgroup of IBS patients reveals psychological disturbances which may interfere with the symptoms are dealt with.[4, 11] Although all these causes probably overlap and vary in importance from one patient to another, visceral hypersensitivity appears to be a key pathophysiological factor.[12]

A recent review of available IBS treatments in Europe concluded that the efficacy of most is limited by a low level of evidence[2] for several reasons: a multifactorial pathophysiology resulting in heterogeneous patients groups, a variety of symptoms leading to very diverse expectations, a strong placebo effect[13, 14] and a lack of tools with sufficient validity, reliability and sensitivity to change to allow for proper symptom assessment.

The alverine citrate/simeticone (ACS) combination (Meteospasmyl; Mayoly-Spindler, France) has been available in Europe since 1990 for the treatment of symptoms related to functional bowel disorders (FBDs). It combines 60 mg of alverine citrate, an active substance derived from papaverine with 300 mg of simeticone (dimeticone enriched with silicon dioxide) in a soft capsule. In pharmacological studies, alverine citrate has been shown to exert an effect on intestinal motility and intestinal sensitivity, two factors recognized as involved in the onset of FBD, without exhibiting the potential drawbacks of a medication with systemic effects.[15–19] Alverine citrate affects basal and stimulated motility via a calcium-dependent and -independent inhibition of neuronal excitability[15] as well as direct inactivation of L-type Ca^{2+} of smooth muscle cells.[19] Experimental findings support an antinociceptive action by selective receptor-mediated mechanisms. Alverine has been shown to bind to 5-HT1A receptors thereby acting as an antagonist that reduces the visceral pronociceptive effect of 5-HT.[18] This mechanism of action may account for its antinociceptive effects in postinflammatory visceral hypersensitivity.[16] Simeticone is an inert substance with antifoaming activity. Additionnally, simeticone is able to reduce stress-induced increase in colonic permeability in animals (unpublished data). By limiting mucosal entry of immune stimulating substances, simeticone is likely to reduce the sensitization of primary afferent nerve endings.

In previous double-blind, clinical studies, ACS has been shown to have a therapeutic effect in patients with FBDs (cited by Coelho *et al.*[18]) when compared with other antispasmodics. However, these studies were performed in patients suffering from FBD not strictly defined as IBS. Moreover, these studies were not consistent with current recommendations for IBS clinical studies.[20]

Our double-blind study was designed to assess the symptomatic efficacy of ACS, when administered three times daily for 4 weeks, for the relief of abdominal pain/discomfort in any subgroup of IBS patients meeting Rome III criteria.

METHODS

The design and methods of this study were consistent with the recommendations of Rome III, EMEA and expert groups.[20–23]

Study design

This multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted in 17 gastroenterological sites in Hungary and Poland from July 2007 to July 2008. The final protocol and amendments were approved by each country's central independent ethics committee and the study was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice, the Declaration of Helsinki and applicable local regulations. Before entry, patients received detailed information on the study and signed a written consent form.

After a 2-week run-in treatment-free period, patients satisfying the eligibility criteria were randomized to either ACS combination or matching placebo, in a 1:1 ratio. Patients were treated for 4 weeks.

Randomization, stratified by country, was centralized through an Interactive Voice Response System.

Patient selection

Patients were eligible for inclusion if they met the following criteria: adult patient (aged 18–75 years), suffering from IBS as defined by Rome III criteria[24] and for no longer than 5 years. At the end of the run-in period, IBS patients were randomized into one of the two treatment groups if they exhibited:

(i) Abdominal pain/discomfort for at least 2 days/week during the run-in period;

(ii) Intensity of abdominal pain/discomfort ≥60 mm on a visual analogue scale (VAS) at randomization (based on the previous 7 days).

Patients were excluded from participation for the following reasons: if their diagnosis was not IBS, if they presented alarming signs (anaemia, rectal bleeding, unexplained weight loss, general health status impairment) or in case of any underlying cause raising doubt as to the IBS diagnosis (diabetes, thyroid dysfunction, biliary or pancreatic disorders or infectious diarrhoea), history of gastro-intestinal cancer or significant gastro-intestinal surgery, acute/uncontrolled systemic pathology or liver function tests ≥3 times the upper normal limits. Patients with known intolerance to ACS combination or one of its components were also excluded from entry, as were patients with regular use of ACS combination during the 6 months prior to the study.

Drug treatment

During the active treatment period, patients took either ACS (alverine citrate 60 mg + simeticone 300 mg) or matching placebo. ACS and placebo were identical in appearance and taste and administered orally as soft capsules three times a day, prior to meals for 4 weeks. No study drug was administered during the run-in period.

Randomization and blinding

The randomization scheme was performed by a specific contractor (Cardinal Systems, Paris, France), who was independent from the Contract Research Organization (I3 Research) in charge of the study conduct and analysis. Cardinal Systems generated the randomization scheme (stratified by country) using SAS program (SAS Institute Inc., Cary, NC, USA). Codes were held by their statistician. Patients were equally allocated to treatment in block sizes of 4. When a patient was eligible for randomization, investigator contacted the randomization centre through the Interactive Voice Response System. The IVRS prompted the user for key information: VAS value in millimeters, number of pain/discomfort episode during the first and second week of run-in period. If randomization criteria were met, randomization was confirmed and IVRS allocated the appropriate treatment kit number and a notification was sent by fax to the investigator to confirm treatment kit number to be dispensed. All study personnel and participants were blinded to the true identity of the treatment assigned until database was locked.

Prohibited/authorized treatment

Prohibited treatments during the study were those likely to jeopardize study drug evaluation, i.e. antispasmodics, antidiarrhoea drugs and laxatives. Antidepressants and anxiolytics were allowed, if they were started prior to the study and had been taken at a stable dosage over the last 3 and 1 months respectively. Their dosage had to be stable during the 4-week study. Patients were advised not to change their diet throughout the study.

Data collection

Visits were scheduled at inclusion (week −2), randomization (week 0), and then at weeks 1, 2 and 4. Throughout the duration of the study (from weeks −2 to 4), patients had to report in a paper diary on a daily basis: abdominal pain/discomfort, bloating, any other symptoms, number and form of stools, medications used and study drug intake. At each visit, patients rated their abdominal pain/discomfort on a 0–100 mm VAS relating to the previous week. Discomfort was defined as an uncomfortable, but not painful sensation. In IBS patients, the 0–100 mm VAS of abdominal pain was shown to be a valid and a reliable tool,[25] with discriminatory power.[26] At randomization and end of treatment (week 4), patients quantified the impact of IBS on their daily life; they assessed overall treatment efficacy at week 4.

Efficacy endpoints

Primary efficacy endpoint. The primary efficacy endpoint was the difference in the magnitude of change in

abdominal pain/discomfort VAS scores from weeks 0 to 4 between treatment groups. In addition, a patient was defined as responder if abdominal pain/discomfort VAS score decreased by at least 50% at week 4 compared to week 0. This definition of responder is considered accurate.[21, 27] In the statistical analysis plan, the difference in responder rates between both groups was taken into account in the secondary analysis of the primary efficacy endpoint.

Secondary efficacy criteria. Secondary end-points included intensity of abdominal pain assessed by VAS at weeks 1 and 2, overall patient assessment regarding symptom relief, IBS impact on daily life and changes in remaining IBS symptoms as compared to week 0.

Patients were asked to assess the outcome of their IBS symptoms at the end of week 4 by responding to the following statement, 'The treatment helped to improve my bowel problems' using a 5-point Likert scale: 'strongly disagree', 'disagree', 'neither agree nor disagree', 'agree' and 'strongly agree'.

At randomization (week 0) and end of treatment (week 4), patients were also asked to grade the impact of IBS on their daily life by responding to the following statement: 'My bowel problems limit my life and everyday activities'. A 5-point Likert scale was used, with scores ranging from 1 to 5: 'extremely', 'quite a bit', 'moderately', 'a little' or 'not at all'.

Each day, patients recorded the frequency and form of stools in a paper diary. At each visit the investigator assessed the weekly average frequency and the most frequent type of stools by using the Bristol Stool Form Scale (BSFS).

The presence of other IBS symptoms (bloating, straining, urgency and feeling of incomplete defecation) was also noted.

Concomitant factors

Although psychological factors are not required for IBS diagnosis, they may influence GI symptoms.[11, 28, 29] The Hamilton Rating Scales for Depression (HAM-D) and Anxiety (HAM-A) were used to detect symptoms of depressive or anxiety disorders and if present to explore their potential impact on the treatment's effect. Trained and certified raters conducted patient's interviews and filled in the HAM-D and HAM-A questionnaires at weeks 0 and 4.

Safety

All adverse events (AEs) were actively sought at each visit. Standard laboratory tests for haematology and biochemistry were performed at inclusion (week −2) and at end of treatment (week 4). Haematology included haemoglobin, total white blood cell count, platelet count and a differential count including neutrophiles, lymphocytes, monocytes, eosinophiles and basophiles. Biochemistry included serum creatinine, alkaline phosphatases, aspartate amino transferase, alanine amino transferase and total bilirubin.

Statistical analysis

Analyses were performed on three sets: safety analysis set, full analysis set (FAS) and per protocol set. The safety analysis set included all randomized patients who received at least one dose of study treatment. The FAS included all randomized patients who took at least one dose of study treatment and for whom at least one on-treatment main criterion measure was available. The FAS population corresponded to the recommended intention-to-treat (ITT) population. The per-protocol set (PP) included a subgroup of the FAS population fulfilling the following criteria: minimal time of exposure to treatment (≥3 weeks), minimal treatment compliance during minimal study drug exposure time (≥66%) and evaluation of the main criterion (abdominal pain/discomfort VAS score at week 4).

Primary efficacy criterion was assessed using two analyses. The primary analysis focused on the between-group difference in the degree of change in abdominal pain/discomfort VAS scores from weeks 0 to 4. Due to the non-normality of the VAS score change distribution, a rank-based nonparametric analysis of covariance (ANCOVA, Quade's analysis)[30] was performed on week 4 VAS values in the ITT population. This was conducted after imputing missing values by last-observation-carried-forward (LOCF). The nonparametric analysis of the week 4 VAS values adjusted for week 0 VAS values is equivalent to the nonparametric analysis of the VAS score changes adjusted for week 0 value. The secondary analysis of the primary efficacy criterion focused on responder rates using a Cochran-Mantel-Haenszel Test adjusted for country. For consistency, responder rates were calculated, after imputing missing values using the LOCF-based method. This analysis was also performed with a 60% cut-off value. A logistic

regression model adjusting for treatment and country was used and the odds ratio for the treatment effect with 95% confidence interval was calculated.

The efficacy analyses were primarily performed on the ITT population and secondarily on the PP population.

The safety analysis was performed on the safety population.

The study was planned to assess superiority of ACS combination over placebo. The sample size was calculated based on the primary end point. Notably, there are no guidelines specifying the threshold considered clinically significant for IBS. Considering a conservative expected standard deviation of 25 mm of VAS score change from weeks 0 to 4, and a conventional two-sided type-1 error of 5%, the sample size was established at 200 patients in each group, enabling the detection of a minimal clinically significant effect of 7 mm with a guaranteed 80% power. All statistical analyses were performed using the SAS software version 9. As no direct action on any specific subtype was expected, no subgroup analysis on bowel habit subtypes was performed and the different IBS subtypes were not taken into account for the calculation of the study sample size.

RESULTS

Baseline patient characteristics

Between July 2007 and June 2008, 429 patients were selected and entered the 2-week treatment-free run-in period. Among these patients, 17 (4.0%) were not randomized for the following reasons: VAS <60 mm (five patients), consent withdrawal (10 patients), serious AE (one patient) and lost to follow-up (one patient). Among the remaining 412 patients, 207 were randomly assigned to ACS, and 205 to placebo. A total of 399 (97.0%) patients completed the study, whereas 13 (3.0%) discontinued the study. The most common reasons for study discontinuation were: lack of efficacy in five patients (ACS: one patient; placebo: four patients) and AEs in three patients (ACS: one patient; placebo: two patients). One patient in each group was lost to follow-up. The flow chart of the study is shown in Figure 1. Of the randomized patients, all 412 comprised the safety set (207 in ACS and 205 in placebo groups), 409 formed the ITT set (205 in the ACS and 204 in the placebo groups) and 386 comprised the PP set (194 in the ACS and 192 in the placebo groups).

Baseline patient characteristics of ITT population are displayed in Tables 1 and 2. Mean age was 46.2 ± 13.9 years (mean ± s.d.). No differences were observed between both groups regarding demographic characteristics, abdominal pain/discomfort score, occurrence of other gastrointestinal symptoms, bowel habit disorders, and anxiety (HAM-A) and depression (HAM-D) scores. Concomitant medical conditions were mainly hypertension (27.7%), gastroesophageal reflux disease (18.0%) and psychological disorders (14.3%). The most common concomitant drugs were: cardiovascular agents (33.3%) antiacids, including mainly proton pump inhibitors (26.7%), anxiolytics (10.7%) and antidepressants (8%). Concomitant pathologies and drugs were comparable between both groups.

Primary efficacy criterion

Intention-to-treat population:

A greater effect on abdominal pain/discomfort VAS scores from weeks 0 to 4 was observed following ACS compared to placebo, with a week 4 median of: 40.0 mm (range: 0–95) and 50.0 mm (range: 0–100) respectively. The VAS score analysis at week 4 showed a statistically significant difference in favour of ACS combination ($P = 0.047$) (Figure 2).

The responder rates at week 4 were significantly higher with ACS than placebo: 46.8% vs. 34.3% (OR: 1.30; 95% CI: 1.06–1.59; $P = 0.01$). Sensitivity analyses of responders with a 60% cut-off value showed a statistically significant difference (Figure 3).

Per-protocol population

A greater reduction in abdominal pain/discomfort VAS score was observed following ACS [median at week 4: 39.0 mm (range: 3–95)] than placebo [median at week 4: 49.5 mm (range: 0–90)], the difference being statistically significant ($P = 0.036$).

Responder rates at week 4 were significantly higher with ACS than placebo: 49.0% vs. 35.9% (OR: 1.31; 95% CI: 1.07–1.60; $P = 0.01$).

Secondary efficacy criteria

Abdominal pain/discomfort at weeks 1 and 2. At week 1, VAS scores reduction and responder rates were greater with ACS group than with placebo, although the difference was not statistically significant.

At week 2, abdominal pain/discomfort VAS scores were significantly ($P = 0.02$) in favour of ACS [median: 51.0 mm (range: 2–93)] as compared with placebo

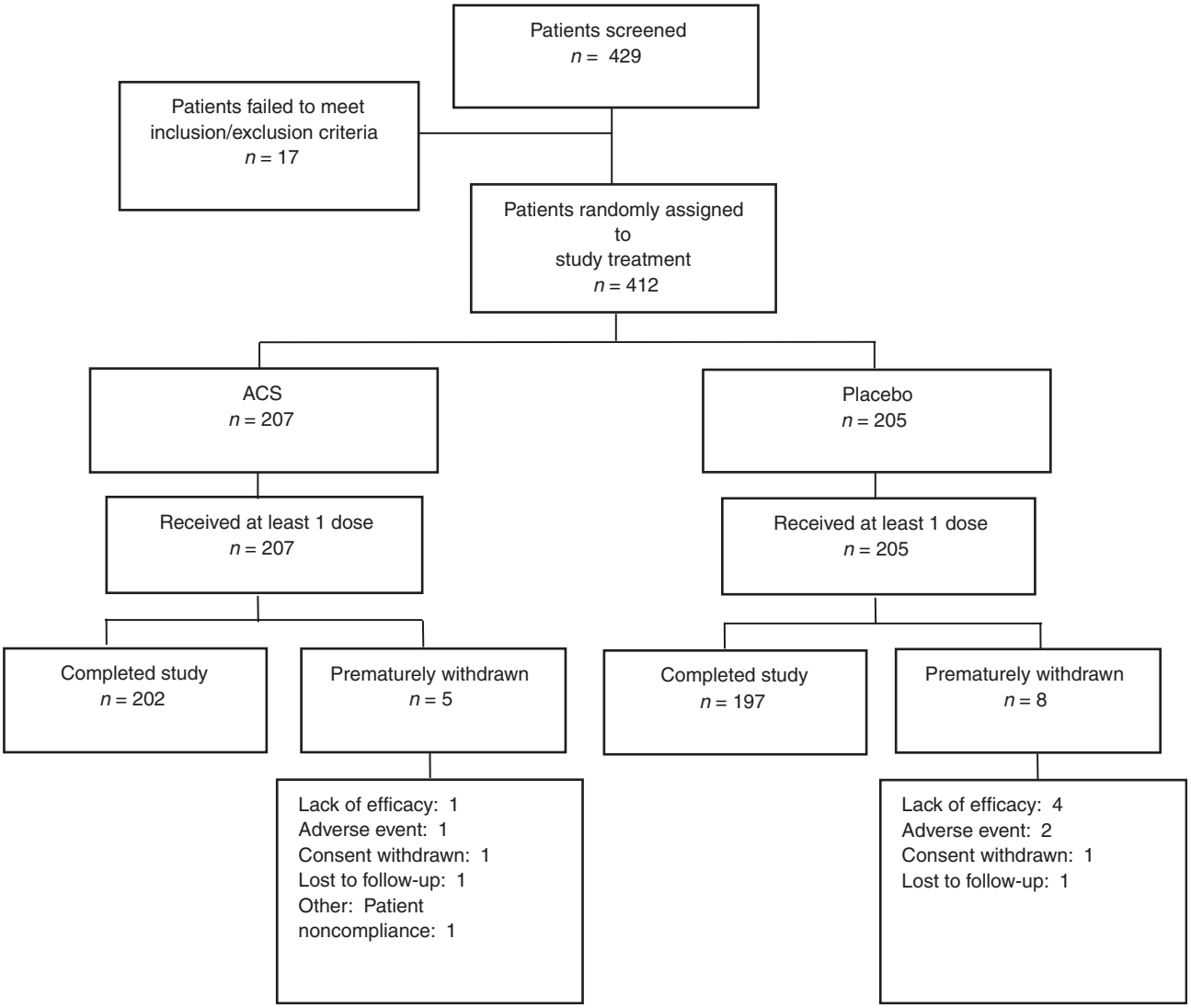

Figure 1. Flow chart of patients screened and randomized in the study.

[median: 59.0 mm (range: 0–100)] (Figure 2). A statistically significant difference in favour of ACS was also observed on the responder rates (27.9% vs. 17.2%; $P = 0.01$).

Overall treatment assessment. Positive overall treatment assessments were reported more frequently in the ACS-treated group, while negative assessments were more common in the placebo group, the difference being highly significant ($P = 0.0001$; Table 3).

IBS life impact score. From weeks 0 to 4, there was a trend towards greater improvements in IBS life impact scores following ACS as compared with placebo (0.97 vs. 0.76), although the difference was not statistically significant ($P = 0.08$) (Table 4).

Stool assessment and other IBS symptoms. The number and rate of patients who reported constipation as the most frequent stool type during the last 7 days (score 1 or 2) decreased from weeks 0 to 4, from 45 (21.9%) to 29 (14.1%) in the ACS group and from 51 (25%) to 23 (11.3%) in the placebo group. The number and rate of patients who reported diarrhoea (score 6 or 7) decreased from weeks 0 to 4, from 45 (21.9%) to 18 (8.8%) in the ACS group and from 47 (23%) to 32 (15.7%) in the placebo group. No significant difference between the groups was observed with regard to the

Table 1. Baseline characteristics of the intention-to-treat population

	ACS combination (n = 205)	Placebo (n = 204)
Females (%)	147 (71.7)	145 (71.1)
Age (years, mean ± s.d.)	46.5 ± 13.5	46.0 ± 14.3
Time elapsed since IBS diagnosis (months, mean ± s.d.)	22.7 ± 21.0	18.7 ± 19.1
Number of days with symptoms/month (mean ± s.d.)	22.1 ± 7.9	23.4 ± 7.5
Week 0 abdominal pain/discomfort (VAS scores)		
Mean ± s.d.	72.2 ± 7.5	74.2 ± 8.5
Median	71.0	73.5
Associated complaints (%)		
Bloating	192 (93.7)	195 (95.6)
Bowel habits disorders*	174 (84.9)	171 (83.8)
Stool form type (BSFS)† (%)		
1–2	45 (21.9)	51 (25.0)
6–7	45 (21.9)	47 (23.0)
Other GI symptom	53 (25.9)	57 (27.9)
Number of patients having taken a specific treatment for IBS in the 6 months prior to the study	43 (21.0)	50 (24.5)

N, number; ITT, intention to treat; ACS, alverine citrate/simeticone; s.d., standard deviation; GI, gastro-intestinal; IBS, irritable bowel syndrome; BSFS, Bristol Stool Form Scale.
* Patient self-reporting.
† Investigator estimation based on the patient diary.

Table 2. Baseline levels for depression and anxiety in the intention-to-treat population

	ACS	Placebo
Depression levels (HAM-D)*		
Mild		
n	112	113
VAS score (mean ± s.d.)	71.5 ± 7.6	73.8 ± 8.6
Moderate		
n	88	88
VAS score (mean ± s.d.)	73.3 ± 7.5	74.7 ± 8.4
Severe		
n	5	3
VAS score (mean ± s.d.)	71.0 ± 6.3	74.0 ± 4.6
Anxiety levels (HAM-A)†		
Mild		
n	143	144
VAS score (mean ± s.d.)	71.8 ± 7.4	73.8 ± 8.4
Moderate		
n	38	45
VAS score (mean ± s.d.)	72.9 ± 6.6	74.3 ± 9.0
Severe		
n	24	15
VAS score (mean ± s.d.)	73.7 ± 9.2	78.4 ± 6.9

VAS, visual analogue scale, s.d., standard deviation; ACS, alverine citrate/simeticone; HAM-D, Hamilton Rating Scales for Depression; HAM-A, Hamilton Rating Scales for Anxiety.
* Total HAM-D score: <13 = mild, 13–25 = moderate, >25 = severe.
† Total HAM-A score: <18 = mild, 18–24 = moderate, 25–30 = severe.

progression of bowel habit disorders or other IBS symptoms.

Concomitant factors. Reductions in HAM-A and HAM-D scores from weeks 0 to 4 were observed in both groups, although the difference was not statistically significant.

Safety. The incidence of AEs was similar in both groups with 17.9% and 24.4% of patients reporting at least one treatment emergent adverse events (TEAE) under ACS and placebo respectively. TEAEs reported by at least 2% of patients are presented in Table 5. Seven (3.4%) patients in the ACS group and 12 (5.9%) in the placebo group reported treatment related TEAEs, as considered by the investigator. There were no deaths or other drug-related serious adverse events (SAE) in this study. Only one (0.2%) patient (ACS group) reported a SAE (traumatic tendon rupture), which was not considered drug-related. Three patients (one in the ACS group and two in the placebo group) withdrew from the study due to TEAEs, namely eye swelling in the ACS patient, and dizziness and pain in the extremities in the placebo patients.

DISCUSSION

This multicentre, double blind, placebo-controlled, randomized study was the first to assess an antispasmodic drug in IBS patients using Rome III criteria. Patients from hospital databases were prescreened for eligibility. About 50% of these patients were not selected as they did not meet eligibility criteria, in particular, absence of ACS administration in the 6 months prior to inclusion. Furthermore, many patients did not accept to be referred to a psychiatrist for anxiety and depression symptoms rating as they denied any

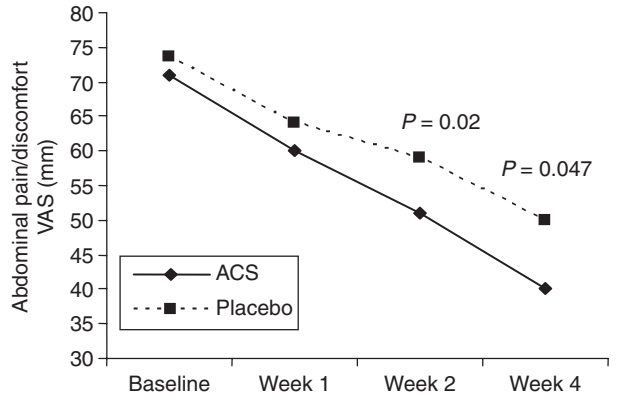

Figure 2. Evolution of weekly abdominal pain assessment.

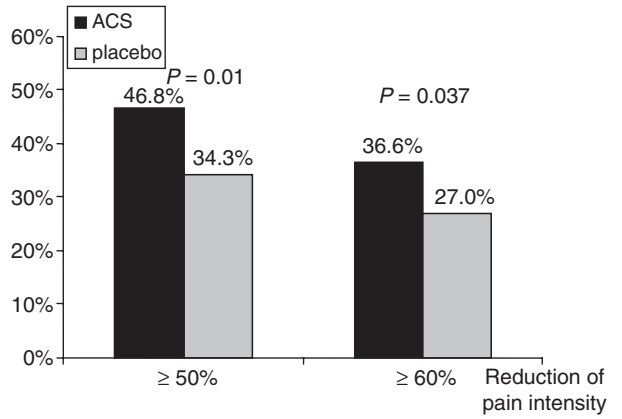

Figure 3. Percentage of responders at week 4 in the intention-to-treat population.

Table 3. Global assessment of treatment at week 4 (intention-to-treat population)

	Treatment group	
Global evaluation [*n* (%)]	ACS combination	Placebo
Strongly disagree	10 (5.0)	10 (5.1)
Disagree	11 (5.5)	46 (23.2)
Neither agree nor disagree	54 (27.0)	46 (23.2)
Agree	74 (37.0)	72 (36.4)
Strongly agree	51 (25.5)	24 (12.1)
P-value*	=0.0001	

n, number, ITT, intention to treat; ACS, alverine citrate/simeticone.
Patients answered the following statement: 'The treatment helped to improve my bowel problems': 'strongly disagree', 'disagree', 'neither agree nor disagree', 'agree' and 'strongly agree'.
* Cochran–Mantel–Haenszel adjusted for country.

Table 4. Irritable bowel syndrome life impact in the intention-to-treat population (mean ± s.d.)

	ACS combination	Placebo
Week 0	2.33 ± 0.78 (*n* = 205)	2.33 ± 0.81 (*n* = 203)
Week 4	3.32 ± 1.09 (*n* = 203)	3.10 ± 0.99 (*n* = 199)
Change	0.97 ± 1.09 (*n* = 203)	0.76 ± 1.04* (*n* = 198)

ACS, alverine citrate/simeticone.
* *P*-value: 0.08 (Van Elteren test).

psychological component in their IBS symptoms. This strict screening may account for the low screen failure rate. In the study population, at the end of a 4-week treatment period, the relief of abdominal pain/discomfort was greater with ACS than placebo. This superior efficacy was associated with significantly higher responder rates in the ACS group (46.8%) compared with placebo (34.3%) at week 4. This resulted in a number needed to treat (NNT) of 8, which is close to the NNT related to pain relief (8.3) previously determined by a meta-analysis of other smooth muscle relaxant studies meta analysis.[31, 32] The overall treatment assessment by patients showed a higher rate of symptoms improvement with ACS compared with placebo. However, because of the lack of severity measurement of symptoms other than pain, particularly bloating, no further evidence could be collected. Because of the lack of comparative data between ACS combination and alverine citrate or simeticone, the ACS effect cannot be attributed to one particular component or to a combination. This issue should be addressed in future clinical studies including both pain/discomfort assessment and objective bloating measurements.

At baseline, bowel habit disorders were self-reported by 84% patients. IBS subtype estimation done by investigators based on patient diaries and using BSFS revealed that 23% of patients were IBS-C and 22% IBS-D. Other patients reported stool types 3, 4 and 5 as the most frequent during the 7 days preceding estimation. The discrepancy between the percentages may be explained by the difficulty in assessing bowel habit disorders as perceived by patients, as previously reported by Hungin *et al.*[33] As our patients mainly complained of severe pain/discomfort, and patients with IBS-M pattern have been reported to exhibit greater pain/discomfort severity than patients with other stool patterns,[34] it may be hypothesized that these patients suffered from mixed type (IBS-M) or unsubtyped IBS, although our

Table 5. Treatment emergent adverse events occurring in ≥2% of patients (safety population)

System organ class* Preferred term (%)	ACS combination (n = 207)	Placebo (n = 205)	Total (n = 412)
Gastrointestinal disorders			
Nausea	2.9	5.4	4.1
Abdominal pain upper	1.4	3.4	2.4
Nervous system disorders			
Headache	3.4	5.9	4.6
General disorders			
Asthenia	0.5	2.0	1.2
Ear and labyrinth disorders			
Vertigo	1.9	2.0	1.9

* MedDRA V 11.0 (Northrop Grumman Corporation, New York, NY, USA) applied.

data do not allow us to draw conclusions on this issue. The number of patients meeting the BSFS definition of diarrhoea or constipation decreased to 30%. As the decrease was comparable in both the ACS and the placebo groups, it is unlikely to be related to drug itself. In our view, the decrease is more likely related to the natural fluctuations of IBS as reported by Garrigues *et al.*[35] However, it cannot be excluded that some patients changed from one subgroup to another, although changes from constipation to diarrhoea subgroups and vice versa are uncommon.[34, 35]

Patients included in the study had been suffering from IBS for less than 5 years and presented abdominal pain/discomfort ≥60 mm on VAS. We decided to exclude patients with IBS history longer than 5 years, as they are a subgroup of patients with a more complex clinical profile, and have often used multiple therapies.[14] Moreover, the selected population was thought to be representative of IBS patients seen by general practitioners or gastroenterologists in primary and secondary care. Large epidemiological surveys have reported symptom duration of less than 5 years in a large subset of IBS patients, particularly among those seeking a medical advice for the first time.[33, 36] This also appears to apply to our patients, as more than three-quarters did not receive any drug for IBS within the 6 months preceding enrolment. For inclusion, pain/discomfort had to be severe enough to detect a difference between the two groups. Even among patients likely to experience positive changes, the severity of IBS symptoms had to be sufficiently marked to distinguish between treatment and placebo. Previous randomized controlled studies have revealed a large positive placebo response in IBS patients, ranging from 30% to 40%.[13] In our study, the results obtained in the placebo group (which displayed a high 50% responder rate (34.3%) on abdominal pain/discomfort at week 4) are in accordance with previously published results. Hence, the positive overall results of our study cannot be explained by a lower placebo response.

Our selection criteria likely account for the baseline characteristics of the IBS population included in this trial. In our study population, IBS had a moderate impact on quality of life and approximately 10% of patients experienced severe anxiety or depression symptoms. This figure is close to the lower range of psychological co-morbidity reported for IBS.[11] Consequently, we acknowledge that our results may not be applicable to long-standing sufferers.

In conclusion, ACS combination administered orally three times daily for 4 weeks, significantly improves abdominal pain/discomfort in IBS patients irrespective of the IBS subgroup. Our results support the conclusion that ACS is a therapeutic option for IBS patients seen in primary and secondary care.

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