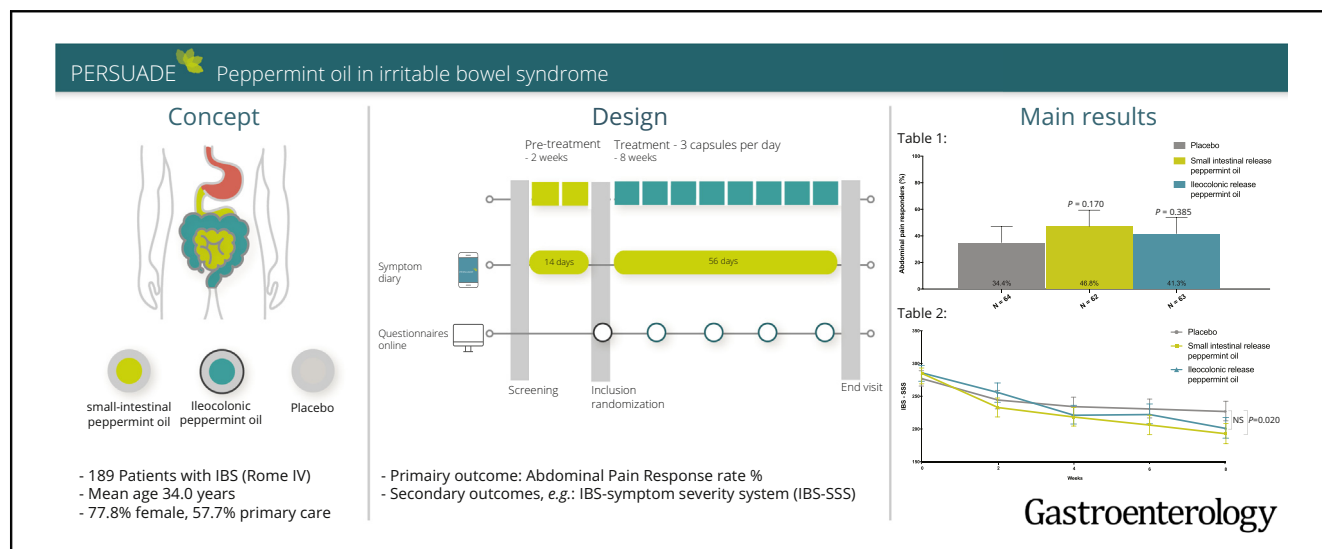# Efficacy and Safety of Peppermint Oil in a Randomized, Double-Blind Trial of Patients With Irritable Bowel Syndrome

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PERSUADE — Peppermint oil in irritable bowel syndrome

Concept
- 189 Patients with IBS (Rome IV)
- Mean age 34.0 years
- 77.8% female, 57.7% primary care

small-intestinal peppermint oil / Ileocolonic peppermint oil / Placebo

Design
Pre-treatment - 2 weeks
Treatment - 3 capsules per day - 8 weeks
Symptom diary — 14 days — 56 days
Questionnaires online
Screening — Inclusion randomization — End visit
- Primary outcome: Abdominal Pain Response rate %
- Secondary outcomes, e.g.: IBS-symptom severity system (IBS-SSS)

Main results
Table 1: P = 0.170 / P = 0.385 / 34.4% N = 64 / 46.8% N = 62 / 41.3% N = 63
Table 2: NS / P=0.020

Gastroenterology

BACKGROUND & AIMS: Peppermint oil is frequently used to treat irritable bowel syndrome (IBS), despite a lack of evidence for efficacy from high-quality controlled trials. We studied the efficacy and safety of small-intestinal–release peppermint oil in patients with IBS and explored the effects of targeted ileocolonic-release peppermint oil. **METHODS:** We performed a double-blind trial of 190 patients with IBS (according to Rome IV criteria) at 4 hospitals in The Netherlands from August 2016 through March 2018; 189 patients were included in the intent-to-treat analysis (mean age, 34.0 years; 77.8% female; 57.7% in primary care), and 178 completed the study. Patients were randomly assigned to groups given 182 mg small-intestinal–release peppermint oil, 182 mg ileocolonic-release peppermint oil, or placebo for 8 weeks. The primary endpoint was abdominal pain response, as defined by the US Food and Drug Administration: at least a 30% decrease in the weekly average of worst daily abdominal pain compared with baseline in at least 4 weeks. The co-primary endpoint was overall relief of IBS symptoms, as defined by the European Medicines Agency. Secondary endpoints included abdominal pain, discomfort, symptom severity, and adverse events. **RESULTS:** Abdominal pain response did not differ significantly between the peppermint oil and placebo groups: 29 of 62 patients in the small-intestinal–release peppermint oil group had a response (46.8%,

$P = .170$ vs placebo), 26 of 63 patients in the ileocolonic-release peppermint oil group had a response (41.3%, $P = .385$ vs placebo), and 22 of 64 patients in the placebo group had a response (34.4%). We did not find differences among the groups in overall relief (9.7%, $P = .317$ and 1.6%, $P = .351$ vs 4.7% for placebo). The small intestinal peppermint oil did, however, produce greater improvements than placebo in secondary outcomes of abdominal pain ($P = .016$), discomfort ($P = .020$), and IBS severity ($P = .020$). Adverse events, although mild, were more common in both peppermint oil groups ($P < .005$). **CONCLUSIONS:** In a randomized trial of patients with IBS, we found that neither small-intestinal–release nor ileocolonic-release peppermint oil (8 weeks) produced statistically significant reductions in abdominal pain response or overall symptom relief, when using US Food and Drug Administration/European Medicines Agency recommended endpoints. The small-intestinal–release peppermint oil did, however, significantly reduce abdominal pain, discomfort, and IBS severity. These findings do not support further development of ileocolonic-release peppermint oil for treatment of IBS. Clinicaltrials.gov, Number: NCT02716285.

Keywords: Functional Gastrointestinal Disorder; PERSUADE Study; RCT; Treatment.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Peppermint oil is frequently used to treat irritable bowel syndrome (IBS), despite a lack of high quality evidence for efficacy. We studied the efficacy and safety of small intestinal-release peppermint oil in patients with IBS (Rome-IV) and explored the effects of targeted ileocolonic-release peppermint oil according to guidelines from regulatory authorities.

NEW FINDINGS

In a randomized trial of patients with IBS, we found that neither small-intestinal-release nor ileocolonic-release peppermint oil (8 weeks) produced statistically significant reductions in abdominal pain response or overall symptom relief. The small intestinal-release peppermint oil did, however, significantly reduce abdominal pain, discomfort, and IBS symptom severity.

LIMITATIONS

The primary outcome of this trial was a negative result. Improvements in secondary explorative endpoints should be interpreted with appropriate caution.

IMPACT

Peppermint oil can be considered a treatment option with moderate efficacy for patients with IBS.

Irritable bowel syndrome (IBS) is a disorder of the gut-brain axis characterized by recurrent chronic abdominal pain and altered bowel habits.[1] IBS is highly prevalent, with an estimated prevalence in the general population of 5%–6%, according to Rome IV criteria.[2,3] IBS has a profound negative impact on quality of life and carries a substantial socioeconomic burden.[4] Although the number of therapeutic options has grown recently,[5] treatment of abdominal pain remains challenging and is often unsatisfactory. One of the pharmacotherapeutic entities currently used is peppermint oil. This agent of herbal origin has menthol as its main constituent and is presumed to have several mechanisms of action, including intestinal smooth muscle relaxation,[6] modulation of transient receptor potential (TRP) channel–mediated visceral nociception,[7–9] 5-hydroxytryptamine antagonism,[10] antimicrobial and antifungal effects,[11–13] and κ-opioid receptor agonism.[14] Enteric-coated capsules that release peppermint oil in the small intestine are currently available as an over-the-counter drug in Europe[15] and as a medical food–labeled product in the United States and Canada.[16]

Guideline recommendations[17] regarding the use of small-intestinal–release peppermint oil in IBS treatment are currently based on prior studies showing highly favorable results in terms of abdominal pain reduction and global improvement of symptoms.[16,18–22] Most of these studies, however, were hampered by significant methodologic shortcomings that impede the ability to draw firm conclusions. Moreover, the US Food and Drug Administration (FDA)[23] and the European Medicines Agency (EMA)[24] have defined robust, albeit provisional, endpoints for IBS trials since 2012, and the Rome diagnostic criteria for IBS were updated in 2016. Taken together, there is a need for a well-designed trial in patients with Rome IV–defined IBS that investigates efficacy according to these stringent endpoints to refute or validate earlier findings. Thus, the primary objective of this multicenter, randomized, placebo-controlled study was to determine the efficacy and safety of small-intestinal–release peppermint oil in a population with Rome IV IBS according to FDA and EMA guidelines. We hypothesized that, in patients with Rome IV IBS, conventional small-intestinal–release peppermint oil would be more effective than placebo.

A secondary aim was to explore the efficacy and safety of a novel soft gel peppermint oil capsule with a predominant distal ileocolonic release. The pharmacokinetic profile of this formulation has been described recently.[25] The rationale for using ileocolonic release was based on experimental findings that peppermint oil has a direct local antinociceptive effect in the colon through an interaction of menthol with TRPM8 and/or TRPA1 channels on sensory afferents.[7] We therefore hypothesized that a higher exposure of the colonic afferents through targeted ileocolonic delivery of peppermint oil would enhance antinociceptive effects and thereby improve efficacy. In addition, small-

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intestinal–release peppermint oil therapy is often discontinued due to mild but burdensome upper gastrointestinal adverse events (AEs) that are assumed to be related to the relaxation of the lower esophageal sphincter[26] and can hamper therapy adherence. We therefore also postulated that the ileocolonic-release formulation would decrease these AEs.

Materials and Methods

Study Design, Setting, and Patients

The **PE**ppe**R**mint Oil for the treatment of Irritable Bowel **S**yndrome: optimizing therape**U**tic str**A**tegies using targeted **DE**livery (PERSUADE) study was a randomized, double-blind, placebo-controlled trial and was performed in 4 Dutch hospitals: 1 academic with a combined secondary and tertiary care function (Maastricht University Medical Center+ [MUMC+]) and 3 secondary care hospitals (Hospital Gelderse Vallei, Ede; Alrijne Hospital, Leiden; and Medical Center Leeuwarden). The study protocol was approved by the MUMC+ ethics committee (applicable to all centers). All study procedures were performed in compliance with good clinical practice guidelines and according to the revised Declaration of Helsinki. All participants gave written informed consent before participation. All authors had access to the study data and reviewed and approved the final manuscript.

Patients between 18 and 75 years of age, fulfilling the Rome IV criteria for IBS, and without alarm symptoms were recruited via primary care; via the outpatient clinics of the above-mentioned hospitals; or via self-referral through public advertisements, social media, and the Dutch IBS Patient Federation. Detailed inclusion and exclusion criteria are given in the Supplementary Material. Patients were screened for eligibility in a prescreening (telephone interview) and a medical screening that included history taking and a physical examination. After the screening, eligible patients entered a 14-day pretreatment period during which they scored their daily worst abdominal pain in a digital symptom diary, scored on an 11-point numerical rating scale (NRS) from 0 (no pain) to 10 (worst possible pain). Subsequently, those with a mean worst abdominal pain score of at least 3 were then randomly assigned to 182 mg of small-intestinal–release peppermint oil (Tempocol, WillPharma SA, Wavre, Belgium), 182 mg of ileocolonic-release peppermint oil (Tempocol, core capsules, coated with a ColoPulse [WillPharma SA, Wavre, Belgium] coating layer[25,27]), or placebo (microcrystalline cellulose) intake orally. Randomization was done with ALEA (Abcoude, The Netherlands) Screening and Enrolment Application software using the minimization method, accounted for inclusion center, IBS subtypes (diarrhea, mixed, constipation, undefined), sex, and age. All study medication was over-encapsulated with identical hard gelatin capsules and packaged in identical blisters to ensure allocation concealment by Tiofarma SA (Oud-Beijerland, The Netherlands). Patients were instructed to self-administer 3 capsules daily, 30 minutes before breakfast, lunch, and dinner, for 8 weeks. An 8-week treatment period was chosen because we expected the clinical effect to occur within this period based on previous studies.[16,20] This treatment duration was also selected to mitigate potential hazardous effects of long-term peppermint administration related to certain constituents.[26] Nevertheless, safety issues were refuted by the EMA during a later period of the trial.[28] To decrease

possible AEs, particularly heartburn and belching, a gradual titration schedule was followed in the first week of 1, 1, 2, 2, 2, 3, and 3 capsules per day, respectively. Patients, investigators, and health care providers were blinded to treatment allocation.

Patients were instructed to refrain from lifestyle changes (eg, a change in diet or exercise routine) throughout the study. Rescue medication, that is, acetaminophen alone or a combination with nonsteroidal anti-inflammatory drugs, proton pump inhibitors, antacids, histamine H2 receptor antagonists, loperamide, polyethylene glycol and psyllium, were allowed after consultation with the investigator (ZZRMW). All rescue medication had to be documented in the digital diary.

Study visits were conducted at the start of the pretreatment period (screening), at randomization, and at the end of the treatment period (end visit). Throughout the pretreatment and 8-week treatment periods, patients had to complete daily questions on worst abdominal pain (scored on the 11-point NRS from 0 [no pain] to 10, [worst possible pain]), stool evacuation frequency and consistency assessed by the Bristol Stool Form Scale, and presence of AEs in a digital diary. Relief of IBS symptoms (scored on a 7-point NRS from 1 [no relief] to 7 [completely relieved]) and abdominal discomfort, abdominal bloating, abdominal cramping, belching, nausea, and urgency (all scored on an 11-point NRS from 0 [no symptoms] to 10 [worst possible symptoms]) were assessed once weekly. In addition, at weeks 1, 2, 4, 6, and 8 and at months 3 and 6 of follow-up after the treatment period, patients were asked to complete several Web-based questionnaires, including the IBS Severity Scoring System (IBS-SSS),[29] Irritable Bowel Syndrome Quality of Life,[30] the EuroQoL-5D,[31,32] the Generalized Anxiety Disorder-7,[33] and the Patient Health Questionnaire-9.[34] At the beginning of weeks 2, 4, and 6, patients were contacted by telephone for follow-up and safety assessment. The treatment period was followed by a 6-month follow-up period in which no treatment was given. An overview of the study design and timing of the questionnaires is given in Supplementary Figure 1.

Electronic Data Capture and Data Storage

Investigators documented all research findings in an electronic case report file. An electronic smartphone application was developed for the digital symptom diary in which entering data from previous days was impossible. The electronic case report file, Web-based questionnaires, and diary all featured built-in routing, data validation, and response requirements to stimulate data quality and completeness.

Efficacy Assessment

Primary Endpoints. The primary endpoint was the percentage of abdominal pain responders, according to the FDA definition,[23] with a *responder* being a patient with at least 30% decrease in the weekly average of worst daily abdominal pain (scored on an 11-point NRS) compared with baseline for at least 50% of the treatment period, that is, in 4 of the 8 weeks.

In line with EMA recommendations to use a global (overall) improvement outcome in trials treating 2 or more IBS subtypes,[24] response to global relief of IBS symptoms was included as a coprimary endpoint, using a 7-point NRS. A *global relief responder* was defined as a patient with a weekly relief of threshold 6 or 7 on the NRS in at least 50% of the treatment period, that is, 4 weeks.

We expected that peppermint oil would not influence bowel habit substantially. Therefore, improvements in bowel movements and stool consistency were not included in a combined primary efficacy endpoint[23] but were analyzed separately as secondary outcome measures.

Secondary Endpoints. Secondary endpoints included symptom improvement of abdominal pain, abdominal discomfort, abdominal bloating, abdominal cramping, belching, nausea, and urgency. IBS symptom severity, stool frequency and consistency (based on the Bristol Stool Form Scale), use of rescue medication, quality of life, and comorbid anxiety and depression scores were also assessed. Another secondary endpoint was defined as moderate relief of IBS symptoms, with a patient considered a responder if he or she met a threshold of 5 or greater for symptom relief on the 7-point NRS in at least 4 of the treatment weeks. In addition, a different threshold for the abdominal pain response was included, with a patient considered a responder with at least 50% decrease in worst daily abdominal pain for at least 4 of the 8 weeks. Primary efficacy outcomes were also evaluated according to IBS subtype as secondary outcomes.

Treatment adherence was quantified by counting returned capsules at the study end visit. Patients were deemed adherent if at least 80% of the study medication was taken during the treatment period or until discontinuation of the study. The compliance rate for the digital diary was defined by the percentage of entry days completed during the treatment period or until discontinuation from the study.

Safety Assessment

Safety was assessed by the incidence, nature, and severity of AEs occurring during the treatment period. Researchers

Table 1. Summary of Patient Demographic and Baseline Characteristics (ITT Population)

Characteristics	Placebo (n = 64)	Small-intestinal–release peppermint oil (n = 62)	Ileocolonic-release peppermint oil (n = 63)
Demographic data			
Age, y			
Mean (SD)	35.5 (15.2)	32.0 (11.1)	34.4 (13.1)
Range	19–70	18–66	18–64
Sex, n (%)			
Female	49 (76.6)	51 (82.3)	47 (74.6)
Male	15 (23.4)	11 (17.7)	16 (25.4)
Race, n (%)			
White	63 (98.4)	60 (96.8)	58 (92.1)
Mixed[a]	1 (1.6)	2 (3.2)	5 (7.9)
Body mass index, kg/m^2, mean (SD)	24.6 (5.2)	25.6 (5.7)	26.5 (5.1)
Educational level, n (%)			
No education	0	0	1 (1.6)
Low	0	4 (6.5)	11 (17.5)
Moderate	32 (50.0)	23 (37.1)	25 (39.7)
High	32 (50.0)	35 (56.5)	26 (41.3)
Employment status, n (%)			
Currently studying	12 (18.8)	10 (16.1)	10 (15.9)
Employed, full-time or part-time	41 (64.1)	40 (64.6)	40 (63.5)
Unemployed	3 (4.7)	3 (4.8)	4 (6.3)
Incapacitated for work	2 (3.1)	4 (6.5)	7 (11.1)
Homemaker	1 (1.6)	4 (6.5)	2 (3.2)
Retired	5 (7.8)	1 (1.6)	0
Setting, n (%)			
Primary care	39 (60.9)	36 (58.1)	34 (54.0)
Secondary care	16 (25.0)	14 (22.6)	11 (17.5)
Combined secondary and tertiary care	9 (14.1)	12 (19.4)	18 (28.6)
IBS subtype, n (%)[b]			
Diarrhea	29 (45.3)	25 (40.3)	29 (46.0)
Constipation	14 (21.9)	12 (19.4)	16 (25.4)
Mixed	12 (18.8)	15 (24.2)	13 (20.6)
Undefined	9 (14.1)	10 (16.1)	5 (9.7)
Abdominal symptoms, mean (SD)			
Abdominal pain[c]	5.3 (1.3)	5.5 (1.2)	5.4 (1.4)
Abdominal discomfort[d]	6.3 (1.4)	6.4 (1.3)	6.5 (1.2)
Abdominal bloating[d]	6.4 (1.8)	6.4 (2.0)	6.7 (1.9)
Abdominal cramping[d]	6.2 (1.8)	6.0 (2.1)	6.3 (1.6)
Belching[d]	3.3 (2.5)	3.5 (2.4)	3.3 (2.7)
Nausea[d]	3.0 (2.4)	3.5 (2.7)	3.7 (2.5)
Bowel symptoms, mean (SD)			
Urgency[d]	6.2 (1.7)	6.3 (1.7)	6.6 (1.6)

Table 1. Continued

Characteristics	Placebo (n = 64)	Small-intestinal–release peppermint oil (n = 62)	Ileocolonic-release peppermint oil (n = 63)
IBS severity[e]			
Mean score (SD)	270.8 (74.2)	277.0 (73.6)	281.8 (68.7)
Mild, n (%)	7 (10.9)	3 (4.8)	5 (7.9)
Moderate, n (%)	34 (53.1)	35 (56.5)	31 (49.2)
Severe, n (%)	23 (35.9)	24 (38.7)	27 (42.9)
IBS Quality of Life, mean score (SD)[f]	74.0 (14.2)	72.2 (14.7)	72.8 (16.6)
EQ-5D-5L, mean utility score (SD)[g]	0.72 (0.2)	0.74 (0.2)	0.74 (0.2)
Psychological comorbidities[h]			
Anxiety, mean (SD)	6.0 (4.4)	4.5 (3.9)	5.7 (4.6)
Depression, mean (SD)	7.0 (4.7)	6.6 (4.4)	6.7 (4.6)

EQ-5D-5L, EuroQoL-5D; SD, standard deviation.

[a]Self-reported race. Placebo group: 1 participant reported mixed race of one quarter Asian. Small-intestinal–release peppermint oil group: 1 participant reported mixed race of one quarter Asian, and 1 participant reported mixed race that is one half unknown. Ileocolonic-release peppermint oil group: 4 participants reported mixed race of one quarter Asian, and 1 participant reported mixed race of one half Asian.

[b]Determined in a face-to-face interview (Rome IV).

[c]Assessed daily during the pretreatment period with an 11-point NRS in the digital diary from 0 (no symptoms) to 10 (worst possible pain).

[d]Assessed weekly during the pretreatment period using an 11-point NRS in the digital diary from 0 (no symptoms) to 10 (worst imaginable symptoms).

[e]The IBS-SSS consists of 5 items with a maximum score of 100; higher scores indicate more severe symptoms.

[f]The IBS Quality of Life consists of 34 items with a 5-point Likert-like scale from 1 (good) to 5 (worst quality of life).

[g]The EQ-5D-5L measures 5 dimensions of IBS Quality of Life. Raw scores are transformed to utility scores,[31] which vary from 1 (perfect health) to 0 (death).

[h]For anxiety, the 7-item Generalized Anxiety Disorder-7 was used, and for depression, the 9-item Patient Health Questionnaire-9 was used. Both have a 4-point response scale from 0 (not at all) to 3 (almost every day).

documented AEs during all telephone follow-ups (weeks 2, 4, and 6) and during the end visit at week 8. In addition, participants were asked to report AEs in the digital symptom diary.

Statistical Analysis

The sample size calculation was based on the most recent meta-analysis[35] available at the time of study design, indicating that 57% of the peppermint oil group had abdominal pain improvement (vs no improvement), compared with 27% in the placebo group. A sample size of 42 in both the placebo and the small-intestinal–release peppermint oil group was required to detect a 30% efficacy difference between groups, with a power of 80% at the 2-sided 0.05 α level. Anticipating that ileocolonic release would increase efficacy, we chose the same sample of 42 to compare this group with placebo. To account for heterogeneity, an inflation factor of 1.23 was applied.[36] To account for a 13% dropout, an additional 1.15 inflation factor was applied. Therefore, 60 patients per group were required.

All analyses were based on the intention-to-treat (ITT) principle, with correction for the minimization variables of sex, inclusion center, IBS subtype, and age. The responder outcomes were analyzed by using multiple logistic regression. Odds ratios (ORs), 2-sided 95% confidence intervals (CIs), and corresponding P values are reported. Patients with fewer than 4 weekly diary entries were considered to be nonresponders for that week, regardless of their score. To account for multiple comparisons (both intervention groups with placebo and 2 primary outcomes), 2-sided P values of $\leq 0.05/4 = 0.0125$ were considered statistically significant for the primary outcomes. Additionally, a per-protocol (PP) analysis was performed. The PP population included all randomized patients who had at least 80% adherence to treatment and had completed the treatment period. A detailed description of the statistical analysis of secondary outcomes, for which a multiplicity correction was applied, resulting in a significance level of $\alpha < .025$, is given in the Supplementary Material. Statistical analyses were carried out using IBM (Armonk, NY) SPSS Statistics, version 25.0, for Macintosh.

Results

Patient Disposition, Demographics, and Baseline Characteristics

Between August 2016 and March 2018, 622 patients were screened for participation in this study, of whom 190 were randomized (Supplementary Figure 2). One patient was erroneously randomized (ie, without having a mean worst abdominal score of more than 3 during the pretreatment period) and was excluded from further analyses. Therefore, the modified ITT population consisted of 189 patients. Baseline characteristics are shown in Table 1 and were balanced across treatment groups (mean overall age, 34.0 years; standard deviation, 13.3; 77.8% female; 95.8% white; 57.7% primary care). In total, 11 patients withdrew from the study: 9 discontinued as a result of AEs, 1 because of insufficient therapeutic response, and 1 for personal reasons.

Of the small-intestinal–release peppermint oil group, 90.3% were adherent to study treatment during the

Table 2. Responder Endpoints (ITT Population)

	Responders, n (%)				Responders, n (%)		
Endpoints	Placebo (n = 64)	Small-intestinal–release peppermint oil (n = 62)	P value	OR (95% CI)	Ileocolonic-release peppermint oil (n = 63)	P value	OR (95% CI)
Primary							
Abdominal pain, 30%[a]	22 (34.4)	29 (46.8)	.170	1.68 (0.80–3.51)	26 (41.3)	.385	1.39 (0.66–2.90)
Global relief[b]	3 (4.7)	6 (9.7)	.317	2.12 (0.49–9.17)	1 (1.6)	.351	0.33 (0.03–3.35)
Secondary							
Moderate relief[c]	13 (20.3)	24 (38.7)	.030	2.47 (1.09–5.56)	13 (20.6)	.980	0.99 (0.41–2.38)
Abdominal pain, 50%[d]	8 (12.5)	16 (25.8)	.062	2.51 (0.96–6.59)	13 (20.6)	.220	1.85 (0.69–4.96)

NOTE. P values, ORs, and corresponding 2-sided 95% CIs were calculated by using multiple logistic regression adjusted for minimization variables.
[a]A responder was a patient with at least 30% decrease in mean worst daily abdominal pain in at least 4 out of 8 weeks (FDA recommendation).
[b]A responder was a patient with at least a global relief score of 6 or 7 (on a 7-point NRS) in at least 4 out of 8 weeks (EMA recommendation).
[c]A responder was a patient with at least a global relief score of 5, 6, or 7 (on a 7-point NRS) in at least 4 out of 8 weeks.
[d]A responder was a patient with at least 50% decrease in mean worst daily abdominal pain in at least 4 out of 8 weeks.

complete treatment period or until discontinuation, compared with 92.1% of the ileocolonic-release peppermint oil group and 96.9% of the placebo group (P = .330 between groups) (Supplementary Table 1).

Overall compliance with the digital diary was high and did not differ significantly between the small-intestinal–release peppermint oil, ileocolonic-release peppermint oil, and placebo groups at 88.3% (P = .561), 85.3% (P = .357), and 87.2%, respectively, during the complete treatment period or until discontinuation (Supplementary Table 1). Compliance with the Web-based questionnaires was also high: only a single patient did not complete the questionnaires at the end of the treatment period. All other patients completed the symptom questionnaires with no missing values until the end of the study or until discontinuation.

Primary Efficacy Outcomes

The proportion of abdominal pain responders did not differ significantly between groups: 46.8% in small-intestinal–release peppermint oil group (OR, 1.68; 95% CI, 0.80–3.51; P = .170; number needed to treat [NNT], 8.1) and 41.3% in ileocolonic-release peppermint oil group (OR, 1.39; 95% CI, 0.66–2.90; P = .385; NNT, 14.5), compared with 34.4% in the placebo group (Table 2, Figure 1, Supplementary Table 2).

The proportion of global relief responders also did not differ significantly among groups at 9.7% in small-intestinal–release peppermint oil group (OR, 2.12; 95% CI, 0.49–9.17; P = .317) and 1.6% in ileocolonic-release peppermint oil group (OR, 0.33; 95% CI, 0.03–3.35; P = .351), compared with 4.7% in the placebo group (Table 2 and Figure 1).

In the PP analysis, the primary endpoints did not differ significantly among groups (Supplementary Table 3).

No significant differences in primary efficacy outcomes were observed for each IBS subtype separately (Supplementary Table 4, Supplementary Material section 7).

Secondary Efficacy Outcomes

Results of exploratory secondary outcomes are presented in Table 2 and Supplementary Table 5. The small-intestinal–release peppermint oil resulted in significantly more reduction in daily worst abdominal pain at week 8 compared with placebo, with a corrected difference in change from baseline on an 11-point NRS of –0.63 (95% CI, –1.14 to –0.12; P = .016) (Supplementary Table 5).

The small-intestinal–release peppermint oil was also superior over placebo with respect to abdominal discomfort. This effect appeared at week 6 of treatment, with corrected differences in change from baseline on an 11-point NRS, when compared with placebo, of –0.95 (95% CI, –1.74 to –0.15; P = .020) at 6 weeks, –0.97 (95% CI, –1.71 to –0.24; P = .009) at 7 weeks, and –0.69 (95% CI, –1.36 to –0.03; P = .041, nonsignificant at α = .025) at 8 weeks (Figure 2 and Supplementary Table 5).

A significantly greater improvement in IBS symptom severity was found among those treated with small-intestinal–release peppermint oil, with a corrected difference in change from baseline of –41.8 on the IBS-SSS total score (–91.5 vs –49.8 for small-intestinal release vs placebo; 95% CI for difference, –76.88 to –6.70; P = .020) at week 8 (Figure 3 and Supplementary Table 5). A greater percentage of the small-intestinal–release peppermint oil group reported a symptom relief score of at least 5 (moderate relief) in at least 4 of the treatment weeks (38.7%; P = .030, nonsignificant) compared with placebo (20.3%) (Table 2 and Supplementary Figure 3). In addition, both peppermint oil groups reported using rescue medication for pain fewer times than the placebo group (ie, on average 3.71 (P = .087), 3.16 (P = .039), and 5.16 times for small-
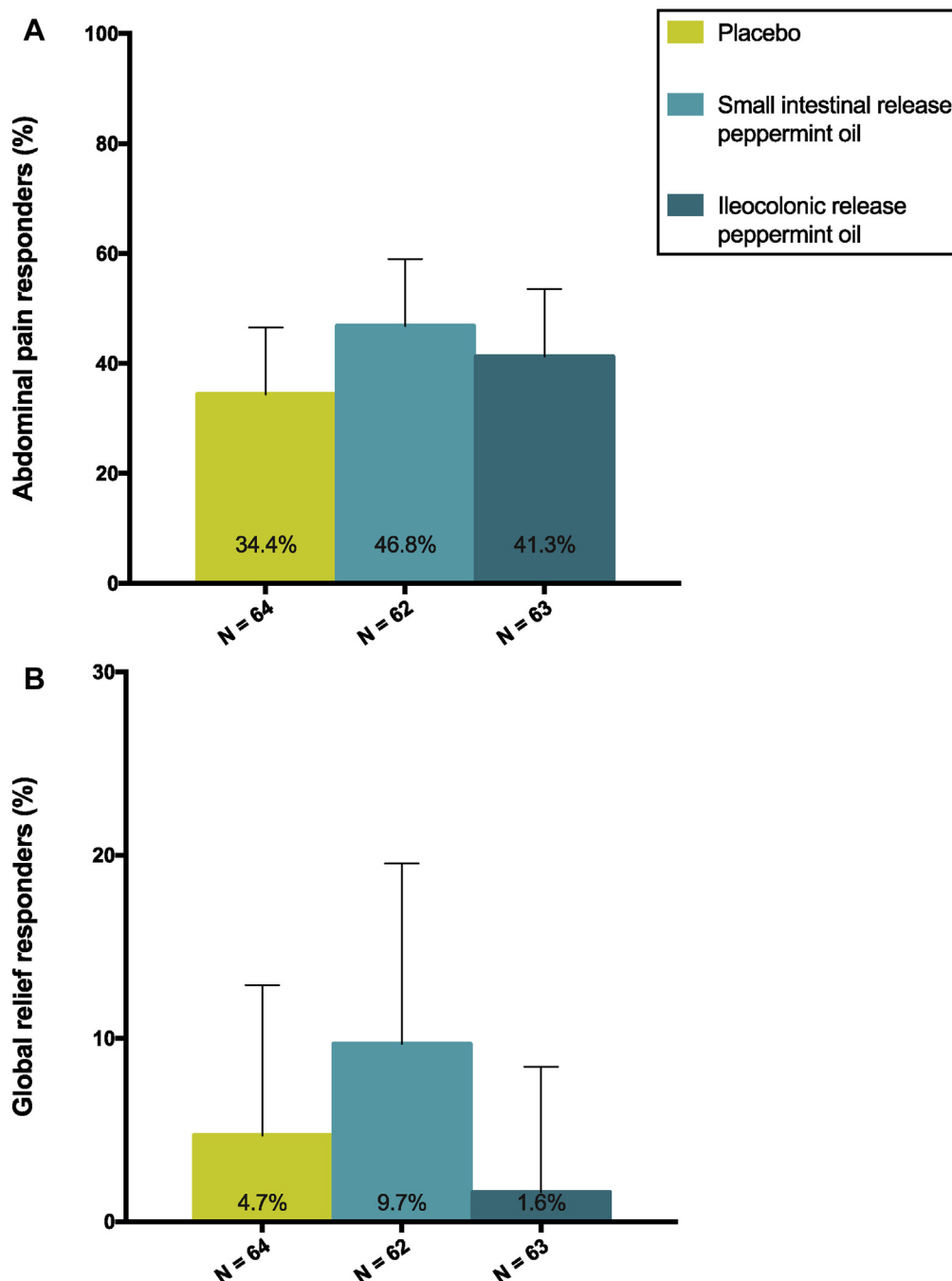
Figure 1. Percentage of patients who were (*A*) abdominal pain responders and (*B*) global (overall) relief responders in the ITT population. An abdominal pain responder was a patient with at least 30% decrease in mean worst daily abdominal pain in at least 4 out of 8 weeks. A global relief responder was a patient with at least a relief score of 6 or 7 (on a 7-point NRS) in at least 4 out of 8 weeks. Values are percentages, and bars represent standard errors.

intestinal–release peppermint oil, ileocolonic-release peppermint oil, and placebo, respectively (Supplementary Table 6). However, this did not reach the prespecified level of significance ($\alpha = .025$).

Ileocolonic-release peppermint oil did not yield significantly more relief, reduction in abdominal discomfort or abdominal pain, or improvement in IBS severity over placebo (Supplementary Table 5). When using a larger abdominal pain decrease threshold (ie, 50% instead of 30%, the proportion of abdominal pain responders did not differ significantly among groups (Table 2). Apart from a few significant changes at single time points, there were no

sustained differences between groups with regard to nausea, abdominal bloating, urgency, or comorbid anxiety and depression (Supplementary Table 5). All treatment groups showed improvements in quality of life that persisted over time, without a significant difference between groups (Supplementary Table 5). No significantly different changes were observed in stool consistency and frequency across treatment groups, apart from a single time point for stool consistency (week 6) (Supplementary Table 7). When analyzing consistency and frequency for each IBS subtype separately, no significant changes were found apart from an increased stool consistency for IBS with diarrhea at a single
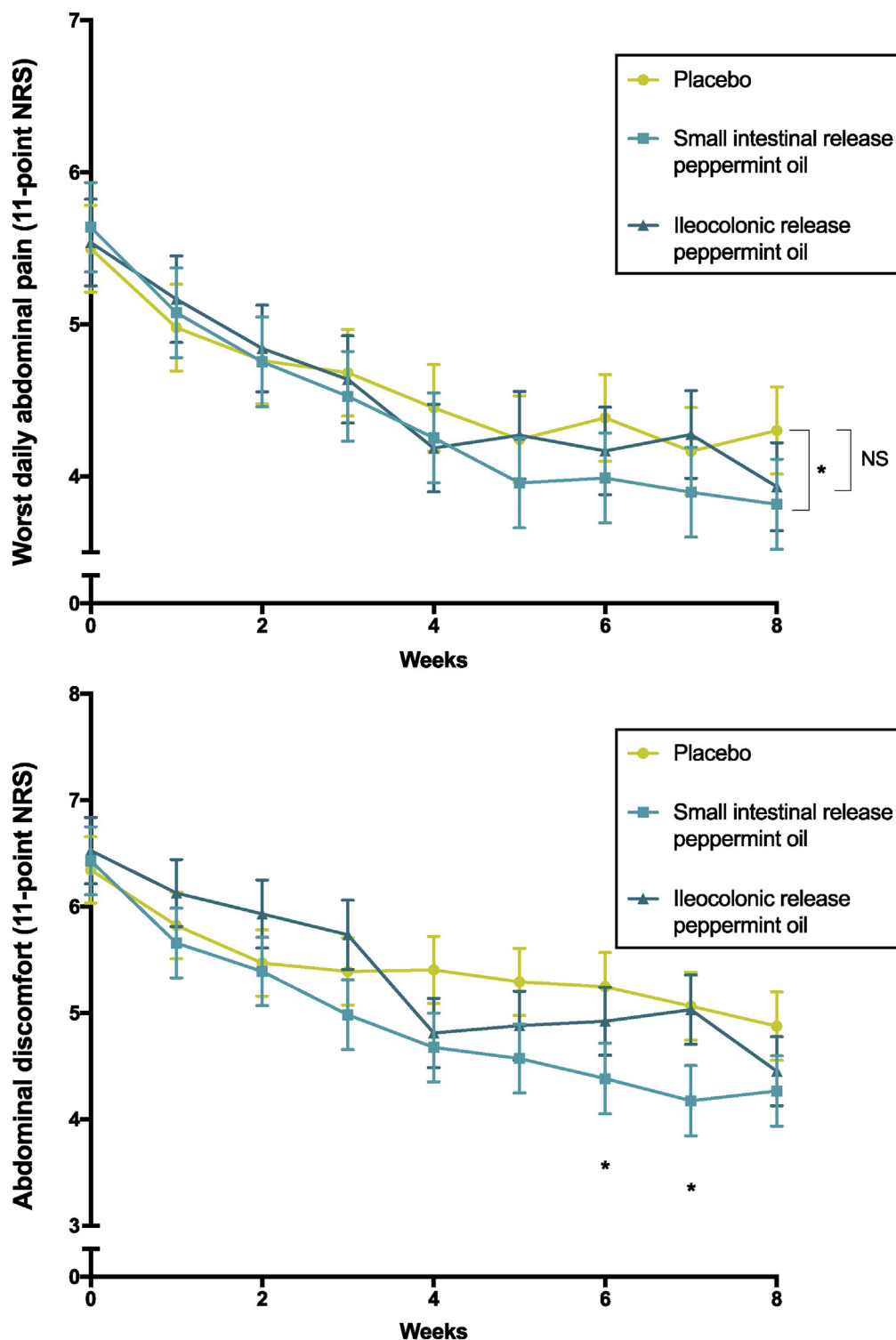
Figure 2. Abdominal pain and discomfort scores in the ITT-population (N = 189). Values are adjusted estimated marginal means derived from the linear mixed model, and bars represent standard errors. The small-intestinal–release peppermint oil group had significantly greater reduction in mean daily worst abdominal pain compared with the placebo group at week 8 (*P* = .016). The small-intestinal–release peppermint oil group also had significantly more reduction in abdominal discomfort compared with the placebo group (*P* = .020, and *P* = .009, at weeks 6, and 7, of treatment, respectively). The ileocolonic-release peppermint oil group did not differ significantly in reduction in abdominal pain and discomfort compared with the placebo group. Abdominal pain and discomfort was assessed weekly with an 11-point NRS in the digital diary. NS, not significant. *P < .025.

time point (week 6 in the small-intestinal–release peppermint oil group and week 3 in the ileocolonic-release peppermint oil group) (Supplementary Tables 8 and 9). Efficacy outcomes did not differ significantly between primary and secondary/tertiary care patients (Supplementary Table 10 and supplementary material section 8). Follow-up measurements until 6 months after treatment cessation

also showed no significant differences between placebo and both forms of peppermint oil (Supplementary Table 5).

Adverse Events/Safety Results

Table 3 summarizes the AEs reported during the treatment period. No serious AEs or deaths were reported. In
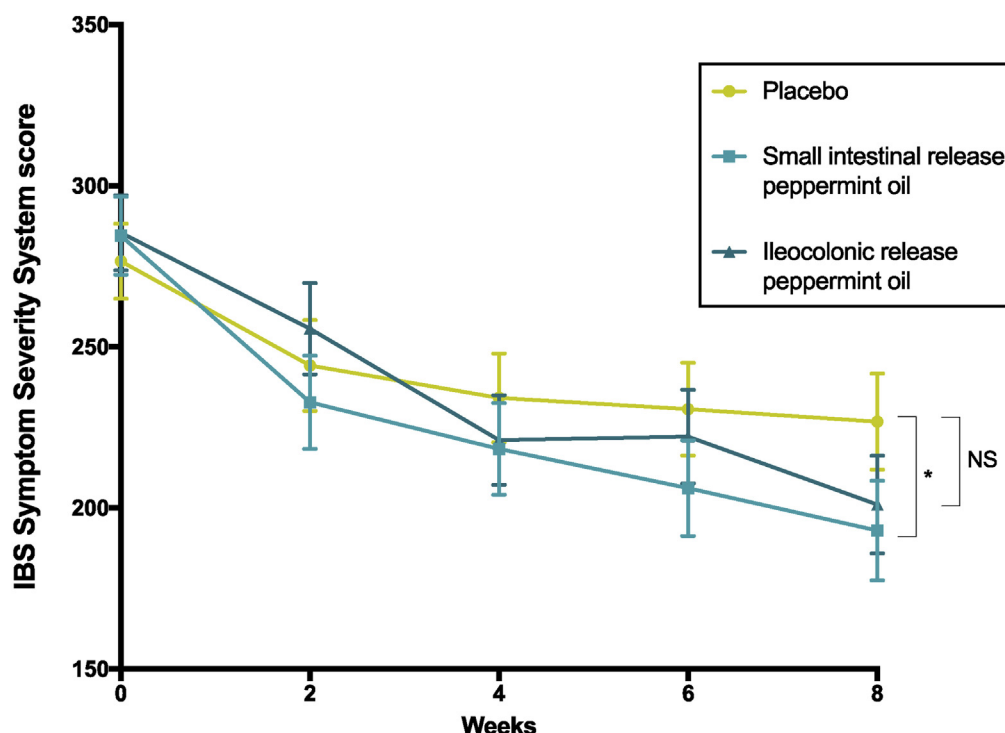
Figure 3. IBS-SSS in the ITT population. IBS-SSS in the ITT population (N = 189). Values are adjusted estimated marginal means derived from the linear mixed model, and bars represent standard errors. The small-intestinal–release peppermint oil group had significantly more reduction in IBS severity at the end of the 8-week treatment period. *P = .020. The absolute change from baseline in the small-intestinal–release peppermint oil group was –91.53 points. The ileocolonic-release peppermint oil group did not differ significantly in severity reduction compared with the placebo group (P = .053). Assessed with the IBS-SSS questionnaire consisting of 5 items, with each a maximum score of 100.

both peppermint oil groups, the total number of AEs was significantly higher compared with placebo (mean [standard error], 4.26 [0.37] for small-intestinal–release [P = .012] and 4.54 [0.45] for ileocolonic-release peppermint oil [P = .001] vs 2.78 [0.34] for placebo). The most common AEs were heartburn or gastroesophageal reflux disease symptoms, belching (with and without a minty taste), and headache with small-intestinal–release peppermint oil and an altered anal sensation or sensitive urethra, headache, and abdominal cramps in ileocolonic-release peppermint oil. Concerning belching, in the first 2 weeks of treatment, the small-intestinal–release peppermint oil group had a larger increase in belching from baseline compared with placebo (P < .001 at week 1, P = .023 at week 2). The severity of this symptom, however, returned to pretreatment levels after 3 weeks and remained there until the end of treatment (Supplementary Figure 6). More patients receiving peppermint oil vs placebo discontinued treatment because of AEs: 3 in the small-intestinal–release peppermint oil group (4.8%) and 5 in the ileocolonic-release peppermint oil group (7.9%), compared with 1 in the placebo group (1.6%).

Discussion

To our knowledge, this is the first randomized, double-blind, placebo-controlled clinical trial of peppermint oil in patients with Rome IV-defined IBS. It showed that neither small-intestinal–release nor ileocolonic-release peppermint oil led to a statistically significant reduction in abdominal pain or increase in global relief based on the prespecified primary outcome measures as defined by FDA and EMA guidelines. Small-intestinal–release, but not ileocolonic, peppermint oil, however, did yield statistically significant improvements in exploratory secondary outcomes of IBS symptom severity, abdominal pain, and abdominal discomfort. AEs occurred more often in both peppermint oil groups compared with placebo, but all were mild and transient.

The treatment effect of small-intestinal–release peppermint oil was not as pronounced as anticipated based on the results of previous meta-analyses,[35,37] which indicated a difference in dichotomous overall abdominal pain improvement of 30% between placebo and peppermint oil.[35] This discrepancy may relate to the more stringent criteria used in the current study, because our primary outcome measure required an abdominal pain reduction compared with baseline of at least 30% in at least 4 out of 8 weeks of treatment. In contrast to our study, none of the earlier trials investigating peppermint oil reported this endpoint. The most recent randomized trial investigated a sustained small-intestinal–release peppermint formulation (182 mg) with pharmacokinetics comparable to the one used in the current study in 72 patients with IBS (Rome III). They used the change from baseline in the Total IBS Symptom Score as a primary endpoint and found a significantly greater reduction of 15.7% in the peppermint oil group compared with the placebo group.[16] In the current

Table 3. Summary of Treatment-Emergent AEs (ITT Population)

AEs	Placebo (n = 64)	Small-intestinal–release peppermint oil (n = 62)	Ileocolonic-release peppermint oil (n = 63)
Total different AEs, mean (SE)	2.78 (0.34)	4.26 (0.37)[a]	4.45 (0.45)[b]
AEs,[c] mean frequency (SE) / n (%)			
Headache	1.56 (0.40) / 21 (32.8)	2.34 (0.59) / 25 (40.3)	2.17 (0.65) / 26 (41.3)
Heartburn/GERD symptoms	0.61 (0.16) / 18 (28.1)	2.84 (0.88) / 31 (50.0)	1.81 (0.60) / 23 (36.5)
Nausea	1.91 (0.78) / 23 (35.9)	1.45 (0.78) / 16 (25.8)	2.21 (0.77) / 18 (28.6)
Belching	1.03 (0.36) / 15 (23.4)	3.71 (1.04) / 28 (45.2)	0.56 (0.21) / 12 (19.0)
Belching with/without minty taste	0.02 (0.02) / 1 (1.6)	4.68 (0.99) / 36 (58.1)	0.51 (0.16) / 14 (22.2)
Abdominal cramps	0.55 (0.22) / 12 (18.8)	1.42 (0.51) / 13 (21.0)	3.76 (0.99) / 29 (46.0)
Altered anal sensation and/or sensitive urethra	0.55 (0.27) / 9 (14.1)	1.48 (0.45) / 22 (35.5)	3.60 (0.95) / 39 (61.9)
Peppermint oil–scented stool	0.02 (0.02) / 1 (1.6)	0.69 (0.22) / 18 (29.0)	2.02 (0.83) / 18 (28.6)
AEs leading to discontinuation, total n	1	3	5
Headache, n	0	1	0
Palpitations, n	1	0	0
Diarrhea and abdominal cramps, n	0	0	1
Combination,[d] n	0	1	2
Combination,[e] n	0	1	0
Combination,[f] n	0	0	2

GERD, gastroesophageal reflux disease; SE, standard error.
[a]The total number of different AEs for small-intestinal–release compared with placebo was significantly higher (P = .012).
[b]The total number of different AEs for ileocolonic-release peppermint oil compared with placebo was significantly higher (P = .001).
[c]Occurrence of AEs was self-reported in the daily symptom diary.
[d]Combination of flatulence, bloating, and abdominal pain.
[e]Combination of headache, tightness of the chest, belching, bloating, and muscle cramp.
[f]Combination of diarrhea, abdominal cramps, altered anal sensation, belching, and altered taste.

study, the placebo response rate according to the stringent FDA definition was 33%, which is similar to previous studies using this outcome measure.[38–40] The therapeutic gain of small-intestinal–release peppermint oil over placebo was 12.4%, corresponding to an NNT of 8. Although nonsignificant, this difference in response rate is numerically comparable to the previous studies in IBS reporting statistically significant differences between linaclotide[38] and plecanatide[39] vs placebo. A recent American College of Gastroenterology monograph[17] mentions an NNT of 4 for peppermint oil (using the data hitherto available), which is considerably better than the NNT we found, but also better than the NNT for linaclotide (6), plecanatide (10), or eluxadoline (12.5). Because we powered the study for an expected 30% difference,[35] it seems plausible that a type II error may exist and that a statistically significant difference among groups would have been identified had we included a larger number of patients. Another reason for the discrepancy may be differences in baseline characteristics of our study population compared with populations previously investigated. In contrast with earlier work, a large part of our population was recruited from primary care, patients had to fulfill the Rome IV diagnostic criteria for IBS,[1] and they had to have an objective mean worst abdominal score of at least 3 on an 11-point NRS. Finally, the overall quality of evidence achieved thus far could explain the conflicting findings throughout the literature. Peppermint oil was evaluated in numerous clinical trials that were hindered by methodologic limitations, including no description of allocation concealment or randomization method used, no

description of how blinding was handled, no use of validated endpoints, or treatment periods of 1 month or shorter.[37,41] As such, treatment effects may have been biased or overestimated, complicating the ability to draw firm conclusions.

Because measuring treatment response in patients with IBS is based on self-reported symptoms, defining optimal outcome measures in IBS trials has been the subject of ongoing debate. It has been postulated that the current recommended provisional FDA/EMA endpoints are limited in their ability to capture all multidimensional aspects of IBS symptoms and treatment response due to the overfocus on certain main symptoms and the dichotomization of continuous responses.[42,43] It is therefore important to take into account various appropriate endpoints to distinguish between clinically relevant and nonrelevant responses, particularly when these are used for clinical decision making. For instance, the small-intestinal–release, but not ileocolonic-release, peppermint oil group had a significantly greater reduction in abdominal pain, discomfort, and IBS symptom severity scores compared with placebo. Furthermore, adherence to study treatment was excellent, and discontinuation due to headache, belching, or other AEs was low (6.4%). In addition, all AEs were mild and transient, and the most common one, belching, subsided after the second week of treatment. This indicates a rather good tolerability of peppermint oil when administered with a gradual titration schedule for the first week. Thereby, the current results show, in our opinion, that small-intestinal–release peppermint oil does have a moderate efficacy in patients with IBS

and should not be ignored as a treatment option in everyday practice.

We had hypothesized that a targeted ileocolonic release of peppermint oil would lead to augmented efficacy of the treatment owing to a more local colonic antinociceptive effect, based on recent experimental evidence suggesting the involvement of TRP channels on colonic sensory afferents.[7] In the current study, however, we found no evidence of symptomatic benefits of ileocolonic-release peppermint oil over placebo. In addition, although upper-gastrointestinal AEs were indeed diminished compared with the small-intestinal–release peppermint oil, the novel formulation resulted in more severe abdominal cramping in the beginning of the treatment period. Therefore, our findings, taken together, do not support the use or further development of this formulation for treatment of patients with IBS. The reason for increased reporting of abdominal cramps upon administration of ileocolonic-release peppermint oil is unclear and unexpected, given the smooth muscle relaxatory effects of the agent. As far as the effects of peppermint oil are concerned and on the basis of these findings, however, we speculate that the small intestine could be of superior importance compared with the colon with regard to pain symptom generation and relief in IBS. In addition, considering the late onset of beneficial effects, we further postulate the involvement of TRP channels on intestinal sensory afferents rather than a primarily antispasmodic effect that is assumed to occur more rapidly.

Currently, treatment of IBS is often tailored toward improvement of a patient's most predominant symptom. If initial treatment fails to achieve satisfactory results, linaclotide and eluxadoline are examples of recent pharmacologic advances that have led to novel drug development and can be used to treat constipation- and diarrheal-type IBS, respectively. Despite high-quality evidence, their somewhat less favorable AE profiles should be considered and may limit applicability.[38,40] Of the therapeutic entities available for IBS, none has been able to cure or alter the disorder in the long term. This reflects our incomplete pathophysiologic understanding of IBS, which leads to the inability to target specific disease mechanisms. In this perspective and in view of our findings, peppermint oil appears to be a favorable initial treatment entity in IBS for the following reasons: (1) peppermint oil is readily available as a low-cost over-the-counter drug, (2) AEs are at most mild and transient in nature, and (3) using a pharmacologic agent of herbal origin without the risk of serious AEs could be attractive to patients. In fact, in The Netherlands, peppermint oil was the most preferred treatment option when patients were given the choice of 10 treatment options, including education on IBS, other antispasmodics, antidepressants, and elimination/FODMAP diet included).[44] Because improvements in exploratory secondary outcomes were observed toward the end of the treatment period, and belching arises at the beginning of treatment but normalizes soon after, patients should be encouraged to continue treatment. Finally, to avoid disappointment, providers could communicate that there is little evidence for long-term beneficial effects after discontinuing peppermint oil treatment. Future research should investigate the safety and efficacy of longer treatment periods.

This study has several limitations. First, the population was relatively young, female, and predominantly white; therefore, data may not necessarily be generalizable to more diverse populations with IBS. We speculate that the use of social media as a recruitment strategy may have contributed to this relatively young study population. Nevertheless, the subtype distribution was in line with epidemiologic findings in IBS.[45] Future studies are required to ascertain the effect in populations from different geographic regions; a current trial in the United States investigating placebo responses uses a peppermint oil comparator.[46] However, because we have recruited patients with IBS from primary, secondary, and tertiary care, and via social media accounts of the participating centers, we argue that the current study population is representative of the Dutch IBS population seeking help for their symptoms. However, caution is necessary when applying these results to clinical practice because they might apply only to patients who have a certain level of pain symptoms, corresponding to both the Rome IV and the FDA pain entry criteria. Second, blinding of the patients may not have been entirely successful due to the smell and taste of peppermint oil and other recognizable AEs. We tried to limit a confounding effect through the identical appearance of capsules by over-encapsulation. Third, because of possible power limitations and increase in type I error (multiple testing), secondary endpoint analyses should be considered exploratory. Fourth, the treatment period was relatively short compared with that of other IBS trials; therefore, potential benefits from a longer treatment period (ie, 12–26 weeks) could not be ascertained.

Strengths of the current study include the soundness of the experimental design and compliance with recent guidelines on IBS drug trials and, as such, reporting on stringent primary outcomes according to FDA and EMA guidelines and ITT analyses; the meticulous use of state-of-the-art electronic data capture, ensuring data quality and completeness; and a well-characterized patient population composed of both primary and secondary/tertiary care patients with diagnoses made according to Rome IV diagnostic criteria for IBS with a low drop-out rate.

In summary, peppermint oil compared with placebo was not superior in patients with IBS when the prespecified outcome measures of abdominal pain response and global relief of IBS symptoms were used, based on recommendations by the FDA and EMA. We found no benefits of a targeted ileocolonic-release peppermint oil formulation for treatment of IBS. Conventional small-intestinal–release peppermint oil did, however, improve secondary outcomes such as abdominal pain, abdominal discomfort, and IBS symptom severity, with a minimal AE profile and high tolerability. Peppermint oil may thus be considered as a worthwhile treatment option for symptom management in IBS.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at

www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.08.026.

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CLINICAL AT