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A trial-based economic evaluation of peppermint oil for the treatment of irritable bowel syndrome

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Abstract

Background: Irritable Bowel Syndrome (IBS) is a prevalent, chronic gastrointestinal disorder that imposes a substantial socioeconomic burden. Peppermint oil is a frequently used treatment for IBS, but evidence about cost-effectiveness is lacking.

Objective: We aimed to assess cost-effectiveness of small-intestinal release peppermint oil versus placebo in IBS patients.

Methods: In a multicenter randomized placebo-controlled trial, cost-effectiveness was evaluated from a societal perspective. The incremental cost-effectiveness ratios (ICERs) were expressed as (1) incremental costs per Quality Adjusted Life Years (QALY), and (2) incremental costs per successfully treated patient, that is per abdominal pain responder (according to FDA definitions), both after an eight-week treatment period with placebo versus peppermint oil. Cost-utility and uncertainty were estimated using non-parametric bootstrapping. Sensitivity analyses were performed.

Results: The analysis comprised 126 patients (N = 64 placebo, N = 62 small-intestinal release peppermint oil). Peppermint oil was a dominant treatment compared to placebo in 46% of bootstrap replications. Peppermint oil was also more effective but at higher cost in 31% of replications. The net-benefit acceptability curve showed that peppermint oil has a 56% probability of being cost-effective at a conservative willingness-to-pay threshold of €10.000/QALY. Peppermint oil was also a dominant treatment per additional successfully treated patient according to FDA definitions, that is in 51% of replications. In this case, the acceptability curve showed an 89% probability of being cost-effective.

Conclusions: In patients with IBS, small-intestinal release peppermint oil appears to be a cost-effective treatment although there is uncertainty surrounding the ICER. When using abdominal pain responder as outcome measure for the ICER, peppermint oil has a high probability of being cost-effective. The use of peppermint oil, which is a

low-cost treatment, can be justified by the modest QALY gains and slightly higher proportion of abdominal pain responders. More research and long-term data are necessary to confirm the cost-effectiveness of peppermint oil. **NCT02716285**.

KEYWORDS
Abdominal pain, cost-effectiveness, economic burden, ICER, irritable bowel syndrome, peppermint oil, QALY

Key summary

Summarize the established knowledge on this subject

- Peppermint oil is among the most frequently used therapeutics to treat pain in irritable bowel syndrome (IBS).
- Data on cost-effectiveness are lacking.

What are the significant and/or new findings of this study?

- In a large RCT with peppermint oil in IBS, cost-effectiveness analyses using incremental costs per quality adjusted life years and costs per successfully treated patient showed that small-intestinal release peppermint capsules appear to be cost-effective.
- When choosing a treatment that targets abdominal pain in IBS, it is important to consider the low-cost and moderate efficacy of small-intestinal release peppermint oil.

INTRODUCTION

Irritable Bowel Syndrome (IBS) is a prevalent and chronic disorder of brain-gut-interaction characterized by chronic abdominal pain and altered bowel habits.[1] IBS has a negative impact on quality of life (QoL)[2] and is associated with considerable costs for patients, healthcare systems and society.[3–5]

Regarding direct costs to healthcare systems, IBS patients are reported to have increased numbers of consultations, ER visits, hospitalizations, and prescribed medications, when compared to patients without IBS.[2,6] Additionally, a large proportion of patients use over-the-counter (OTC) drugs or complementary medicine leading to high out of pocket costs.[6] Regarding indirect costs,[3,4] IBS patients are more likely to be both absent from work (absenteeism) and impaired during work (presenteeism) when compared to non-IBS patients.[6] Summed with the reduced QoL in patients, IBS leads to a high socioeconomic burden.[2,7,8]

Effective therapies are therefore crucial to decrease this burden. Generally, symptom improvement should result in a better health-related QoL, less resource use and less productivity loss. Peppermint oil is a frequently used treatment for IBS and we previously reported the results of the largest randomized clinical trial (RCT) with peppermint oil to date.[9] A recent meta-analysis, including data from this trial, confirmed the therapeutic superiority of small-intestinal peppermint oil over placebo in IBS.[10] Trial-based data on the cost-effectiveness of peppermint oil however, are lacking so far. The objective of this trial-based economic evaluation was therefore to assess the cost-effectiveness of peppermint oil compared with placebo, in patients with IBS.

MATERIALS AND METHODS

This economic evaluation was performed in a multicenter, placebo-controlled, double-blind RCT on clinical efficacy of peppermint oil as a secondary outcome. The study was performed in four Dutch hospitals, one academic with a combined secondary/tertiary care function (Maastricht University Medical Center+, MUMC+), and three secondary care (Hospital Gelderse Vallei, Ede; Alrijne Hospital, Leiden; Medical Center Leeuwarden, Leeuwarden). The research protocol had been approved by the MUMC + Ethics Committee and has been registered (Clinicaltrials.gov, NCT02716285). All study procedures were performed in compliance with GCP and the Declaration of Helsinki. All subjects gave written informed consent prior to participation. Full details of the clinical trial have been published elsewhere[9] and are briefly summarized below.

Patients, setting and interventions

IBS patients, between 18 and 75 years of age were eligible for inclusion if they fulfilled the Rome IV criteria.[11] Patients had to have a mean daily worst abdominal pain score ≥3 during a two-week run-in period (on an eleven-point numerical rating scale [NRS]). Randomization was done with ALEA Screening and Enrollment software using the minimization method accounted for inclusion center, IBS subtypes, gender, and age. Patients were assigned to 182 mg of small-intestinal release peppermint oil in enteric-coated soft gel capsules (Tempocol, WillPharma S.A.), ileocolonic release peppermint oil (Tempocol core capsules, coated with ColoPulse coating layer[12]), or placebo. The study consisted of two-weeks run-in period, an eight-week treatment period, followed by a six-month follow-up period with no study medication. Patients were asked to refrain from lifestyle changes and new treatments. Standard care, however, could be continued in a stable manner. Patient inclusion took place between August 2016 and March 2018.

Economic evaluation

The economic evaluation was performed in accordance with the Dutch guidelines for cost-calculations,[13,14] the CHEERS checklist and ISPOR guidelines, based on intention-to-treat analysis. Costs were calculated from the societal perspective and expressed in 2017 euros. The primary outcome was the incremental cost-effectiveness ratio (ICER), calculated as difference in costs between peppermint oil and placebo divided by the difference in QALY between peppermint oil and placebo, over the eight-week treatment period. As the newly formulated ileocolonic release peppermint oil did not yield any benefits over small-intestinal release peppermint oil,[9] this formulation will not be developed further and will not be available to patients. Consequently, this formulation was not taken into account into this economic evaluation.

Costs included all IBS-related direct costs (*i.e.*, outpatient consultations, general practice consultation, dietician, and mental healthcare) and indirect costs (*i.e.*, absenteeism, presenteeism, and impaired unpaid work). Additionally, cost of treatment assigned was included (peppermint oil or placebo). An overview of costs per unit is given in Table 1.

Health-related resource use was assessed using the iMTA Medical Consumption Questionnaire (MCQ), which is designed to measure costs in the Dutch healthcare system (see https://www.imta.nl). The MCQ was completed at baseline and after eight-weeks of treatment. As the recall-period of the MCQ is three months, the recall period was adjusted to eight weeks for assessment at the end of the treatment period. A distinction was made between IBS-unrelated and potentially related costs based on expert opinion; for example, drugs for comorbid cardiovascular disease were not included, whereas visits to a gastroenterologist or GP, or mental healthcare were. Direct costs were calculated by multiplying resource use by the cost price per resource unit, adopting reference prices derived from the Dutch costing manual (Table 1). Medication costs were obtained from the Dutch Pharmacotherapeutic Compass (Healthcare Insurance Board, 2017). Additionally, for each visit to a care provider, travel expenses were calculated using a standard cost of €0.19 per average kilometer.

Indirect health-related costs were measured using the iMTA Productivity Cost Questionnaire (PCQ), which was designed and validated for the Dutch situation (see https://www.imta.nl).[15] The PCQ was completed at baseline and at four and eight-weeks of treatment. The PCQ includes questions on productivity loss of paid work (absenteeism and presenteeism) and productivity loss of unpaid work (*e.g.*, voluntary work, or homemaking and caregiving). Indirect costs were calculated by multiplying the hours absent (using self-reported dates of sick-leave) or impaired (using a self-reported inefficiency score) by average wages per hour derived from the Dutch costing manual (Table 1). Since most costs and outcomes were measured within one year, no discounting was applied and all costs were indexed for inflation to 2017. A detailed description of indirect cost calculation is given in the Supplementary file.

The EuroQol-5D (EQ-5D-5 L) was used to measure health-related QoL at baseline, four and eight weeks of treatment. The EQ-5D-5 L measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and has shown good performance in IBS.[16] Dutch social tariffs were used to transform EQ-5D-5L scores to utility scores.[17] The IBS-QoL questionnaire consists of 34 items, and was used to determine the impact of IBS and treatment on QoL.[18]

All data were collected electronically using web-based questionnaires and a smartphone-based symptom diary.

Statistical analysis

Statistical analyses were performed using SPSS and Microsoft Excel. The proportion of missing data and the missing data pattern were investigated using descriptives and patterns function in SPSS, and associations between missingness and baseline and outcome variables were investigated with logistic regression, to inform on the missing data mechanism. Missing values missing (completely) at random were handled by multivariate imputation by chained equations using predictive mean matching[19] with gender, IBS-subtype, age, baseline IBS severity, baseline utility, and treatment group. QALYs were calculated by the area under the curve, in which the time in a certain health state was multiplied by the utility of this state. The time horizon was the eight-week treatment. For QALY calculation, utility values were corrected for baseline differences between groups with the mean absolute difference method.[20] ICER was calculated as the difference in costs divided by the difference in QALYs. Nonparametric bootstrapping with 10.000 and 1.000 simulations was used to calculate the difference in costs between groups and to examine uncertainty surrounding the ICER, respectively. This method requires resampling and derives a cost-effectiveness ratio from each of the samples,[21] thereby increasing the robustness of the results and accounting for within and between imputation variability.[19] Results of the bootstrap analysis are presented in cost-effectiveness planes and net-benefit acceptability curves. A cost-effectiveness plane is a scatterplot of simulated ICERs and presents the four situations of additional costs and additional QALY's of peppermint oil compared to placebo. If the majority of the ICERs appear in the southeast quadrant, this indicates higher effectiveness at lower costs, that is, peppermint oil dominates placebo. The northwest quadrant indicates lower effectiveness at higher costs, that is peppermint oil is inferior compared to placebo. With regard to the other two quadrants (lower effectiveness at lower costs, and higher effectiveness at higher costs), the choice for peppermint oil depends on the threshold value, that is, the maximum amount society/decision maker is willing to pay for a health gain. The net-benefit acceptability curve shows the probability that the treatment is cost-effective compared to placebo over various willingness to pay (WTP) values. The net monetary benefit (NMB) is calculated as follows: WTP*difference in QALY-difference in costs. Commonly used WTP-thresholds per QALY (one year in perfect health) in the Netherlands are €20.000 for mild, €50.000 for moderately severe

TABLE 1 Overview of costs per unit of resource use

Resource use	Unit	Cost (euro)	Reference
Study treatment			
Placebo	168 capsules	0.00	Manufacturer
Small-intestinal release peppermint oil	168 capsules	41.86	Manufacturer
General practitioner consultation	consultation/visit	34.00	Dutch costing manual
Gastroenterologist consultation	consultation/visit	93.00	Dutch costing manual
Social work consultation	consultation/visit	67.00	Dutch costing manual
Mental healthcare consultation	consultation/visit	94.60	Dutch costing manual
Travel cost car or public transport	kilometer	0.19	Dutch costing manual
Parking cost	visit	3.07	Dutch costing manual
Average wage women	hour	32.36	Dutch costing manual
Average wage men	hour	38.82	Dutch costing manual
Productivity cost unpaid work	hour	14.34	Dutch costing manual

and €80.000 for a severe condition.[22] As IBS does not increase mortality and our study includes a relatively short time horizon, a WTP-threshold of €10.000 (estimated €65.000 per year) was chosen for the calculation of NMB. Prior studies investigating cost-effectiveness in IBS have applied thresholds between £30.000[23] and $80.000[24] per QALY with the last study covering a treatment period of 10 weeks.

Sensitivity analyses

Several sensitivity analyses were performed. First, the main clinical effectiveness outcome, that is, the proportion of responders instead of QALY, was used. According to the Food and Drug Administration (FDA) definition, a responder had at least a 30% decrease in the mean weekly worst daily abdominal pain (measured daily, on an 11-point NRS) compared to baseline, in at least four (out of eight) weeks. As this endpoint does not capture a generic health-related QoL, a lower WTP-threshold was chosen to calculate the NMB, that is, €5.000. For the second sensitivity analysis, unadjusted QALYs were used, that is no correction for baseline differences in QALYs between groups. The final sensitivity analysis was a cost-effectiveness analysis from the healthcare perspective, that is, considering only direct costs.

RESULTS

Overall, the intention-to-treat population of the clinical trial with three treatment arms consisted of 189 patients.[9] Of these 189, 126 patients were included in this cost-effectiveness study (N = 64 placebo, N = 62 small-intestinal release peppermint), of whom 120 completed the study. Baseline characteristics are presented in Table 2. Compliance and missing data are described in the Supplementary file.

Overall, a somewhat greater improvement in QoL was found in the small-intestinal release peppermint oil group compared to placebo, although these differences did not reach statistical significance (Table S2).

Mean costs per category are presented in Table 3. During the treatment period, direct healthcare costs differed with the peppermint oil group showing significantly lower costs compared to placebo. Differences were mainly caused by mental healthcare utilization (Table 3). There were no significant differences between groups in indirect costs during treatment, except for more productivity loss in unpaid work in the small-intestinal peppermint oil group (Table 3).

Cost-effectiveness analysis

The incremental cost-savings of small-intestinal peppermint oil were €40.00, with an incremental corrected QALY gain of 0.004 compared to placebo. The cost-effectiveness plane is presented in Figure 1 and shows that small-intestinal release peppermint oil is a dominant treatment compared to placebo in 46% of simulations (southeast quadrant, greater effectiveness at lower costs). Peppermint oil is more effective, but at a higher cost (northeast quadrant) in 31% of the simulated ratios, while it is inferior in 18% of simulations (northwest quadrant, less effective and higher costs). The net-benefit acceptability curve showed that the probability of peppermint being cost-effective was 50% at a WTP-threshold of €1.000 and increased to 56% at a WTP-threshold of €10.000 (Figure 2).

Sensitivity analyses

Sensitivity analyses are presented in Table 4. When using the main clinical outcome instead of QALY, no statistically significant difference was observed in the proportion of abdominal pain responders

TABLE 2 Summary of patient demographic, baseline characteristics, and baseline quality of life (ITT population)

	Placebo *N* = 64	Small-intestinal release Peppermint oil *N* = 62
Demographic data		
Age, years		
Mean (SD)	35.5 (15.2)	32.0 (11.1)
Range	19–70	18–66
Gender, *n* (%)		
Female	49 (76.6)	51 (82.3)
Setting, *n* (%)		
Primary care	39 (60.9)	36 (58.1)
Secondary care	16 (25.0)	14 (22.6)
Combined secondary & tertiary care	9 (14.1)	12 (19.4)
Employment status, *n* (%)		
Currently studying	12 (18.8)	10 (16.1)
Employed, full- or part-time	41 (64.1)	40 (64.6)
Unemployed	2 (3.1)	3 (4.8)
Incapacitated for work	2 (3.1)	4 (6.5)
Homemaker	1 (1.6)	4 (6.5)
Retired	5 (7.8)	1 (1.6)
Missing	1 (1.6)	0
IBS Quality of Life, mean score (SD) on IBS-QoL	74.0 (14.2)	72.2 (14.7)
Psychological comorbidities		
Anxiety, mean (SD) on GAD-7	6.0 (4.4)	4.5 (3.9)
Minimal anxiety, *n* (%)	26 (40.6)	36 (58.1)
Mild anxiety, *n* (%)	29 (45.3)	18 (29.0)
Moderate anxiety, *n* (%)	4 (6.3)	6 (9.7)
Severe anxiety, *n* (%)	5 (7.8)	2 (3.2)
Depression, mean (SD) on PHQ-9	7.0 (4.7)	6.6 (4.4)
Minimal depression, *n* (%)	22 (34.4)	27 (43.5)
Mild depression, *n* (%)	27 (42.2)	24 (38.7)
Moderate depression, *n* (%)	8 (12.5)	7 (11.3)
Moderately severe depression, *n* (%)	6 (9.4)	3 (4.8)
Severe depression, *n* (%)	1 (1.6)	1 (1.6)

between both groups: 22/64, 29/62 in the placebo and small-intestinal peppermint oil group, respectively.[9] The cost-effectiveness plane showed that small-intestinal release peppermint oil is dominant in 51% of ICER simulations and more effective at higher cost in 41% of simulations. At a WTP-threshold of €5.000 per additional responder, the probability of small-intestinal release peppermint oil being cost-effective is 89% (Figure 3).

When using uncorrected (for baseline differences) QALYs, peppermint oil is dominant in 51% of simulations and more effective at higher cost in 40% of simulations. When comparing uncorrected QALYs to corrected ones, the probability of peppermint oil being a cost-effective treatment for a threshold of €10.000 increases slightly from 56% to 58%.

When assessing cost-effectiveness from a healthcare perspective, small-intestinal peppermint oil is dominant compared to placebo in 65% of ICER simulations. Peppermint oil has an 85% probability of being cost-effective at a WTP-threshold of €10.000.

TABLE 3 Total costs per category (ITT-population)

	Placebo *N* = 64	Small-intestinal release Peppermint oil *N* = 62	Difference in means[a] (€) (95% Confidence Interval)
Costs, mean (SD) (€)			
Total direct costs	355 (90)	161 (11)	−194 (−392;−35)[b]
Mental healthcare	287 (90)	69 (8)	−218 (−411;-57)[b]
General practice	29 (33)	19 (33)	−11 (−17;−5)[b]
Rehabilitation	0 (33)	0 (33)	0 (33)
Outpatient consultation	3 (1)	4 (1)	0 (−2; 3)
Company doctor	7 (33)	8 (33)	0 (−5; 6)
Homeopathy	7 (33)	8 (34)	0 (−6; 7)
Medication	2 (33)	1 (33)	−1 (−2;0)
Dietician	1 (33)	5 (1)	4 (33)[b]
Travelling-expenses	2 (33)	1 (33)	−1 (−2;0)
Treatment or diagnostics	17 (6)	6 (33)	−11 (−24;0)
Hospitalization	-	-	-
Study treatment costs	N.A.	42 (33)	-
Total indirect costs	818 (73)	975 (78)	157 (−55;370)
Absenteeism	386 (59)	453 (71)	71 (−103;256)
Presenteeism	364 (20)	371 (21)	7 (−50;65)
Productivity loss unpaid work	68 (10)	145 (19)	77 (37;120)[b]
Total costs, mean (SD)	1.175 (113)	1.132 (82)	−40 (−226;322)

[a]Bootstrapped differences (means and confidence intervals) between small-intestinal release peppermint oil and placebo.
[b]significant (no zero in confidence interval).

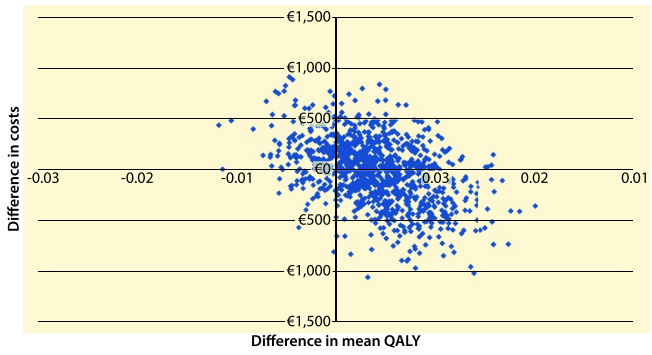

FIGURE 1 Cost-effectiveness plane of small-intestinal release peppermint oil compared with placebo. Each data-point represents one bootstrapped estimate of incremental costs and baseline corrected quality adjusted life years. The bootstrapped incremental cost-effectiveness ratios cover all four quadrants in both planes, indicating some uncertainty of the data. 46% of simulations lie in the south-east quadrant, the quadrant indicating dominance of peppermint oil. 31% of simulations lie in the north-east quadrant, indicating higher efficacy but at higher cost. The cost-effectiveness acceptability curve (Figure 2) shows the probability peppermint oil is cost-effective at different willingness to pay-thresholds

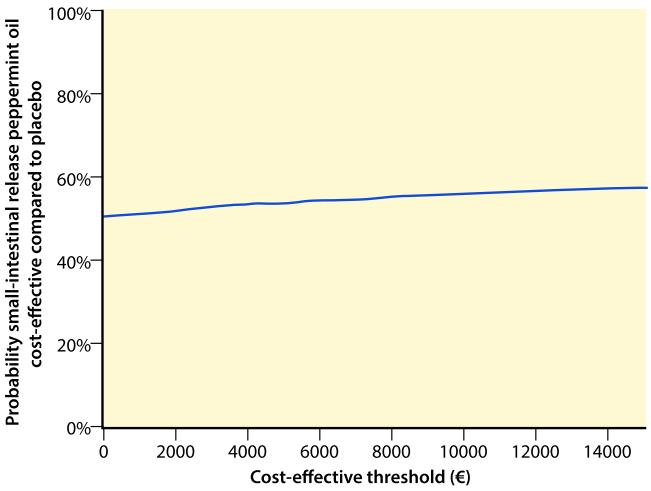

FIGURE 2 Cost-effectiveness acceptability curve. The line indicates the probability (*y*-axis) of a treatment being cost-effective, that is, the proportion of replications small-intestinal release peppermint oil has the highest net monetary benefit, given various levels of willingness to pay (cost-effectiveness thresholds (*x*-axis)

DISCUSSION

Here, we report the results of the first trial-based economic evaluation of peppermint oil for IBS conducted in a multicenter, placebo-controlled RCT. The results show that small-intestinal release peppermint oil may be considered cost-effective compared to placebo during an eight-week treatment, from a societal perspective at a conservative WTP-threshold of €10.000 per QALY. However, there is an uncertainty surrounding the incremental cost-effectiveness ratios (ICERs). At a lower and highly conservative WTP-threshold of €1.000 per QALY, peppermint oil and placebo have an equal chance of being cost-effective. Sensitivity analyses showed similar results indicating uncertainty surrounding the cost-effectiveness of peppermint oil with the exception of the analyses using abdominal pain responder according to FDA-definition, and costs from a healthcare perspective. In these cases, peppermint oil has a much higher probability of being cost-effective compared to placebo.

IBS is highly prevalent and one of the most expensive conditions in gastroenterology.[25] We recently demonstrated that peppermint oil is moderately effective in patients with IBS, decreasing abdominal pain, discomfort, and IBS-symptom severity.[9] Although non-significant, small-intestinal release peppermint showed an abdominal pain response rate (FDA-defined) of 12.4%, which is numerically comparable to studies reporting statistically significant differences between linaclotide,[26] plecanatide[27] and tenapanor[28] versus placebo. These findings further warrant a trial-based economic evaluation such as the current study.

Peppermint oil is available as an OTC drug without reimbursement from healthcare insurance in many countries. Peppermint oil is relatively inexpensive and this study indicates that it is likely cost-effective, showing that its use can be justified by the (albeit modest) gains in health-related QoL and cost-savings. Moreover, in light of its favorable adverse event profile, peppermint oil can be a worthwhile treatment option. Peppermint oil seems particularly suited for primary care or as an initial step in therapy since more than half of patients were recruited in this setting. Our findings are further supported by a preliminary model-based study suggesting cost-effectiveness of peppermint oil.[29] Other treatments with a high probability of being cost-effective for IBS are anti-depressants, the low-FODMAP diet, and cognitive behavioral therapy.[25] No direct comparisons can be made due to different study designs and patient populations.

The ICER of eight weeks peppermint oil treatment was dominant, indicating cost savings with a small health-related QoL gain with the bootstrap analysis showing uncertainty surrounding the ratio. This short-term evaluation might underestimate cost-effectiveness, since long-term savings and QALY gains are not considered. However, as guidelines do not currently recommend peppermint usage for longer than three months,[30] we did not perform any long-term analysis and did not extrapolate the data. Future studies should investigate the safety, effect, and QALY gains of longer treatment periods.

This economic evaluation additionally investigated cost-effectiveness based on a clinical parameter in addition to traditional QALYs. We used the stringent abdominal pain response outcome (FDA-defined) at a WTP of €5000 and showed that while using this outcome, peppermint oil has an 89% probability of being cost-effective. Currently, healthcare policymakers have not defined WTP-threshold values when clinical effect measures are used instead of QALYs.[22] Nevertheless, given that the FDA-endpoint is recommended by drug regulatory authorities[31,32] and widely accepted as a primary outcome in IBS trials, we anticipate that more economic evaluations will present ICERs based on this endpoint in addition to ICERs based on more traditional QALY endpoints. This would enhance comparisons between treatments further.

The results of the current study should be considered in light of potential limitations. First, for the estimation of costs, we relied on self-reported healthcare usage and productivity losses, which may lead to recall- and social desirability bias. However, studies in the UK and the Netherlands have shown good agreement between health registry and self-reported data.[33,34] In addition, the bias would have been present in both groups and is therefore unlikely to have a noticeable effect. Second, a substantial part of the cost-savings within healthcare perspective was driven by differences in mental healthcare costs. This difference results in a higher probability of peppermint oil being cost-effective from a healthcare perspective as shown in the sensitivity analysis. It is questionable however, whether the difference in mental healthcare costs is a mere result of the treatment with peppermint oil in the relatively short period of 8 weeks. Baseline depression and anxiety scores were slightly higher in the placebo compared to the peppermint oil group. Therefore, despite using a valid randomization method stratified for potential effect modifiers, we cannot exclude the difference in mental healthcare costs to be caused by chance and not treatment effect. Clinical gastroenterologists should take this into account when interpreting the results. Third, missing data regarding presenteeism (Table S1), limits the validity of the results. Fourth, it is not always clear whether patients can make a distinction between IBS-related productivity loss and other comorbidities. Although we used expert opinion to make such distinction for medical consumption, this is not possible for the productivity questionnaire because of the generic questions. Fifth, since this was a trial-based cost-effectiveness study we only compared to peppermint oil to placebo. A valid comparison to other treatments such as the low-FODMAP diet or cognitive behavioral therapy would require a model-based study. Sixth, patients were relatively young, female, and predominantly white. Half of the population was recruited from primary care. Results may therefore not reflect cost-effectiveness in other populations. Nevertheless, inclusion led to a population highly representative for IBS patients seeking treatment in daily routine clinical practice. Thereby our results are applicable to everyday practice and informative for both healthcare policy makers and providers.

In summary, treatment of IBS with small-intestinal release peppermint oil appears to be cost-effective, both from a societal and healthcare perspective, although there is uncertainty surrounding the ICER. When using abdominal pain responder instead of QALY as an outcome measure, peppermint oil has a very high probability of being

TABLE 4 Results of primary and sensitivity analyses (ITT-population)

			Quadrant (%)[a]				Probability of cost effectiveness at willingness-to-pay (%)	
	Δ Effect	Δ Costs (€)	NE	NW	SE	SW	€5.000	€10.000
Cost utility, primary analysis (corrected QALY)	0.004	−40	31	18	**46**	5	53	56
Sensitivity analysis								
Cost-effectiveness, responder ratio[b]	12.4	−40	41	5	**51**	3	89	92
Cost utility, uncorrected QALY	0.006	−40	40	6	**51**	3	56	58
Cost utility, health-care perspective	0.004	−195	15	5	**65**	15	83	85

Note: Bold dignifies the percentage of replications in the south-east quadrant, *i.e.* indicating dominance.

Abbreviations: ICER incremental cost effectiveness ratio; NE, North-east; NW, North-west; PO Peppermint oil; QALY quality adjusted life years; SE, south-east; SW, south-west.

[a]The four quadrants represent four different situations of cost-effectiveness compared to placebo. If the majority of the bootstrapped ICERs appear in the south-east quadrant of the figure, this indicates that treatment is dominant. If the majority of the bootstrapped ICERs appear in the north-west quadrant of the figure, this indicates that treatment is inferior.

[b]The primary clinical endpoint was the percentage (%) of abdominal pain responders, according to FDA definition, 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 to baseline, in at least 50% of the treatment period, in this study that is four weeks.

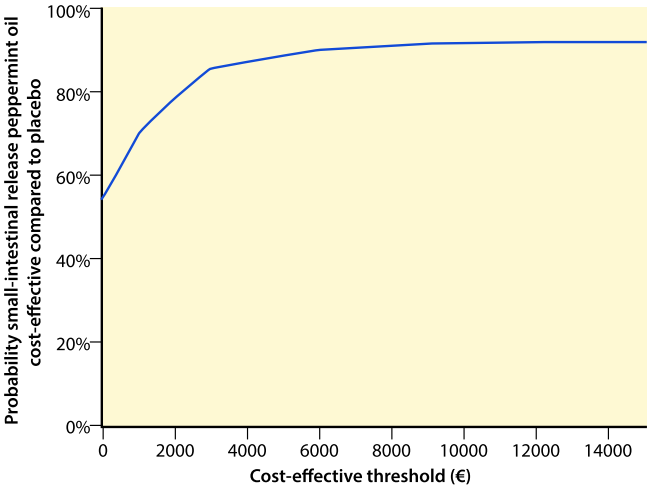

FIGURE 3 Cost-effectiveness acceptability curve of costs and abdominal pain responder (food and drug administration definition). The line indicates the probability (*y*-axis) of small-intestinal release peppermint oil being cost-effective. At a WTP-threshold of 5.000, small-intestinal release has a probability of 89% of being cost effective when using the main clinical parameter, abdominal pain responder, as effect outcome

cost-effective. The use of peppermint oil, which is a low-cost treatment, can be justified by the modest QALY gains and the slightly higher proportion of abdominal pain responders. More research and long-term data are necessary to confirm the cost-effectiveness of peppermint oil.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

Daniel Keszthelyi, Brigitte A. B. Essers, Ad A. M. Masclee, Daisy M. A. E. Jonkers and Zsa Zsa R. M. Weerts designed the study. Zsa Zsa R. M. Weerts, Jeresa I. A. Willems and Deborah J. P. A. Janssen collected the data. Zsa Zsa R. M. Weerts and Brigitte A. B. Essers analyzed the data. Zsa Zsa R. M. Weerts wrote the manuscript. Brigitte A. B. Essers, Daisy M. A. E. Jonkers, Ben J. M. Witteman, Cees H. M. Clemens, Audrey Westendorp, Ad A. M. Masclee and Daniel

Keszthelyi revised the manuscript. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available for scientific researchers upon reasonable request through the first or last author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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