Clinical trial results:
Peppermint oil for the treatment of Irritable Bowel Syndrome: optimizing therapeutic strategies using targeted delivery

Summary

EudraCT number	2015-005467-16
Trial protocol	NL
Global end of trial date	01 May 2018

Results information

Result version number	v1 (current)
This version publication date	01 December 2021
First version publication date	01 December 2021
Summary attachment (see zip file)	Weerts_Gastroenterol_2020 (Weerts_Gastroenterol_2019.pdf) Weerts_JMU_2020 (Weerts_JMU_2020.pdf) Weerts_UEG_2021 (Weerts-2021-A trial-based economic evaluation.pdf)

Trial information

Trial identification

Sponsor protocol code	55995

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02716285
WHO universal trial number (UTN)	-
Other trial identifiers	ABR form number (CCMO): 56000

Notes:

Sponsors

Sponsor organisation name	Maastricht university
Sponsor organisation address	Universiteitssingel 50, Maastricht, Netherlands, 6229 ER
Public contact	Coordinating investigator, Z Weerts, Maastricht University, 0031 3882284, z.weerts@maastrichtuniversity.nl
Scientific contact	Coordinating investigator, Z Weerts, Maastricht University, 0031 3882284, z.weerts@maastrichtuniversity.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2018
Global end of trial reached?	Yes
Global end of trial date	01 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To assess the efficacy and safety profile of treatment of IBS symptoms with peppermint oil compared to placebo. Thereby superiority of peppermint oil can be scientifically supported, leading to increased recognition of this therapy in IBS.
2. To ascertain whether treatment of IBS symptoms with colon-targeted-delivery peppermint oil results in a greater reduction of IBS symptoms and reduction of side effects, compared to enteric-coated capsules delivering the oil in the small intestine.

Protection of trial subjects:

Patients received treatment with peppermint oil or placebo. There were no invasive measurements. Side effects were monitored.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 190
Worldwide total number of subjects	190
EEA total number of subjects	190

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	184

From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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 participating hospitals; or via self-referral through public advertisements, social media, and the Dutch IBS Patient Federation.

Pre-assignment

Screening details:

Prescreening (telephone interview) and a medical screening: 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 NRS. If mean abdominal pain>3. They were included.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Data analyst, Subject

Blinding implementation details:

Capsules were over-encapsulated to ensure equal appearance of placebo and peppermint oil capsules. Packaging info only contained blinded information.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

182mg

Arm title	Small-intestinal release peppermint oil

Arm description:

Small-intestinal release peppermint oil treatment

Arm type	Experimental
Investigational medicinal product name	Tempocol
Investigational medicinal product code	
Other name	Small-intestinal release peppermint oil
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

3 times daily 182mg

Arm title	Ileocolonic release peppermint oil

Arm description:

Ileocolonic release peppermint oil

Arm type	Experimental

Investigational medicinal product name	Tempocol-colopulse
Investigational medicinal product code	
Other name	Ileocolonic-release peppermint oil
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

3 times daily 182mg

Number of subjects in period 1	Placebo	Small-intestinal release peppermint oil	Ileocolonic release peppermint oil
Started	64	62	64
Completed	61	59	59
Not completed	3	3	5
personal reason	1	-	-
Adverse event, non-fatal	1	3	5
Lack of efficacy	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	Small-intestinal release peppermint oil
Reporting group description:	
Small-intestinal release peppermint oil treatment	
Reporting group title	Ileocolonic release peppermint oil
Reporting group description:	
Ileocolonic release peppermint oil	

Reporting group values	Placebo	Small-intestinal release peppermint oil	Ileocolonic release peppermint oil
Number of subjects	64	62	64
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	35.5	32.0	34.4
standard deviation	± 15.2	± 11.1	± 13.1
Gender categorical			
Units: Subjects			
Female	49	51	48
Male	15	11	16
IBS-SSS score			
The IBS-SSS consists of 5 items with a maximum score of 100; higher scores indicate more severe symptoms.			
Units: symptom severity score			
arithmetic mean	270.8	277.0	282.8
standard deviation	± 74.2	± 73.6	± 68.7

Reporting group values	Total		
Number of subjects	190		
Age categorical			
Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	148		
Male	42		
IBS-SSS score			
The IBS-SSS consists of 5 items with a maximum score of 100; higher scores indicate more severe symptoms.			
Units: symptom severity score			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Small-intestinal release peppermint oil
Reporting group description: Small-intestinal release peppermint oil treatment	
Reporting group title	Ileocolonic release peppermint oil
Reporting group description: Ileocolonic release peppermint oil	

Primary: Abdominal pain responder (FDA)

End point title	Abdominal pain responder (FDA)
End point description: An abdominal pain responder is someone who has a >30% in mean daily worst abdominal pain, scored on a 11 point NRS, in at least 50% of the time in which treatment is given.	
End point type	Primary
End point timeframe: 0-8 weeks	

End point values	Placebo	Small-intestinal release peppermint oil	Ileocolonic release peppermint oil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	62	63[1]	
Units: Responders				
Abdominal pain responder	22	29	26	
Abdominal pain non-responder	42	33	37	

Notes:

[1] - 1 person excluded from analysis due to unjustified randomization

Statistical analyses

Statistical analysis title	Abdominal Pain responder (FDA)
Statistical analysis description: The responder outcomes were analyzed by using multiple logistic regression, with correction for the minimization variables of sex, center, IBS subtype, age. Ors, 2-sided 95% 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 comparison 2-sided P values of 0.05/4 1/4 0.0125 were considered statistically significant for the primary outcome.	
Comparison groups	Placebo v Small-intestinal release peppermint oil v Ileocolonic release peppermint oil

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0125 [2]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Notes:

[2] - To account for multiple comparisons (both intervention groups with placebo and 2 primary outcomes), 2-sided P values of 0.05/4 1/4 0.0125 were considered statistically significant for the primary outcomes.

Statistical analysis title	Global relief

Statistical analysis description:

The responder outcomes were analyzed by using multiple logistic regression, with correction for the minimization variables of sex, center, IBS subtype, age. Ors, 2-sided 95% 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 comparison 2-sided P values of 0.05/4 1/4 0.0125 were considered statistically significant for the primary outcome.

Comparison groups	Placebo v Small-intestinal release peppermint oil v Ileocolonic release peppermint oil
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0125 [3]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Notes:

[3] - To account for multiple comparisons (both intervention groups with placebo and 2 primary outcomes), 2-sided P values of 0.05/4 1/4 0.0125 were considered statistically significant for the primary outcomes.

Primary: Global relief responder

End point title	Global relief responder

End point description:

A global relief responder was defined as a patient with a weekly relief of threshold 6 or 7 on the 11 point NRS in at least 50% of the treatment period, that is, 4 weeks.

End point type	Primary

End point timeframe:

0-8 weeks

End point values	Placebo	Small-intestinal release peppermint oil	Ileocolonic release peppermint oil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	62	63[4]	
Units: Global relief responder				
Global Relief responder	3	6	1	
Global Relief non-responder	61	56	62	

Notes:

[4] - 1 person was excluded from the ITT analysis due to unjustified randomization

Statistical analyses

Statistical analysis title	Global relief responder
Comparison groups	Small-intestinal release peppermint oil v Ileocolonic release peppermint oil v Placebo
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0125 [5]
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Notes:

[5] - To account for multiple comparisons (both intervention groups with placebo and 2 primary outcomes), 2-sided P values of 0.05/4 1/4 0.0125 were considered statistically significant for the primary outcomes.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

0-8 weeks

Adverse event reporting additional description:

Patients were asked to score any side effects daily into the daily symptom diary (digital application) (question: did you experience any side effects today?). In addition, at the end of the week - prespecified questions were asked about side effects such as belching, nausea, etc.

Assessment type	Systematic

Dictionary used

Dictionary name	Own codebook
Dictionary version	x

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Small-intestinal release peppermint oil

Reporting group description:

Small-intestinal release peppermint oil treatment

Reporting group title	Ileocolonic release peppermint oil

Reporting group description:

Ileocolonic release peppermint oil

Serious adverse events	Placebo	Small-intestinal release peppermint oil	Ileocolonic release peppermint oil
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 64 (0.00%)	0 / 62 (0.00%)	0 / 63 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placebo	Small-intestinal release peppermint oil	Ileocolonic release peppermint oil
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 64 (78.13%)	59 / 62 (95.16%)	61 / 63 (96.83%)
General disorders and administration site conditions			
Headache			

subjects affected / exposed	21 / 64 (32.81%)	25 / 62 (40.32%)	26 / 63 (41.27%)
occurrences (all)	21	25	26
Gastrointestinal disorders			
Heartburn			
subjects affected / exposed	18 / 64 (28.13%)	31 / 62 (50.00%)	23 / 63 (36.51%)
occurrences (all)	18	31	23
Belching			
subjects affected / exposed	15 / 64 (23.44%)	28 / 62 (45.16%)	12 / 63 (19.05%)
occurrences (all)	15	28	12
Belching with minty taste			
subjects affected / exposed	1 / 64 (1.56%)	36 / 62 (58.06%)	14 / 63 (22.22%)
occurrences (all)	1	36	14
Abdominal cramps			
subjects affected / exposed	12 / 64 (18.75%)	13 / 62 (20.97%)	29 / 63 (46.03%)
occurrences (all)	12	13	29
Altered anal sensation/sensitive urethra			
subjects affected / exposed	9 / 64 (14.06%)	22 / 62 (35.48%)	39 / 63 (61.90%)
occurrences (all)	9	22	39
Peppermint oil-scented stool			
subjects affected / exposed	1 / 64 (1.56%)	18 / 62 (29.03%)	18 / 63 (28.57%)
occurrences (all)	1	18	18

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31470006

http://www.ncbi.nlm.nih.gov/pubmed/34468079

http://www.ncbi.nlm.nih.gov/pubmed/33030150