Clinical trial results:
Double blind, randomized, placebo-controlled, parallel group study to evaluate the effect of a 4-week treatment with oral doses of MEN15596 in irritable bowel syndrome.

Summary

EudraCT number	2008-000214-71
Trial protocol	GB ES SK LV DE DK IT
Global end of trial date	18 February 2009

Results information

Result version number	v1 (current)
This version publication date	09 June 2019
First version publication date	09 June 2019

Trial information

Trial identification

Sponsor protocol code	NAK-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00761007
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LABORATORIOS MENARINI, S.A. (Menarini Group)
Sponsor organisation address	Alfonso XII, 587, BADALONA (BARCELONA), Spain, 08918
Public contact	Dr. Isabel Paredes, LABORATORIOS MENARINI, S.A. (Menarini Group), 34 934628800, iparedes@menarini.es
Scientific contact	Dr. Isabel Paredes, LABORATORIOS MENARINI, S.A. (Menarini Group), 34 934628800, iparedes@menarini.es

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	15 March 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 February 2009
Global end of trial reached?	Yes
Global end of trial date	18 February 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of three doses of MEN 15596 on IBS symptoms relief as compared to placebo in the broad population of irritable bowel syndrome (IBS) patients following a 4 week oral treatment.

Protection of trial subjects:

If any event(s) related to the conduct of the study or the development of the IMP which affected the safety of the study participants, the sponsor and the investigator were to take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/ECs were to be informed forthwith about these new events and the measures taken. For patients participating in the study, the Sponsor had stipulated an insurance policy in accordance with local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 July 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 22
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	United Kingdom: 52
Country: Number of subjects enrolled	Denmark: 148
Country: Number of subjects enrolled	Germany: 80
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Latvia: 72
Country: Number of subjects enrolled	Russian Federation: 72
Country: Number of subjects enrolled	Ukraine: 88
Worldwide total number of subjects	554
EEA total number of subjects	394

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)	508
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient in (screening) 15th July 2008, last patient out 18th February 2009.

Pre-assignment

Screening details:

The study design included a 2-week run-in period, starting from Screening on Day -14 until Day – 1 (start of the treatment).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo oral film-coated tablet, (three tablets), once daily in the morning.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo oral film-coated tablet, (three tablets), once daily in the morning.

Arm title	Ibodutant 10mg

Arm description:

Ibodutant 10mg, oral film-coated tablet, three tablets (one ibodutant 10 mg tablet plus two placebo tablets), once daily in the morning.

Arm type	Experimental
Investigational medicinal product name	Ibodutant
Investigational medicinal product code	MEN15596
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ibodutant 10 mg: oral film-coated tablet, three tablets (one ibodutant 10 mg tablet plus two placebo tablets), once daily in the morning.

Arm title	Ibodutant 30mg

Arm description:

Ibodutant 30mg, oral film-coated tablet, three tablets (one ibodutant 30 mg tablet plus two placebo tablets), once daily in the morning.

Arm type	Experimental

Investigational medicinal product name	Ibodutant
Investigational medicinal product code	MEN15596
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ibodutant 30mg, oral film-coated tablet, three tablets (one ibodutant 30 mg tablet plus two placebo tablets), once daily in the morning.

Arm title	Ibodutant 60mg

Arm description:

Ibodutant 60mg, oral film-coated tablet, three tablets (one ibodutant 60 mg tablet plus two placebo tablets), once daily in the morning.

Arm type	Experimental
Investigational medicinal product name	Ibodutant
Investigational medicinal product code	MEN15596
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ibodutant 60mg, oral film-coated tablet, three tablets (one ibodutant 60 mg tablet plus two placebo tablets), once daily in the morning.

Number of subjects in period 1[1]	Placebo	Ibodutant 10mg	Ibodutant 30mg
Started	136	140	133
Completed	114	117	112
Not completed	22	23	21
Protocol deviation	22	23	21

Number of subjects in period 1[1]	Ibodutant 60mg
Started	135
Completed	112
Not completed	23
Protocol deviation	23

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Overall, 763 patients were screened. Among them, 554 were randomised to receive the study drug and therefore considered as enrolled. 3 patients did not take any dose of study drug, and 7 more patients who did take medication withdrew their consent. Intention to treat (ITT) population was composed of 544 patients. ITT were all patients of the Safety population who had at least one response to the binary question after randomisation.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo oral film-coated tablet, (three tablets), once daily in the morning.	
Reporting group title	Ibodutant 10mg
Reporting group description:	
Ibodutant 10mg, oral film-coated tablet, three tablets (one ibodutant 10 mg tablet plus two placebo tablets), once daily in the morning.	
Reporting group title	Ibodutant 30mg
Reporting group description:	
Ibodutant 30mg, oral film-coated tablet, three tablets (one ibodutant 30 mg tablet plus two placebo tablets), once daily in the morning.	
Reporting group title	Ibodutant 60mg
Reporting group description:	
Ibodutant 60mg, oral film-coated tablet, three tablets (one ibodutant 60 mg tablet plus two placebo tablets), once daily in the morning.	

Reporting group values	Placebo	Ibodutant 10mg	Ibodutant 30mg
Number of subjects	136	140	133
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	43.7	43.9	45
standard deviation	± 13.73	± 13.43	± 12.66
Gender categorical Units: Subjects			
Female	94	104	79
Male	42	36	54
Race Units: Subjects			
Caucasian	135	140	131
Black	1	0	2

Reporting group values	Ibodutant 60mg	Total	
Number of subjects	135	544	

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	44.4		
standard deviation	± 12.97	-	
Gender categorical Units: Subjects			
Female	90	367	
Male	45	177	
Race Units: Subjects			
Caucasian	134	540	
Black	1	4	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo oral film-coated tablet, (three tablets), once daily in the morning.	
Reporting group title	Ibodutant 10mg
Reporting group description:	
Ibodutant 10mg, oral film-coated tablet, three tablets (one ibodutant 10 mg tablet plus two placebo tablets), once daily in the morning.	
Reporting group title	Ibodutant 30mg
Reporting group description:	
Ibodutant 30mg, oral film-coated tablet, three tablets (one ibodutant 30 mg tablet plus two placebo tablets), once daily in the morning.	
Reporting group title	Ibodutant 60mg
Reporting group description:	
Ibodutant 60mg, oral film-coated tablet, three tablets (one ibodutant 60 mg tablet plus two placebo tablets), once daily in the morning.	

Primary: Response (50% rule) at week 4

End point title	Response (50% rule) at week 4
End point description:	
The response for relief of overall IBS symptoms was measured at the end of 4 weeks of treatment, where response was defined as at least two weeks with satisfactory relief during four weeks of treatment (50% rule).	
End point type	Primary
End point timeframe:	
4 weeks	

End point values	Placebo	Ibodutant 10mg	Ibodutant 30mg	Ibodutant 60mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136[1]	140[2]	133[3]	135[4]
Units: 544				
number (not applicable)	78	79	61	61

Notes:

[1] - Total number of subjects analysed. Number (not applicable) stands for responders.

[2] - Total number of subjects analysed. Number (not applicable) stands for responders.

[3] - Total number of subjects analysed. Number (not applicable) stands for responders.

[4] - Total number of subjects analysed. Number (not applicable) stands for responders.

Statistical analyses

Statistical analysis title	Mantel-Haenzel Chi2 Statistics
Comparison groups	Ibodutant 10mg v Ibodutant 30mg v Ibodutant 60mg

Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Mantel-Haenszel

Secondary: Response (75% rule) at week 4.

End point title	Response (75% rule) at week 4.

End point description:

The response for relief of overall IBS symptoms were measured at the end of 4 weeks of treatment, where response was defined as at least three weeks with satisfactory relief during four weeks of treatment (75% rule).

End point type	Secondary

End point timeframe:

4 weeks

End point values	Placebo	Ibodutant 10mg	Ibodutant 30mg	Ibodutant 60mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136[5]	140[6]	133[7]	135[8]
Units: 544				
number (not applicable)	48	53	39	37

Notes:

[5] - Total number of subjects analysed. Number (not applicable) stands for responders.

[6] - Total number of subjects analysed. Number (not applicable) stands for responders.

[7] - Total number of subjects analysed. Number (not applicable) stands for responders.

[8] - Total number of subjects analysed. Number (not applicable) stands for responders.

Statistical analyses

Statistical analysis title	Mantel-Haenszel Chi 2 Statistics
Comparison groups	Ibodutant 10mg v Ibodutant 30mg v Ibodutant 60mg
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Mantel-Haenszel

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
1+/-3 days	
Adverse event reporting additional description:	
Analyzed for the Safety population (all patients who received study treatment)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo oral film-coated tablet, (three tablets), once daily in the morning, before breakfast (in fasting condition).	
Reporting group title	MEN15596 10mg
Reporting group description:	
MEN15596 10mg, oral film-coated tablet, three tablets (only one being MEN15596 10mg), once daily in the morning, before breakfast (in fasting condition).	
Reporting group title	MEN15596 30mg
Reporting group description:	
MEN15596 30mg, oral film-coated tablet, three tablets (only one being MEN15596 30mg), once daily in the morning, before breakfast (in fasting condition).	
Reporting group title	MEN15596 60mg
Reporting group description:	
MEN15596 60mg, oral film-coated tablet, three tablets (only one being MEN15596 60mg), once daily in the morning, before breakfast (in fasting condition).	

Serious adverse events	Placebo	MEN15596 10mg	MEN15596 30mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 137 (0.00%)	0 / 140 (0.00%)	3 / 135 (2.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 137 (0.00%)	0 / 140 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrilation			

subjects affected / exposed	0 / 137 (0.00%)	0 / 140 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 137 (0.00%)	0 / 140 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	0 / 137 (0.00%)	0 / 140 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	MEN15596 60mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 139 (0.72%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrilation			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Pneumonia			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	MEN15596 10mg	MEN15596 30mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 137 (32.85%)	44 / 140 (31.43%)	45 / 135 (33.33%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 137 (0.00%)	1 / 140 (0.71%)	5 / 135 (3.70%)
occurrences (all)	0	1	5
Headache			
subjects affected / exposed	8 / 137 (5.84%)	9 / 140 (6.43%)	7 / 135 (5.19%)
occurrences (all)	10	12	10
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 137 (1.46%)	2 / 140 (1.43%)	1 / 135 (0.74%)
occurrences (all)	2	2	1
Urinary tract infection			
subjects affected / exposed	0 / 137 (0.00%)	3 / 140 (2.14%)	3 / 135 (2.22%)
occurrences (all)	0	3	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 137 (0.73%)	4 / 140 (2.86%)	5 / 135 (3.70%)
occurrences (all)	1	5	5
Abdominal pain upper			
subjects affected / exposed	2 / 137 (1.46%)	0 / 140 (0.00%)	1 / 135 (0.74%)
occurrences (all)	2	0	1
Diarrhoea			
subjects affected / exposed	3 / 137 (2.19%)	5 / 140 (3.57%)	1 / 135 (0.74%)
occurrences (all)	3	5	1
Dyspepsia			

subjects affected / exposed	1 / 137 (0.73%)	2 / 140 (1.43%)	2 / 135 (1.48%)
occurrences (all)	1	2	12
Flatulence			
subjects affected / exposed	2 / 137 (1.46%)	0 / 140 (0.00%)	1 / 135 (0.74%)
occurrences (all)	2	0	1
Nausea			
subjects affected / exposed	4 / 137 (2.92%)	5 / 140 (3.57%)	6 / 135 (4.44%)
occurrences (all)	5	5	7
Vomiting			
subjects affected / exposed	3 / 137 (2.19%)	1 / 140 (0.71%)	0 / 135 (0.00%)
occurrences (all)	4	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 137 (0.73%)	3 / 140 (2.14%)	1 / 135 (0.74%)
occurrences (all)	1	3	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 137 (1.46%)	3 / 140 (2.14%)	1 / 135 (0.74%)
occurrences (all)	2	3	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 137 (5.11%)	5 / 140 (3.57%)	6 / 135 (4.44%)
occurrences (all)	9	6	7

Non-serious adverse events	MEN15596 60mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 139 (31.65%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 139 (1.44%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	5 / 139 (3.60%)		
occurrences (all)	6		
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	3 / 139 (2.16%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 139 (3.60%)		
occurrences (all)	5		
Abdominal pain upper			
subjects affected / exposed	3 / 139 (2.16%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	2 / 139 (1.44%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	3 / 139 (2.16%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	3 / 139 (2.16%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	3 / 139 (2.16%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 139 (1.44%)		
occurrences (all)	2		

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 4 / 139 (2.88%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2008	There were 3 protocol amendments but just one of them was substantial to the Final Protocol (Amendment nº 3) that affected the conditions for subject's participation in the trial, the Patient Information Leaflet/Informed Consent Form (PIL/ICF) was accordingly amended to incorporate this modification and participating subjects were required to consider and sign the amended version indicating that they re-consented to participate in the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported