Clinical trial results:
A 12-week double-blind, randomised, placebo-controlled, parallel group phase III study, followed by a 4-week randomised withdrawal period to evaluate the efficacy and safety of oral ibodutant 10 mg once daily in female patients with irritable bowel syndrome with diarrhoea (IBS-D).

Summary

EudraCT number	2013-000894-56
Trial protocol	CZ IT DE ES GB PL RO
Global end of trial date	22 June 2015

Results information

Result version number	v1 (current)
This version publication date	08 July 2016
First version publication date	08 July 2016
Summary attachment (see zip file)	NAK-06_CSR Synopsis_Final 21JUN2016 (NAK-06_CSR Synopsis_Final 21JUN2016_Signed.pdf)

Trial information

Trial identification

Sponsor protocol code	NAK-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02107196
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini Ricerche S.p.A.
Sponsor organisation address	Via Sette Santi, 1, Florence, Italy, 50131
Public contact	Clinical Research, Menarini Ricerche S.p.A., +39 05556809990, acapriati@menarini-ricerche.it
Scientific contact	Clinical Research, Menarini Ricerche S.p.A., +39 05556809990, acapriati@menarini-ricerche.it

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	18 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2015
Global end of trial reached?	Yes
Global end of trial date	22 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of ibodutant on IBS symptoms as compared to placebo in IBS-D female patients over a 12 week oral treatment period.

Protection of trial subjects:

If any event(s) related to the conduct of the study or the development of the IMP affects the safety of the study participants, the Sponsor and the Investigator will take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/ECs will be informed forthwith about these new events and the measures taken.

For patients participating in the study, Menarini Ricerche S.p.A. has stipulated an insurance policy in accordance with local regulatory requirements. Details on the insurance company, the insurance number and conditions will be made available to patients in the ICF and/or provided as a separate document, in accordance with national requirements.

Overall, the risk-benefit for eligible patients to participate in study NAK-06 is considered favourable. No risk is expected as consequence of drug safety profile or study procedures while a clinically significant benefit is anticipated based on the results of Phase II study; finally no detrimental effect or even a benefit is expected for patients who are randomised to receive placebo because of lack of efficacious and safe treatment versus the high placebo response observed in IBS patients.

Examinations to be performed in the course of the study such as 12-Lead ECGs and blood draws are not associated with any specific risks.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 February 2014
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	Poland: 9
Country: Number of subjects enrolled	Romania: 18
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Bulgaria: 35
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 8

Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	United States: 400
Worldwide total number of subjects	535
EEA total number of subjects	112

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)	509
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was screened on 27th February 2014 and; the first patient randomized on 21st March 2014. The last patient completed the study on 22nd June 2015. The study was conducted at 158 clinical sites in 11 countries (Bulgaria, Czech Republic, France, Germany, Italy, Poland, Romania, Russia, Spain, the USA and the United Kingdom).

Pre-assignment

Screening details:

A total of 1237 entered a 2-week Screening period; 1034 of them entered the 2-week run-in period. A total of 535 patients were actually randomized (enrolled); 453 of them were re-randomized to a 4-week randomized withdrawal period after 12 weeks of study treatment.

Pre-assignment period milestones

Number of subjects started	535
Number of subjects completed	535

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Eligible patients were randomised at the end of the 2-week run-in period and after rechecking eligibility criteria, as per the treatment code provided by the IVRS/IWRS in accordance with the randomisation list.

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline_Ibodutant

Arm description:

DAY1-before first dose of Ibodutant, oral tablet to begiven once daily for 12 weeks of treatment. Patients randomized to the Ibodutant 10 mg arm will be re-randomized at week 13 in a 1:1 ratio to either Ibodutant 10 mg or placebo for additional 4 weeks of treatment.

Arm type	Baseline_Ibodutant
Investigational medicinal product name	not applicable
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

not applicable for baseline group

Arm title	Baseline_Placebo

Arm description:

DAY1-before first dose of placebo, oral tablet to be given once daily for 12 weeks of treatment. Patients randomized to the placebo arm will be mock-re-randomized (switched in blinded conditions) to ibodutant at week 13 for additional 4 weeks of treatment.

Arm type	Baseline _Placebo

Investigational medicinal product name	not applicable
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

not applicable for baseline population

Number of subjects in period 1	Baseline_Ibodutant	Baseline_Placebo
Started	271	264
Completed	271	264

Period 2

Period 2 title	12-week Study Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Blinding implementation details:

Double-blind conditions were maintained by the identical appearance and weight of the ibodutant and placebo tablets. To preserve the double-blind conditions of the study, individuals involved in the preparation or handling of the randomisation lists were not involved in the study conduct or statistical analysis. This remained in effect until the database was completed and locked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ibodutant

Arm description:

Ibodutant, oral tablet to begiven once daily for 12 weeks of treatment.
Patients randomized to the Ibodutant 10 mg arm will be re-randomized at week 13 in a 1:1 ratio to either Ibodutant 10 mg or placebo for additional 4 weeks of treatment.

Arm type	Experimental
Investigational medicinal product name	Ibodutant
Investigational medicinal product code	MEN 15596
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ibodutant 10 mg: Oral tablet, to be given once daily.

Arm title	Placebo

Arm description:

Placebo, oral tablet to be given once daily for 12 weeks of treatment. Patients randomized to the placebo arm will be mock-re-randomized (switched in blinded conditions) to ibodutant at week 13 for additional 4 weeks of treatment.

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

Dosage and administration details:

Placebo: Oral tablet, (identical in appearance and weight to ibodutant tablets), to be given once daily.

Number of subjects in period 2	Ibodutant	Placebo
Started	271	264
Completed	227	225
Not completed	44	39
Consent withdrawn by subject	15	12
Physician decision	-	1
Adverse event, non-fatal	6	3
Lost to follow-up	3	6
Reason missing	11	8
Lack of efficacy	2	1
Protocol deviation	7	8

Period 3

Period 3 title	4-week Randomized Withdrawal
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Double-blind conditions were maintained by the identical appearance and weight of the ibodutant and placebo tablets. To preserve the double-blind conditions of the study, individuals involved in the preparation or handling of the randomisation lists were not involved in the study conduct or statistical analysis. This remained in effect until the database was completed and locked.

Arms

Are arms mutually exclusive?	Yes
Arm title	RW-Placebo

Arm description:

All patients included in the Ibodutant 10 mg arm (period 2), who were re-randomized at week 13 to placebo for additional 4 weeks of treatment.

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral tablet, (identical in appearance and weight to ibodutant tablets), to be given once daily for 4 weeks.

Arm title	RW-Ibodutant

Arm description:

All patients included in both the placebo arm and the ibodutant arm (period 2), who were re-randomized at week 13 to Ibodutant for additional 4 weeks of treatment.

Arm type	Experimental
Investigational medicinal product name	Ibodutant
Investigational medicinal product code	MEN 15596
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ibodutant 10 mg: Oral tablet, to be given once daily.

Number of subjects in period 3[1][2]	RW-Placebo	RW-Ibodutant
Started	114	264
Completed	109	316
Not completed	5	23
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	2
Reason missing	5	18
Protocol deviation	-	2
Joined	0	75
Transferred in from other group/arm	-	75

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: At randomisation (Visit 3), patients commenced 12 weeks of double-blind treatment in a 1:1 ibodutant : placebo ratio, during which Visits 4 (Day 29) and 5 (Day 57) occurred.
Patients were re-randomised for the 4-week RW period at Visit 6 (Day 85): those previously randomised to placebo were mock-randomised to ibodutant; those previously randomised to ibodutant were re-randomised in a 1:1 ibodutant : placebo ratio.
For further details, refer to attached CSR-Synopsis.

[2] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: At randomisation (Visit 3), patients commenced 12 weeks of double-blind treatment in a 1:1 ibodutant : placebo ratio, during which Visits 4 (Day 29) and 5 (Day 57) occurred.

Patients were re-randomised for the 4-week RW period at Visit 6 (Day 85): those previously randomised to placebo were mock-randomised to ibodutant; those previously randomised to ibodutant were re-randomised in a 1:1 ibodutant : placebo ratio.
For further details, refer to attached CSR-Synopsis.

Baseline characteristics

Reporting groups	
Reporting group title	Baseline_Ibodutant

Reporting group description:

DAY1-before first dose of Ibodutant, oral tablet to begiven once daily for 12 weeks of treatment. Patients randomized to the Ibodutant 10 mg arm will be re-randomized at week 13 in a 1:1 ratio to either Ibodutant 10 mg or placebo for additional 4 weeks of treatment.

Reporting group title	Baseline_Placebo

Reporting group description:

DAY1-before first dose of placebo, oral tablet to be given once daily for 12 weeks of treatment. Patients randomized to the placebo arm will be mock-re-randomized (switched in blinded conditions) to ibodutant at week 13 for additional 4 weeks of treatment.

Reporting group values	Baseline_Ibodutant	Baseline_Placebo	Total
Number of subjects	271	264	535
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	258	251	509
From 65-84 years	13	13	26
85 years and over	0	0	0
Age continuous			
Age, Continuous			
Units: years			
arithmetic mean	42.5	43.8	
standard deviation	± 12.81	± 12.47	-
Gender categorical Units: Subjects			
Female	271	264	535
Male	0	0	0
Region of Enrollment Units: Subjects			
Europe	69	66	135
North America	202	198	400
Ethnicity Units: Subjects			
Hispanic or Latino	149	136	285
Not Hispanic or Latino	122	128	250
Abdominal Pain Severity Score Units: Subjects			
<5	46	37	83

>=5 to < 8	176	187	363
>= 8	49	40	89
IBS-SSS Score Units: Subjects			
Mild IBS (<175)	2	6	8
Moderate IBS (175 to < 300)	35	44	79
Severe IBS (>= 300)	233	212	445
Missing	1	2	3

End points

End points reporting groups

Reporting group title	Baseline_Ibodutant

Reporting group description:

DAY1-before first dose of Ibodutant, oral tablet to begiven once daily for 12 weeks of treatment.
Patients randomized to the Ibodutant 10 mg arm will be re-randomized at week 13 in a 1:1 ratio to either Ibodutant 10 mg or placebo for additional 4 weeks of treatment.

Reporting group title	Baseline_Placebo

Reporting group description:

DAY1-before first dose of placebo, oral tablet to be given once daily for 12 weeks of treatment. Patients randomized to the placebo arm will be mock-re-randomized (switched in blinded conditions) to ibodutant at week 13 for additional 4 weeks of treatment.

Reporting group title	Ibodutant

Reporting group description:

Ibodutant, oral tablet to begiven once daily for 12 weeks of treatment.
Patients randomized to the Ibodutant 10 mg arm will be re-randomized at week 13 in a 1:1 ratio to either Ibodutant 10 mg or placebo for additional 4 weeks of treatment.

Reporting group title	Placebo

Reporting group description:

Placebo, oral tablet to be given once daily for 12 weeks of treatment. Patients randomized to the placebo arm will be mock-re-randomized (switched in blinded conditions) to ibodutant at week 13 for additional 4 weeks of treatment.

Reporting group title	RW-Placebo

Reporting group description:

All patients included in the Ibodutant 10 mg arm (period 2), who were re-randomized at week 13 to placebo for additional 4 weeks of treatment.

Reporting group title	RW-Ibodutant

Reporting group description:

All patients included in both the placebo arm and the ibodutant arm (period 2), who were re-randomized at week 13 to Ibodutant for additional 4 weeks of treatment.

Primary: Weekly Response for Abdominal Pain Intensity AND Stool Consistency in at least 50% of the weeks of treatment (6 out of 12 weeks)

End point title	Weekly Response for Abdominal Pain Intensity AND Stool Consistency in at least 50% of the weeks of treatment (6 out of 12 weeks)

End point description:

Weekly Response for Abdominal Pain Intensity AND Stool Consistency Over 12 Weeks of Treatment in at least 50% of theWeeks of Treatment (6 out of 12 Weeks)

End point type	Primary

End point timeframe:

over 12 weeks of treatment

End point values	Ibodutant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	216		
Units: Number of Responders				
Responder	79	75		
Non Responder	142	141		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test

Statistical analysis description:

The primary endpoint was analysed using the Cochran-Mantel-Haenszel (CMH) test in a 2x2 contingency table to compare ibodutant with placebo. The number and percentage of responders and non-responders for each treatment group, the difference in responder rates between the treatment groups, the odds ratio with corresponding 95% two-sided confidence interval for each, and p-value associated with the CMH test were presented.

Comparison groups	Ibodutant v Placebo
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Weekly Abdominal Pain Responder in at least 50% of the weeks of treatment (6 out of 12 weeks)

End point title	Weekly Abdominal Pain Responder in at least 50% of the weeks of treatment (6 out of 12 weeks)

End point description:

The patient will be considered a weekly abdominal pain responder if she meets the following criterion:

-Decrease in weekly average of worst abdominal pain score in the past 24 hours of at least 30% compared with baseline.

End point type	Secondary

End point timeframe:

over 12 weeks of treatment

End point values	Ibodutant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	216		
Units: number of patients				
Responder	106	103		
Non Responder	115	113		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test

Statistical analysis description:

It was analysed using the Cochran-Mantel-Haenszel (CMH) test in a 2x2 contingency table to compare ibodutant with placebo. The number and percentage of responders and non-responders for each treatment group, the difference in responder rates between the treatment groups, the odds ratio with corresponding 95% two-sided confidence interval for each, and p-value associated with the CMH test were presented.

Comparison groups	Ibodutant v Placebo
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Weekly Response for Stool Consistency in at least 50% of the weeks of treatment (6 out of 12 weeks)

End point title	Weekly Response for Stool Consistency in at least 50% of the weeks of treatment (6 out of 12 weeks)

End point description:

The patient will be considered a weekly stool consistency responder if she meets the following criterion:

-Decrease of at least 50% in the number of days per week with at least one stool that has a consistency of Type 6 or 7 compared with baseline.

End point type	Secondary

End point timeframe:

over 12 weeks of treatment

End point values	Ibodutant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	216		
Units: Number of responders				
Responder	99	93		
Non-responder	122	123		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test

Statistical analysis description:

All secondary endpoints were analysed using the Cochran-Mantel-Haenszel (CMH) test in a 2x2 contingency table to compare ibodutant with placebo. The number and percentage of responders and non-responders for each treatment group, the difference in responder rates between the treatment groups, the odds ratio with corresponding 95% two-sided confidence interval for each, and p-value associated with the CMH test were presented.

Comparison groups	Placebo v Ibodutant
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Weekly Response for Relief of overall IBS Signs and Symptoms in at least 50% of weeks of treatment (6 out of 12 weeks)

End point title	Weekly Response for Relief of overall IBS Signs and Symptoms in at least 50% of weeks of treatment (6 out of 12 weeks)

End point description:

The patient will be considered a weekly responder if she has an IBS degree-of relief equal to "completely relieved/improved" or "considerably relieved/improved".

End point type	Secondary

End point timeframe:

over 12 weeks of treatment

End point values	Ibodutant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	216		
Units: number of responders				
Responder	47	41		
Non-responder	174	175		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test

Statistical analysis description:

All secondary endpoints were analysed using the Cochran-Mantel-Haenszel (CMH) test in a 2x2 contingency table to compare ibodutant with placebo. The number and percentage of responders and non-responders for each treatment group, the difference in responder rates between the treatment groups, the odds ratio with corresponding 95% two-sided confidence interval for each, and p-value associated with the CMH test were presented.

Comparison groups	Ibodutant v Placebo
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Rebound effect evaluation for abdominal pain

End point title	Rebound effect evaluation for abdominal pain

End point description:

Evaluation of rebound effect by comparison between average abdominal pain intensity and stool consistency during 4 weeks of randomized withdrawal treatment period and baseline in patients who are re-randomized to placebo after being treated with ibodutant.

End point type	Secondary

End point timeframe:

over 4 weeks of randomized withdrawal treatment

End point values	RW-Placebo	RW-Ibodutant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	316		
Units: units on a scale				
arithmetic mean (standard deviation)				
Abdominal Pain Score (NRS, 0-10 points)	-3.11 (± 2.21)	0 (± 0)		
Bristol Stool Scale (NRS, 1-7 points)	-1.38 (± 1.37)	0 (± 0)		

Statistical analyses

Statistical analysis title	Paired t-test for rebound effect

Statistical analysis description:

The analysis only included the patients randomised to ibodutant in the 12-week treatment period and re-randomised to placebno for the 4-week RW period. Baseline was considered as the average abdominal pain intensity/stool consistency in the 2-week Run-in period.

Comparison groups	RW-Placebo v RW-Ibodutant
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.01
Method	paired t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	2-sided
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
12-week double blind treatment period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Ibodutant
Reporting group description:	
Ibodutant, oral tablet to begiven once daily for 12 weeks of treatment. Patients randomized to the Ibodutant 10 mg arm were re-randomized at week 13 in a 1:1 ratio to either Ibodutant 10 mg or placebo for additional 4 weeks of treatment.	
Reporting group title	Placebo
Reporting group description:	
Placebo, oral tablet to be given once daily for 12 weeks of treatment. Patients randomized to the placebo arm were mock-re-randomized (switched in blinded conditions) to ibodutant at week 13 for additional 4 weeks of treatment.	

Serious adverse events	Ibodutant	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 271 (0.00%)	2 / 264 (0.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Circulatory Collaps			
subjects affected / exposed	0 / 271 (0.00%)	1 / 264 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 271 (0.00%)	1 / 264 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ibodutant	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 271 (12.92%)	33 / 264 (12.50%)	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 271 (1.11%)	0 / 264 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 271 (1.11%)	10 / 264 (3.79%)	
occurrences (all)	3	11	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 271 (1.11%)	0 / 264 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	3 / 271 (1.11%)	1 / 264 (0.38%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 271 (1.11%)	1 / 264 (0.38%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 271 (0.37%)	4 / 264 (1.52%)	
occurrences (all)	1	4	
Muscle spasms			
subjects affected / exposed	3 / 271 (1.11%)	1 / 264 (0.38%)	
occurrences (all)	3	1	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 271 (0.37%)	3 / 264 (1.14%)	
occurrences (all)	1	3	
Nasopharyngitis			
subjects affected / exposed	7 / 271 (2.58%)	6 / 264 (2.27%)	
occurrences (all)	7	6	
Urinary tract infections			

subjects affected / exposed occurrences (all)	8 / 271 (2.95%) 8	7 / 264 (2.65%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2013	Amendment n°1: Besides others, an exclusion criterion (no. 22) was amended in order to provide more detailed guidance to the Investigators.
05 December 2013	Amendment n°2: Besides others, the procedure to be used for the follow-up of the Adverse Events was amended.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported