Clinical trial results:
A 52-week, double-blind, randomised, placebo-controlled, parallel-group phase III study with re-randomisation at week 25 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	2013-000895-14
Trial protocol	HU SE LV CZ SK DE GB
Global end of trial date	03 November 2015

Results information

Result version number	v1 (current)
This version publication date	04 December 2016
First version publication date	04 December 2016
Summary attachment (see zip file)	NAK07 CSR Synopsis_Final version 1.0_02NOV2016 (NAK07 CSR Synopsis_Final version_02NOV2016.pdf)

Trial information

Trial identification

Sponsor protocol code	NAK-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02120027
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	03 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 November 2015
Global end of trial reached?	Yes
Global end of trial date	03 November 2015
Was the trial ended prematurely?	Yes

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 24-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 would have affected the safety of the study participants, the Sponsor and the Investigator would have taken appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/ECs would be informed forthwith about these new events and the measures taken.
For patients participating in the study, Menarini Ricerche S.p.A. had stipulated an insurance policy in accordance with local regulatory requirements. Details on the insurance company, the insurance number and conditions were 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-07 was considered favourable. No risk was expected as consequence of drug safety profile or study procedures while a clinically significant benefit was anticipated based on the results of Phase II study (NAK-04); finally no detrimental effect or even a benefit was expected for patients who were to be randomised to 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 were not associated with any specific risks.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 February 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Slovakia: 11
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Czech Republic: 25
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Latvia: 8
Country: Number of subjects enrolled	United States: 425

Worldwide total number of subjects	558
EEA total number of subjects	133

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)	540
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was consented on 26th February 2014; the first patient was randomised on 24th March 2014. The last patient completed the study on 03rd November 2015. The study was conducted at 139 clinical sites in 9 countries (Czech Republic, Germany, Hungary, Latvia, Poland, Slovakia, Sweden, United Kingdom and USA).

Pre-assignment

Screening details:

Following the screening period of up to 2 weeks, patients entered a 2-week run-in period. A total of 1300 patients were actually screened, of whom 558 patients were randomised to enter the first 24-week treatment period; only 321 of them were re-randomised to enter the second 28-week treatment period due to premature study termination.

Period 1

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

Blinding implementation details:

Following the screening period of up to 2 weeks, patients entered a 2-week run-in period which served as a treatment-free prospective baseline period to characterise IBS symptom severity. 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 be given once daily for 24 weeks of double-blind treatment.
Patients randomised to the ibodutant 10 mg arm will continue on ibodutant 10 mg for additional 28 weeks of treatment via mock re-randomisation at week 25.

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 population.

Arm title	Baseline_Placebo

Arm description:

DAY1- before first dose of placebo, oral tablet to be given once daily for 24 weeks of treatment.
Patients randomised to the placebo arm will be re-randomised at week 25 in a 1:1 ratio to ibodutant or placebo for additional 28 weeks.

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[1]	Baseline_Ibodutant	Baseline_Placebo
Started	277	279
Completed	277	279

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: A total opf 558 patients were randomised: 277 randomised to ibodutant and 281 to placebo group. Two patients randomised to placebo never took the study medication.
Intent-to-treat (ITT) Population (n=556): all randomised patients who received at least 1 dose of study drug.

Period 2

Period 2 title	24-week Study Treatment
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	Ibodutant

Arm description:

Ibodutant, oral tablet to be given once daily for 24 weeks of treatment.
Patients randomised to the ibodutant 10 mg arm were to be continued on ibodutant 10 mg for additional 28 weeks of treatment via mock-re-randomisation at week 25 .

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 24 weeks of treatment.
Patients randomised to the placebo arm were to be re-randomised at week 25 in a 1:1 ratio to ibodutant or placebo for additional 28 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	277	279
Completed	161	160
Not completed	116	119
Physician decision	4	3
Consent withdrawn by subject	33	25
Study terminated by Sponsor	45	47
Adverse event, non-fatal	4	5
Unknown	4	-
Lost to follow-up	5	13
Lack of efficacy	3	5
Protocol deviation	18	21

Baseline characteristics

Reporting groups	
Reporting group title	Baseline_Ibodutant
Reporting group description:	
DAY1-before first dose of Ibodutant, oral tablet to be given once daily for 24 weeks of double-blind treatment. Patients randomised to the ibodutant 10 mg arm will continue on ibodutant 10 mg for additional 28 weeks of treatment via mock re-randomisation at week 25.	
Reporting group title	Baseline_Placebo
Reporting group description:	
DAY1- before first dose of placebo, oral tablet to be given once daily for 24 weeks of treatment. Patients randomised to the placebo arm will be re-randomised at week 25 in a 1:1 ratio to ibodutant or placebo for additional 28 weeks.	

Reporting group values	Baseline_Ibodutant	Baseline_Placebo	Total
Number of subjects	277	279	556
Age categorical Units: Subjects			
Adults (18-64 years)	269	269	538
From 65-84 years	8	10	18
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	42.6	43.8	
standard deviation	± 12.2	± 11.8	-
Gender categorical Units: Subjects			
Female	277	279	556
Male	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	124	131	255
Not Hispanic or Latino	153	148	301
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	3	2	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	32	28	60
White	241	247	488
More than one race	0	0	0
Other	1	1	2
Geographic Region Units: Subjects			
Eastern Europe	35	30	65
North America	211	214	425
Western Europe	31	35	66
Abdominal Pain Severity			

Worst abdominal pain on a 0 to 10 scale, where 0 corresponds to no pain and 10 corresponds to worst possible pain.			
Units: Subjects			
Abdominal Pain Severity < 5	55	54	109
Abdominal Pain Severity ≥ 5 and < 8	172	172	344
Abdominal Pain Severity ≥ 8	50	53	103
IBS-Signs and Symptoms Score			
IBS-SSS score calculated from the questionnaire evaluating primarily the intensity of IBS symptoms during a 10-day period:abdominal pain, distension, stool frequency and consistency, and interference with life in general.The IBS-SSS calculates the sum of these 5 items each scored on a visual analog scale from 0 to 100.All four domains contribute equally to the total score, yielding a range of 0 to 500 to categorize patients into three severity groups:mild (below 175), moderate (175-300), and severe (above 300).			
Units: Subjects			
Mild IBS	7	7	14
Moderate IBS	60	58	118
Severe IBS	210	214	424
Body Mass Index			
Units: kg/m²			
arithmetic mean	29.6	29.6	
standard deviation	± 6.92	± 7.02	-

End points

End points reporting groups

Reporting group title	Baseline_Ibodutant

Reporting group description:

DAY1-before first dose of Ibodutant, oral tablet to be given once daily for 24 weeks of double-blind treatment.
Patients randomised to the ibodutant 10 mg arm will continue on ibodutant 10 mg for additional 28 weeks of treatment via mock re-randomisation at week 25.

Reporting group title	Baseline_Placebo

Reporting group description:

DAY1- before first dose of placebo, oral tablet to be given once daily for 24 weeks of treatment.
Patients randomised to the placebo arm will be re-randomised at week 25 in a 1:1 ratio to ibodutant or placebo for additional 28 weeks.

Reporting group title	Ibodutant

Reporting group description:

Ibodutant, oral tablet to be given once daily for 24 weeks of treatment.
Patients randomised to the ibodutant 10 mg arm were to be continued on ibodutant 10 mg for additional 28 weeks of treatment via mock-re-randomisation at week 25 .

Reporting group title	Placebo

Reporting group description:

Placebo, oral tablet to be given once daily for 24 weeks of treatment.
Patients randomised to the placebo arm were to be re-randomised at week 25 in a 1:1 ratio to ibodutant or placebo for additional 28 weeks of treatment.

Primary: Weekly Response for Abdominal Pain Intensity AND Stool Consistency Over the First 24 Weeks of Treatment in at Least 50% of the Weeks of Treatment (12 Out of 24 Weeks).

End point title	Weekly Response for Abdominal Pain Intensity AND Stool Consistency Over the First 24 Weeks of Treatment in at Least 50% of the Weeks of Treatment (12 Out of 24 Weeks).

End point description:

The patient was considered a weekly responder if she met both of the following criteria in the same week:
• Abdominal pain response: decrease in weekly average of worst abdominal pain score in the past 24 hours of at least 30% compared with baseline (patients reported their worst abdominal pain on a 0 to 10 NRS scale, where 0 corresponds to no pain and 10 corresponds to worst possible pain);
• Stool consistency response: 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 (patients reported their stool consistency response using the Bristol Stool Chart score based on a 1 to 7 NRS scale where 1 corresponds to hard stool and 7 corresponds to watery diarrhoea).

End point type	Primary

End point timeframe:

over 24 weeks of treatment

End point values	Ibodutant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236[1]	238[2]		
Units: Number of Responders				
Responder	51	52		
Non Responder	185	186		

Notes:

[1] - Modified ITT population (n=474): ITT population (n=556) excluding patients of two disqualified sites
[2] - Modified ITT population (n=474): ITT population (n=556) excluding patients of two disqualified sites

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	Ibodutant v Placebo
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.986
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.53
Variability estimate	Standard deviation

Notes:

[3] - Analysis population description: Modified (mITT) Population: all patients in the ITT population excluding patients from site 00179 (N=48), where a potential serious breach of Good Clinical Practice was reported, and site 00186 (N=34), where disqualification proceedings against the Investigator were initiated by the US Food and Drug Administration.

Secondary: Weekly Response for Abdominal Pain Intensity Over the First 24 Weeks of Treatment in at Least 50% of the Weeks of Treatment (12 Out of 24 Weeks).

End point title	Weekly Response for Abdominal Pain Intensity Over the First 24 Weeks of Treatment in at Least 50% of the Weeks of Treatment (12 Out of 24 Weeks).

End point description:

The patient was considered a weekly abdominal pain responder if she met 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 24 weeks of treatment

End point values	Ibodutant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236[4]	238[5]		
Units: Number of Responders				
Responder	96	83		
Non Responder	140	155		

Notes:

[4] - Modified ITT Population (n=474): ITT population (n=556) excluding patients of 2 disqualified sites

[5] - Modified ITT Population (n=474): ITT population (n=556) excluding patients of 2 disqualified sites

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	Ibodutant v Placebo
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.86
Variability estimate	Standard deviation

Secondary: Weekly Response for Stool Consistency Over the First 24 Weeks of Treatment in at Least 50% of the Weeks of Treatment (12 Out of 24 Weeks).

End point title	Weekly Response for Stool Consistency Over the First 24 Weeks of Treatment in at Least 50% of the Weeks of Treatment (12 Out of 24 Weeks).

End point description:

The patient was considered a weekly stool consistency responder if she met 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 24 weeks of treatment

End point values	Ibodutant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236[6]	238[7]		
Units: Number of Responders				
Responder	72	71		
Non Responder	164	167		

Notes:

[6] - Modified ITT (n=474): ITT population (n=556) excluding patients of 2 disqualified sites

[7] - Modified ITT (n=474): ITT population (n=556) excluding patients of 2 disqualified sites

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	Ibodutant v Placebo
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.53
Variability estimate	Standard deviation

Secondary: Weekly Response for Relief of Overall IBS Signs and Symptoms Over the First 24 Weeks of Treatment in at Least 50% of the Weeks (12 Out of 24)

End point title	Weekly Response for Relief of Overall IBS Signs and Symptoms Over the First 24 Weeks of Treatment in at Least 50% of the Weeks (12 Out of 24)

End point description:

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

End point type	Secondary

End point timeframe:

over 24 weeks of treatment

End point values	Ibodutant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236[8]	238[9]		
Units: Number of Responders				
Responder	37	29		
Non Responder	199	209		

Notes:

[8] - Modified ITT Population (n=474): ITT Population (n=556) excluding patients of 2 disqualified sites

[9] - Modified ITT Population (n=474): ITT Population (n=556) excluding patients of 2 disqualified sites

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	Ibodutant v Placebo

Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.339
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.26
Variability estimate	Standard deviation

Secondary: Sustained Analysis of Response for Abdominal Pain AND Stool Consistency Over First 24-week Double-blind Treatment Period

End point title	Sustained Analysis of Response for Abdominal Pain AND Stool Consistency Over First 24-week Double-blind Treatment Period

End point description:

Weekly response for abdominal pain intensity AND stool consistency over the first 24 weeks of treatment applying the 50% rule with at least 2 weeks of response in the last 4 weeks of treatment (week 21 to 24). The patient was considered a weekly responder as defined for the primary endpoint.

End point type	Secondary

End point timeframe:

over 24 weeks of treatment

End point values	Ibodutant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236[10]	238[11]		
Units: Number of Responders				
Responder	50	45		
Non Responder	186	193		

Notes:

[10] - Modified ITT Population (n=474): ITT Population (n=556) excluding patients of 2 disqualified sites

[11] - Modified ITT Population (n=474): ITT Population (n=556) excluding patients of 2 disqualified sites

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Comparison groups	Ibodutant v Placebo
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.153

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.81
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are reported for the safety population (all enrolled patients who received at least 1 dose of study drug) over a period of 24 weeks. The SAE incidence did not change over the entire 52-weeks with respect to the first 24-week period.

Adverse event reporting additional description:

AEs were categorized as Treatment-Emergent Signs and Symptoms (TESS) or Non-TESS for each of the study periods based on the onset date/time of AE. Number of events and number of patients (%) are presented herein by System Organ Class (SOC) and Preferred Term (PT).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Ibodutant 10 mg for 24-week treatment

Reporting group description:

Adverse Events were reported for the safety population (all enrolled patients who received at least 1 dose of study drug) over a period of 24 weeks (first 24-week double-blind treatment period).

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

Reporting group title	Placebo for 24-week treatment

Reporting group description:

Adverse Events were reported for the safety population (all enrolled patients who received at least 1 dose of study drug) over a period of 24 weeks (first 24-week double-blind treatment period).
Placebo: Oral tablet, (identical in appearance and weight to ibodutant tablets), to be given once daily.

Serious adverse events	Ibodutant 10 mg for 24-week treatment	Placebo for 24-week treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 277 (1.08%)	2 / 279 (0.72%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Occipital neuralgia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Dyspnoe			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
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 10 mg for 24-week treatment	Placebo for 24-week treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 277 (27.08%)	82 / 279 (29.39%)	
Investigations			
Weight increased			
subjects affected / exposed	0 / 277 (0.00%)	3 / 279 (1.08%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 277 (1.08%)	7 / 279 (2.51%)	
occurrences (all)	3	8	
Dizziness			

subjects affected / exposed	1 / 277 (0.36%)	3 / 279 (1.08%)	
occurrences (all)	1	3	
Migraine			
subjects affected / exposed	4 / 277 (1.44%)	0 / 279 (0.00%)	
occurrences (all)	10	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 277 (0.00%)	3 / 279 (1.08%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 277 (1.08%)	3 / 279 (1.08%)	
occurrences (all)	3	4	
Gastroenteritis			
subjects affected / exposed	6 / 277 (2.17%)	1 / 279 (0.36%)	
occurrences (all)	7	1	
Nausea			
subjects affected / exposed	7 / 277 (2.53%)	5 / 279 (1.79%)	
occurrences (all)	9	5	
Diarrhoea			
subjects affected / exposed	2 / 277 (0.72%)	3 / 279 (1.08%)	
occurrences (all)	2	3	
Dyspepsia			
subjects affected / exposed	3 / 277 (1.08%)	2 / 279 (0.72%)	
occurrences (all)	4	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 277 (1.44%)	1 / 279 (0.36%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	2 / 277 (0.72%)	3 / 279 (1.08%)	
occurrences (all)	3	3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 277 (0.72%)	4 / 279 (1.43%)	
occurrences (all)	8	4	
Arthralgia			

subjects affected / exposed	4 / 277 (1.44%)	1 / 279 (0.36%)	
occurrences (all)	4	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 277 (0.36%)	3 / 279 (1.08%)	
occurrences (all)	1	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 277 (2.89%)	19 / 279 (6.81%)	
occurrences (all)	9	21	
Sinusitis			
subjects affected / exposed	2 / 277 (0.72%)	4 / 279 (1.43%)	
occurrences (all)	2	4	
Upper respiratory tract infection			
subjects affected / exposed	6 / 277 (2.17%)	4 / 279 (1.43%)	
occurrences (all)	6	4	
Urinary tract infection			
subjects affected / exposed	9 / 277 (3.25%)	9 / 279 (3.23%)	
occurrences (all)	9	9	
Bronchitis			
subjects affected / exposed	3 / 277 (1.08%)	1 / 279 (0.36%)	
occurrences (all)	3	1	
Influenza			
subjects affected / exposed	2 / 277 (0.72%)	3 / 279 (1.08%)	
occurrences (all)	2	3	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	3 / 277 (1.08%)	0 / 279 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2013	Besides others, better specification that the primary endpoint and all efficacy data collected after 12 and 24 weeks of treatment will be analysed after Visit 9 of the 500th randomised patient and that, therefore, the database will undergo two lock procedures (after 24 weeks of treatment and at study end).
05 December 2013	Besides others, the procedure to be used for the follow-up of the Serious Adverse Events was amended.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The Sponsor decided on 03 September 2015 to prematurely terminate the study because of negative results of the contemporaneous sister study NAK-06 and the definitely lower than expected overall (ibodutant/placebo) response rate at week 24.

Notes: