Clinical trial results:
Multicentric, randomized double blind clinical trial and paralell groups to compare Adalimub vs Azatioprina efficacy prevention in Crhon disease post-surgical recurrency after 52 weeks of treatment

Summary

EudraCT number	2011-000885-36
Trial protocol	ES
Global end of trial date	17 April 2015

Results information

Result version number	v1 (current)
This version publication date	14 March 2020
First version publication date	14 March 2020

Trial information

Trial identification

Sponsor protocol code	APPRECIA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01564823
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GETECCU
Sponsor organisation address	C/Gran Via 81, 5º Dpto. 10, Bilbao (Vizcaya), Spain, 48011
Public contact	Clinical trials, GETECCU (Spanish Crohn's Disease and Ulcerative Colitis Working Group), +34 944278855,
Scientific contact	Clinical trials, GETECCU (Spanish Crohn's Disease and Ulcerative Colitis Working Group), +34 944278855,

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	17 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 April 2015
Global end of trial reached?	Yes
Global end of trial date	17 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of Adalimumab vs. Azathioprine in the prevention of endoscopic relapse (quantified using the Rutgeerts score and defined as an score of 2b, 3 or 4) in Cohn’s disease after 52 weeks of treatment.

Protection of trial subjects:

The study was in compliance with ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

Metronidazole PO: 250 mg/8h, for 3 months.
The severity grading for dyspepsia that may occur in patients treated with metronidazole is left to the investigator's discretion. If the investigator considers the dyspepsia to be mild, treatment will not be adjusted. If it is classified as moderate, the dose of metronidazole will be reduced by half, and if it is considered serious, metronidazole will be discontinued. The appearance of paraesthesia in the hands or feet, as well as any side effects attributable to metronidazole at the discretion of the investigator, will lead to discontinuation of the drug, but the patient will remain in the study.

Evidence for comparator: -

Actual start date of recruitment	13 June 2012
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	Spain: 91
Worldwide total number of subjects	91
EEA total number of subjects	91

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)	88
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First randomization/first study treatment administration took place on 22/06/2012 and last randomization/last study treatment administration took place on 03/01/2014.
91 patients were screened; 85 were randomized at 22 sites. 1 patient did not receive the study treatment, so 84 were analyzed.

Pre-assignment

Screening details:

Signed the IC;Age≥18 years;Patients with Crohn’s disease who have undergone an ileocecal/ileocolic resection (L1 or L3);Surgical reconstruction by ileocolic anastomosis.

Period 1

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

Blinding implementation details:

Randomisation was centralised and the investigator was blinded to allocation of each patient until enrolment. From then on, this was an open-label study at site.

Arms

Are arms mutually exclusive?	Yes
Arm title	Azathioprine

Arm description:

Azathioprine: 2.5 mg/kg body weight/day PO throughout the full duration of the Trial

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

Dosage and administration details:

Azathioprine: 2.5 mg/kg body weight/day PO throughout the full duration of the Trial

Arm title	Adalimumab

Arm description:

Adalimumab SC 160 mg followed by 80 mg 2 weeks later and then 40 mg every 2 weeks as maintenance throughout the full duration of the Trial.

Arm type	Experimental
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Adalimumab SC 160 mg followed by 80 mg 2 weeks later and then 40 mg every 2 weeks as maintenance throughout the full duration of the Trial.

Number of subjects in period 1[1]	Azathioprine	Adalimumab
Started	39	45
Completed	27	41
Not completed	12	4
Adverse event, serious fatal	-	1
Physician decision	2	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	9	1
Lost to follow-up	1	-

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: 7 patients were not analyzed: 6 failure of screening and 1 patient was not treated

Baseline characteristics

Reporting groups	
Reporting group title	Azathioprine
Reporting group description:	
Azathioprine: 2.5 mg/kg body weight/day PO throughout the full duration of the Trial	
Reporting group title	Adalimumab
Reporting group description:	
Adalimumab SC 160 mg followed by 80 mg 2 weeks later and then 40 mg every 2 weeks as maintenance throughout the full duration of the Trial.	

Reporting group values	Azathioprine	Adalimumab	Total
Number of subjects	39	45	84
Age categorical			
Units: Subjects			
Adults (18-64 years)	37	44	81
From 65-84 years	2	1	3
Age continuous			
Units: years			
median	37	35	
full range (min-max)	20 to 68	19 to 65	-
Gender categorical			
Units: Subjects			
Female	16	26	42
Male	23	19	42
Ethnicity			
Units: Subjects			
Caucasian	36	42	78
Arab	2	2	4
Gypsy	1	1	2
Smoking			
Units: Subjects			
Non smoker	10	13	23
Former smoker	20	21	41
Smoker	9	11	20
Alcohol intake			
Units: Subjects			
Abstemious	18	22	40
Occasional	20	21	41
Regular	1	1	2
Unknown	0	1	1
Localization of disease			
Units: Subjects			
Ileum	23	26	49
Ileum + Colon	16	19	35
Upper urinary tract affections			
Units: Subjects			
Yes	3	2	5
No	36	43	79

Perforating disease Units: Subjects			
Yes	11	20	31
No	28	25	53
Perianal affections Units: Subjects			
Yes	8	4	12
No	31	41	72
Previous surgery Units: Subjects			
Yes	3	3	6
No	36	42	78
Phenotypes L Units: Subjects			
L1	21	25	46
L1+L4	2	1	3
L3	15	18	33
L3+L4	1	1	2
Phenotypes B Units: Subjects			
No B3	22	23	45
No B3+p	6	2	8
B3	9	18	27
B3+p	2	2	4
Time of disease			
Between diagnosis and consent inform			
Units: Years			
median	4	6	
full range (min-max)	0 to 34	0 to 28	-
Crohn affected length Units: cm			
median	32.5	25	
full range (min-max)	11 to 100	9 to 70	-

End points

End points reporting groups

Reporting group title	Azathioprine
Reporting group description:	
Azathioprine: 2.5 mg/kg body weight/day PO throughout the full duration of the Trial	
Reporting group title	Adalimumab
Reporting group description:	
Adalimumab SC 160 mg followed by 80 mg 2 weeks later and then 40 mg every 2 weeks as maintenance throughout the full duration of the Trial.	

Primary: Endoscopic recurrence

End point title	Endoscopic recurrence
End point description:	
Endoscopic recurrence was defined as having an assessment of the Rutgeerts index of 2b or 3 or 4 past 52 weeks. Patients without evaluable images after 52 weeks or early discontinuation were considered as therapy failure.	
End point type	Primary
End point timeframe:	
After 52 weeks of treatment	

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	45		
Units: subjects				
Yes	23	19		
No	16	26		

Statistical analyses

Statistical analysis title	Endoscopic recurrence between groups
Comparison groups	Azathioprine v Adalimumab
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1257
Method	Chi-squared

Primary: Endoscopic recurrence - PP

End point title	Endoscopic recurrence - PP

End point description:

Endoscopic recurrence was defined as having an assessment of the Rutgeerts index of 2b or 3 or 4 past 52 weeks
Per Protocol population (PP): Consisted of randomized patients who toke at least one dose of treatment and they had an evaluation of the primary endpoint (evaluable colonoscopy) at Visit 9 (52 weeks).

End point type	Primary

End point timeframe:

After 52 weeks of treatment

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[1]	37[2]		
Units: subjects				
Yes	8	11		
No	16	26		

Notes:

[1] - PPC population

[2] - PPC population

Statistical analyses

Statistical analysis title	Endoscopic recurrence between groups
Comparison groups	Azathioprine v Adalimumab
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7665
Method	Chi-squared

Primary: Serious endoscopic recurrence

End point title	Serious endoscopic recurrence

End point description:

It was defined the event serious endoscopic recurrence as having an assessment of the Rutgeerts index of 3 or 4.

End point type	Primary

End point timeframe:

After 52 weeks of treatment

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	45		
Units: Subjects				
Yes	17	13		
No	22	32		

Statistical analyses

Statistical analysis title	Serious endoscopic recurrence between groups
Comparison groups	Azathioprine v Adalimumab
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1608
Method	Chi-squared

Primary: Combined endpoint of both endoscopic recurrence and MRI enterography

End point title	Combined endpoint of both endoscopic recurrence and MRI enterography

End point description:

It was also defined the combined endpoint of both endoscopic recurrence and MRI enterography, considering recurrence all patients who had an assessment after 52 weeks either of the Rutgeerts index of 2b, 3 or 4 or the Sailer index of mr2 or mr3.

End point type	Primary

End point timeframe:

After 52 weeks of treatment

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	45		
Units: subjects				
Yes	30	27		
No	9	18		

Statistical analyses

Statistical analysis title	Recurrence by endoscopy or MRI between groups
Comparison groups	Adalimumab v Azathioprine

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0977
Method	Chi-squared

Secondary: Clinical remission in week 52

End point title	Clinical remission in week 52

End point description:

It was defined clinical remission as having Cohn’s Disease Activity Index ≤200.

End point type	Secondary

End point timeframe:

in week 52 of treatment

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	45		
Units: subjects				
Yes	25	38		
No	2	0		
Unknown	12	7		

Statistical analyses

Statistical analysis title	Clinical remission between groups
Comparison groups	Azathioprine v Adalimumab
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1687
Method	Chi-squared

Secondary: MRI enterography recurrence

End point title	MRI enterography recurrence

End point description:

MRI enterography recurrence was defined as having an assessment of the Sailer index of mr2 or mr3 past 52 weeks. Patients without evaluable images after 52 weeks or early discontinuation were considered as therapy failure.

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	45		
Units: subjects				
Yes	25	22		
No	14	23		

Statistical analyses

Statistical analysis title	MRI enterography recurrence between groups
Comparison groups	Azathioprine v Adalimumab
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1613
Method	Chi-squared

Secondary: Requirement of hospitalization

End point title	Requirement of hospitalization

End point description:

End point type	Secondary

End point timeframe:

During the 52 weeks of treatment

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	45		
Units: subjects				
Yes	4	9		
No	35	36		

Statistical analyses

Statistical analysis title	Requirement of hospitalization between groups
Comparison groups	Azathioprine v Adalimumab

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2182
Method	Chi-squared

Secondary: Requirement of surgery

End point title	Requirement of surgery

End point description:

End point type	Secondary

End point timeframe:

During the 52 weeks of treatment

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	45		
Units: subjects				
Yes	3	2		
No	36	43		

Statistical analyses

Statistical analysis title	Requirement of surgery between groups
Comparison groups	Azathioprine v Adalimumab
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6594
Method	Chi-squared

Secondary: Markers of disease activity: C reactive protein

End point title	Markers of disease activity: C reactive protein

End point description:

End point type	Secondary

End point timeframe:

in week 52 of treatment

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	40		
Units: mg/L				
arithmetic mean (confidence interval 95%)	1.84 (1.06 to 2.62)	4.61 (-0.24 to 9.47)		

Statistical analyses

Statistical analysis title	C reactive protein between groups
Comparison groups	Azathioprine v Adalimumab
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6513
Method	t-test, 2-sided

Secondary: Markers of disease activity: Fecal calprotectin

End point title	Markers of disease activity: Fecal calprotectin

End point description:

End point type	Secondary

End point timeframe:

in week 52 of treatment

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	19		
Units: µg/g				
arithmetic mean (confidence interval 95%)	99.8 (20.6 to 178.9)	120.5 (-7.9 to 249.0)		

Statistical analyses

Statistical analysis title	Fecal calprotectin between groups
Comparison groups	Azathioprine v Adalimumab

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6096
Method	t-test, 2-sided

Secondary: Markers of disease activity: Erythrocyte sedimentation rate

End point title	Markers of disease activity: Erythrocyte sedimentation rate

End point description:

End point type	Secondary

End point timeframe:

in week 52 of treatment

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	29		
Units: units				
arithmetic mean (confidence interval 95%)	13.5 (6.6 to 20.5)	11.4 (7.9 to 15.0)		

Statistical analyses

Statistical analysis title	ESR between groups
Comparison groups	Azathioprine v Adalimumab
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8236
Method	t-test, 2-sided

Secondary: Quality of life by EuroQoL

End point title	Quality of life by EuroQoL

End point description:

Improvement respect to baseline of quality of life measured by EuroQoL questionnaire

End point type	Secondary

End point timeframe:

week 52 of treatment

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	40		
Units: percentage				
arithmetic mean (confidence interval 95%)	12.1 (3.7 to 20.5)	13.2 (6.7 to 19.7)		

Statistical analyses

Statistical analysis title	QoL between treatment
Comparison groups	Azathioprine v Adalimumab
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4951
Method	Wilcoxon (Mann-Whitney)

Secondary: Quality of life by SIBDQ

End point title	Quality of life by SIBDQ
End point description:	
Improvement respect to baseline of quality of life measured by SIBDQ questionnaire	
End point type	Secondary
End point timeframe:	
after 52 weeks of treatment	

End point values	Azathioprine	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	40		
Units: percent				
arithmetic mean (confidence interval 95%)	17.2 (9.6 to 24.7)	15.1 (8.2 to 22.0)		

Statistical analyses

Statistical analysis title	QoL between treatment
Comparison groups	Azathioprine v Adalimumab

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6949
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Azathioprine
Reporting group description:	
Azathioprine: 2.5 mg/kg body weight/day PO throughout the full duration of the Trial	
Reporting group title	Adalimumab
Reporting group description:	
Adalimumab SC 160 mg followed by 80 mg 2 weeks later and then 40 mg every 2 weeks as maintenance throughout the full duration of the Trial.	

Serious adverse events	Azathioprine	Adalimumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 39 (10.26%)	9 / 45 (20.00%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 39 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	1 / 39 (2.56%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 39 (2.56%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periureteral collection			

subjects affected / exposed	0 / 39 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 39 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 39 (2.56%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 39 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal hemorrhage			
subjects affected / exposed	1 / 39 (2.56%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subocclusive syndrome			
subjects affected / exposed	0 / 39 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal mass			
subjects affected / exposed	0 / 39 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 39 (2.56%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 39 (2.56%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Frequent bowel movements			
subjects affected / exposed	0 / 39 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 39 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 39 (0.00%)	1 / 45 (2.22%)	
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: 5 %

Non-serious adverse events	Azathioprine	Adalimumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 39 (89.74%)	37 / 45 (82.22%)	
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	2 / 39 (5.13%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 39 (2.56%)	4 / 45 (8.89%)	
occurrences (all)	1	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 45 (2.22%)	
occurrences (all)	4	1	
Iron deficiency anaemia			
subjects affected / exposed	0 / 39 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	
Leukopenia			
subjects affected / exposed	4 / 39 (10.26%)	1 / 45 (2.22%)	
occurrences (all)	10	1	
Neutropenia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 39 (2.56%)	4 / 45 (8.89%)	
occurrences (all)	1	4	
Pyrexia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 39 (2.56%)	4 / 45 (8.89%)	
occurrences (all)	1	4	
Abdominal distension			

subjects affected / exposed	1 / 39 (2.56%)	4 / 45 (8.89%)	
occurrences (all)	1	4	
Abdominal pain			
subjects affected / exposed	3 / 39 (7.69%)	6 / 45 (13.33%)	
occurrences (all)	3	7	
Abdominal pain lower			
subjects affected / exposed	3 / 39 (7.69%)	3 / 45 (6.67%)	
occurrences (all)	5	5	
Rectal haemorrhage			
subjects affected / exposed	2 / 39 (5.13%)	2 / 45 (4.44%)	
occurrences (all)	2	2	
Nausea			
subjects affected / exposed	3 / 39 (7.69%)	0 / 45 (0.00%)	
occurrences (all)	5	0	
Vomiting			
subjects affected / exposed	1 / 39 (2.56%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 39 (2.56%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Eczema			
subjects affected / exposed	2 / 39 (5.13%)	4 / 45 (8.89%)	
occurrences (all)	2	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 39 (23.08%)	3 / 45 (6.67%)	
occurrences (all)	9	3	
Back pain			
subjects affected / exposed	2 / 39 (5.13%)	3 / 45 (6.67%)	
occurrences (all)	2	3	
Pain in extremity			

subjects affected / exposed	2 / 39 (5.13%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
Limb discomfort			
subjects affected / exposed	2 / 39 (5.13%)	0 / 45 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2012	1- Elimination of redundant selection criteria and greater specification of others 2- Specification of the accounting record procedure of the medication in the trial

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.

A limitation of our study is the lack of a placebo-controlled arm to assess if the observed benefits depend on the post-operative prophylactic drugs used or on the surgery itself.

Notes: