Clinical trial results:
Double-blind, double-dummy, randomised, placebo-controlled, multi-centre phase III study on the efficacy and tolerability of a 8-week treatment with 9 mg budesonide vs. 3 g mesalazine vs. placebo in patients with lymphocytic colitis

Summary

EudraCT number	2008-005994-36
Trial protocol	DE HU SE BE DK CZ LT ES NL IT
Global end of trial date	16 January 2017

Results information

Result version number	v1 (current)
This version publication date	30 March 2018
First version publication date	30 March 2018

Trial information

Trial identification

Sponsor protocol code	BUG-1/LMC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01209208
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstrasse 5, Freiburg, Germany, 79288
Public contact	Department of Clinical Research, Dr. Falk Pharma GmbH, 0049 7611514-0, zentrale@drfalkpharma.de
Scientific contact	Department of Clinical Research, Dr. Falk Pharma GmbH, 0049 7611514-0, zentrale@drfalkpharma.de

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 November 2016
Global end of trial reached?	Yes
Global end of trial date	16 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to evaluate the efficacy of 9 mg budesonide/day and 3 g mesalazine/day compared to placebo for the induction of remission in lymphocytic colitis.

Protection of trial subjects:

Close supervision of subjects by implementing interim visits every 14 days to guarantee their safety and wellbeing. Prior to recruitment of patients, all relevant documents of the clinical study were submitted and proved by the Independent Ethics Committees (IECs) responsible for the participating investigators. Written consent documents embodied the elements of informed consent as described in the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (GCP) and were in accordance with all applicable laws and regulations. The informed consent form and patient information sheet described the planned and permitted uses, transfers and disclosures of the patient's personal data and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet further explained the nature of the study, its objectives and potential risks and benefits as well as the date informed consent was given. Before being enrolled in the clinical trial, every patient was informed that participation in this trial was voluntary and that he/she could withdraw from the study at any time without giving a reason and without having to fear any loss in his/her medical care. The patient’s consent was obtained in writing before the start of the study. By signing the informed consent, the patient declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator and to answer the questions asked during the course of the trial.

Background therapy:

None

Evidence for comparator:

Not applicable

Actual start date of recruitment	06 May 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Lithuania: 4

Worldwide total number of subjects	57
EEA total number of subjects	57

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)	35
From 65 to 84 years	21
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

In total 57 patients were randomized from Germany, Sweden, Denmark, Hungary, Lithuania, Spain, Czech Republic and the Netherlands.

Pre-assignment

Screening details:

Patients signing the informed consent form were screened for up to 2 weeks to evaluate eligibility for the study. A total of 105 patients was screened for enrolment into the study. Forty-eight patients could not be randomised. The most frequent reason for screening failure was violation of eligibility criteria.

Period 1

Period 1 title	8-week double-blind treatment phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The study was to be conducted using the double-dummy technique to guarantee the double-blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A

Arm description:

8-week treatment with 1x sachet Budenofalk® 9 mg granules and 2x sachets Salofalk® 1.5g placebo granules

Arm type	Experimental
Investigational medicinal product name	Budenofalk® 9 mg granules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant granules
Routes of administration	Oral use

Dosage and administration details:

One sachet Budenofalk® 9 mg granules once daily in the morning

Investigational medicinal product name	Salofalk® 1.5g placebo granules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant granules
Routes of administration	Oral use

Dosage and administration details:

Two sachets Salofalk® 1.5g placebo granules once daily in the morning

Arm title	Treatment B

Arm description:

8-week treatment with 1x sachet Budenofalk® 9 mg placebo granules and 2x sachets Salofalk® 1.5g granules

Arm type	Experimental
Investigational medicinal product name	Budenofalk® 9 mg placebo granules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant granules
Routes of administration	Oral use

Dosage and administration details: One sachet Budenofalk® 9 mg placebo granules once daily in the morning.	
Investigational medicinal product name	Salofalk® 1.5g granules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant granules
Routes of administration	Oral use
Dosage and administration details: Two sachets Salofalk® 1.5g granules once daily in the morning.	
Arm title	Treatment C
Arm description: 8-week treatment with 1x sachet Budenofalk® 9 mg placebo granules and 2x sachets Salofalk® 1.5g placebo granules	
Arm type	Placebo
Investigational medicinal product name	Budenofalk® 9 mg placebo granules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant granules
Routes of administration	Oral use
Dosage and administration details: One sachet Budenofalk® 9 mg placebo granules once dail in the morning	
Investigational medicinal product name	Salofalk® 1.5g placebo granules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant granules
Routes of administration	Oral use
Dosage and administration details: Two sachets Salofalk® 1.5g placebo granules once daily in the morning	

Number of subjects in period 1	Treatment A	Treatment B	Treatment C
Started	19	19	19
Completed	15	15	14
Not completed	4	4	5
Adverse event, non-fatal	2	3	-
Other reasons	1	-	-
Lack of patient's co-operation	1	1	-
Lack of efficacy	-	-	5

Period 2

Period 2 title	4-week open-label treatment phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

NA

Arms

Arm title	Open-label treatment

Arm description:

4-week open-label (OL) treatment phase with 1x sachet Budenofalk® 9 mg granules, once daily, for patients who were
• prematurely withdrawn from the double-blind treatment phase due to lack of efficacy,
• not in clinical remission at the end of the double-blind treatment phase or
• experiencing a clinical relapse during the follow-up phase.

Arm type	Experimental
Investigational medicinal product name	Budenofalk® 9 mg granules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gastro-resistant granules
Routes of administration	Oral use

Dosage and administration details:

One sachet Budenofalk® 9 mg granules once daily in the morning

Number of subjects in period 2[1]	Open-label treatment
Started	19
Completed	17
Not completed	2
Adverse event, non-fatal	1
Lack of patient's co-operation	1

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: The 4-week open-label treatment phase could only be entered by a subset of patients of the preceding period.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A
Reporting group description:	
8-week treatment with 1x sachet Budenofalk® 9 mg granules and 2x sachets Salofalk® 1.5g placebo granules	
Reporting group title	Treatment B
Reporting group description:	
8-week treatment with 1x sachet Budenofalk® 9 mg placebo granules and 2x sachets Salofalk® 1.5g granules	
Reporting group title	Treatment C
Reporting group description:	
8-week treatment with 1x sachet Budenofalk® 9 mg placebo granules and 2x sachets Salofalk® 1.5g placebo granules	

Reporting group values	Treatment A	Treatment B	Treatment C
Number of subjects	19	19	19
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)	11	10	14
From 65-84 years	8	9	4
85 years and over	0	0	1
Age continuous Units: years			
arithmetic mean	60.8	57.4	59.0
standard deviation	± 11.5	± 18.5	± 12.7
Gender categorical Units: Subjects			
Female	15	14	12
Male	4	5	7

Reporting group values	Total		
Number of subjects	57		
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)	35		
From 65-84 years	21		
85 years and over	1		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	41		
Male	16		

Subject analysis sets

Subject analysis set title	FAS
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The full analysis set (FAS) defined according to the intention-to-treat principle includes all randomised patients (as randomised) who received at least one dose of the investigational medicinal product.

Subject analysis set title	OL analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The open-label (OL) analysis set includes all patients of the FAS who entered the open-label phase and
• received at least one dose of the investigational medicinal product during the open-label phase and
• have at least one evaluable assessment of efficacy or safety data during the open-label phase.

Reporting group values	FAS	OL analysis set	
Number of subjects	57	19	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	35	12	
From 65-84 years	21	6	
85 years and over	1	1	
Age continuous			
Units: years			
arithmetic mean	59.1	60.0	
standard deviation	± 14.4	± 13.8	
Gender categorical			
Units: Subjects			
Female	41	11	
Male	16	8	

End points

End points reporting groups

Reporting group title	Treatment A
Reporting group description:	
8-week treatment with 1x sachet Budenofalk® 9 mg granules and 2x sachets Salofalk® 1.5g placebo granules	
Reporting group title	Treatment B
Reporting group description:	
8-week treatment with 1x sachet Budenofalk® 9 mg placebo granules and 2x sachets Salofalk® 1.5g granules	
Reporting group title	Treatment C
Reporting group description:	
8-week treatment with 1x sachet Budenofalk® 9 mg placebo granules and 2x sachets Salofalk® 1.5g placebo granules	
Reporting group title	Open-label treatment
Reporting group description:	
4-week open-label (OL) treatment phase with 1x sachet Budenofalk® 9 mg granules, once daily, for patients who were • prematurely withdrawn from the double-blind treatment phase due to lack of efficacy, • not in clinical remission at the end of the double-blind treatment phase or • experiencing a clinical relapse during the follow-up phase.	
Subject analysis set title	FAS
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The full analysis set (FAS) defined according to the intention-to-treat principle includes all randomised patients (as randomised) who received at least one dose of the investigational medicinal product.	
Subject analysis set title	OL analysis set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The open-label (OL) analysis set includes all patients of the FAS who entered the open-label phase and • received at least one dose of the investigational medicinal product during the open-label phase and • have at least one evaluable assessment of efficacy or safety data during the open-label phase.	

Primary: Clinical remission at week 8 / EOT

End point title	Clinical remission at week 8 / EOT
End point description:	
Percentage of patients being in clinical remission at week 8 / EOT. Clinical remission was defined as a maximum of 21 stools, thereof not more than 6 watery stools in the last 7 days prior to the week 8 / EOT.	
End point type	Primary
End point timeframe:	
After 8-week treatment: week 8 / EOT	

End point values	Treatment A	Treatment B	Treatment C	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	19	19	19	57
Units: patients	15	12	8	35

Statistical analyses

Statistical analysis title	Confirmative analysis I
Statistical analysis description:	
Confirmative comparison between Treatment A (Budenofalk® granules) and Treatment C (placebo).	
Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0101 [2]
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	0.368
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.031
upper limit	0.633

Notes:

[1] - Superiority is shown if the lower bound of the 95% repeated confidence interval for the treatment difference with respect to clinical remission is > 0. This corresponds to a local significance level of 0.0164 for the interim analysis / final analysis (incl. overrunning patients).

[2] - As the p-value is lower than the local significance level of 0.0164 for the interim analysis / final analysis (incl. overrunning patients), superiority has been proven.

Statistical analysis title	Confirmative analysis II
Statistical analysis description:	
Confirmative comparison between Treatment B (Salofalk® granules) and Treatment C (placebo).	
Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0969
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	0.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.132
upper limit	0.508

Notes:

[3] - Superiority is shown if the lower bound of the 95% repeated confidence interval for the treatment difference with respect to clinical remission is > 0. This corresponds to a local significance level of 0.0164 for the interim analysis / final analysis (incl. overrunning patients).

Secondary: Histological remission at week 8 / EOT

End point title	Histological remission at week 8 / EOT

End point description:

Percentage of patients beeing in histological remission at week 8 / EOT. Histological remission was defined as ≤ 20 intraepithelial lymphocytes (IELs)/100 epithelial cells.

End point type	Secondary

End point timeframe:

After 8-week treatment: week 8 / EOT

End point values	Treatment A	Treatment B	Treatment C	FAS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	19	19	19	57
Units: patients	13	5	4	22

Statistical analyses

Statistical analysis title	Explorative analysis I

Statistical analysis description:

Explorative comparison between Treatment A (Budenfalk® granules) and Treatment C (placebo).

Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0081
Method	Fisher exact

Statistical analysis title	Explorative Analysis II

Statistical analysis description:

Explorative comparison between Treatment B (Salofalk® granules) and Treatment C (placebo)

Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Clinical remission at end of OL phase

End point title	Clinical remission at end of OL phase

End point description:

The proportion of patients with clinical remission, defined as a maximum of 21 stools, thereof not more than 6 watery stools in the last 7 days prior to the end of the open-label phase.

End point type	Secondary

End point timeframe:

After 4-week open-label treatment

End point values	Open-label treatment	OL analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	17	17		
Units: patients	15	15		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatments A, B, C: from baseline to week 8 / EOT
Open-label treatment: from start of open-label treatment phase to week 4 / EOT

Adverse event reporting additional description:

Treatments A, B, C: all adverse events which occurred from the first drug administration to week 8 / EOT.
Open-label treatment: all adverse events which occurred from the first drug administration of open-label treatment to week 4 / EOT.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Treatment A

Reporting group description:

8-week treatment with 1x sachet Budenofalk® 9 mg granules and 2x sachets Salofalk® 1.5 g placebo granules once daily.

Reporting group title	Treatment B

Reporting group description:

8-week treatment with 1x sachet Budenofalk® 9 mg placebo granules and 2x sachets Salofalk® 1.5 g granules once daily.

Reporting group title	Treatment C

Reporting group description:

8-week treatment with 1x sachet Budenofalk® 9 mg placebo granules and 2x sachets Salofalk® 1.5g placebo granules once daily.

Reporting group title	Open-label treatment

Reporting group description:

4-week open-label treatment with 1x sachet Budenofalk® 9 mg granules once daily.

Serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 19 (10.53%)	2 / 19 (10.53%)	1 / 19 (5.26%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			

subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Metatarsalgia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-label treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Alcohol abuse			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Metatarsalgia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 19 (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: 0 %

Non-serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 19 (42.11%)	13 / 19 (68.42%)	7 / 19 (36.84%)
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Blood urea increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Weight increased			

subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Traumatic haematoma			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Headache			
subjects affected / exposed	1 / 19 (5.26%)	2 / 19 (10.53%)	0 / 19 (0.00%)
occurrences (all)	1	7	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Abdominal pain lower			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Abdominal pain upper			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Colitis microscopic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1

Nausea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Vomiting			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Rash			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			
subjects affected / exposed	2 / 19 (10.53%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
Haemarthrosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Tendon pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Musculoskeletal discomfort			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Furuncle			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
Nasopharyngitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Pneumonia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Sinusitis			

subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Tooth infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Hyperphagia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Open-label treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 19 (26.32%)		
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Blood urea increased			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Glomerular filtration rate decreased			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Hepatic enzyme increased			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Traumatic haematoma			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Abdominal pain lower			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		

Colitis microscopic			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Night sweats			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Haemarthrosis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Tendon pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Musculoskeletal discomfort			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Infections and infestations			
Furuncle			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Tooth infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Clostridium difficile infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Hyperphagia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2010	Primary reason for amendment no. 1 was that lymphocytic colitis may be associated with the use of certain drugs. A high level of likelihood of being able to cause microscopic colitis is attributed to acarbose, aspirin, Cyclo3Fort, lansoprazole, nonsteroidal anti-inflammatory drugs, ranitidine, sertraline, and ticlopidine. Therefore, the previous and concomitant medication section has been amended.
10 June 2013	Amendment 2 was required to take into account the new information of the latest Investigator's Brochure for Salofalk® (oral formulations). Some administrative additions were also included in the protocol to verbalize more detailed guidance as per the current status quo.
30 September 2015	Amendment no. 3 which was requested by the Italian competent authority, agenzia italiana del farmaco (AIFA), was applicable only for Italy and only submitted to the IECs of Italy. It focused on live vaccination and diagnosis of chickenpox, herpes zoster or measles. Additional exclusion and withdrawal criteria were included.
22 June 2016	Amendment no. 4 referred to the fact that the planned interim analysis was to be performed after inclusion of 54 patients who were evaluable in the intention-to-treat analysis (approximately 18 patients in each treatment group), instead of 60 patients.
16 August 2016	Substantial amendment no. 5 was submitted to the IECs of Germany, Hungary, Spain and Lithuania and referred to basic clarifications of the study protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported