Clinical trial results:
Double-blind, double-dummy, randomised, multi-centre, comparative phase III clinical study on the efficacy and tolerability of an 8-week oral treatment with three times daily 1000 mg mesalazine versus three times daily 2x500 mg mesalazine in patients with active ulcerative colitis.

Summary

EudraCT number	2012-001830-32
Trial protocol	DE HU LV LT PL
Global end of trial date	06 October 2014

Results information

Result version number	v1 (current)
This version publication date	20 July 2016
First version publication date	20 July 2016

Trial information

Trial identification

Sponsor protocol code	SAT-25/UCA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01745770
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstraße 5, Freiburg, Germany, 79108
Public contact	Department of Medical Science, Dr. Falk Pharma GmbH, 0049 7611514-0,
Scientific contact	Department of Medical Science, Dr. Falk Pharma GmbH, 0049 7611514-0,

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	23 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2014
Global end of trial reached?	Yes
Global end of trial date	06 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to proof the non-inferiority of an 8-week treatment with three times daily 1000mg mesalazine versus three times daily 2x500 mg mesalazine in patients with active ulcerative colitis.

Protection of trial subjects:

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:

No concomitant background therapy was allowed during the trial.

Evidence for comparator:

Eudragit-L-coated 500 mg mesalazine tablets (Salofalk® 500 mg tablets) were selected as comparator because this galenical principle was demonstrated to be effective in mildly to moderately active UC in several trials and are approved for the treatment of mildly to moderately active UC.

Actual start date of recruitment	03 January 2013
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	Poland: 10
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 32
Country: Number of subjects enrolled	Latvia: 34
Country: Number of subjects enrolled	Lithuania: 29
Country: Number of subjects enrolled	Russian Federation: 122
Country: Number of subjects enrolled	Ukraine: 73

Worldwide total number of subjects	306
EEA total number of subjects	111

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)	1
Adults (18-64 years)	282
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This clinical trial was conducted in 42 sites in 7 countries in Europe. The first patient was enrolled on 03 January 2013.

Pre-assignment

Screening details:

A screening period up to 7 days prior to randomisation was implemented to evaluate eligibility of patients. A total of 374 patients were screened for enrolment into the study. Sixty-eight patients could not be randomised, mainly due to violation of in-/exclusion criteria (41 patients). 306 patients were randomised to either of both treatments.

Period 1

Period 1 title	Treatment Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, 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	M1000

Arm description:

8-week treatment with three times daily 1000 mg mesalazine

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

Dosage and administration details:

Three times daily 1000 mg mesalazine

Arm title	M2x500

Arm description:

8-week treatment with three times daily 2x500 mg mesalazine

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

Dosage and administration details:

Three times daily 2x500 mg mesalazine

Number of subjects in period 1	M1000	M2x500
Started	151	155
Completed	143	149
Not completed	8	6
Adverse event, non-fatal	2	1
Other	-	1
Lack of patient's co-operation	4	2
Lack of efficacy	2	2

Baseline characteristics

Reporting groups	
Reporting group title	M1000
Reporting group description:	
8-week treatment with three times daily 1000 mg mesalazine	
Reporting group title	M2x500
Reporting group description:	
8-week treatment with three times daily 2x500 mg mesalazine	

Reporting group values	M1000	M2x500	Total
Number of subjects	151	155	306
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)	1	0	1
Adults (18-64 years)	141	141	282
From 65-84 years	9	14	23
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	41.4	43.3	
standard deviation	± 12.9	± 14	-
Gender categorical Units: Subjects			
Female	72	82	154
Male	79	73	152
Type of disease Units: Subjects			
New	29	26	55
Established	122	129	251
Localisation of disease Units: Subjects			
Proctosigmoiditis	93	76	169
Left-sided colitis	22	32	54
Subtotal/total colitis	29	41	70
Not assessable	7	6	13
Body mass index Units: kg/m²			
arithmetic mean	25.2	24.5	
standard deviation	± 4.8	± 4.4	-
Time since first symptoms Units: years			

median	3.5	3.6	
inter-quartile range (Q1-Q3)	1.1 to 8.9	1.4 to 10.2	-
Clinical Activity Index (CAI)			
The clinical activity index (CAI) combines clinical findings (ESR, temperature, haemoglobin, extraintestinal manifestations) and patient reported outcomes (number of [bloody] stools per week, degree of abdominal pain and general well-being). The total score ranges from 0 to 31 points.			
Units: points			
arithmetic mean	7.5	7.7	
standard deviation	± 1.7	± 1.9	-
Endoscopic Index (EI)			
The following endoscopic asssessments are performed for calculation of the endoscopic index (EI): granulation scattering reflected light, vascular pattern, vulnerability of mucosa, mucosal damage (mucus, fibrin, exudate, erosions, ulcers). The EI ranges between 0 and 12 points, with high (low) values indicating high (low) impairment of the mucosa.			
Units: points			
arithmetic mean	6.9	6.7	
standard deviation	± 1.7	± 1.7	-
Histological Index (HI)			
The histological index (HI) is represented by the total histological assessment (0 = no signs of UC, 1 = remission, 2 = mild activity, 3 = moderate activity, 4 = severe activity).			
Units: points			
arithmetic mean	2.5	2.4	
standard deviation	± 1	± 0.9	-

End points

End points reporting groups

Reporting group title	M1000
Reporting group description:	
8-week treatment with three times daily 1000 mg mesalazine	
Reporting group title	M2x500
Reporting group description:	
8-week treatment with three times daily 2x500 mg mesalazine	

Primary: Clinical remission at week 8 / EOT (PP interim)

End point title	Clinical remission at week 8 / EOT (PP interim)
End point description:	
Percentage of patients being in clinical remission at week 8 / EOT. Clinical remission was defined as clinical activity index (CAI) ≤ 4 with stool frequency subscore of 0 (i.e. < 18 stools/week [CAI subscore 1]) and rectal bleeding subscore of 0 (i.e. 0-1 stools with blood in or on the stool [CAI subscore 2]). This is the primary analysis, as non-inferiority was proven already for the first interim analysis. The analysis set is the per-protocol analysis set for the first interim analysis (N = 217).	
End point type	Primary
End point timeframe:	
After 8-week treatment: week 8 / EOT	

End point values	M1000	M2x500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	114		
Units: patients	48	44		

Statistical analyses

Statistical analysis title	Non-inferiority test
Statistical analysis description:	
For statistical testing a non-inferiority margin of 15% was defined. Hence, non-inferiority is shown if the lower bound of the 95% repeated confidence interval for the treatment difference with respect to clinical remission (πM1000 – πM2x500) is above -15%. This corresponds to a local significance level of 0.0043 for the first interim analysis. This is the primary analysis, as non-inferiority was proven already at stage 1 of the 3 stage adaptive study design.	
Comparison groups	M1000 v M2x500
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0003 [1]
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.6
upper limit	25.2

Notes:

[1] - As the p-value is lower than the local significance level of 0.0043 for interim analysis 1, non-inferiority has been proven for the PP analysis set for interim analysis I.

Primary: Clinical remission at week 8 / EOT (PP final)

End point title	Clinical remission at week 8 / EOT (PP final)

End point description:

Percentage of patients being in clinical remission at week 8 / EOT. Clinical remission was defined as clinical activity index (CAI) ≤ 4 with stool frequency subscore of 0 (i.e. < 18 stools/week [CAI subscore 1]) and rectal bleeding subscore of 0 (i.e. 0-1 stools with blood in or on the stool [CAI subscore 2]). This is a sensitivity analysis. The analysis set is the per-protocol analysis set for the final analysis (N = 278), taking into account the 68 overrunning patients who have been included into the study during interim analysis I.

End point type	Primary

End point timeframe:

After 8-week treatment: week 8 / EOT

End point values	M1000	M2x500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	144		
Units: Patients	64	61		

Statistical analyses

Statistical analysis title	Non-inferiority test

Statistical analysis description:

For statistical testing a non-inferiority margin of 15% was defined. Hence, non-inferiority is shown if the lower bound of the 95% repeated CI for the treatment difference with respect to clinical remission (пM1000 – пM2x500) is above -15%. This corresponds to a local significance level of 0.0043 for the first interim analysis. This is a sensitivity analysis, taking into account the 68 overrunning patients who have been included into the study during interim analysis I.

Comparison groups	M1000 v M2x500
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0003 [2]
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	20.8

Notes:

[2] - As the p-value is lower than the local significance level of 0.0043, non-inferiority has been proven for the PP analysis set inlcuding overrunning patients.

Primary: Clinical remission at week 8 / EOT (FAS final)

End point title	Clinical remission at week 8 / EOT (FAS final)

End point description:

Percentage of patients being in clinical remission at week 8 / EOT. Clinical remission was defined as clinical activity index (CAI) ≤ 4 with stool frequency subscore of 0 (i.e. < 18 stools/week [CAI subscore 1]) and rectal bleeding subscore of 0 (i.e. 0-1 stools with blood in or on the stool [CAI subscore 2]). This is a sensitivity analysis. The analysis set is the full analysis set for the final analysis (N = 306).

End point type	Primary

End point timeframe:

After 8-week treatment: week 8 / EOT

End point values	M1000	M2x500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	155		
Units: Patient	68	65		

Statistical analyses

Statistical analysis title	Non-inferiority test

Statistical analysis description:

For statistical testing a non-inferiority margin of 15% was defined. Hence, non-inferiority is shown if the lower bound of the 95% repeated CI for the treatment difference with respect to clinical remission (πM1000 – πM2x500) is above -15%. This corresponds to a local significance level of 0.0043 for the first interim analysis. This is a sensitivity analysis for the full analysis set, taking into account the 68 overrunning patients who were included into the study during interim analysis I.

Comparison groups	M2x500 v M1000
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0006 [3]
Method	Normal approximation test
Parameter estimate	Risk difference (RD)
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	17.8

Notes:

[3] - As the p-value is lower than the local significance level of 0.0043, non-inferiority has been proven for the full analysis set including overrunning patients.

Secondary: Clinical improvement in CAI

End point title	Clinical improvement in CAI

End point description:

Percentage of patients with clincal improvement, defined as increase of clinical activity index (CAI) by ≥ 3 points from baseline to week 8 / EOT. The analysis set is the full analysis set for the final analysis (N = 306).

End point type	Secondary

End point timeframe:

From baseline to week 8 / EOT

End point values	M1000	M2x500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	155		
Units: Patients	116	123		

Statistical analyses

Statistical analysis title	Confidence interval for risk difference
Comparison groups	M1000 v M2x500
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Wald 95% confidence interval
Parameter estimate	Risk difference (RD)
Point estimate	-2.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.8
upper limit	6.73

Secondary: Endoscopic remission (mucosal healing)

End point title	Endoscopic remission (mucosal healing)

End point description:

Percentage of patients being in endoscopic remission at week 8 / EOT, defined as endoscopic index (EI) < 4. The analysis set is the full analysis set for the final analysis (N = 306).

End point type	Secondary

End point timeframe:

After 8-week treatment: week 8 / EOT

End point values	M1000	M2x500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	155		
Units: patients	104	106		

Statistical analyses

Statistical analysis title	Confidence interval for risk difference

Statistical analysis description:

The Wald 95% confidence interval is calculated for the difference in remission rates between M1000 and M2x500.

Comparison groups	M1000 v M2x500
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.91
upper limit	10.89

Secondary: Endoscopic improvement

End point title	Endoscopic improvement

End point description:

Percentage of patients with endoscopic improvement, defined as decrease of endoscopic index (EI) by ≥ 1 point from baseline to week 8 / EOT. The analysis set is the full analysis set for the final analysis (N = 306).

End point type	Secondary

End point timeframe:

After 8-week treatment: week 8 / EOT

End point values	M1000	M2x500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	155		
Units: patients	120	129		

Statistical analyses

Statistical analysis title	Confidence interval for risk difference
Statistical analysis description:	
The Wald 95% confidence interval is calculated for the difference in improvement rates between M1000 and M2x500.	
Comparison groups	M1000 v M2x500
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	-3.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.48
upper limit	4.97

Secondary: Histological improvement	
End point title	Histological improvement
End point description:	
Percentage of patients with histological improvment, defined as decrease of histological index (HI) by ≥ 1 point from baseline to week 8 / EOT. The analysis set is the full analysis set for the final analysis (N = 306).	
End point type	Secondary
End point timeframe:	
After 8-week treatment: week 8 / EOT	

End point values	M1000	M2x500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	155		
Units: patients	75	84		

Statistical analyses

Statistical analysis title	Confidence interval for risk difference
Comparison groups	M1000 v M2x500
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Risk difference (RD)
Point estimate	-4.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.71
upper limit	6.66

Notes:

[4] - The Wald 95% confidence interval is calculated for the difference in improvement rates between M1000 and M2x500.

Secondary: Tablet preference

End point title	Tablet preference

End point description:

Patients had to assess their tablet preference: one big mesalazine tablet or two smaller mesalazine tablets.

End point type	Secondary

End point timeframe:

After 8-week treatment: week 8 / EOT

End point values	M1000	M2x500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	155		
Units: patients				
One big mesalazine tablet	73	73		
Two smaller mesalazine tablets	12	20		
No preference	62	62		
Missing	4	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline to week 8 / EOT	
Adverse event reporting additional description:	
All treatment emergent adverse events which occurred from the first drug administration to week 8 / EOT.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	M1000
Reporting group description:	
8-week treatment with three times daily 1000 mg masalazine	
Reporting group title	M2x500
Reporting group description:	
8-week treatment with three times daily 2x500 mg mesalazine	

Serious adverse events	M1000	M2x500	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 151 (0.00%)	0 / 155 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	M1000	M2x500	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 151 (19.87%)	29 / 155 (18.71%)	
Investigations			
C-reactive protein increased			
subjects affected / exposed	4 / 151 (2.65%)	0 / 155 (0.00%)	
occurrences (all)	4	0	
Faecal calprotectin increased			
subjects affected / exposed	4 / 151 (2.65%)	1 / 155 (0.65%)	
occurrences (all)	4	1	
Lipase increased			

subjects affected / exposed	3 / 151 (1.99%)	3 / 155 (1.94%)	
occurrences (all)	3	3	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 151 (1.99%)	2 / 155 (1.29%)	
occurrences (all)	3	2	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 151 (1.99%)	2 / 155 (1.29%)	
occurrences (all)	3	2	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 151 (2.65%)	4 / 155 (2.58%)	
occurrences (all)	4	4	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	3 / 151 (1.99%)	5 / 155 (3.23%)	
occurrences (all)	3	5	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 151 (1.99%)	0 / 155 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 151 (2.65%)	1 / 155 (0.65%)	
occurrences (all)	4	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2013	Clinical study protocol amendment 1, version 1.0 of 08 Apr 2013, became necessary in order to incorporate changes due to the update of the Investigator's Brochure for Salofalk® (oral formulations) and Summary of Product Characteristics for Salofalk® 500 mg tablets. This amendment was also used to increase clarity of the study protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported