Clinical Study Report Synopsis

Study Title:	Double-blind, randomised, placebo-controlled, parallel group, multi-centre Phase III clinical study on the efficacy and tolerability of mesalazine granules vs. placebo for the prevention of recurrence of diverticulitis
Short title:	Mesalazine granules vs. placebo for the prevention of recurrence of diverticulitis
Investigational drug:	Mesalazine granules (Salofalk® 1.5 g granules)
Reference drug:	Placebo granules
Indication:	Prevention of recurrence of diverticulitis
Phase of study:	III
First patient enrolled:	07 Jan 2008
Last patient completed:	15 Nov 2011
EudraCT No.:	2007-000680-22
Date of final report:	25 September 2015
Sponsor:	Dr. Falk Pharma GmbH Leinenweberstr. 5 79108 Freiburg Germany
Medical Expert/LKP according to §40 AMG:	Prof. Dr. med. Wolfgang Kruis Medical Department Evang. Krankenhaus Kalk Buchforststr 2 51103 Köln Germany

GCP Statement: This study was conducted in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.

SYNOPSIS

Title of Study:
Double-blind, randomised, placebo-controlled, parallel group, multi-centre Phase III clinical study on the efficacy and tolerability of mesalazine granules vs. placebo for the prevention of recurrence of diverticulitis

Methodology:
This was a double-blind, randomized, placebo-controlled, parallel group, multi-centre Phase III clinical study with 2 treatment groups.

Group A (investigational drug): 3 g mesalazine granules (Salofalk® 1.5 g granules) OD
Group B (reference drug): Placebo granules OD

The study was planned to be performed according to a 2-stage group sequential test design with possible sample size adjustments after the interim analysis.

Protocol version:
Study protocol version 2.0/28.06.2007
Amendment No. 1, final version 1.0, dated 10 Nov 2008
Amendment No. 2, final version, dated 13 Jan 2010
Amendment No. 3, final version, dated 13 Jan 2011

Study Centres:
57 centres enrolled patients in following countries (number of patients): Czech Republic (36), Estonia (8), Germany (100), Hungary (68), Israel (34), Latvia (9), Lithuania (9), The Netherlands (38), Poland (3), Romania (9), Slovakia (31), United Kingdom (0)

Study Period:	**Phase of Development:**
First patient enrolled: 07 Jan 2008 Last patient completed: 15 Nov 2011	III

Objectives:
- To compare the efficacy and tolerability of mesalazine granules (3 g 5-aminosalicylic acid (5-ASA)/once daily (OD)) vs. placebo for the prevention of recurrence of diverticulitis
- To study safety and tolerability in the form of adverse events (AEs) and laboratory parameters
- To assess patients' quality of life (QoL)

Number of Patients (Total and for Each Treatment):
Planned/Adapted during Interim Analyses:
According to the original Clinical Study Protocol (CSP), a 2-stage group sequential adaptive design was used. The interim analysis was planned to be performed after observation of 2 x 66 patients who were evaluable in the full analysis set (FAS). The final analysis was planned to be performed after observation of further 2 x 134 patients who were evaluable in the FAS. The estimated sample size, without sample size adaptation, was 200 evaluable patients in each treatment group.
The planned interim analysis was performed on 133 evaluable patients in the FAS. It showed that the primary objective of the study could not be reached. Recruitment of the study was stopped after the result of the interim analysis was available. However, as recruitment continued during the time the interim analysis was performed, about 200 patients were still in the study. The study was carried on in these patients, a second interim analysis was performed on a total of 233 evaluable patients in the FAS, and the final analysis was performed on a total of 333 evaluable patients in the FAS. The second interim analysis was introduced with Amendment No. 3 due to recommendations of the Independent Data Monitoring Committee (IDMC).

Analysed in the Final Analysis:

Number of patients	Mesalazine	Placebo	Total
Randomised	171	174	345
Treated	170	172	342
Safety	170	172	342
FAS	165	168	333
PP	133	137	270

In total, 342 patients received study medication and were included in the safety analysis set (SAF). Nine patients were excluded from the SAF to form the FAS because they did not fulfil inclusion criterion no. 5 defined as most recent attack of left-sided uncomplicated diverticulitis responding to antibiotics and/or dietary modifications within the last 6 months.

Diagnosis and Main Criteria for Inclusion

Main Inclusion Criteria:

- Signed informed consent,
- Men or women aged 40 to 80 years,
- Diagnosis of left-sided uncomplicated diverticular disease (DD)
- Presence of at least one diverticulum of the left colon
- Most recent attack of left-sided uncomplicated diverticulitis responding to antibiotics and/or dietary modification within the last 6 months
- C-reactive protein (CRP) >upper limit of normal (ULN) or leucocytosis at the start of the most recent attack

Duration of Treatment:

48 weeks

Criteria for Evaluation:

Primary Efficacy Variable:

- Proportion of recurrence-free patients within 48 weeks: recurrence of diverticulitis was defined as CRP >ULN or leukocytosis and recurrence of diverticulitis-like symptoms (left lower quadrant pain, fever) with associated clinical, biochemical parameters or confirmation by ultrasound or CT.

Secondary Efficacy Variables:

- Proportion of patients with recurrence
- Time in study
- Time to recurrence
- Time to recurrence or discontinuation, due to lack of efficacy of the study medication or an AE with certain or probable/likely or possible causal relationship with the study medication, or intolerable AE which was a deterioration of the study disease
- Course of erythrocyte sedimentation rate (ESR)
- Course of CRP
- Course of leukocytosis
- Occurrence of diverticulitis-associated fever
- Number of days with left lower quadrant pain
- Number of days with stools of solid consistency
- Number of days with stools of soft or solid consistency
- Number of days with diarrhoea (>3 stools per day)
- Number of days with stools of watery consistency
- Average frequency of stools per week
- Amount of used spasmolytics
- Amounts of used analgesics
- Worsening of symptoms, e.g. symptoms recorded in the diary, use of antibiotics, hospitalisation for underlying disease, surgery
- QoL
- Health assessment
- Assessment of efficacy by investigator and patient.

Safety:

- AEs,
- Vital signs (blood pressure, pulse rate) and body weight
- Standard haematology, blood chemistry, and urinalysis
- Assessment of tolerability by investigator and patient.

Statistical Methods:

This was a confirmatory study. The aim was to demonstrate superiority of mesalazine granules compared to placebo in terms of proportion of recurrence-free patients within 48 weeks. H_0 ($\pi_{placebo} \geq \pi_{mesalazine}$) was tested against the alternative hypothesis ($\pi_{placebo} < \pi_{mesalazine}$) with π = the proportion of recurrence-free patients within 48 weeks in the respective treatment group. The study was conducted using an adaptive 2-stage group sequential design.

According to the IDMC recommendations after the planned interim analysis an additional interim analysis was to be performed including approximately further 100 patients. The critical values for the new second interim analysis as well as for the final analysis were calculated on the basis of the results of the first interim analysis. Rejection of the null hypothesis was possible at the second interim analysis if the inverse normal test statistic for the second stage exceeded critical value.

Summary:

Demographic and baseline characteristics (FAS)		**Mesalazine (n = 165)**	**Placebo (n = 168)**	**Total (n = 333)**
Sex				
Male	n (%)	63 (38.2%)	74 (44.0%)	137 (41.1%)
Female	n (%)	102 (61.8%)	94 (56.0%)	196 (58.9%)
Race				
White	n (%)	165 (100.0%)	167 (99.4%)	332 (99.7%)
Asian	n (%)	0	1 (0.6%)	1 (0.3%)
Age	Mean (SD)	58.8 (9.1)	58.3 (9.5)	58.6 (9.3)
Weight	Mean (SD)	78.98 (15.05)	79.99 (16.57)	79.49 (15.82)
Height	Mean (SD)	168.55 (9.95)	168.51 (10.66)	168.53 (10.30)
BMI	Mean (SD)	27.75 (4.56)	28.06 (4.57)	27.90 (4.56)
CRP of the most recent attack [mg/l]	Mean (SD)	72.48 (108.62) n = 151	76.85 (97.21) n = 155	74.69 (102.85) n = 306
>ULN	n (%)	148 (89.7%)	152 (90.5%)	300 (90.1%)
≤ULN	n (%)	3 (1.8%)	3 (1.8%)	6 (1.8%)
No remark	n (%)	14 (8.5%)	13 (7.7%)	27 (8.1%)
CRP at baseline [mg/l]	Mean (SD)	3.71 (4.40) n = 165	4.40 (5.98) n = 166	4.06 (5.26) n = 331
>ULN	n (%)	63 (38.2%)	70 (41.7%)	133 (39.9%)
≤ULN	n (%)	102 (61.8%)	96 (57.1%)	198 (59.5%)
No remark	n (%)	0	2 (1.2%)	2 (0.6%)
Leukocyte count at baseline [/cmm]	Mean (SD)	6884.7 (2685.5) n = 165	6803.9 (1847.0) n = 164	6844.4 (2302.8) n = 329
Number of stools [/week]	Mean (SD)	13.21 (7.52) n = 161	12.38 (5.62) n = 165	12.79 (6.63) n = 326

* For the calculation, missing data regarding day or month of start of diverticulitis were replaced by '1'. Diverticulitis attacks without documentation of the start date were excluded from the calculation.

Efficacy Results:

Primary Efficacy Evaluation:

Recurrence-free patients at the interim analyses in the FAS and at the final analysis in the FAS and in the PP analysis set:

		Number (%) of recurrence-free patients within 48 weeks		**Testing of H_0***	
		Mesalazine	**Placebo**	**Critical value**	**Inverse normal**
1st interim analysis (original design)	**FAS**	49/73 (67.1%)	46/60 (76.7%)	3.416	-1.212
2nd interim analysis (recursive design)	**FAS**	34/46 (73.9%)	39/54 (72.2%)	4.581	0.190
Final analysis (recursive design)	**FAS**	30/46 (65.2%)	40/54 (74.1%)	3.239	0.719
	PP	27/34 (79.4%)	38/42 (90.5%)	3.540	-1.809

* Testing of H_0 ($\pi_{placebo} \geq \pi_{mesalazine}$) by means of the normal approximation test for comparing two rates.

Proportions of recurrence-free patients did not show meaningful differences in favour of the mesalazine group in subgroups with a relevant number of patients.

Secondary Efficacy Evaluation (FAS):

- Patients with recurrence of diverticulitis within 48 weeks (FAS) was 31/165 (18.8%) in mesalazine group and 20/168 (11.9%) in placebo group.

- ESR showed a very small increase from baseline to Visit 7 (LOCF) in the mesalazine group, while no meaningful change in ESR was observed in the placebo group. Proportions of patients with ESR >ULN increased from baseline to Visit 7 (LOCF) in both treatment groups. This increase was larger in the mesalazine group than in the placebo group.
- CRP showed comparable increase from baseline to Visit 7 (LOCF) in both treatment groups. The proportion of patients with CRP >ULN at Visit 7 (LOCF) was comparable in both treatment groups.
- Both treatment groups showed no relevant difference in leukocyte count at Visit 7 (LOCF). Furthermore, the proportion of patients with a leukocyte count >10000 /cmm at Visit 7 (LOCF) was nearly identical.
- The mean number of days and the mean percentage of documented diary days with a temperature >38°C was larger in the mesalazine than in the placebo group.
- The mean number of days and the mean percentage of documented diary days with left lower quadrant pain was larger in the mesalazine than in the placebo group.
- The mean number of days with stools of solid consistency and with stools of soft or solid consistency was smaller in the mesalazine than in the placebo group. In contrast, the mean number of days with diarrhoea and with stools of watery consistency was larger in the mesalazine than in the placebo group. The mean percentage of documented diary days with diarrhoea was slightly larger in the mesalazine than in the placebo group. No meaningful difference between treatment groups was observed regarding the mean percentage of documented diary days with stools of solid consistency, stools of soft or solid consistency, and stools of watery consistency.
- The mean number of stools per week did not show a meaningful change across the treatment period in both treatment groups (mesalazine: 13.21 stools/week in week 1 and 13.04 stools/week in week 48; placebo: 12.38 stools/week in week 1 and 12.59 stools/week in week 48).

Safety Results:

In total, 486 treatment-emergent AEs (TEAEs) occurred in 145 patients (85.3%) taking mesalazine and 423 TEAEs occurred in 136 patients (79.1%) taking placebo. Based on preferred terms (PTs), the most frequently reported TEAEs were abdominal pain, headache, diverticulitis, and nasopharyngitis. The vast majority of patients experienced TEAEs of mild (mesalazine: 119 patients (70.0%); placebo: 123 patients (71.5%)) or moderate (mesalazine: 76 patients (44.7%); placebo: 53 patients (30.8%)) intensity. Severe TEAEs occurred in 16 patients (9.4%) taking mesalazine and 8 patients (4.7%) taking placebo. The investigators were asked for a causality assessment. In total, 25 TEAEs in 20 patients (11.8%) in the mesalazine group and 20 TEAEs in 14 patients (8.1%) in the placebo group were assessed as adverse drug reactions (ADRs).

One patient died during the course of the trial (metastatic bronchial carcinoma, placebo group).

Twenty-nine serious AEs (SAEs) occurred in 24 patients (14.1%) taking mesalazine and 17 SAEs occurred in 15 patients (8.7%) taking placebo. There was one serious suspected ADR in the mesalazine group (agranulocytosis, expected reaction).

Increases in laboratory parameters of inflammation reflected lack of efficacy in each treatment group. Only in the mesalazine group there were slight increases in transaminases and parameters of cholestasis which is in line with the known hepatic side effects of mesalazine.

No patient showed a new abnormal clinically significant laboratory value at Visit 7 (LOCF) assessed as at least possibly related to the intake of study medication.

Tolerability of the study medication was assessed as very good or good in the vast majority of patients by both the patients and investigators.

Conclusions:

- The study failed to prove superiority of 3 g mesalazine OD compared to placebo for the prevention of recurrence of diverticulitis within 48 weeks of treatment.
- None of the secondary endpoints showed any advantage for mesalazine over placebo.

• Overall, 3 g mesalazine OD was well tolerated in this patient group. • Based on efficacy results, this study does not support the use of mesalazine for the prevention of recurrence of diverticulitis.	
Publication:	Kruis W, Eisenbach T, Löhr H, et al. 808 Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial of Mesalamine for the Prevention of Recurrence of Diverticulitis. Gastroenterology. 2013;144(5):S-139.