Clinical Study Report Synopsis

Study Title:	Double-blind, dose-response, 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/3.0 g granules)
Reference drug:	Placebo granules
Indication:	Prevention of recurrence of diverticulitis
Phase of study:	III
First patient enrolled:	26 May 2010
Last patient completed:	29 Jan 2013
EudraCT No.:	2009-015158-39
Date of final report:	30 August 2016
Sponsor:	Dr. Falk Pharma GmbH Leinenweberstr. 5 79108 Freiburg Germany
Coordinating Investigator/ 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, dose-response, 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, dose-response, randomized, placebo-controlled, multi-centre, comparative, Phase III clinical trial with 3 treatment groups.

Group A (investigational drug):	1.5 g mesalazine granules (Salofalk® 1.5 g granules) once daily (OD) for 96 weeks
Group B (investigational drug):	3.0 g mesalazine granules (Salofalk® 3.0 g granules) OD for 96 weeks
Group C (reference drug):	Placebo granules OD for 96 weeks

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

Protocol version:
Clinical study protocol version1.0/17 Nov 2009
Amendment No. 1, version 2.0, dated 01 Jun 2010
Amendment No. 2, version 3.0, dated 29 Jul 2011
Amendment No. 3, final version, dated 19 Jul 2012

Study Centres:
74 centres enrolled patients in following countries (number of patients): 9 centres in Australia (42), 6 centres in Belgium (11), 2 centres in Finland (7), 6 centres in Germany (34), 2 centres in Greece (3), 2 centres in Spain (11), 2 centres in Sweden (11), 39 centres in USA (173), and 6 centres in Ukraine (38).

Study Period:		**Phase of Development:**
First patient enrolled:	26 May 2010 [1]	III
Last patient completed:	29 Jan 2013	

Objectives:
- To compare the efficacy and tolerability of mesalazine granules (1.5 g 5-aminosalicylic acid (5-ASA)/day) vs. mesalazine granules (3.0 g 5-ASA/day) 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 3 x 100 patients who were evaluable in the full analysis set (FAS). The final analysis was planned to be performed after observation of further 3 x 140 patients. The estimated sample size, without sample size adaptation, was 240 evaluable patients in each treatment group.
With Amendment No. 3, the interim analysis was brought forward and a rule for stopping the study due to futility (non-binding) was introduced. According to Amendment No. 3, the interim analysis was planned to be performed after observation of 3 x 60 patients who were evaluable in the FAS. The final analysis was planned to be performed after observation of further 3 x 180 patients. The estimated sample size, without sample size adaptation, was still 240 evaluable patients in each treatment group.
The planned interim analysis was performed on 180 evaluable patients in the FAS. It showed that the

[1] The earliest documented date of a visit to the study centre was 05 Jan 2010 (Visit 3 in Patient No. 2521114). This was a typing error. Visit 1 and Visit 2 were documented on 01 Dec 2010 and 15 Dec 2010, respectively, and the actual date of Visit 3 was 05 Jan 2011.

primary objective of the study could not be reached. The study was stopped due to futility. This meant an immediate stop of treatment and premature study termination in all patients that had not yet completed the study.
The final analysis was performed on a total of 324 evaluable patients in the FAS. This included 180 patients evaluable for the FAS at the interim analysis plus all patients not evaluable for the FAS at the interim analysis and all patients recruited during the time the interim analysis was performed.

Analysed in the Final Analysis:

Number of patients	Mesalazine 1.5 g	Mesalazine 3.0 g	Placebo	Total
Randomised	125	92	113	330
Treated	125	92	113	330
Safety	125	92	113	330
FAS	123	90	111	324
MFAS48	87	75	81	243
MFAS96	58	51	52	161
PP	79	59	80	218
MPP48	44	46	55	145
MPP96	25	25	27	77

In total, 330 patients received study medication and were included in the safety analysis set (SAF). Six patients were excluded from the SAF to form the FAS because they did not fulfil inclusion criterion no. 5 defined as documented attack of left-sided uncomplicated diverticulitis responding to antibiotics and/or dietary modification within 6 months prior to baseline.
In order to avoid that patients with termination due to stopping of the study would be analysed as patients with recurrence of diverticulitis, 2 modified versions of both the FAS and PP analysis set were defined. The modified versions of the FAS (MFAS48 and MFAS96) and PP analysis set (MPP48 and MPP96) were subsets of the FAS and PP analysis set excluding patients who terminated the study due to stopping of the study before week 48 and week 96, respectively.

Diagnosis and Main Criteria for Inclusion:
Main Inclusion Criteria:
- Signed informed consent
- Men or women aged 30 to 80 years
- Diagnosis of left-sided uncomplicated diverticular disease (DD) confirmed by ultrasonography or computed tomography (CT)
- 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 leukocytosis at the start of the most recent attack

Duration of Treatment:
96 weeks

Criteria for Evaluation:
Primary Efficacy Variables:
The study was designed to investigate 2 primary efficacy variables:
- Proportion of recurrence-free patients within 48 weeks
- Proportion of recurrence-free patients within 96 weeks

Recurrence of diverticulitis was defined as CRP >ULN or leukocytosis (>10000 /cmm) and recurrence of diverticulitis-like symptoms (LLQ pain, fever) and confirmation by 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
- 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

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	• Amount of used spasmolytics • Amount 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, 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 the 2 primary efficacy variables 'proportion of recurrence-free patients within 48 weeks' and 'proportion of recurrence-free patients within 96 weeks'. The 2 treatment arm comparisons were performed for the 2 primary efficacy variables in a priori fixed order: 1st mesalazine 3.0 g vs. placebo, 2nd mesalazine 1.5 g vs. placebo. Accordingly, the 4 null hypotheses (H_{01}: $\pi_{placebo\ 48} \geq \pi_{mesalazine\ 3.0\ g\ 48}$, H_{02}: $\pi_{placebo\ 48} \geq \pi_{mesalazine\ 1.5\ g\ 48}$, H_{03}: $\pi_{placebo\ 96} \geq \pi_{mesalazine\ 3.0\ g\ 96}$, H_{04}: $\pi_{placebo\ 96} \geq \pi_{mesalazine\ 1.5\ g\ 96}$) were tested against their respective alternative hypotheses where $\pi_{48/96}$ denoted the proportion of recurrence-free patients within 48/96 weeks in the respective treatment arm.

The study was conducted using an adaptive 2-stage group sequential design. The interim analysis was planned after observation of 180 patients who were evaluable in the FAS (approximately 60 patients per treatment arm).

According to the IDMC recommendation after the interim analysis, the study was stopped due to futility. This meant an immediate stop of treatment and premature study termination in all patients that had not yet completed the study.

Summary:

Demographic and baseline characteristics (FAS)		**Mesalazine 1.5 g (n = 123)**	**Mesalazine 3.0 g (n = 90)**	**Placebo (n = 111)**	**Total (n = 324)**
Sex					
Male	n (%)	38 (30.9%)	39 (43.3%)	49 (44.1%)	126 (38.9%)
Female	n (%)	85 (69.1%)	51 (56.7%)	62 (55.9%)	198 (61.1%)
Race					
White	n (%)	116 (94.3%)	87 (96.7%)	107 (96.4%)	310 (95.7%)
Asian	n (%)	2 (1.6%)	---	---	2 (0.6%)
Black or African American	n (%)	4 (3.3%)	3 (3.3%)	4 (3.6%)	11 (3.4%)
Native Hawaiian or other Pacific Islander	n (%)	1 (0.8%)	---	---	1 (0.3%)
Age	Mean (SD)	55.6 (10.4)	55.2 (11.3)	55.4 (10.3)	55.4 (10.6)
Weight	Mean (SD)	83.32 (19.38)	83.08 (17.15)	85.79 (20.10)	84.10 (19.03)
Height	Mean (SD)	167.05 (9.16)	168.39 (9.44)	168.58 (9.49)	167.95 (9.35)
BMI	Mean (SD)	29.74 (5.90)	29.18 (4.70)	30.17 (6.68)	29.73 (5.88)
CRP of the most recent attack [mg/l]	Mean (SD)	80.34 (89.52) n = 62	49.58 (42.90) n = 38	71.83 (63.39) n = 56	69.79 (71.87) n = 156
>ULN	n (%)	61 (49.6%)	37 (41.1%)	54 (48.6%)	152 (46.9%)
≤ULN	n (%)	1 (0.8%)	1 (1.1%)	2 (1.8%)	4 (1.2%)
No remark	n (%)	61 (49.6%)	52 (57.8%)	55 (49.5%)	168 (51.9%)

CRP at baseline [mg/l]	Mean (SD)	4.56 (7.06) n = 122	4.43 (7.92) n = 90	6.80 (16.35) n = 110	5.29 (11.32) n = 322
>ULN	n (%)	34 (27.6%)	22 (24.4%)	33 (29.7%)	89 (27.5%)
≤ULN	n (%)	88 (71.5%)	68 (75.6%)	77 (69.4%)	233 (71.9%)
No remark	n (%)	1 (0.8%)	---	1 (0.9%)	2 (0.6%)
Leukocyte count at baseline [/cmm]	Mean (SD)	6871.6 (2127.1) n = 118	6975.1 (2108.4) n = 90	6992.5 (1981.4) n = 109	6942.6 (2066.9) n = 317
Number of stools [/week]	Mean (SD)	13.45 (6.25) n = 121	14.34 (10.66) n = 88	14.55 (8.02) n = 105	14.07 (8.26) n = 314

Efficacy Results:

Primary Efficacy Evaluation:

Recurrence-free patients at the interim analysis in the FAS and at the final analysis in the MFAS48 and MFAS96 and in the MPP48 and MPP96 analysis sets:

			Number (%) of recurrence-free patients within 48 weeks/96 weeks			**Testing of H_0***	
		Within…	**Mesalazine 1.5 g**	**Mesalazine 3.0 g**	**Placebo**	**Critical value**	**Inverse normal**
Interim analysis	**FAS**	**48 weeks**	34/68 (50.0%)	32/58 (55.2%)	34/54 (63.0%)	4.483	-0.837
	FAS	**96 weeks**	0/41 (0.0%)	2/34 (5.9%)	5/30 (16.7%)	4.483	-1.379
Final analysis	**MFAS48**	**48 weeks**	40/87 (46.0%)	39/75 (52.0%)	47/81 (58.0%)	4.483	-0.756
	MFAS96	**96 weeks**	4/58 (6.9%)	5/51 (9.8%)	12/52 (23.1%)	4.483	-1.814
	MPP48	**48 weeks**	24/44 (54.5%)	27/46 (58.7%)	42/55 (76.4%)	4.483	-1.901
	MPP96	**96 weeks**	3/25 (12.0%)	3/25 (12.0%)	10/27 (37.0%)	4.483	-2.083

* Testing of H_{01} ($\pi_{placebo\ 48} \geq \pi_{mesalazine\ 3.0\ g\ 48}$) and H_{03} ($\pi_{placebo\ 96} \geq \pi_{mesalazine\ 3.0\ g\ 96}$) by means of the normal approximation test for comparing two rates.

The interim analysis was performed based on 180 patients included in the FAS in stage 1. Proportions of recurrence-free patients were smaller in both mesalazine groups than in the placebo group both within 48 weeks and within 96 weeks at the interim analysis. The IDMC recommended to stop the study.

The final analysis was performed based on 243 and 161 patients included in MFAS48 and MFAS96, respectively, and based on 145 and 77 patients included in MPP48 and MPP96, respectively. The overrun patients were included in Stage 1 of the adaptive analysis. Based on both modified analysis sets, proportions of recurrence-free patients were smaller in both mesalazine groups than in the placebo group both within 48 weeks and within 96 weeks at the final analysis. Based on both modified analysis sets, the inverse normal for the comparison between the mesalazine 3.0 g and the placebo group was lower than the critical value, so that H_0 could not be rejected.

Proportions of recurrence-free patients did not show meaningful differences in favour of the mesalazine groups in any subgroup.

Main Secondary Efficacy Evaluation:

- Patients with recurrence of diverticulitis within 48 weeks (MFAS48) was 15/87 (17.2%) in mesalazine 1.5 g group, 15/75 (20.0%) in mesalazine 3 g group, and 17/81 (21.0%) in placebo group.
- Patients with recurrence of diverticulitis within 96 weeks (MFAS96) was 16/58 (27.6%) in mesalazine 1.5 g group, 17/51 (33.3%) in mesalazine 3 g group, and 20/52 (38.5%) in placebo group.
- Both the mean (median) time to recurrence and the mean (median) time to recurrence or study discontinuation due to lack of efficacy or intolerable AE was longest in the mesalazine 3.0 g group followed by the placebo group and the mesalazine 1.5 g group in descending order.
- Patients in the 3 treatment groups showed increases in CRP from baseline to Visit 8 (LOCF) and Visit 12 (LOCF). The increases in CRP from baseline to Visit 8 (LOCF) and Visit 12 (LOCF) were largest in the mesalazine 3.0 g group.
- Proportions of patients with CRP >ULN showed small increases from baseline to Visit 8 (LOCF) and Visit 12 (LOCF) in the mesalazine 3.0 g and placebo groups and no meaningful changes from

baseline to Visit 8 (LOCF) and Visit 12 (LOCF) in the mesalazine 1.5 g group.

- Both from baseline to Visit 8 (LOCF) and from baseline to Visit 12 (LOCF), the leukocyte count showed a very small decrease in the mesalazine 1.5 g group, no meaningful change in the mesalazine 3.0 g group, and a very small increase in the placebo group.
- Proportions of patients with a leukocyte count >10000 /cmm showed small decreases from baseline to Visit 8 (LOCF) and Visit 12 (LOCF) in the mesalazine 3.0 g group, small increases from baseline to Visit 8 (LOCF) and Visit 12 (LOCF) in the placebo group, and no meaningful changes from baseline to Visit 8 (LOCF) and Visit 12 (LOCF) in the mesalazine 1.5 g group.
- Both from baseline to Visit 8 (LOCF) and from baseline to Visit 12 (LOCF), ESR did not show a meaningful change in either treatment group.
- Fifteen patients (12.2%) in the mesalazine 1.5 g group, 6 patients (6.7%) in the mesalazine 3.0 g group, and 8 patients (7.2%) in the placebo group experienced at least one episode (including 1 day episodes) of diverticulitis-associated fever defined as body temperature >38°C in the FAS.
- At week 48, the mean number of days per week with mild/moderate/severe LLQ pain decreased to around half of the baseline value in the 3 treatment groups. Patients in the mesalazine 1.5 g and mesalazine 3.0 g groups showed a clear shift towards less time with moderate/severe to mild LLQ pain and more time with mild LLQ pain from baseline to week 48.
- From baseline to week 48, patients in the placebo group showed an increase in mean numbers of days per week with solid stools and patients in the mesalazine 1.5 g and placebo groups showed a decrease in mean numbers of days per week with watery stools from baseline to week 48. Other changes in mean numbers of days per week by consistency of stools were small compared to baseline values.
- Patients in the mesalazine 1.5 g group showed a small decrease in the mean number of stools per week from baseline to week 48. In the mesalazine 3.0 g and placebo groups, no meaningful change in the mean number of stools per week from baseline to week 48 was observed.
- From baseline to week 48, mean number of days per week with diarrhoea showed a decrease in the mesalazine 1.5 g group and no meaningful change in the mesalazine 3.0 g and placebo groups.
- Similar proportions of patients in both treatment groups reported concomitant intake of analgesics (23.1%, 21.1%, and 20.1% in the mesalazine 1.5 g, 3.0 g, and placebo groups, respectively) or spasmolytics (4.7%, 5.3%, and 6.7% in the mesalazine 1.5 g, 3.0 g, and placebo groups, respectively).

Safety Results:

In total, 337 TEAEs occurred in 107 patients (85.6%) in the 1.5 g mesalazine group and 297 TEAEs occurred in 75 patients (81.5%) in the 3.0 g mesalazine goup, and 295 TEAEs occurred in 89 patients (78.8%) taking placebo. Based on preferred terms (PTs), the most frequently reported TEAEs were diverticulitis, abdominal pain, headache, and nasopharyngitis. The vast majority of patients with an AE experienced a TEAE of mild (62.4%, 63.0%, and 61.9%) or moderate (46.4%, 46.7%, and 45.1%) intensity. Severe TEAEs occurred in 15.2%, 14.1%, and 13.3% of the patients in the mesalazine 1.5 g, 3.0 g, and placebo groups. Most patients with a severe TEAE experienced diverticulitis assessed as severe (9.6%, 6.5%, and 8.0%). The investigators were asked for a causality assessment. In total, 51 TEAEs in 21 patients (16.8%) in the mesalazine 1.5 g group, 25 TEAEs in 14 patients (15.2%) in the mesalazine 3.0 g group, and 23 TEAEs in 14 patients (12.4%) in the placebo group were rated as ADRs.

No patient died during the course of this study.

Most patients with an SAE experienced a serious TEAE of diverticulitis (7.2%, 5.4%, and 3.5%). Serious TEAEs of other preferred terms (PTs) were observed at most in 2 patients each. All SAEs were serious because they involved or prolonged inpatient hospitalisation. Metastatic breast cancer in one patient was additionally assessed as life threatening.

Increases in laboratory parameters of inflammation reflected lack of efficacy in each treatment group. Few patients showed a new abnormal clinically significant laboratory value with a suspected causal relationship to the study medication and no difference between patients receiving 1.5 g or 3.0 g mesalazine and patients receiving placebo could be concluded.

Tolerability of the study medication was assessed as very good or good in around 70% of patients by both the investigators and patients.
Conclusions: • The study failed to prove superiority of 3.0 g mesalazine OD compared to placebo for the prevention of recurrence of diverticulitis within 48 weeks and within 96 weeks of treatment. • Some secondary endpoints showed (small) differences to the advantage of mesalazine 3.0 g vs. placebo treatment for the prevention of recurrence of diverticulitis. • The results for the mesalazine 1.5 g group were not consistent with the results for the mesalazine 3.0 g group. • Overall, this study does not support the use of mesalazine for the prevention of recurrence of diverticulitis. • Mesalazine treatment at doses of 1.5 g OD and 3.0 g OD was well tolerated in this study.

Publication:	Kruis W, Kardalinos V, Curtin A, Dorofeyev AE, Zakko SF, Wölkner J, et al. 1052 Daily Mesalamine Fails to Prevent Recurrent Diverticulitis in a Large Placebo Controlled Multicenter Trial. Gastroenterology. 2014;146(5, Supplement 1):S-187.