

# Investigation of a High-Dose pH-Dependent-Release Mesalazine on the Induction of Remission in Active Crohn's Disease

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## Abstract

**Introduction** The effect of mesalazine in treating active Crohn's disease (CD) remains controversial, possibly due to the various formulae of mesalazine used to treat inflammation located in different regions of the digestive tract.

**Methods** This exploratory, multicenter, uncontrolled, open-label study included 17 patients with active CD. The inclusion criteria were patients with a CD activity index (CDAI) of  $\geq 200$  and  $< 350$ , and in whom mucosal lesions were observed in the area from the terminal ileum to the rectum using colonoscopy (CS). Each patient was treated with pH-dependent-release mesalazine at 4.8 g/day. The drug was administered three times daily for 12 weeks. Efficacy was evaluated by the change in CDAI at the time of final observation (at week 12 or at discontinuation), and safety was evaluated by the incidence of adverse events (AEs) and adverse drug reactions (ADRs).

**Results** In the full analysis set ( $n = 17$ ), the change in CDAI at the time of final observation was  $-67.4$ , and the

mean change in CDAI from baseline was  $-49.3$  at week 2,  $-61.8$  at week 4,  $-78.3$  at week 8, and  $-101.1$  at week 12. A statistically significant improvement was observed from week 2 to week 12 compared with baseline, and the incidences of AEs and ADRs were 94.1 and 58.8 %, respectively. All events were known events, as the results suggested, which is in line with the known safety profile of pH-dependent-release mesalazine.

**Conclusions** The results suggest that the administration of pH-dependent-release mesalazine 4.8 g/day for 12 weeks could be an effective and highly safe treatment option for patients with mild to moderately active CD in whom mucosal lesions were observed in the area from the terminal ileum to the rectum.

**Trial registration number.** JapicCTI-111460.

## 1 Introduction

Crohn's disease (CD) is an inflammatory bowel disease that can cause inflammation at any site in the gastrointestinal tract, although the most commonly affected locations are the terminal ileum and the colon. Typically, those suffering from CD have recurrent attacks, with acute exacerbations interspersed with periods of remission or less active disease. The main treatment is symptomatic therapy, primarily focusing on the control of symptoms because the cause of the disease is not yet understood and a curative therapy has not been established [1].

The treatment for CD varies between countries based on the approved medication and status of healthcare; however, treatments are performed following specific guidelines, taking into consideration the activity of the disease and the site of the lesion [2, 3]. Oral mesalazine has long been used as a treatment for CD, and although its efficacy is said to be

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limited, it has a good safety profile. Mesalazine acts locally; therefore, to date, preparations with various release profiles have been developed and selection of the preparation depends on the site of the lesion. Because pH-dependent-release mesalazine releases 90 % of the mesalazine after it reaches the terminal ileum where the pH exceeds 7 [4], it may be an effective treatment option for lesions in the terminal ileum and beyond, where CD lesions occur most frequently.

Furthermore, the European Crohn's and Colitis Organisation (ECCO) guideline on the diagnosis and management of CD states that "mesalazine should be considered clinically no more effective than placebo for active ileal or colonic Crohn's disease" [2]. To confirm the efficacy of pH-dependent-release mesalazine in patients with CD, an exploratory study was performed to investigate the efficacy of administering 4.8 g/day of the study drug for 12 weeks for inducing remission in patients with mild to moderately active CD with mucosal lesions situated at any site from the terminal ileum to the rectum.

## 2 Methods

### 2.1 Study Design

This was a multicenter, uncontrolled, open-label study conducted at 15 facilities in Japan from June 2011 to May 2013. The study period consisted of a 1- to 3-week screening period and a 12-week treatment period. The investigators calculated subjects' CD activity index (CDAI) during the observation period, and eligible patients received oral administration of four tablets of the study drug, three times daily after each meal for 12 weeks. Patients visited the trial site at weeks 2, 4, 8, and 12 (or at discontinuation) of treatment. At each visit, the investigators calculated the CDAI, performed laboratory tests, and confirmed and recorded the incidences of adverse events (AEs) and adverse drug reactions (ADRs).

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 1975, as revised in 2013. All subjects provided written informed consent prior to participating in the study. This trial was registered with the JapicCTI under registration no. JapicCTI-111460.

### 2.2 Subjects

Patients who met all of the following inclusion criteria were enrolled: (1) CDAI score of  $\geq 200$  and  $< 350$  at the time of screening; (2) mucosal lesions at any site from the terminal ileum to the rectum observed using colonoscopy (CS) at the time of screening; and (3) aged between 16 and 64 years at

the time of providing informed consent. Patients with any of the following criteria were excluded: (1) longitudinal ulcer, cobblestone appearance, or stenosis on the proximal side of the small intestine from the terminal ileum observed using intestinal imaging (contrast X-ray or CS) at the time of screening, or CT or ultrasound scan performed after the intestinal imaging at the time of screening; (2) the terminal ileum could not be observed using CS at the time of screening; (3) comorbid perforation, fistula, or abscess; (4) comorbid colitis other than CD; (5) received oral mesalazine at a dose above 3 g/day, oral salazosulfapyridine at a dose above 6 g/day, enema or suppository mesalazine or salazosulfapyridine, corticosteroids (oral, enema, suppository, or injection), metronidazole, ciprofloxacin, levofloxacin, intravenous hyperalimentation, enteral nutrition (calorie intake  $\geq 1200$  kcal/day), or changed the drug or calorie intake of enteral nutrition within 2 weeks before screening; (6) received azathioprine or 6-mercaptopurine within 3 weeks before screening; (7) underwent cytapheresis, laparotomy, or laparoscopic surgery within 8 weeks before screening; (8) received cyclosporine, tacrolimus, methotrexate, mycophenolate mofetil, infliximab, adalimumab, tocilizumab, or etanercept within 12 weeks before screening; (9) a history of intestinal resection; (10) hypersensitivity to mesalazine or salicylate drugs; (11) moderate comorbid hepatic or renal disease; (12) severe comorbid disease such as gastrointestinal, hematologic, cardiovascular, and neuropsychiatric diseases; (13) undergoing treatment for a malignant tumor or being followed up for less than 5 years; (14) pregnant and nursing women, or women planning to get pregnant; and (15) a history of using the aforementioned drugs (including Asacol<sup>®</sup> tablets 400 mg).

### 2.3 Study Drug

Patients were administered pH-dependent-release mesalazine (Asacol<sup>®</sup> tablets; Tillotts Pharma AG, Ziefen, Switzerland) consisting of Eudragit-S<sup>®</sup>-coated pH-dependent-release mesalazine containing 400 mg of mesalazine per tablet. Eudragit-S<sup>®</sup> dissolves at a pH  $\geq 7$ , and the study drug (Asacol<sup>®</sup> tablets 400 mg) is designed to release mesalazine at the terminal ileum and beyond, where the pH exceeds 7. Asacol<sup>®</sup> tablets used in this study were supplied by Zeria Pharmaceutical Co., Ltd, Tokyo, Japan.

### 2.4 Efficacy Assessment

#### 2.4.1 Crohn's Disease Activity Index (CDAI)

During the study period, patients recorded the number of liquid or soft stools and completed an abdominal pain rating, as well as a rating for their general well-being, into a diary every day. Patients visited the trial site at the time of

screening and at weeks 2, 4, 8, and 12 (or at discontinuation), and, based on the information obtained from the entries in the patients' diaries and clinical examinations, the investigators calculated the CDAI [5]. The change in CDAI from screening was also calculated at each of the visits. Patients with a CDAI <150 were defined as being in clinical remission, and the clinical remission proportion was calculated.

#### 2.4.2 Colonoscopy (CS)

Endoscopic findings were assessed at the time of screening and at week 12 (or at discontinuation) if possible. The investigators compared the endoscopic findings from the terminal ileum to the rectum before and after drug administration. The findings were assessed as total (not by region) assessment between the terminal ileum and the rectum, and were classified into three stages: 'improved', 'unchanged', or 'worsened'. Images of the mucosa from the examination were submitted to a central reviewer who was independent from this study; this reviewer evaluated the endoscopic findings in the same manner as the investigators. At the time of evaluation, the reviewer was blinded from any information that may have affected the assessment of the endoscopic findings, such as the investigator's assessment, the timing of CS, and the CDAI at the time of CS.

#### 2.5 Safety Assessment

For the assessment of safety, the subjective symptoms or objective findings and laboratory tests were investigated at weeks 2, 4, 8, and 12 (or at discontinuation) of treatment. For the laboratory tests, changes in values falling under the Criteria for Classification of Abnormal Laboratory Values in this study were categorized as AEs. The presence/absence of AEs and ADRs were recorded by investigators at each visit.

#### 2.6 Statistical Analysis

For the efficacy endpoints, the change in the CDAI at the time of final observation (at week 12 or at discontinuation), clinical remission proportion, and endoscopic improvement proportion were investigated. For the safety endpoints, the frequency distribution and proportion of AEs and ADRs were calculated.

No statistical rationale for the sample size was set for the study because this was an exploratory study. A paired *t* test was performed for the change in the CDAI. The significance level of 0.05 (two-tailed) was used, and  $p < 0.05$  was considered statistically significant. The multiplicity of the tests was not taken into consideration, although the confidence level of 0.95 (two-tailed) was used to calculate the confidence interval (CI). The safety analysis was performed on the safety analysis set (SAF), which

included subjects who received at least one tablet of the study drug, with the exception of those who were non-compliant to good clinical practices or had no safety data after study treatment. The full analysis set (FAS) included the subjects in the SAF, with the exception of those who had no efficacy data after study treatment, were found to not have CD after treatment, or were found to not have any mucosal lesions beyond the terminal ileum after treatment. The per-protocol set (PPS) included the subjects in the FAS, with the exception of those who were found to not meet the inclusion criteria (1) or (3) after treatment, were found to fall under the exclusion criteria after treatment, used a prohibited concomitant drug or therapy, during the treatment phase had a treatment compliance <80 %, or discontinued within 1 week from the start of the study treatment. The CS set included subjects in the FAS, with the exception of those who did not undergo CS at week 12 or at discontinuation. Statistical analysis was performed at Zeria Pharmaceutical Co., Ltd. All statistical calculations were performed using SAS release 9.2 (SAS Institute Inc., Cary, NC, USA).

### 3 Results

#### 3.1 Subjects

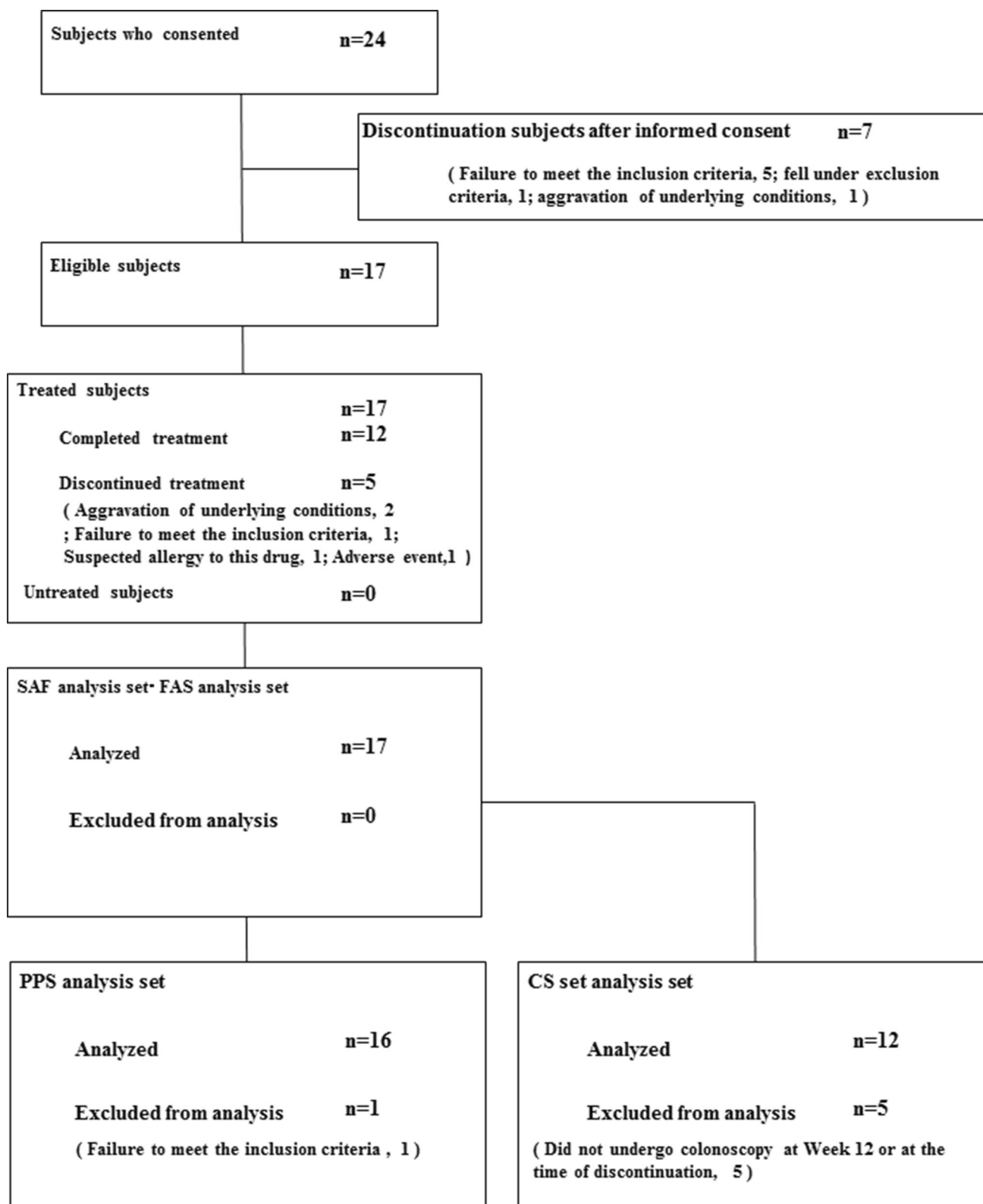
Among the 24 patients who provided informed consent, 7 subjects were ineligible and 17 subjects were eligible and received the study treatment. Of the treated subjects, 12 subjects completed the study treatment and 5 subjects discontinued the treatment. Reasons for discontinuation were aggravation of underlying conditions in two subjects, AEs of 'chest pain' and 'C-reactive protein (CRP) increased', suspected allergy to the drug, and failure to meet the inclusion criteria in one subject each. The disposition of each analysis set is shown in Fig. 1. The results of the data analysis were similar between the FAS and PPS; therefore, the analysis results of the FAS will hereafter be shown for efficacy analyses other than the assessment of endoscopic findings. The patient demographics of this study are shown in Table 1.

#### 3.2 Efficacy

##### 3.2.1 CDAI

Analysis was performed in 17 subjects who were included in the FAS.

*Transition of CDAI* The mean values by time point were 228.6 (95 % CI 209.6–247.5) at screening, 182.9 (95 % CI 131–233.8) at week 2, 161.9 (95 % CI 114.7–209.1) at week 4, 145.4 (95 % CI 103.6–187.2) at week 8, and 122.7 (95 % CI 80.8–164.5) at week 12; therefore, a decrease in



**Fig. 1** Enrollment and analysis of study subjects. *FAS* full analysis set, *PPS* per-protocol set, *SAF* safety analysis set, *CS set* colonoscopy set

the CDAI score over time was observed from screening to week 12. The mean CDAI values at week 8 and week 12 were <150, which suggests clinical remission (CDAI

<150) [6, 7]; however, the mean CDAI at the time of the final observation was 161.2 (95 % CI 107.5–215.0), which exceeded 150 (Fig. 2).

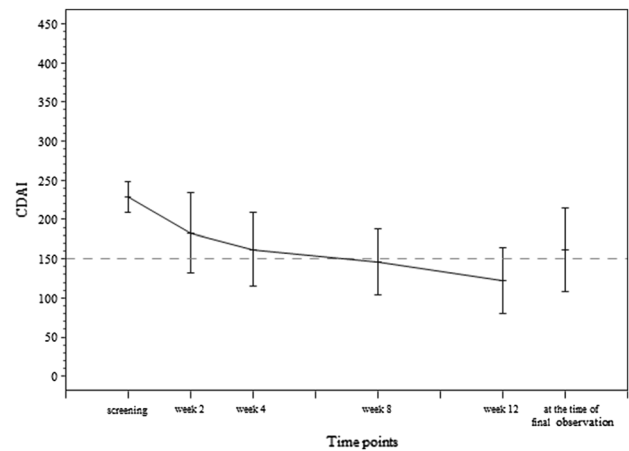
**Table 1** Patient background

Parameter	%	
Sex		
Male	12	70.6
Female	5	29.4
Age (years)		
No. of subjects	17	
Mean value	31.2	
Standard deviation	11.6	
Maximum value	60	
Median	29.0	
Minimum value	16	
Weight (kg)		
No. of subjects	17	
Mean value	55.90	
Standard deviation	8.74	
Maximum value	70.0	
Median	56.60	
Minimum value	37.0	
Duration of Crohn's disease (months)		
No. of subjects	17	
Mean value	53.0	
Standard deviation	70.5	
Maximum value	197	
Median	18.0	
Minimum value	1	
Clinical course of Crohn's disease		
First-time	11	64.7
Relapse	6	35.3
Duration of active phase until eligibility determination (months)		
No. of subjects	17	
Mean value	13.4	
Standard deviation	15.6	
Maximum value	52	
Median	7.0	
Minimum value	1	
Type of intestinal involvement in Crohn's disease		
Small intestine	1	5.9
Small and large intestines	6	35.3
Large intestine	10	58.8
Other	0	0.0
CDAI at eligibility determination		
No. of subjects	17	
Mean value	228.6	
Standard deviation	36.9	
Maximum value	302	
Median	214.0	
Minimum value	162	
Under 220 (mild)	10	58.8
220 and over under 350 (moderate)	7	41.2

**Table 1** continued

Parameter	%	
CRP at screening time point (mg/dL)		
No. of subjects	17	
Mean value	1.459	
Standard deviation	1.437	
Maximum value	5.15	
Median	1.010	
Minimum value	0.05	
Presence/absence of treatments administered to patients with Crohn's disease in the active phase before eligibility determination		
Absence	4	23.5
Presence	13	76.5
Mesalazine preparation	11	64.7
Corticosteroid	3	17.6
Other drug	5	29.4

CDAI Crohn's Disease Activity Index, CRP C-reactive protein



**Fig. 2** Transition of CDAI. CDAI Crohn's disease Activity Index

*Change in CDAI* The mean value with respect to time was  $-49.3$  at week 2,  $-61.8$  at week 4,  $-78.3$  at week 8, and  $-101.1$  at week 12; therefore, there was a decrease over time in the mean change in CDAI from week 2 to week 12. The change in CDAI at the time of final observation was  $-67.4$ . A statistically significant difference was found for all time points compared with screening (Table 2).

### 3.3 Clinical Remission Proportion

The change in the proportion of clinical remission is shown in Table 3. This proportion increased over time between week 2 and week 12, from 40.0 to 66.7 %, respectively, and was 58.8 % at the time of the final observation.

**Table 2** Change in CDAI

Time point	Change in CDAI						95 % CI of mean value	Paired <i>t</i> test	Data missing
	No. of subjects	Mean value	Standard deviation	Minimum value	Median	Maximum value			
Week 2	15	-49.3	76.1	-146	-38.0	111	-91.4 to -7.2	<i>p</i> = 0.025	0
Week 4	12	-61.8	65.6	-162	-47.5	54	-103.5 to -20.2	<i>p</i> = 0.007	0
Week 8	12	-78.3	53.9	-157	-79.0	51	-112.5 to -44.1	<i>p</i> < 0.001	0
Week 12	12	-101.1	48.7	-167	-101.5	2	-132.0 to -70.2	<i>p</i> < 0.001	0
At the time of final observation	17	-67.4	88.6	-167	-95.0	124	-112.9 to -21.9	<i>p</i> = 0.006	0

At the time of final observation: At week 12 or at the time of discontinuation. Change in CDAI = CDAI at each examination time point - CDAI at screening

CDAI Crohn's disease activity index, CI confidence interval

**Table 3** Change in clinical remission

Time point and no. of subjects in analysis set	Clinical remission			Clinical remission proportion [%] (95 % CI)	Data missing
	Clinical remission	Non-clinical remission			
Week 2	15	6	9	40.0 (16.4-67.7)	0
Week 4	12	5	7	41.7 (15.2-72.3)	0
Week 8	12	7	5	58.3 (27.7-84.8)	0
Week 12	12	8	4	66.7 (34.9-90.0)	0
At the time of final observation	17	10	7	58.8 (33.0-81.5)	0

At the time of final observation: at week 12 or at the time of discontinuation. Clinical remission: CDAI <150

CDAI Crohn's disease activity index, CI confidence interval

### 3.3.1 CS

The CS set included a total of 12 subjects. The result of the evaluation by the investigators was improved in four subjects, unchanged in seven subjects, and worsened in one subject, and the endoscopic improvement proportion was 33.3 % (4 of 12 subjects).

In contrast, the result of the evaluation by the central reviewer was improved in six subjects, unchanged in three subjects, and worsened in three subjects, and the endoscopic improvement proportion was 50.0 % (6 of 12 subjects).

One subject was assessed as having improved by both the investigators and the reviewer; a deep irregular ulcer, which was observed at the time of screening, had almost healed at week 12, showing marked efficacy of the drug.

## 3.4 Safety

All 17 treated subjects were included in the SAF; treatment compliance was  $\geq 80$  % in all subjects throughout

the study period. The list of AEs and ADRs that occurred during the study are shown in Table 4. The incidence of AEs and ADRS was 94.1 % (16 of 17 subjects) and 58.8 % (10 of 17 subjects), respectively. The majority of these events corresponded with abnormal changes in laboratory values. All AEs and ADRs that occurred during the study were known from the ADR information of the study drug.

A serious AE of drug hypersensitivity, i.e. a clinically significant AE (AE leading to the discontinuation of study treatment), occurred in one subject.

Other clinically significant AEs of 'chest pain' and 'CRP increased' occurred in another subject. These AEs were considered to be definitely related to the study drug.

With respect to severity, AEs were mild in 4 subjects (61 cases), moderate in 11 subjects (26 cases), and severe in 1 subject (1 case). Moreover, ADRs were mild in 5 subjects (22 cases), moderate in 4 subjects (9 cases), and severe in 1 subject (1 case). The severe AE and ADR was drug hypersensitivity.

**Table 4** List of adverse events and adverse drug reactions

No. of subjects in the analysis set	17					
	Adverse events			Adverse drug reactions		
	No. of onsets	No. of patients affected	Incidence (%)	No. of onsets	No. of patients affected	Incidence (%)
Total	88	16	94.1	32	10	58.8
Infections and infestations	10	9	52.9	0	0	0.0
Bronchitis	1	1	5.9	0	0	0.0
Cystitis	1	1	5.9	0	0	0.0
Nasopharyngitis	4	4	23.5	0	0	0.0
Anal abscess	1	1	5.9	0	0	0.0
Gingival abscess	1	1	5.9	0	0	0.0
Enteritis infectious	2	2	11.8	0	0	0.0
Immune system disorders	1	1	5.9	1	1	5.9
Drug hypersensitivity	1	1	5.9	1	1	5.9
Metabolism and nutrition disorders	1	1	5.9	0	0	0.0
Diabetes mellitus	1	1	5.9	0	0	0.0
Eye disorders	1	1	5.9	0	0	0.0
Corneal disorder	1	1	5.9	0	0	0.0
Gastrointestinal disorders	5	4	23.5	1	1	5.9
Upper abdominal pain	1	1	5.9	0	0	0.0
Constipation	1	1	5.9	1	1	5.9
Dental caries	1	1	5.9	0	0	0.0
Gastric ulcer	1	1	5.9	0	0	0.0
Gastritis	1	1	5.9	0	0	0.0
Musculoskeletal and connective tissue disorders	2	2	11.8	1	1	5.9
Neck pain	2	2	11.8	1	1	5.9
Reproductive system and breast disorders	1	1	5.9	0	0	0.0
Vulval ulceration	1	1	5.9	0	0	0.0
General disorders and administration site conditions	6	4	23.5	4	2	11.8
Chest pain	1	1	5.9	1	1	5.9
Local swelling	1	1	5.9	0	0	0.0
Pyrexia	4	2	11.8	3	1	5.9
Investigations	61	16	94.1	25	9	52.9
Alanine aminotransferase increased	1	1	5.9	0	0	0.0
$\beta$ -N-acetyl-D-glucosaminidase increased	8	8	47.1	5	5	29.4
Bilirubin conjugated increased	2	2	11.8	0	0	0.0
Blood amylase increased	2	2	11.8	2	2	11.8
Blood bilirubin increased	2	2	11.8	0	0	0.0
Blood potassium decreased	5	5	29.4	2	2	11.8
Blood urea increased	1	1	5.9	0	0	0.0
C-reactive protein increased	12	12	70.6	4	4	23.5
Eosinophil count increased	5	4	23.5	1	1	5.9
$\gamma$ -Glutamyltransferase increased	1	1	5.9	0	0	0.0
Lymphocyte count decreased	8	8	47.1	4	4	23.5
Monocyte count increased	2	2	11.8	0	0	0.0
Neutrophil count increased	1	1	5.9	1	1	5.9
White blood cell count increased	5	5	29.4	2	2	11.8
Platelet count increased	1	1	5.9	1	1	5.9

**Table 4** continued

No. of subjects in the analysis set	17					
	Adverse events			Adverse drug reactions		
	No. of onsets	No. of patients affected	Incidence (%)	No. of onsets	No. of patients affected	Incidence (%)
Protein urine present	3	3	17.6	3	3	17.6
Blood alkaline phosphatase increased	2	2	11.8	0	0	0.0

Event name: MedDRA/J Ver.13.1. If the same adverse event occurred more than once in a subject, the subject was counted once for that event. Summary of all events: if one event occurs more than once in a subject, the subject was counted once for that event

MedDRA Medical Dictionary for Regulatory Activities

## 4 Discussion

In the efficacy assessment using CDAI, a decrease in CDAI over time was observed from week 2, with the CDAI decreasing to <150 at week 8 (145.4) and week 12 (122.7), which is defined as remission of CD. However, at the time of the final observation, which included subjects who discontinued the treatment, the CDAI was 161.2; therefore, the threshold for CD remission was not reached. The reason for this may have been the inclusion of the two subjects who discontinued the study because of aggravation of underlying conditions.

The percentage of those reaching clinical remission increased over time from week 2, i.e. 66.7 % (8 of 12 subjects) at week 12 and 58.8 % (10 of 17 subjects) at the time of the final observation, which included the subjects who discontinued treatment.

Two other clinical studies have been reported in which the study drug was administered to patients with active CD. In one study [8] where the study drug was administered to patients with active CD for 12 weeks, with the dose tapering from 4 g/day (from the beginning of the study to week 6: 4.0 g/day; week 7–9: 3.2 g/day; week 10–12: 2.4 g/day), clinical remission was reported in 60.0 % of subjects (21 of 35 subjects), which was comparable to the results from this study. In another study [9], 3.2 g/day of the study drug was administered to patients with active CD for 16 weeks, with 60.0 % of subjects (12 of 20 subjects) showing a reduction in CDAI of  $\geq 70$ , and 45.0 % (9 of 20 subjects) showing a reduction in CDAI of  $\geq 70$  in addition to reaching a CDAI of below 150. When these assessment criteria are applied to the data from the present study, the results are 64.7 % (11 of 17 subjects) and 52.9 % (9 of 17 subjects), respectively, which are comparable; therefore, the results of the present study are similar to those obtained from other clinical studies.

In the CS findings, the findings were assessed as total (not by region) assessment between the terminal ileum and the rectum. Some of the subjects showed an improvement

from monotherapy administration of the study drug based on the evaluation by both the investigators and the central reviewer. Of the four subjects who were assessed as 'improved' by both the investigators and the reviewer, three achieved clinical remission (CDAI <150) and tended to have decreased levels of CRP. Of these three subjects, remarkable efficacy of the drug was found in one subject (large intestine-type CD patient); it was confirmed that the deep irregular ulcer observed between the cecum and sigmoid colon at screening had disappeared after the study treatment, with the patient achieving an almost healed state (the change in CDAI and CRP from screening to week 12 in this subject was CDAI 208  $\rightarrow$  109, CRP 1.01  $\rightarrow$  0.03).

In addition, although one small intestine-type CD patient (who had a lesion of the terminal ileum only) had improvement of CDAI, the patient had no improvement of endoscopic finding (assessed as 'unchanged' by the investigator and 'worsened' by the reviewer) and CRP (the change in CDAI and CRP from screening to week 12 in this patient was CDAI 205  $\rightarrow$  43, CRP 1.49  $\rightarrow$  1.36).

The above results suggest that the study drug could have sufficient therapeutic efficacy in patients with mild to moderately active CD, with a major mucosal lesion subjected to treatment at any site from the terminal ileum to the rectum.

The present study examined the small and large intestine. Due to the properties of the pH-dependent-release mesalazine (releasing at pH >7), subjects were limited to those who had mucosal lesions from the terminal ileum to the rectum. When treating CD with mesalazine, it is important to select a preparation of the drug that has a release profile that best suits the specific mucosal lesion [10]; this may have been the reason that efficacy was determined from this study.

The incidences of AEs and ADRs were relatively high, at 94.1 and 58.8 %, respectively. The reason for this may have been that the events were summarized in accordance with the study protocol, which specified that any changes in laboratory values falling under the Criteria for



Classification of Abnormal Laboratory Values be classified as AEs. Furthermore, the criteria specifies that events other than those assessed as 'unrelated' should be treated as ADRs. None of the AEs related to the laboratory tests required treatment. Many of the AEs and ADRs were mild or moderate in severity and were known events. Moreover, there was no apparent increase in the number of cases of AEs or ADRs associated with the duration of treatment. Therefore, the safety profile of 4.8 g/day of the study drug administered over 12 weeks in patients with mild to moderately active CD was similar to the safety profile of the study drug obtained in the past, and suggested high safety of the study drug.

In interpreting the results of this study, it must be taken into account that this was an uncontrolled, open-label study with a small sample size (17 subjects), and the efficacy of the drug was evaluated without setting a primary endpoint because this was an exploratory study. However, because no previous studies have demonstrated the therapeutic efficacy of pH-dependent-release mesalazine administered at 4.8 g/day in patients with mild to moderately active CD, this study could be seen as providing valuable new findings.

## 5 Conclusions

The results from this study suggest that 12-week administration of 4.8 g/day of a high-dose of pH-dependent-release mesalazine could provide an effective and highly safe treatment for patients with mild to moderately active CD with major mucosal lesions in the area from the terminal ileum to the rectum. The formulation of mesalazine and the location of inflammation must be considered when treating CD with mesalazine.

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## Compliance with Ethical Standards

**Conflicts of Interest** Drs. Suzuki and Iida declare that they have no conflicts of interest. Dr. Ito has received consulting fees from Zeria Pharmaceutical Co., Ltd; Naoto Tachikawa is an employee of Zeria Pharmaceutical Co., Ltd; and Dr. Hibi has received advisory fees, speaker fees, and grant support from Zeria Pharmaceutical Co., Ltd.

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**Ethics Statements** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 1975, revised in 2013. Springer's policy concerning informed consent has been followed. Documented approval from appropriate Institutional Review Boards was obtained for all participating sites.

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