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Original Article

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Long-Term Efficacy and Safety of Multi-Matrix Mesalazine Maintenance Therapy in Pediatric Patients with Ulcerative Colitis

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ABSTRACT

Purpose: This study aimed to evaluate the efficacy and safety of multi-matrix mesalazine in pediatric patients with ulcerative colitis (UC) in remission.
Methods: A multicenter, open-label, uncontrolled study was conducted in Japan, in which multi-matrix mesalazine 40 mg/kg was administered orally once daily for 48 weeks to 23 patients with UC in remission, aged <17 years. The primary endpoint was the nonoccurrence of rectal bleeding based on the Ulcerative Colitis Disease Activity Index (UC-DAI) score.
Results: The percentage of patients without rectal bleeding, based on the UC-DAI score in the full analysis set, was 73.9% (two-sided 95% confidence interval [CI]: 51.6%, 89.8%; n=17/23). The lower limit of the two-sided 95% CI exceeded the predetermined threshold of 50%, derived from placebo group data in previous clinical studies involving adult patients with UC. The incidence of adverse events (AEs) and study drug-related AEs was 87.0% (n=20/23) and 13.0% (n=3/23), respectively. No deaths were reported. None of the study drug-related AEs were severe or serious, nor did they lead to discontinuation of the study drug.
Conclusion: This study demonstrated the long-term efficacy of multi-matrix mesalazine in pediatric patients with UC in remission in Japan. No noteworthy safety concerns beyond those known to be associated with mesalazine were observed.

Keywords: Ulcerative colitis; Child; Mesalamine; Maintenance; Once-daily; Clinical trial

INTRODUCTION

Ulcerative colitis (UC) is a chronic disease characterized by the diffuse inflammation of the colonic and rectal mucosae [1]. This disease tends to present to a greater extent and severity in children than in adults [2].

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Conflict of Interest
The authors have no financial conflicts of interest.

Oral mesalazine (5-aminosalicylic acid [5-ASA]) is the first-line therapy for UC in both adults and children [2-6]. This medication is available in formulations with different drug delivery systems and is classified according to its active ingredient delivery mechanisms into time-dependent, pH-dependent, and multi-matrix types. In Japan, all are approved for the treatment of adult UC; however, only time-dependent formulations (Pentasa®; Kyorin Pharmaceutical Co., Ltd.) are approved for pediatric UC [2]. The approval of time-dependent formulations for pediatric UC in Japan is based solely on postmarketing surveillance data [7], with no company-sponsored clinical trials conducted in Japanese pediatric patients.

The time-dependent formulation of mesalazine available in Japan typically needs to be administered three times daily for both the induction and maintenance of remission.

Multi-matrix mesalazine has been shown to be effective and safe in clinical studies involving adult patients with UC, leading to its approval in numerous countries, including the United States (US), Canada, Europe, and Japan. In Japan, it has been approved for use in patients with UC aged 16 years and older, based on its demonstrated efficacy and safety in both active and remission phase studies [8,9]. Its efficacy and safety for pediatric use have been established in clinical studies conducted in the US and Europe [10], leading to its approval for pediatric patients in 18 countries, including the US and countries in Europe, but not in Japan. In the US and Europe, multi-matrix mesalazine is the only oral formulation that can be administered once daily during both the active and remission phases in adults and children. This study investigated the efficacy and safety of multi-matrix mesalazine in pediatric patients with UC in remission in Japan.

MATERIALS AND METHODS

Study design

This multicenter, open-label, uncontrolled, phase 2/3 study was conducted at 30 sites in Japan from March 2018 to July 2021. The study design is illustrated in **Fig. 1**. Multi-matrix mesalazine (Lialda®; Mochida Pharmaceutical Co., Ltd.) was administered at a dose of 40 mg/kg/day once daily for 48 weeks, according to the body weight categories in **Table 1**. The 40 mg/kg/day dose of multi-matrix mesalazine was based on an approved dose of 2,400 mg/day for adult patients with UC in remission, assuming an adult body weight of 60 kg.

Written assent was obtained from pediatric patients, and written informed consent was obtained from legal representatives aged ≥20 years, including the parents, partner, guardian, or equivalent of the patient. The study protocol was approved by the institutional review boards at each of the 30 participating study sites, and the appropriateness of conducting

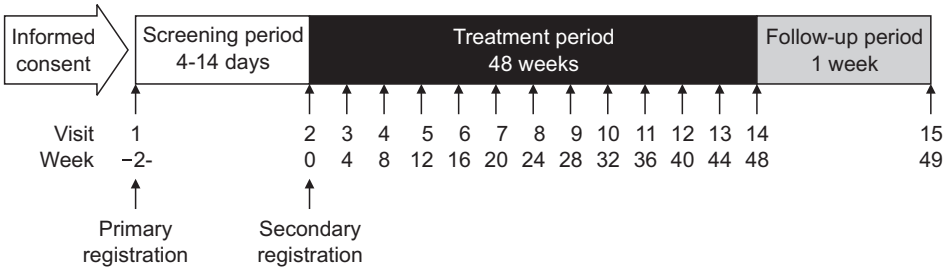

Fig. 1. Study design.

Table 1. Dosage, type, and number of tablets of the study drug for each body weight classification

Body weight classification	Dosage	Type and number of tablets
18 to ≤23 kg	900 mg/day	Multi-matrix mesalazine 300 mg tablet, 3 tablets
>23 to ≤35 kg	1,200 mg/day	Multi-matrix mesalazine 600 mg tablet, 2 tablets
>35 to ≤50 kg	1,800 mg/day	Multi-matrix mesalazine 600 mg tablet, 3 tablets
>50 to ≤90 kg	2,400 mg/day	Multi-matrix mesalazine 1,200 mg tablet, 2 tablets

the clinical study was confirmed at all sites prior to study initiation. This study was conducted in accordance with the Ministerial Ordinance on Good Clinical Practice for Drugs, and conformed to the principles outlined in the Declaration of Helsinki. This study was registered in the Japan Registry of Clinical Trials (jRCT2080223747).

Patients

The study included male and female patients with UC aged <17 years, weighing 18 to 90 kg, who were in remission, defined as the Ulcerative Colitis Disease Activity Index (UC-DAI) score of ≤2 and a rectal bleeding score based on the UC-DAI score of 0. The major exclusion criteria included the use of oral formulations of mesalazine or salazosulfapyridine at doses exceeding those listed in **Table 1** within two weeks prior to secondary registration; the use of topical formulations of mesalazine, salazosulfapyridine, corticosteroids (oral, rectal, suppository, hemorrhoid treatment, or injection) or cytapheresis therapy within four weeks prior to secondary registration; the use of immunomodulators (oral or injectable) within 12 weeks prior to secondary registration; prior use of biologics for UC treatment; and concomitant moderate to severe renal or hepatic impairment.

Efficacy endpoints

Efficacy was assessed every four weeks, with end-of-treatment data recorded at week 48 or at the time of discontinuation.

Efficacy endpoints were evaluated using the UC-DAI and pediatric ulcerative colitis activity index (PUCAI) scores. The UC-DAI score (range: 0–12) comprises four components: stool frequency, rectal bleeding, sigmoidoscopic findings regarding mucosal appearance, and physician's global assessment. Due to the invasive nature of colonoscopy, end-of-treatment colonoscopy is recommended (to the extent possible), although not mandatory. The PUCAI score (range: 0–85) comprises six components: abdominal pain, rectal bleeding, stool consistency, stool frequency, nocturnal bowel movement, and activity level.

The primary endpoint was the absence of rectal bleeding based on the UC-DAI score (rectal bleeding scores <1 at all visits during the treatment period). Secondary endpoints included the duration of nonoccurrence of rectal bleeding based on the UC-DAI score, change in the UC-DAI score, relapse based on the UC-DAI score (UC-DAI score ≥3 and rectal bleeding score ≥1 at the end of the treatment period), change in each UC-DAI component score, and remission based on the PUCAI score (PUCAI score <10 at the end of the treatment period).

Safety endpoints

Adverse events (AEs), study drug-related AEs, AEs leading to fatalities, serious AEs (SAEs), and AEs leading to study drug discontinuation are summarized. Height, body weight, laboratory test results, and vital signs were assessed. AEs were categorized using the preferred terms from the international standardized medical terminology by ICH (Medical Dictionary for Regulatory Activities; MedDRA), version 26.1 (MeDRA MSSO).

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Statistical analyses

The Full Analysis Set (FAS) was used for the primary efficacy analysis. The FAS was defined as patients who received at least one dose of the study drug and underwent at least one efficacy assessment after treatment initiation. The safety analysis set included patients who received at least one dose of the study drug and had safety data available during the treatment period.

The threshold for the percentage of patients without rectal bleeding was set at 50%, based on the results of placebo-controlled studies in adult patients with UC in remission [11-15], which reported that approximately 50% of placebo-treated patients did not experience rectal bleeding.

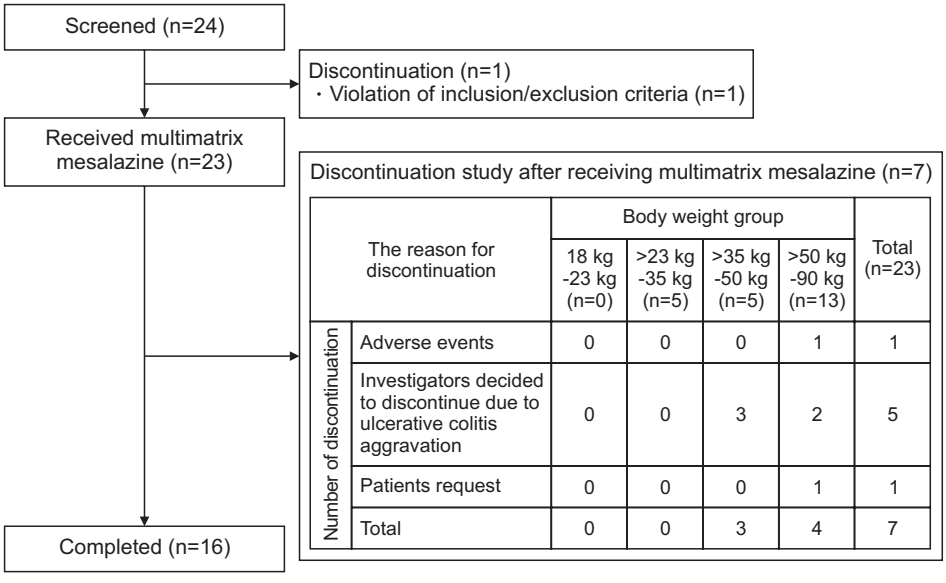
All statistical analyses were performed using the SAS software (version 9.4; SAS Institute Inc.).

Based on a Japanese clinical study of multi-matrix mesalazine in adult patients with UC in remission [9], in which 84.8% of patients treated with 2,400 mg/day of multi-matrix mesalazine did not experience rectal bleeding, and the results of clinical studies of multi-matrix mesalazine in adult patients with UC in remission [16,17], which reported remission rates of 69.7% and 68.0%, respectively, the target sample size was set at 26 patients. This sample size was designed to estimate the effect with a precision of ±20%, assuming that 80% of patients would achieve the primary endpoint absence of rectal bleeding.

RESULTS

The disposition of patients is shown in **Fig. 2**. A total of 23 patients received the study drug, which comprised the FAS and Safety Analysis Set during the treatment period.

The demographic and baseline characteristics of the FAS are shown in **Table 2**. The FAS group comprised 43.5% males (n=10/23) and 56.5% females (n=13/23). The mean (±standard deviation [SD]) age was 12.7±3.1 years. The mean (±SD) body weight was 46.18±13.19 kg.



Discontinuation study after receiving multimatrix mesalazine (n=7)

	The reason for discontinuation	Body weight group: 18 kg -23 kg (n=0)	>23 kg -35 kg (n=5)	>35 kg -50 kg (n=5)	>50 kg -90 kg (n=13)	Total (n=23)
Number of discontinuation	Adverse events	0	0	0	1	1
	Investigators decided to discontinue due to ulcerative colitis aggravation	0	0	3	2	5
	Patients request	0	0	0	1	1
	Total	0	0	3	4	7

Fig. 2. Disposition of patients.

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Table 2. Demographics and baseline characteristics (full analysis set)

Variable	Multi-matrix mesalazine (n=23)
Sex	
Male	10 (43.5)
Female	13 (56.5)
Age (yr)	
Mean ± standard deviation	12.7±3.1
Age category	
≤10 yr	6 (26.1)
>10 to <17 yr	17 (73.9)
Weight at baseline (kg)	
Mean ± standard deviation	46.18±13.19
Weight category	
18 to ≤23	0 (0.0)
>23 to ≤35	5 (21.7)
>35 to ≤50	5 (21.7)
>50 to ≤90	13 (56.5)
Height at baseline (cm)	
Mean ± standard deviation	153.10±16.58
Disease course	
First attack*	15 (65.2)
Relapsing-remitting†	8 (34.8)
Extent of disease	
Proctitis	1 (4.3)
Left-sided colitis	5 (21.7)
Pancolitis	16 (69.6)
Right-sided colitis	1 (4.3)
Duration of current remission (yr)	
Mean ± standard deviation	2.08±1.83
<24 mo	12 (52.2)
≥24 mo	11 (47.8)
UC-DAI score at baseline	
Mean ± standard deviation	1.0±0.9
PUCAI score at baseline	
Mean ± standard deviation	1.09±2.11

Values are presented as number (%) or mean±standard deviation.
UC-DAI: ulcerative colitis disease activity index, PUCAI: pediatric ulcerative colitis activity index.
*Patients in remission after the first episode of ulcerative colitis, †Patients in remission after a relapse of ulcerative colitis.

Of the patients, 65.2% (n=15/23) were in remission after the first UC attack, and 34.8% (n=8/23) were in remission after a UC relapse. The extent of the disease was as follows: proctitis, 4.3% (n=1/23); left-sided colitis, 21.7% (n=5/23); pancolitis, 69.6% (n=16/23); and right-sided colitis, 4.3% (n=1/23). The mean (±SD) duration of current remission was 2.08±1.83 years, with 52.2% (n=12/23) of patients remaining in remission for <24 months and 47.8% (n=11/23) in remission for ≥24 months. The mean (±SD) baseline UC-DAI score was 1.0±0.9, and the mean (±SD) baseline PUCAI score was 1.09±2.11.

The median treatment compliance rate in the FAS was 99.4%, with 100.0% (n=23/23) of patients achieving a compliance rate of ≥75%.

Efficacy

1. Primary endpoint

The percentage of patients without rectal bleeding based on the UC-DAI score in the FAS was 73.9% (two-sided 95% confidence interval [CI]: 51.6%, 89.8%; n=17/23) (**Table 3**), and the lower limit of the two-sided 95% CI exceeded the predefined threshold of 50%.

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Table 3. Efficacy results (full analysis set) (the end of treatment period)

Variable	Multi-matrix mesalazine
Nonoccurrence of rectal bleeding based on the UC-DAI score	(n=23)
Proportion of patients	17 (73.9)
95% CI	51.6 to 89.8
Duration of nonoccurrence of rectal bleeding based on the UC-DAI score	(n=23)
25th percentile	267.0 d
95% CI	18.0 d to -*
Relapse based on the UC-DAI score†	(n=23)
Proportion of patients	15 (65.2)
95% CI	42.7 to 83.6
Change in the UC-DAI score	(n=10)
Mean ± standard deviation	1.0±2.5
95% CI	−0.8 to 2.8
UC-DAI component score: change in stool frequency score	(n=23)
Mean ± standard deviation	0.0±0.6
95% CI	−0.2 to 0.3
UC-DAI component score: change in rectal bleeding score	(n=23)
Mean ± standard deviation	0.3±0.7
95% CI	0.0 to 0.7
UC-DAI component score: change in sigmoidoscopy score	(n=10)
Mean ± standard deviation	0.2±0.6
95% CI	−0.3 to 0.7
UC-DAI component score: change in the PGA score	(n=10)
Mean ± standard deviation	0.3±0.8
95% CI	−0.3 to 0.9
Remission based on the PUCAI score	(n=23)
Proportion of patients	18 (78.3)
95% CI	56.3 to 92.5

Values are presented as number (%).
UC-DAI: ulcerative colitis disease activity index, CI: confidence interval, PGA: physician's global assessment, PUCAI: pediatric ulcerative colitis activity index.
*Not calculable, †Participants with no data available at the end of treatment were classified as having relapsed.

2. Secondary endpoints

The 25th percentile of the duration of the nonoccurrence of rectal bleeding, defined as the time point when 75% of patients remained free of rectal bleeding, based on the UC-DAI score in the FAS, was 267.0 days (**Table 3**). The Kaplan–Meier plot for the duration of nonoccurrence of rectal bleeding is shown in **Fig. 3**. The remission rate in the FAS based on the PUCAI score at the end of the treatment period was 78.3% (two-sided

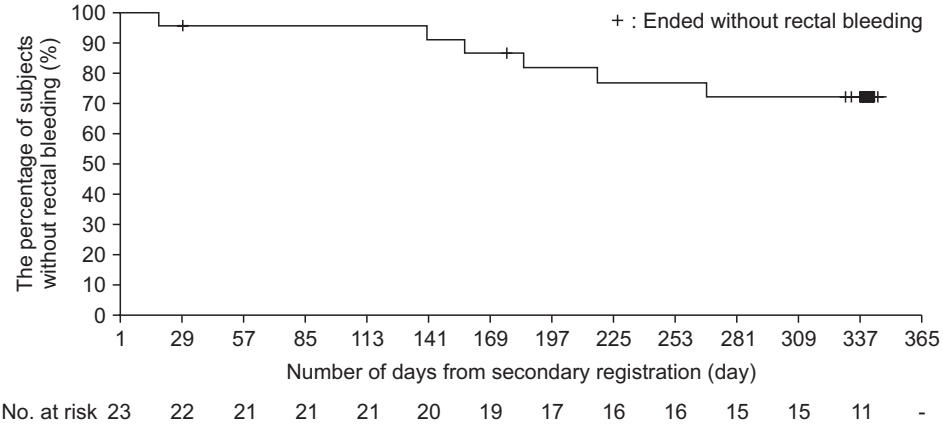

Fig. 3. Kaplan–meier plot for the duration of nonoccurrence of rectal bleeding (full analysis set).

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95% CI: 56.3%, 92.5%; n=18/23). One patient was not evaluated for the PUCAI and was considered a "non-remission" case. The results for the other secondary endpoints are summarized in **Table 3**.

Safety

The incidences of AEs and study drug-related AEs during the treatment period were 87.0% (n=20/23) and 13.0% (n=3/23), respectively. AEs reported in ≥2 patients included nasopharyngitis (39.1%, n=9/23), influenza, upper respiratory tract inflammation, ulcerative colitis, vomiting (21.7%, n=5/23 each), headache, diarrhea (13.0%, n=3/23 each), varicella, abdominal pain, dental caries, and ligament sprains (8.7%, n=2/23 each) (**Table 4**). Among the AEs reported in two or more patients, except for one case each of headache, abdominal pain, and diarrhea, none were related to the study drug.

No deaths were reported. The incidence of SAEs was 8.7% (n=2/23), including cerebral hemorrhage and brain herniation in one patient (the same individual) and ulcerative colitis

Table 4. Incidence of adverse events (treatment period: 48 wk)

Preferred terms	Multi-matrix mesalazine (n=23)
Nasopharyngitis	9 (39.1)
Influenza	5 (21.7)
Upper respiratory tract inflammation	5 (21.7)
Ulcerative colitis	5 (21.7)
Vomiting	5 (21.7)
Headache	3 (13.0)
Diarrhea	3 (13.0)
Varicella	2 (8.7)
Abdominal pain	2 (8.7)
Dental caries	2 (8.7)
Ligament sprain	2 (8.7)
Gastroenteritis viral	1 (4.3)
Otitis externa	1 (4.3)
Sinusitis	1 (4.3)
Vulvovaginal candidiasis	1 (4.3)
Herpes ophthalmic	1 (4.3)
Seasonal allergy	1 (4.3)
Decreased appetite	1 (4.3)
Insomnia	1 (4.3)
Delirium febrile	1 (4.3)
Cerebral hemorrhage	1 (4.3)
Ear pain	1 (4.3)
Ear discomfort	1 (4.3)
Cough	1 (4.3)
Haemoptysis	1 (4.3)
Oropharyngeal discomfort	1 (4.3)
Anal fissure	1 (4.3)
Constipation	1 (4.3)
Nausea	1 (4.3)
Stomatitis	1 (4.3)
Anal eczema	1 (4.3)
Acne	1 (4.3)
Mass	1 (4.3)
Arthropod sting	1 (4.3)
Brain herniation	1 (4.3)
Contusion	1 (4.3)
Meniscus injury	1 (4.3)

Values are presented as number (%).
Medical Dictionary for Regulatory Activities, version 26.1

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Table 5. Incidence of adverse events of special interest (treatment period: 48 wk)

Category*	Multi-matrix mesalazine (n=23)	
	Adverse events	Adverse drug reactions
Hypersensitivity reaction	5 (21.7)	1 (4.3)
Renal and urinary tract disorder	0 (0.0)	0 (0.0)
Hepatobiliary disorder	0 (0.0)	0 (0.0)
Blood cell decreased	0 (0.0)	0 (0.0)
Pericarditis, myocarditis, pleurisy	0 (0.0)	0 (0.0)
Interstitial lung disease	0 (0.0)	0 (0.0)
Pancreatitis	0 (0.0)	0 (0.0)
Toxic epidermal necrolysis, oculomucocutaneous syndrome	0 (0.0)	0 (0.0)
Drug-induced hypersensitivity syndrome	0 (0.0)	0 (0.0)

Values are presented as number (%).
*The category "Hypersensitivity reaction" includes adverse events that meet any of the following criteria: those classified as Preferred Term (PT) "Drug Intolerance," PTs "Hypersensitivity," or "Drug Hypersensitivity," PT "Pyrexia," events that include terms such as "Rash," "Eczema," or "Urticaria" in the PTs, events that include "Abdominal Pain" in the PTs, events that include "Diarrhea" in the PTs, and events that include "Eosinophils" in the PTs (excluding events related to eosinophil decrease). The category "Renal and urinary tract disorder" includes events that meet any of the following criteria: those included in the System Organ Class (SOC) "Renal and Urinary Disorders," events that contain the terms "Renal" or "Urinary" in the PTs (excluding those related to diabetes), and events related to renal and urinary tract disorders included in the SOC "Investigations" findings. The category "Hepatobiliary disorder" includes events that meet any of the following criteria: those included in the SOC "Hepatobiliary Disorders," events that contain the term "Hepatic" in the PTs, and events related to hepatobiliary disorders included in the SOC "Investigations" findings. The category "Blood cell decreased" includes events that fall under the Standardised Medical Dictionary for Regulatory Activities Query (SMQ) "Hematopoietic cytopenias" (broad and narrow). The category "Pericarditis, myocarditis, pleurisy" includes events that contain the terms "Pericar-ditis," "Myocarditis," or "Pleurisy" in the PTs. The category "Interstitial lung disease" includes events that fall under the SMQ "Interstitial Lung Disease" (broad and narrow). The category "Pancreatitis" includes events that meet any of the following criteria: events that contain "Pancreatitis" in the PTs, and events related to pancreatitis included in the SOC "Investigations" findings. The category "Toxic epidermal necrolysis, oculomucocutaneous syndrome" includes events classified as PT "Toxic Epidermal Necrolysis" or "Oculomucocutaneous Syndrome." Lastly, the category "Drug-induced hypersensitivity syndrome" includes events classified as PT "Drug reaction with eosinophilia and systemic symptoms."
Medical Dictionary for Regulatory Activities, version 26.1.

in another. The incidence of AEs leading to study drug discontinuation was 26.1% (n=6/23), with ulcerative colitis in five patients, and cerebral hemorrhage and brain herniation in one patient (the same patient). The incidence of severe AEs was 4.3% (n=1/23, including cerebral hemorrhage and brain herniation in one patient [the same patient]). None of the SAEs, AEs leading to discontinuation of the study drug, or severe AEs were considered related to the study drug. Based on a report from the hospital to which the patient was transported, which identified an arteriovenous malformation on postoperative angiography, cerebral hemorrhage and brain herniation were determined by the principal investigator as events that occurred due to the patient's congenital arteriovenous malformation.

Known adverse drug reactions to multi-matrix mesalazine were defined and tabulated as AEs of special interest (**Table 5**). There were AEs classified under "hypersensitivity reactions," with diarrhea and abdominal pain reported in one patient (the same individual), assessed as related to the study drug. Both events were mild and non-serious, did not lead to the discontinuation of the study drug, and resolved without intervention.

No laboratory test results, vital signs, physical findings, or other safety observations revealed noteworthy trends related to the study drug.

DISCUSSION

In this study, the primary endpoint was the nonoccurrence of rectal bleeding (rectal bleeding score <1 during the treatment period), and the percentage of patients without rectal bleeding was evaluated. Rectal bleeding is a significant indicator used to determine remission and relapse in the Japanese guidelines for UC treatment [18]. As it can be continuously

monitored, it was selected as the primary endpoint in a Japanese clinical study involving adult patients with UC in remission [9].

In the present study, the primary endpoint was achieved based on the prespecified efficacy criteria, which were derived from the percentage of patients without rectal bleeding in the placebo group of clinical studies involving adult patients with UC, indicating that multi-matrix mesalazine is also effective in pediatric patients with UC.

In pediatric UC, the PUCAI score is widely used to guide treatment strategies [2,4] and evaluate the activity of pediatric UC [19]. The Japanese treatment guidelines for pediatric UC stipulate that the medium-term treatment goal is a PUCAI score of <10 [2]. Moreover, according to the European treatment guidelines for pediatric UC, a PUCAI score <10 indicates a good long-term prognosis [4]. Therefore, remission based on a PUCAI score (<10) was established as the secondary endpoint in this study.

In the present study, the remission rate based on the PUCAI score was 78.3%, which demonstrated favorable outcomes in the maintenance of remission during long-term administration of multi-matrix mesalazine in patients who maintained remission with oral 5-ASA. A prospective registry study of pediatric inflammatory bowel disease, which was a non-interventional observational study, reported that the PUCAI-based remission rate after one year of treatment with oral 5-ASA monotherapy in pediatric patients with UC was 45% [20]. However, this registry study did not provide detailed information on activity levels or other influencing factors, making a direct comparison with the present study difficult.

In the present study, none of the AEs occurring in ≥2 patients were assessed as related to the study drug. No deaths were reported, and no SAEs, AEs leading to study drug discontinuation, or severe AEs related to the study drug were identified. These results indicate no specific safety issues associated with the long-term use of multi-matrix mesalazine in pediatric patients with UC who maintain remission through oral 5-ASA.

In this study, multi-matrix mesalazine was administered at a dose of 40 mg/kg/day (**Table 1**), with high treatment compliance. The majority of pediatric patients with UC are assumed to be school-age children and students aged 7 or older. As multi-matrix mesalazine is administered once daily, it only needs to be taken after breakfast, reducing the likelihood of missed doses due to forgetting to bring the medication to school, thereby improving medication adherence. Given that improving medication adherence with 5-ASA reduces the risk of UC relapse [21], a once-daily regimen of multi-matrix mesalazine may further reduce the risk of relapse.

The limitations of the present study include its open-label design with a single group and a small sample size, as the population of pediatric patients was smaller than that of adult patients with UC. Additionally, because none of the patients were in the low body weight (18–23 kg) category, the efficacy and safety of the study drug in pediatric patients with UC in remission weighing ≤23 kg could not be evaluated. The precision of the estimates was reduced because the target number of patients was not achieved.

In conclusion, this study demonstrated the long-term efficacy of multi-matrix mesalazine in pediatric patients with UC in remission in Japan. No noteworthy safety concerns beyond the known risks associated with mesalazine were observed. Multi-matrix mesalazine, which

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is suitable for once-daily administration, may serve as a new option for oral mesalazine treatment in pediatric patients with UC.

Only a limited number of published reports have described clinical studies on oral mesalazine formulations in pediatric patients with UC. This study contributes to the clinical management of pediatric UC by providing valuable clinical data on the use of mesalazine in pediatric patients with UC in remission.

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