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Comparison of efficacy of once daily multimatrix mesalazine 2.4 g/day and 4.8 g/day with other 5-aminosalicylic acid preparation in active ulcerative colitis: a randomized, double-blind study

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Background/Aims: This study compared the efficacy of multimatrix mesalazine 2.4 g/day and 4.8 g/day with controlled-release mesalazine 2.25 g/day. **Methods:** In this multicenter, randomized, double-blind study, 251 patients with mildly to moderately active ulcerative colitis received multimatrix mesalazine 2.4 g/day once daily (Multimatrix-2.4), 4.8 g/day once daily (Multimatrix-4.8), or controlled-release (time-dependent) mesalazine 2.25 g/day 3 times daily (Time-2.25) for 8 weeks. The primary efficacy endpoint was the change in the ulcerative colitis-disease activity index (UC-DAI) score. **Results:** The mean change in the UC-DAI score and standard deviation in the per protocol set was −1.9±2.5 for Multimatrix-2.4 and −2.4±2.8 for Time-2.25. The difference between Multimatrix-2.4 and Time-2.25 was 0.3 (two-sided 95% confidence interval [CI], −0.5 to 1.1), thus non-inferiority was not demonstrated based on the pre-defined non-inferiority margin (1.0). In the full analysis set, the difference between Multimatrix-4.8 and Time-2.25 was −1.2 (two-sided 95% CI, −2.0 to −0.5), and the mean change in UC-DAI score in the FAS was −3.3 (two-sided 95% CI, −3.9 to −2.8) for Multimatrix-4.8 and −1.9 (two-sided 95% CI, −2.5 to −1.3) for Multimatrix-2.4, indicating that Multimatrix-4.8 was more effective than Time-2.25 and Multimatrix-2.4. There was no difference among the treatment groups in terms of safety. **Conclusions:** This study showed that the efficacy of multimatrix mesalazine 2.4 g/day was comparable to controlled release mesalazine 2.25 g/day, although non-inferiority was not demonstrated. Importantly, this was the first study to indicate that multimatrix mesalazine 4.8 g/day was more effective than 2.4g/day with no associated safety concerns. **(Intest Res 2018;16:255-266)**

Key Words: Colitis, ulcerative; Active; Mesalazine; Multimatrix

INTRODUCTION

Multimatrix mesalazine (Lialda® in the United States; Mezavant™ XL in the United Kingdom, Ireland, and Malta; Mezavant™ elsewhere in the European Union) is a once daily (QD) oral formulation of mesalazine, the efficacy of which in mildly to moderately active UC has been demonstrated in 2 placebo-controlled studies.[1,2] Since it has been reported that the therapeutic effect of oral mesalazine correlates with its concentration in the colonic mucosa,[3] a higher dose of oral mesalazine should confer a greater clinical benefit. However, no apparent dose-response relationship was detected between 2 doses of multimatrix mesalazine (2.4 g/day and 4.8 g/day) in the above-mentioned placebo-controlled studies.

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This study was conducted in patients with mildly to moderately active UC to investigate the efficacy and safety of 2 different doses of multimatrix mesalazine (2.4 g/day and 4.8 g/day), compared with time-dependent (controlled-release) mesalazine 2.25 g/day 3 times daily (TID) as an active comparator.

METHODS

1. Patients

Eligible participants were outpatients diagnosed with UC and aged ≥16 years, with a UC disease activity index (UC-DAI) score ≤4 and ≤10 at randomization assignment, sigmoidoscopy score ≥1, rectal bleeding score ≥1, and physician's global assessment (PGA) score ≤2. The UC-DAI consists of the following 4 variables: stool frequency, rectal bleeding, sigmoidoscopic findings regarding the mucosal appearance, and PGA. The UC-DAI employs a 4-point scoring scale from 0 to 3 to evaluate each variable, and the evaluation index score is the total of the 4 variables.[4] Patients were excluded from the study if they had any of the following: history of hypersensitivity to mesalazine and salicylic acid; severe UC; chronic continuous or acute fulminating UC; use of oral mesalazine preparations >2.4 g/day or oral salazosulfapyridine preparations >4.0 g/day, topical mesalazine, topical salazosulfapyridine, adrenal corticosteroid or cytapheresis therapy within 2 weeks before randomization assignment, treatment with an immune-regulating drug or anti-tumor necrosis factor-α antibody within 12 weeks before randomization assignment; previous colonic resection (excluding appendectomy); moderate to severe renal or liver disorders; serious complications including diseases of the blood, respiratory, gastrointestinal, or cardiovascular organs; neuropsychiatric disease; metabolic/electrolyte imbalance or hypersensitivity; or malignant tumor. The following patients were also excluded: women who were pregnant, breastfeeding, or possibly pregnant; female patients who were planning to get pregnant during the study period.

2. Study Drugs

Multimatrix mesalazine tablets (Lialda®; Shire US Inc., Wayne, PA, USA) are red-brown, oval, film-coated tablets containing 1.2 g of mesalazine per tablet. The comparator, time-dependent (controlled-release) mesalazine tablets (Pentasa®; Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan), are white to pale yellow uncoated tablets with grayish-white to pale grayish-yellow maculae containing 250 mg of mesalazine per tablet. The study adopted a double-dummy trial design. Adherence to each study drug was measured based on patient diaries.

3. Study Design

This was a multicenter, randomized, double-blind, active-controlled, and parallel-group study with an 8-week treatment period conducted at 56 study centers in Japan from January 2011 to May 2012 (Japan Pharmaceutical Information Center clinical trial registration number: Japic CTI-101380). After informed consent was obtained, patient eligibility was evaluated based on the inclusion/exclusion criteria, and the study drug was administered to eligible patients. The following 3 groups were given the study drugs: the multimatrix mesalazine 2.4 g/day QD (Multimatrix-2.4) group, the multimatrix mesalazine 4.8 g/day QD (Multimatrix-4.8) group, and the time-dependent (controlled-release) mesalazine 2.25 g/day TID (Time-2.25) group. Patients were randomized to 1 of the 3 groups in a 1:1:1 ratio by the permuted block method, with each study center as 1 block. A double-dummy design was adopted to maintain blinding of the investigators and study participants. The Multimatrix-2.4 group received 2 tablets of multimatrix mesalazine 1.2 g and 2 tablets of multimatrix mesalazine placebo after breakfast. The Multimatrix-4.8 group received 4 tablets of multimatrix mesalazine 1.2 g after breakfast. Both multimatrix groups received 3 tablets of controlled-release mesalazine placebo after each meal. The Time-2.25 group received 4 tablets of multimatrix mesalazine placebo after breakfast and 3 tablets of controlled-release mesalazine 250 mg after each meal.

4. Efficacy and Safety Evaluation

During the study, patients were required to visit the study center at weeks 2, 4, and 8. At each visit, efficacy and safety were evaluated by the investigator. The mean scores of daily stool frequency and rectal bleeding for 3 days before each visit were calculated based on the patient diary in which patients recorded stool frequency and rectal bleeding status. Colonoscopy was performed at the start of the treatment period and at week 8 or at the time of discontinuation, and the sigmoidoscopy score was assessed by the same investigator, with reference to the atlas of mucosal apperarance.[5] The PGA score was evaluated based on the clinical symptoms and endoscopic findings at the beginning of the treatment period and at week 8 or at the time of discontinuation.

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Adverse events (AEs) and vital signs were evaluated at each visit. Body weight and clinical laboratory test results were evaluated every 4 weeks or at the time of discontinuation. AEs were summarized by preferred term using the Medical Dictionary for Regulatory Activities version 15.0.

5. Objective/Endpoints

The primary objective of the efficacy evaluation was to demonstrate the non-inferiority of Multimatrix-2.4 to Time-2.25 and the superiority of Multimatrix-4.8 to Time-2.25 based on the primary efficacy endpoint, which was the change in the UC-DAI score from baseline to the end of the treatment period. The primary safety objective was to evaluate the AEs associated with the 3 treatments during the treatment period.

The secondary efficacy endpoints were: remission (UC-DAI score ≤2 and rectal bleeding score=0 at the end of the treatment period), clinical remission (rectal bleeding score=0 and stool frequency score=0 at the end of the treatment period), endoscopic remission (sigmoidoscopy score=0 at the end of the treatment period), improvement (from baseline, a decrease of at least 2 points in the UC-DAI score at the end of the treatment period), and the change in the score of each variable of the UC-DAI (score at the end of the treatment period–score at baseline). The secondary safety endpoints were adverse drug reactions (side effects) in the treatment period.

6. Statistical Analysis

The full analysis set (FAS) consisted of enrolled patients who received the study drug at least once and received a minimum of 1 efficacy evaluation. The per protocol set (PPS) was the primary analysis set for the efficacy analysis and consisted of patients in the FAS that satisfied the inclusion criteria and did not fall under any exclusion criteria, did not receive prohibited concomitant drugs or therapy, and had a drug adherence of ≥75%. The safety analysis set consisted of patients that received the study drug at least once and underwent safety assessment.

For primary analysis of efficacy, analysis of covariance, using the baseline UC-DAI score as a covariate, was performed on the change in the UC-DAI score, and the two-sided 95% CI of the difference between Multimatrix-2.4 and Time-2.25 was calculated in the PPS to evaluate non-inferiority. The non-inferiority margin (Δ) was set at 1.0 with respect to the change in the UC-DAI score according to previous non-inferiority studies.[6,7] Only if non-inferiority was met, the superiority of Multimatrix-4.8 to Time-2.25 to be investigated in the FAS with a closed testing procedure. With remission, clinical remission, endoscopic remission, and improvement as secondary endpoints, the proportions of patients who achieved each endpoint in the Multimatrix-2.4 and Multimatrix-4.8 groups were compared to the proportions of patients that did so in the Time-2.25 group, along with the two-sided 95% CI of the difference. The changes in each variable of the UC-DAI were analyzed in the same manner as the primary endpoint. Subgroup analyses were performed to support the primary endpoint. For the safety endpoint, the incidence of AEs was compared among the treatment groups.

SAS version 9.2 (SAS Institute, Cary, NC, USA) was used for statistical analysis. Assuming that the difference in the UC-DAI score between Multimatrix-2.4 and the Time-2.25 was –0.5 and the difference in the UC-DAI score between Multimatrix-4.8 and Time-2.25 was –1.6 based on previous studies,[2,6] and the SD was 3.0 in each group, we set the number of patients needed to demonstrate the non-inferiority of Multimatrix-2.4 to Time-2.25 and the superiority of Multimatrix-4.8 to Time-2.25 at 76 patients per group with a one-sided type 1 error (α) of 2.5%, with a power of more than 80% and Δ of 1.0.

7. Ethical Considerations

The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki; the Ministerial Ordinance on Good Clinical Practice for Drugs; and other relevant laws, regulations, and standards. Written informed consent was obtained from each patient. Prior to commencement of the study, the study protocol, a sample case report form, the patient information sheet, and informed consent form were approved by the Institutional Review Board at each study center; the appropriateness of the conduct of the clinical trial was also approved.

RESULTS

1. Patient Disposition and Baseline Characteristics

Patient disposition is shown in Fig. 1. Consent was obtained from 283 patients, and 251 received study drugs (Multimatrix-2.4, 85; Multimatrix-4.8, 81; Time-2.25, 85). Thirty-two patients withdrew from the study before the randomization assignment. Of the 251 patients who received the study drug, 225 patients completed treatment, and 26 pa-

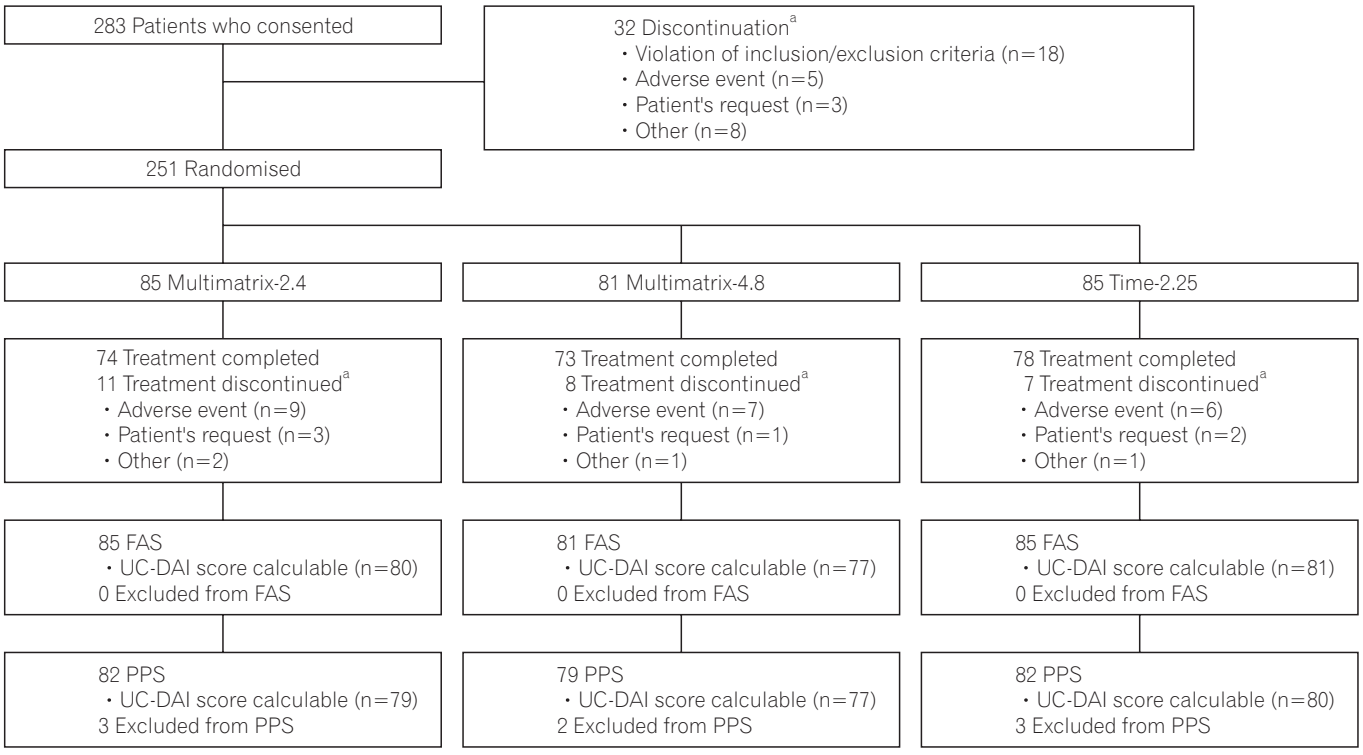

Fig. 1. Patients disposition. [a]Multiple selection is allowed as the reason for discontinuation. Multimatrix-2.4, multimatrix mesalazine 2.4 g/day once daily; Multimatrix-4.8, multimatrix mesalazine 4.8 g/day once daily; Time-2.25, time-dependent (controlled-release) mesalazine 2.25 g/day 3 times daily. FAS, full analysis set; UC-DAI, UC Disease Activity Index; PPS, per protocol set.

tients (Multimatrix-2.4, 11; Multimatrix-4.8, 8; Time-2.25, 7) discontinued during the treatment period. The main reason for discontinuation in all treatment groups was AEs (Multimatrix-2.4, 9; Multimatrix-4.8, 7; Time-2.25, 6). The disposition of the FAS and PPS is shown in Fig. 1. No patients were excluded from the FAS. Eight patients were excluded from the PPS (Multimatrix-2.4, 3; Multimatrix-4.8, 2; Time-2.25, 3). The most common reason for exclusion from the PPS was failure to meet inclusion/exclusion criteria. Thirteen patients in the FAS had a change in the UC-DAI score that was not calculable (Multimatrix-2.4, 5; Multimatrix-4.8, 4; Time-2.25, 4). Seven patients in the PPS had a change in the UC-DAI score was not calculable (Multimatrix-2.4, 3; Multimatrix-4.8, 2; Time-2.25, 2). The mean rates of drug adherence in the PPS were not less than 95% in all treatment groups. There were no intergroup differences in terms of patient background factors in the FAS (Table 1).

2. Efficacy

1) Primary Endpoint

In the PPS, the change in the UC-DAI score at the end of the treatment period (mean±SD) was –1.9±2.5 in the Multimatrix-2.4 group, –3.3±2.5 in the Multimatrix-4.8 group, and –2.4±2.8 in the Time-2.25 group. The difference in the mean change in the UC-DAI score (adjusted) between the Multimatrix-2.4 group and the Time-2.25 group was 0.3 (two-sided 95% CI, –0.5 to 1.1). The upper limit of the two-sided 95% CI of the difference between the treatment groups was not lower than the non-inferiority margin (1.0), indicating that non-inferiority was not met (Table 2). Under the closed testing procedure adopted in this study, since the non-inferiority of the Multimatrix-2.4 group to the Time-2.25 group was not demonstrated, no further attempts were made to show if Multimatrix-4.8 was superior to Time-2.25. In the FAS, the change in the UC-DAI score at the end of the treatment period (mean±SD) was –1.9±2.5 in the Multimatrix-2.4 group, –3.3±2.5 in the Multimatrix-4.8 group, and –2.4±2.8 in the Time-2.25 group. In the ad hoc analysis where multiplicity was not taken into consideration, the difference in the UC-DAI score (adjusted) between the Multimatrix-4.8 group and the Time-2.25 group in the FAS was –1.2 (two-sided 95% CI, –2.0 to –0.5), which was statistically significant (Table 2).

2) Secondary Endpoints

The proportions of patients who achieved remission, clini-

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Table 1 . Patient Demographics (FAS)

	Multimatrix-2.4 (n=85)	Multimatrix-4.8 (n=81)	Time-2.25 (n=85)	*P*-value
Sex				0.169[a]
Male	51 (60.0)	45 (55.6)	39 (45.9)	
Female	34 (40.0)	36 (44.4)	46 (54.1)	
Age (yr)	39.8±13.0	43.0±13.1	40.4±12.4	0.224[b]
Height (cm)	165.9±8.8	164.2±8.5	163.2±9.5	0.143[b]
Weight (kg)	62.1±12.8	60.1±10.5	60.7±13.6	0.569[b]
Disease course				0.928[b]
First attack	16 (18.8)	16 (19.8)	18 (21.2)	
Relapsing-remitting	69 (81.2)	65 (80.2)	67 (78.8)	
Extent of disease				0.256[b]
Proctitis	28 (32.9)	33 (40.7)	29 (34.1)	
Left-sided colitis	40 (47.1)	38 (46.9)	38 (44.7)	
Pancolitis	17 (20.0)	7 (8.6)	15 (17.6)	
Segmental colitis[c]	0	3 (3.7)	3 (3.5)	
UC-DAI score at baseline	6.4±1.8	6.2±1.6	6.7±1.7	0.256[b]
Prior treatment for UC in screening period				0.945[a]
No	14 (16.5)	12 (14.8)	14 (16.5)	
Yes	71 (83.5)	69 (85.2)	71 (83.5)	

Values are presented as number (%) or mean±SD.
[a]Chi-square test.
[b]ANOVA.
[c]Patients with right-sided inflammation in the skip lesion or rectal sparing, and with mucosal findings within at least the range from the rectal to sigmoid colon for UC Disease Activity Index (UC-DAI) scoring were enrolled.
FAS, full analysis set; Multimatrix-2.4, multimatrix mesalazine 2.4 g/day once daily; Multimatrix-4.8, multimatrix mesalazine 4.8 g/day once daily; Time-2.25, time-dependent (controlled-release) mesalazine 2.25 g/day 3 times daily.

Table 2. Change in UC-DAI Score (at End of Treatment)

	Multimatrix-2.4	Multimatrix-4.8	Time-2.25
Per protocol set			
No. of patients	79	77	80
Mean±SD	−1.9±2.5	−3.3±2.5	−2.4±2.8
Differences from Time-2.25 (95% CI)[a]	0.3 (−0.5 to 1.1)	−1.3 (−2.1 to −0.5)	-
P-value		0.001	
Full analysis set			
No. of patients	80	77	81
Mean±SD	−1.9±2.5	−3.3±2.5	−2.4±2.8
Differences from Time-2.25 (95% CI)[a]	0.3 (−0.5 to 1.1)	−1.2 (−2.0 to −0.5)	-
P-value		0.002	

Change in UC-DAI score=UC-DAI score at the end of treatment−UC-DAI score at baseline.
[a]Differences in the mean change in UC-DAI score adjusted for UC-DAI score at baseline between groups.
UC-DAI, UC Disease Activity Index; Multimatrix-2.4, multimatrix mesalazine 2.4 g/day once daily; Multimatrix-4.8, multimatrix mesalazine 4.8 g/day once daily; Time-2.25, time-dependent (controlled-release) mesalazine 2.25 g/day 3 times daily.

cal remission, endoscopic remission, and improvement are shown in Table 3. The proportions of patients who achieved each endpoint were similar between the Multimatrix-2.4 group and the Time-2.25, and a greater proportion of patients in the Multimatrix-4.8 group achieved each endpoint than in the Time-2.25 group. The change in the UC-DAI by variable is shown in Table 4. A decrease was observed in both the rectal bleeding score and the stool frequency score

Table 3. Remission, Clinical Remission, Endoscopic Remission and Improvement (FAS)

	Multimatrix-2.4	Multimatrix-4.8	Time-2.25
Remission			
Proportion of patients (%)	31.8 (27/85)	45.7 (37/81)	28.2 (24/85)
Differences from Time-2.25 (95% CI)	3.5 (−10.2 to 17.3)	17.4 (3.0 to 31.9)	-
Clinical Remission			
Proportion of patients (%)	31.8 (27/85)	38.3 (31/81)	20.0 (17/85)
Differences from Time-2.25 (95% CI)	11.8 (−1.3 to 24.8)	18.3 (4.7 to 31.8)	-
Endoscopic remission			
Proportion of patients (%)	10.6 (9/85)	19.8 (16/81)	14.1 (12/85)
Differences from Time-2.25 (95% CI)	−3.5 (−13.4 to 6.3)	5.6 (−5.8 to 17.0)	-
Improvement			
Proportion of patients (%)	54.1 (46/85)	77.8 (63/81)	57.6 (49/85)
Differences from Time-2.25 (95% CI)	−3.5 (−18.4 to 11.4)	20.1 (6.3 to 34.0)	-

Remission: UC Disease Activity Index (UC-DAI) ≤2 and rectal bleeding score=0; clinical remission: rectal bleeding score=0, stool frequency score=0; endoscopic remission: sigmoidoscopy score=0; improvement: decrease of ≥2 points from baseline in UC-DAI.
FAS, full analysis set; Multimatrix-2.4, multimatrix mesalazine 2.4 g/day once daily; Multimatrix-4.8, multimatrix mesalazine 4.8 g/day once daily; Time-2.25, time-dependent (controlled-release) mesalazine 2.25 g/day 3 times daily.

Table 4. Change in UC-DAI Score Variables (FAS)

	Multimatrix-2.4	Multimatrix-4.8	Time-2.25
Stool frequency score			
Week 2			
No. of patients	79	80	82
Mean±SD	−0.2±0.8	−0.3±0.8	−0.4±0.8
Difference between groups (95% CI)[a]	0.2 (−0.1 to 0.4)	0.0 (−0.2 to 0.2)	-
Week 4			
No. of patients	75	76	80
Mean±SD	−0.3±1.0	−0.4±0.9	−0.6±0.9
Difference between groups (95% CI)[a]	0.1 (−0.1 to 0.4)	−0.1 (−0.3 to 0.2)	-
Week 8			
No. of patients	71	73	77
Mean (SD)	−0.5±1.0	−0.6±1.0	−0.5±1.0
Difference between groups (95% CI)[a]	−0.1 (−0.3 to 0.2)	−0.3 (−0.6 to −0.1)	-
At the end of treatment			
No. of patients	83	81	83
Mean±SD	−0.3±1.0	−0.5±1.0	−0.5±1.0
Difference between groups (95% CI)[a]	0.1 (−0.2 to 0.3)	−0.2 (−0.5 to 0.0)	-

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Table 4. Continued

	Multimatrix-2.4	Multimatrix-4.8	Time-2.25
Rectal bleeding score			
Week 2			
No. of patients	79	80	82
Mean±SD	−0.4±0.7	−0.7±0.8	−0.6±0.8
Difference between groups (95% CI)[a]	0.2 (−0.1 to 0.4)	−0.1 (−0.4 to 0.1)	-
Week 4			
No. of patients	75	76	80
Mean±SD	−0.7±0.8	−0.9±0.8	−0.9±0.9
Difference between groups (95% CI)[a]	−0.1 (−0.1 to 0.4)	−0.1 (−0.3 to 0.1)	-
Week 8			
No. of patients	71	73	77
Mean±SD	−0.9±0.8	−1.2±0.8	−0.8±0.9
Difference between groups (95% CI)[a]	0.0 (−0.3 to 0.2)	−0.4 (−0.6 to −0.1)	-
At the end of treatment			
No. of patients	83	81	83
Mean±SD	−0.8±0.9	−1.1±0.8	−0.8±1.0
Difference between groups (95% CI)[a]	0.0 (−0.3 to 0.3)	−0.4 (−0.6 to −0.1)	-
Sigmoidoscopy score			
At the end of treatment			
No. of patients	82	77	82
Mean±SD	−0.4±0.7	−0.8±0.8	−0.5±0.8
Difference between groups (95% CI)[a]	0.1 (−0.1 to 0.3)	−0.2 (−0.5 to 0.0)	-
PGA score			
At the end of treatment			
No. of patients	80	77	81
Mean±SD	−0.3±0.7	−0.9±0.7	−0.5±0.7
Difference between groups (95% CI)[a]	0.2 (−0.1 to 0.4)	−0.4 (−0.6 to −0.2)	-

Change in each score=score at each evaluation point−score at baseline.
[a]Differences in mean change in scores adjusted for scores at baseline between groups (multimatrix mesalazine−time-dependent release mesalazine).
UC-DAI, UC Disease Activity Index; FAS, full analysis set; Multimatrix-2.4, multimatrix mesalazine 2.4 g/day once daily; Multimatrix-4.8, multimatrix mesalazine 4.8 g/day once daily; Time-2.25, time-dependent (controlled-release) mesalazine 2.25 g/day 3 times daily; PGA, physician's global assessment.

from week 2 in in all 3 treatment groups. The sigmoidoscopy score and the PGA score had also improved from baseline by the end of treatment. Generally, the results of the Multimatrix-2.4 group and the Time-2.25 group appeared to be similar, and the Multimatrix-4.8 group showed greater improvement compared with the other 2 groups for all secondary endpoints.

3) Subgroup Analysis

The results of subgroup analyses for the primary endpoint are shown in Table 5. Concerning the main UC categories (classification by disease course, extent of disease, UC-DAI score at baseline), the Multimatrix-4.8 group showed a trend towards greater improvement in the UC-DAI score than the Time-2.25 group in all subgroups (Table 5).

3. Safety

The incidence of AEs (proportion of patients who experienced at least 1 AE) during the treatment period was 50.6%

Table 5. Change in UC-DAI Score by Subgroup (FAS)

	Multimatrix-2.4	Multimatrix-4.8	Time-2.25
Disease course			
First attack			
No. of patients	16	15	18
Mean±SD	−1.6±2.1	−3.2±3.0	−2.9±2.9
Differences between groups (95% CI)[a]	1.4 (−0.4 to 3.2)	−0.3 (−2.2 to 1.6)	-
Relapse-remitting			
No. of patients	64	62	63
Mean±SD	−2.0±2.6	−3.4±2.3	−2.2±2.8
Differences between groups (95% CI)[a]	0.0 (−0.9 to 0.9)	−1.5 (−2.4 to −0.7)	-
Extent of disease			
Proctitis			
No. of patients	26	33	28
Mean±SD	−2.0±2.0	−2.6±2.3	−2.1±2.6
Differences between groups (95% CI)[a]	0.0 (−1.3 to 1.2)	−0.6 (−1.9 to 0.6)	-
Left-sided colitis			
No. of patients	37	36	36
Mean±SD	−1.7±2.8	−3.9±2.4	−2.2±2.7
Differences between groups (95% CI)[a]	0.2 (−1.0 to 1.5)	−2.2 (−3.2 to −1.1)	-
Pancolitis			
No. of patients	17	5	14
Mean±SD	−2.2±2.8	−3.0±3.9	−2.4±3.1
Differences between groups (95% CI)[a]	0.4 (−1.8 to 2.6)	−0.4 (−4.1 to 3.4)	-
Segmental colitis			
No. of patients	0	3	3
Mean±SD	-	−4.7±0.6	−6.0±1.7
Differences between groups (95% CI)[a]	-	−0.1 (−0.7 to 0.6)	-
UC-DAI score at baseline			
4–5			
No. of patients	32	27	21
Mean±SD	−1.4±2.2	−2.3±1.5	−1.5±2.0
Differences between groups (95% CI)[a]	0.0 (−1.2 to 1.2)	−0.9 (−1.9 to 0.2)	-
6–10			
No. of patients	48	50	59
Mean±SD	−2.2±2.7	−3.9±2.7	−2.7±3.0
Differences between groups (95% CI)[a]	0.5 (−0.5 to 1.6)	−1.5 (−2.5 to −0.4)	-

(43/85 patients) in the Multimatrix-2.4 group, 50.6% (41/81 patients) in the Multimatrix-4.8 group, and 50.6% (43/85 patients) in the Time-2.25 group (Table 6). The most common AEs (more than 5% incidence in any treatment group) were nasopharyngitis, increase in N-acetyl-beta-D-glucosaminidase, and aggravation of UC. The incidence of these AEs in individual treatment groups is shown in Table 6. The incidence of adverse drug reactions (side effects) during the treatment period was 24.7% (21/85) in the Multimatrix-2.4 group, 27.2% (22/81) in the Multimatrix-4.8 group, and 18.8%

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Table 5. Continued

	Multimatrix-2.4	Multimatrix-4.8	Time-2.25
Prior treatment for UC in screening period			
No			
No. of patients	14	12	13
Mean±SD	−2.8±2.3	−4.3±2.2	−3.1±2.6
Differences between groups (95% CI)[a]	0.0 (−1.7 to 1.7)	−1.0 (−2.8 to 0.7)	-
Yes			
No. of patients	66	65	68
Mean±SD	−1.7±2.6	−3.2±2.5	−2.2±2.8
Differences between groups (95% CI)[a]	0.4 (−0.5 to 1.3)	−1.3 (−2.1 to −0.4)	-

Change in UC-DAI score=UC-DAI score at the end of treatment− UC-DAI score at baseline
[a]Differences in mean change in UC-DAI score adjusted for the baseline values between groups (multimatrix mesalazine−time-dependent release mesalazine).
UC-DAI, UC Disease Activity Index; FAS, full analysis set; Multimatrix-2.4, multimatrix mesalazine 2.4 g/day once daily; Multimatrix-4.8, multimatrix mesalazine 4.8 g/day once daily; Time-2.25, time-dependent (controlled-release) mesalazine 2.25 g/day 3 times daily.

Table 6. Incidence of Adverse Events

Event	Multimatrix-2.4 (n=85) No. (%)	Multimatrix-4.8 (n=81) No. (%)	Time-2.25 (n=85) No. (%)
Total	43 (50.6)	41 (50.6)	43 (50.6)
Nasopharyngitis	8 (9.4)	9 (11.1)	20 (23.5)
β-N-acetyl-D-glucosaminidase increased	6 (7.1)	6 (7.4)	6 (7.1)
Headache	3 (3.5)	4 (4.9)	1 (1.2)
Blood bilirubin increased	2 (2.4)	4 (4.9)	1 (1.2)
Aggravation of UC	6 (7.1)	3 (3.7)	4 (4.7)
Blood urine present	1 (1.2)	3 (3.7)	1 (1.2)
White blood cell count increased	1 (1.2)	3 (3.7)	1 (1.2)
CRP increased	2 (2.4)	2 (2.5)	1 (1.2)
Anaemia	1 (1.2)	2 (2.5)	1 (1.2)
Glucose urine present	1 (1.2)	2 (2.5)	1 (1.2)
Weight decreased	1 (1.2)	2 (2.5)	0
Blood ALP increased	0	2 (2.5)	1 (1.2)
Protein urine present	2 (2.4)	1 (1.2)	2 (2.4)
Abdominal distension	2 (2.4)	1 (1.2)	0
Abdominal discomfort	0	1 (1.2)	2 (2.4)
Dizziness postural	0	1 (1.2)	2 (2.4)
Amylase increased	2 (2.4)	0	1 (1.2)
Oral herpes	2 (2.4)	0	1 (1.2)
Alopecia	2 (2.4)	0	0
Haematochezia	2 (2.4)	0	0
Influenza	0	0	2 (2.4)
Seasonal allergy	0	0	2 (2.4)

Adverse events reported by at least 2% of patients in any treatment group during the treatment period are listed.
Multimatrix-2.4, multimatrix mesalazine 2.4 g/day once daily; Multimatrix-4.8, multimatrix mesalazine 4.8 g/day once daily; Time-2.25, time-dependent (controlled-release) mesalazine 2.25 g/day 3 times daily.

(16/85) in the Time-2.25 group.

There were no deaths during the course of the study. Concerning serious AEs during the treatment period, aggravation of UC occurred in 1 patient in the Multimatrix-2.4 group, while aggravation of UC and headache occurred in 1 patient each in the Multimatrix-4.8 group. All of these events were adverse drug reactions. No serious AEs occurred in the Time-2.25 group. During the follow-up period, pericarditis occurred in 1 patient in the Multimatrix-4.8 group. No causal relationship was found between the events and the study drugs.

DISCUSSION

The primary objective of this study was to demonstrate the non-inferiority of Multimatrix-2.4 to Time-2.25, but this was not achieved. It is possible that the failure to demonstrate the non-inferiority could be attributed to the fact that the sample size was determined under the assumption that the difference in change in UC-DAI score between Multimatrix-2.4 and Time-2.25 was –0.5, although actual the difference between 2 groups was found to be 0.3. We estimated the difference between Multimatrix-2.4 to Time-2.25 in the present study based on the results of the 2 previous studies. One was a placebo-controlled study which compared multimatrix mesalamine 2.4 g/day, 4.8 g/day, placebo, and pH-dependent release mesalazine 2.4 g/day as a reference arm, in which the difference in the change in UC-DAI score between multimatrix mesalamine 2.4 g/day and pH-dependent release mesalazine 2.4 g/day was 0.24.[2] The other was a study which compared pH-dependent release mesalazine 2.4 g/day, 3.6 g/day, time-dependent release mesalamine 2.25 g/day, and placebo, in which the difference in the change in UC-DAI score between pH-dependent release mesalazine 2.4 g/day and time-dependent release mesalamine 2.25 g/day was 0.2.6 Based on these results, we estimated the difference between Multimatrix-2.4 and Time-2.25 to be 0.5, but this resulted in the efficacy of Multimatrix-2.4 being overestimated. However, considering the results for the secondary endpoints, Multimatrix-2.4 appeared to have comparable efficacy to that of Time-2.25. This finding is supported by a previous study in which the efficacy of multimatrix mesalazine 2.4 g/day QD was comparable to a similar dose of Asacol tablets 2.4 g/day TID.[2]

In the present study, the mean change in UC-DAI score and two-sided 95% CI in the FAS was –3.3 (–3.9 to –2.8) in the Multimatrix-4.8 group and –1.9 (–2.5 to –1.3) in the Multimatrix-2.4 group (Fig. 2), indicating that multimatrix mesalazine 4.8 g/day is more effective than 2.4 g/day. However, in the previous placebo-controlled studies of multimatrix mesalazine, no dose-response relationship was detected between the 2 doses (2.4 g/day and 4.8 g/day).[1,2] In these studies, patients were permitted to use oral mesalazine at a dose of 2.0 g/day or less if they were receiving this therapy prior to screening. In another report, which assessed the efficacy of multimatrix mesalazine in various patient subgroups using patients pooled from these 2 placebo-controlled studies, among the patients transferring directly from prior low-dose oral 5-aminosalicylic acid (approximately 50% in each treatment group), multimatrix 4.8 g/day was significantly more effective than placebo while the efficacy of multimatrix 2.4 g/day did not reach significance. In contrast, patients who had not received 5-aminosalicylic acid therapy for at least 5 days prior to receiving the study medication responded to both 2.4 g/day and 4.8 g/day.[8] In the present study, the patients were allowed to use oral mesalazine up to a dose of 2.4 g/day during the screening period, and approximately 80% patients were directly transferred to each treatment group from their prior regimen (Table 1). Therefore, the dose-response relationship for the 2 doses (2.4 g/day and 4.8 g/day) of multimatrix mesalazine observed in the present study agrees with the results of the pooled subgroup analysis in the 2 previous placebo-controlled studies.

In the previous study of pH-dependent release controlled mesalamine (ASCEND I, ASCEND II, and ASCEND III), a

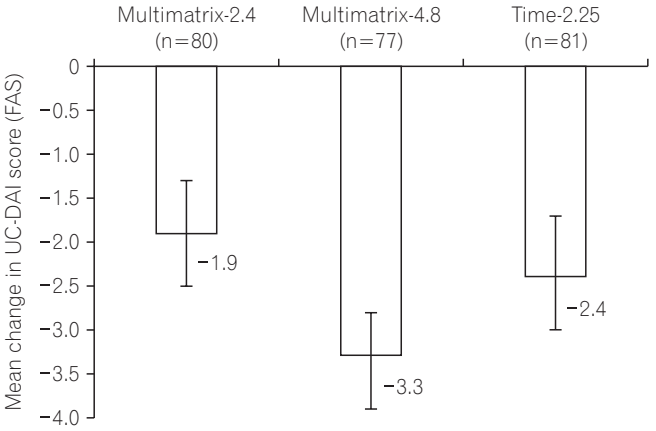

Fig. 2. Change in UC Disease Activity Index (UC-DAI) score. The mean change in UC-DAI score and two-sided 95% CI in the full analysis set (FAS) was –3.3 (–3.9 to –2.8) in the Multimatrix-4.8 group, –1.9 (–2.5 to –1.3) in the Multimatrix-2.4 group, and –2.4 (–3.0 to –1.7) in Time-2.25 group. Error bars indicate 95% CI. Multimatrix-4.8, multimatrix mesalazine 4.8 g/day once daily; Multimatrix-2.4, multimatrix mesalazine 2.4 g/day once daily; Time-2.25, time-dependent (controlled-release) mesalazine 2.25 g/day 3 times daily.

higher dose of mesalamine (4.8 g/day) was observed to be of benefit in moderately active UC.[9-11] In the present study, the change in UC-DAI in the Multimatrix-4.8 group was greater than in the other low-dose treatment groups not only in moderately active UC (UC-DAI score at baseline: 6–10) but also in almost all subgroups, including disease type (first attack, relapsing), disease region (proctitis, left-sided colitis, pancolitis) and mildly active (UC-DAI score at baseline: 4–5) with no associated safety concerns. This suggests that, in general, multimatrix 4.8 g/day is preferable to multimatrix 2.4 g/day for induction treatment in various disease states of mildly to moderately active UC.

In conclusion, the present study showed comparable efficacy between multimatrix mesalazine 2.4 g/day and controlled release mesalazine 2.25 g/day, although non-inferiority was not demonstrated. However, this was the first study to show that multimatrix mesalazine 4.8 g/day is more effective than 2.4 g/day. Moreover, this study also showed that the clinical benefit of multimatrix mesalazine 4.8 g/day in various disease conditions in mildly to moderately active UC with no associated concerns about safety.

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CONFLICT OF INTEREST

H.O. has received consulting, grant, or lecture fees from Mochida Pharmaceutical Co., Ltd., JIMRO, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Kyorin Pharmaceutical, Otsuka Pharmaceutical, Astellas Pharma, Eisai, Zeria Pharmaceutical, AbbVie G.K., EA Pharma, and Boston Scientific Japan K.K. S.M. and A.H. are employees of Mochida Pharmaceutical Co., Ltd. T.H. is editor-in-chief of *Intestinal Research* and has received consulting, grant, lecture, or manuscript preparation fees from Mochida Pharmaceutical Co., Ltd., AbbVie G.K., EA Pharma, AstraZeneca K.K., JIMRO, Mitsubishi Tanabe Pharma, Eisai, Takeda Pharmaceutical, Zeria Pharmaceutical, Janssen Pharmaceutical K.K., Astellas Pharma, and Otsuka Pharmaceutical.

Mochida Pharmaceutical Co., Ltd. provided funding to support the provision of multimatrix mesalazine (Shire US Inc.) and time-dependent controlled-release mesalazine (Kyorin Pharmaceutical Co., Ltd.).

AUTHOR CONTRIBUTION

All the authors participated in drafting of the manuscript or its critical revision. All the authors had full access to all data related to the study and assume final responsibility for the decision to submit the paper for publication. Study design, study supervision, analysis and interpretation of data, principal investigator (H.O.); patient recruitment, data collection (T.Y.); study concept and design, data analysis and interpretation (S.M.); study concept and design, statistical analysis and interpretation (A.H); study design, study supervision, analysis and interpretation of data, principal investigator (T.H).

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See "Comparison of efficacy of once daily multimatrix mesalazine 2.4 g/day and 4.8 g/day with other 5-aminosalicylic acid preparation in active ulcerative colitis: a randomized, double-blind study" on page 255.

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