Report on the Deliberation Results

June 6, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Lialda Tablets 600 mg
	Lialda Tablets 1200 mg
Non-proprietary Name	Mesalazine (JAN*)
Applicant	Mochida Pharmaceutical Co., Ltd.
Date of Application	July 22, 2024

Results of Deliberation

In its meeting held on June 4, 2025, the First Committee on New Drugs concluded that the application for Lialda Tablets 600 mg and the partial change application for Lialda Tablets 1200 mg may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

Lialda Tablets 600 mg is not classified as a biological product or a specified biological product. The drug product is not classified as a poisonous drug or a powerful drug. The re-examination period for Lialda Tablets 600 mg and 1200 mg is 4 years.

** Japanese Accepted Name (modified INN)*

Review Report

May 16, 2025
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	(a) Lialda Tablets 600 mg (b) Lialda Tablets 1200 mg
Non-proprietary Name	Mesalazine
Applicant	Mochida Pharmaceutical Co., Ltd.
Date of Application	July 22, 2024
Dosage Form/Strength	Tablets each containing 600 mg or 1,200 mg of mesalazine
Application Classification	(a) Prescription drug, (6) Drug with a new dosage, (8-2) Drug in an additional dosage form (not in the reexamination period) (b) Prescription drug, (6) Drug with a new dosage
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of ulcerative colitis (non-severe cases), and that the product has acceptable safety in view of its benefits (see Attachment). The product is not classified as a biological product or a specified biological product. The drug product is not classified as a poisonous drug or a powerful drug.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below.

Indication

Ulcerative colitis (non-severe cases)

(No change)

Dosage and Administration

The usual adult dosage is 2,400 mg of mesalazine administered orally once daily after a meal. During the active phase, the usual adult dosage is 4,800 mg of mesalazine administered orally once daily after a meal. The dose may be reduced as necessary according to the patient's condition.

The usual dosage for children weighing >23 kg is 40 mg/kg of mesalazine administered orally once daily after a meal, which however should not exceed 2,400 mg. During the active phase, the usual dosage for children weighing >23 kg is 80 mg/kg of mesalazine administered orally once daily after a meal, which however should not exceed 4,800 mg and may be reduced as necessary according to the patient's condition.

(Underline denotes additions.)

Attachment

Review Report (1)

April 8, 2025

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Lialda Tablets 600 mg Lialda Tablets 1200 mg
Non-proprietary Name	Mesalazine
Applicant	Mochida Pharmaceutical Co., Ltd.
Date of Application	July 22, 2024
Dosage Form/Strength	Tablets each containing 600 mg or 1,200 mg of mesalazine

Proposed Indication

Ulcerative colitis (non-severe cases)

(No change)

Proposed Dosage and Administration

The usual adult dosage is 2,400 mg of mesalazine administered orally once daily after a meal. During the active phase, the usual adult dosage is 4,800 mg of mesalazine administered orally once daily after a meal. The dose may be reduced as necessary according to the patient's condition.

The usual dosage for children weighing >23 kg is 40 mg/kg of mesalazine administered orally once daily after a meal. During the active phase, the usual dosage for children weighing >23 kg is 80 mg/kg of mesalazine administered orally once daily after a meal. The dose may be reduced as necessary according to the patient's condition.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) that is characterized by repeated remission and relapse. Active UC is accompanied by symptoms such as diarrhea, hematochezia, abdominal pain, and pyrexia. In Japan, UC is a designated intractable disease (No. 97, Ministry of Health, Labour and Welfare [MHLW] Ministerial Announcement No. 393, dated October 21, 2014), and treatment for UC (drug therapy, surgical treatment, etc.) is chosen according to the severity and other conditions. The first-line therapy for remission induction and maintenance in patients with mild to moderate UC is 5-aminosalicylate acid (5-ASA) ("Diagnostic Criteria and Treatment Guidelines for Ulcerative Colitis and Crohn's Disease, FY 2023 Revised Edition, dated March 31, 2024" FY 2023 Report "Research on Intractable Inflammatory Bowel Disease" [Hisamatsu group], Research on Policy Planning and Evaluation of Rare and Intractable Diseases, funded by the Health and Labour Sciences Research Grants) (the treatment guidelines).

Mesalazine (5-ASA) has an anti-inflammatory effect on local lesions. However, the administered mesalazine is largely absorbed in the small intestine, and only a small amount of the drug reaches the large intestine where the UC lesions are located. Therefore, various pharmaceutical products have been developed to date. Oral products of mesalazine approved in Japan include Pentasa Tablets/Granules (time-dependent modified release formulation), Asacol Tablets (pH-dependent modified release formulation), and Lialda Tablets 1200 mg (enteric film-coated tablet formulation prepared from the extended-release tablet core of mesalazine). Lialda Tablets 1200 mg deliver mesalazine to the large intestine and allow its sustained release. In Japan, the 1,200 mg formulation was approved for the indication of "ulcerative colitis (non-severe cases)" in September 2016.

The applicant conducted Japanese studies in pediatric UC patients, and has recently filed an application for partial changes of the approved "Lialda Tablets 1200 mg" and an application for the marketing approval of "Lialda Tablets 600 mg," confirming that the studies have demonstrated the efficacy and safety of mesalazine.

As of March 2025, the 1,200 mg formulation of mesalazine has been approved in 35 countries or regions including the United States and Europe, with the approved indication of pediatric UC in 15 countries or regions including the United States (UC patients weighing ≥24 kg) and Europe (UC patients weighing >50 kg and aged ≥10 years). However, the 600 mg formulation of mesalazine has not been approved in any countries or regions.

2. Quality and Outline of the Review Conducted by PMDA

Although this is an application for an additional dosage, data relating to quality have been submitted for the 600 mg formulation of the product, for which application was also submitted for approval as a drug in an additional dosage form. As a result of its review on quality as a drug in an additional dosage form, PMDA has concluded that there were no problems and that the quality of the drug product was controlled in an appropriate manner.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although this is an application for an additional dosage, no additional study results have been submitted because non-clinical pharmacology has already been evaluated at the time of the approval review of the approved product containing mesalazine.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although this is an application for an additional dosage, no additional study results have been submitted because the "data on non-clinical pharmacokinetic studies" have already been evaluated at the time of the approval review of the approved product containing mesalazine.

5. Toxicology and Outline of the Review Conducted by PMDA

Although this is an application for an additional dosage, no additional study results have been submitted because toxicity following oral administration has already been evaluated at the time of the approval review of the approved product containing mesalazine.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The Japanese phase III studies (Studies MD090111P21 and MD090111P22) submitted as the pivotal data for the present application used 300 mg tablets (patients weighing ≥18 kg and ≤23 kg), 600 mg tablets (patients weighing >23 kg and ≤50 kg), and 1,200 mg tablets (patients weighing >50 kg and ≤90 kg). The 600 mg tablets are the proposed commercial formulation, whereas the 1,200 mg tablets have already been approved.

The plasma concentrations of unchanged mesalazine and N-acetyl-5-aminosalicylic acid (Ac-5-ASA), a major metabolite of mesalazine, were measured using liquid chromatography with tandem mass spectrometry (LC/MS/MS), with a lower limit of quantitation of 2.0 or 5.0 ng/mL.[1)]

6.2 Clinical pharmacology

6.2.1 Foreign phase I study in UC patients (CTD 5.3.3.2.1: Study SPD476-112 [October 2010 to June 2013])

A randomized, open-label study was conducted at 12 foreign study sites to investigate the pharmacokinetics and safety following multiple oral doses of mesalazine in non-Japanese UC patients aged 5 to <17 years (target sample size, 45 subjects).

The dosage regimen was as follows: Mesalazine 30, 60, or 100 mg/kg was administered as multiple oral doses once daily for 7 days.[2)]

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1) The lower limit of quantitation for the plasma concentration of both unchanged mesalazine and Ac-5-ASA was 2.0 ng/mL in the Japanese phase III studies (Studies P21 and P22), and 5.0 ng/mL in other studies.

2) Each dose was orally administered as a combination of the 300 mg, 600 mg, and 1,200 mg tablets. Mesalazine was orally administered at a dose of 60 or 100 mg/kg in patients weighing ≥18 kg and <25 kg, 30, 60, or 100 mg/kg in patients weighing ≥25 kg and <50 kg, and 30 or 60 mg/kg in patients weighing ≥50 kg and <82 kg.

All of the 52 subjects who received mesalazine were included in the safety analysis population and the pharmacokinetic analysis population.

Table 1 shows the plasma pharmacokinetic parameters of unchanged mesalazine and Ac-5-ASA following multiple oral doses of mesalazine for 7 days. The C_{max} and $AUC_{0\text{-}24h}$ of unchanged mesalazine and Ac-5-ASA increased in a generally dose-proportional manner between 30 mg/kg and 60 mg/kg, but the increase between 60 mg/kg and 100 mg/kg was less than dose-proportional.

Table 1. Plasma pharmacokinetic parameters of unchanged mesalazine and Ac-5-ASA on Day 7 following multiple oral doses of mesalazine in non-Japanese pediatric UC patients

Analyte	Mesalazine dose	N	C_{max} (ng/mL)	t_{max} [a)] (h)	AUC_{tau} (ng·h/mL)
Unchanged mesalazine	30 mg/kg	21	1,884 ± 1,018	6.00 (0.00, 24.0)	21,411 ± 11,081
	60 mg/kg	22	3,825 ± 1,979	8.98 (0.00, 24.0)	46,173 ± 22,864
	100 mg/kg	9	4,314 ± 2,602	1.98 (0.00, 24.0)	49,213 ± 17,664
Ac-5-ASA	30 mg/kg	21	2,396 ± 1,217	9.00 (0.00, 24.0)	30,942 ± 13,743
	60 mg/kg	22	4,113 ± 1,641	7.48 (0.00, 24.0)	58,119 ± 22,729
	100 mg/kg	9	4,968 ± 2,911	1.98 (0.00, 24.0)	63,067 ± 21,752

Mean ± standard deviation

a) Median (minimum, maximum)

The safety results were as follows: Adverse events were observed in 19.0% (4 of 21) of subjects in the mesalazine 30 mg/kg group, 18.2% (4 of 22) of subjects in the mesalazine 60 mg/kg group, and 22.2% (2 of 9) of subjects in the mesalazine 100 mg/kg group. Adverse drug reactions were observed in 4.8% (1 of 21) of subjects in the mesalazine 30 mg/kg group and 4.5% (1 of 22) of subjects in the mesalazine 60 mg/kg group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.2 Foreign phase I study in healthy adults (CTD 5.3.1.2.2: Study SHP476-122 [April to June 2017])

A randomized, open-label, 2-group 4-period crossover study was conducted at 1 foreign study site to investigate the pharmacokinetics and safety following a single oral dose of mesalazine in non-Japanese healthy adults (target sample size, 36 subjects; 18 subjects per group).

The dosage regimen was as follows: In each period, mesalazine 1,200 mg (600 mg tablet × 2 or 1,200 mg tablet × 1) was orally administered after a meal.[3)] A 10- to 14-day washout period was included between periods.

All of the 36 subjects who received mesalazine were included in the safety analysis population and the pharmacokinetic analysis population.

Table 2 shows the plasma pharmacokinetic parameters of unchanged mesalazine following a single oral dose of mesalazine.

[3)] Subjects were randomized to 1 of 2 treatment groups (Group 1 and Group 2). Over 4 treatment periods, subjects in Group 1 received treatment using 600 mg, 1,200 mg, 600 mg, and 1,200 mg tablets in this order, and subjects in Group 2 received treatment using 1,200 mg, 600 mg, 1,200 mg, and 600 mg tablets in this order.

Table 2. Plasma pharmacokinetic parameters of unchanged mesalazine following a single oral dose of mesalazine in non-Japanese healthy adults

Formulation	N[a)]	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)
600 mg tablet × 2	71	669 ± 794	13.7 ± 8.3[b)]	4,522 ± 3,141
1,200 mg tablet × 1	70	687 ± 788	14.2 ± 8.3[c)]	4,621 ± 3,346

Mean ± standard deviation

a) In each treatment group, each formulation was administered twice to the same participants. One participant in Group 1 withdrew during Period 1.

b) 70 subjects; c) 67 subjects.

The safety results are as follows: Adverse events were observed in 16.7% (6 of 36) of subjects in the mesalazine 600 mg tablet treatment period and 20.0% (7 of 35) of subjects in the mesalazine 1,200 mg tablet treatment period. All of the observed events were assessed as adverse drug reactions. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.3 Japanese phase III study (CTD 5.3.5.2.1: Study MD090111P21 [January 2018 to [redacted] 20[redacted]])

An uncontrolled, open-label study was conducted to evaluate the efficacy and safety of mesalazine in patients with mild to moderate active UC, aged <17 years. The plasma concentrations of unchanged mesalazine and Ac-5-ASA following mesalazine administration were investigated in the study. For a study outline and the efficacy and safety results, see Section 7.1.

The dosage regimen was as follows: Mesalazine 80 mg/kg equivalent[4)] was administered as multiple oral doses once daily after breakfast.

Table 3 shows the pharmacokinetic results (plasma concentrations of unchanged mesalazine and Ac-5-ASA) at the start of the run-in period, at Weeks 4 and 8 of the treatment period, and at the end of the treatment period.

Table 3. Plasma concentrations of unchanged mesalazine and Ac-5-ASA following multiple oral doses of mesalazine in UC patients (ng/mL)[a)]

Analyte	At the start of the run-in period[b)]	Week 4	Week 8	At the end of the treatment period[c)]
Unchanged mesalazine	1,182 ± 1,908 (26)	1,968 ± 1,417 (19)	2,402 ± 2,894 (19)	1,825 ± 2,650 (26)
Ac-5-ASA	1,338 ± 1,735 (26)	2,263 ± 1,410 (19)	2,614 ± 2,100 (19)	2,109 ± 2,033 (26)

Mean ± standard deviation (N)

a) The post-dose time points for plasma concentration measurement were not standardized.

b) Since 18 of the 26 subjects received prior therapy for UC containing mesalazine as the active ingredient, the plasma concentrations of unchanged mesalazine and Ac-5-ASA before the start of mesalazine treatment in this study were measured. The plasma concentrations of unchanged mesalazine and Ac-5-ASA (mean ± standard deviation) before the start of mesalazine treatment in the 18 subjects were 1,707 ± 2,098 and 1,933 ± 1,792 ng/mL, respectively.

c) Including the time of discontinuation of mesalazine treatment.

4) According to the body weight category determined based on body weight at the secondary enrollment, mesalazine was orally administered once daily at a dose of 1,800 mg (300 mg tablet × 6) in patients weighing ≥18 kg and ≤23 kg, 2,400 mg (600 mg tablet × 4) in patients weighing >23 kg and ≤35 kg, 3,600 mg (600 mg tablet × 6) in patients weighing >35 kg and ≤50 kg, and 4,800 mg (1,200 mg tablet × 4) in patients weighing >50 kg and ≤90 kg. No changes to the dose, the formulation used, or the number of tablets were to be made throughout the treatment period.

6.2.4 Japanese phase III study (CTD 5.3.5.2.2: Study MD090111P22 [March 2018 to [redacted] 20[redacted]])

An uncontrolled, open-label study was conducted to evaluate the efficacy and safety of mesalazine in UC patients in remission, aged <17 years. The plasma concentrations of unchanged mesalazine and Ac-5-ASA following mesalazine administration were investigated in the study. For a study outline and the efficacy and safety results, see Section 7.2.

Multiple doses of Mesalazine 40 mg/kg equivalent[5)] were administered orally once daily after breakfast.

Table 4 shows the pharmacokinetic results (plasma concentrations of unchanged mesalazine and Ac-5-ASA) at the start of the run-in period, at Weeks 4, 24, and 48 of the treatment period, and at the end of the treatment period.

Table 4. Plasma concentrations of unchanged mesalazine and Ac-5-ASA following multiple oral doses of mesalazine in UC patients (ng/mL)[a)]

Analyte	At the start of the run-in period[b)]	Week 4	Week 24	Week 48	At the end of the treatment period[c)]
Unchanged mesalazine	757 ± 1,604 (23)	1,716 ± 2,335 (22)	852 ± 779 (18)	797 ± 1,435 (15)	960 ± 1,553 (23)
Ac-5-ASA	1,350 ± 1,558 (23)	2,146 ± 2,217 (22)	1,244 ± 887 (18)	1,329 ± 1,616 (15)	1,409 ± 1,521 (23)

Mean ± standard deviation (N)

a) The post-dose time points for plasma concentration measurement were not standardized.
b) All of the 23 subjects had received prior therapy containing mesalazine as the active ingredient since ≥2 weeks before enrollment in this study, and the plasma concentrations of unchanged mesalazine and Ac-5-ASA before the start of mesalazine treatment in the study were measured.
c) Including the time of discontinuation of mesalazine treatment.

6.2.5 Foreign phase III study (CTD 5.3.5.1.1: Study SPD476-319 [December 2014 to November 2018])

A randomized, double-blind, parallel-group study was conducted at 50 foreign study sites to evaluate the efficacy and safety of mesalazine in non-Japanese patients with mild to moderate active UC, aged 5 to <17 years. The plasma concentrations of unchanged mesalazine and Ac-5-ASA following mesalazine administration were investigated in the study.

This study consisted of a double-blind acute (DBA) period, a double-blind maintenance (DBM) period, and an open-label acute (OLA) period. Participants were enrolled in the DBA or DBM period, and those who showed a clinical response in the DBA period were switched to the DBM period. Participants in the DBA period who did not show a clinical response or who discontinued the treatment at or after Week 2 and were assessed to have no response to the study drug were switched to the OLA period. Participants who showed a clinical response in the 8-week OLA period were switched to the DBM period.

5) According to the body weight category determined based on body weight at the secondary enrollment, mesalazine was orally administered once daily at a dose of 900 mg (300 mg tablet × 3) in patients weighing ≥18 kg and ≤23 kg, 1,200 mg (600 mg tablet × 2) in patients weighing >23 kg and ≤35 kg, 1,800 mg (600 mg tablet × 3) in patients weighing >35 kg and ≤50 kg, and 2,400 mg (1,200 mg tablet × 2) in patients weighing >50 kg and ≤90 kg. No changes to the dose, the formulation used, or the number of tablets were to be made throughout the treatment period.

The dosage regimen was as follows: In the DBA and DBM periods, mesalazine 40 mg/kg equivalent[6] or 80 mg/kg equivalent[7] was administered as multiple oral doses once daily. In the OLA period, mesalazine 80 mg/kg equivalent[7] was administered in the same regimen as above.

Table 5 shows the pharmacokinetic results (plasma concentrations of unchanged mesalazine and Ac-5-ASA) at Week 8 of the DBA period, Week 26 of the DBM period, and Week 8 of the OLA period.

Table 5. Plasma concentrations of unchanged mesalazine and Ac-5-ASA following multiple oral doses of mesalazine in UC patients (ng/mL)[a]

Analyte	Treatment group	Week 8 of the DBA period	Week 26 of the DBM period	Week 8 of the OLA period
Unchanged mesalazine	40 mg/kg equivalent	718 ± 795 (12)	1,446 ± 1,744 (25)	-
	80 mg/kg equivalent	2,543 ± 2,962 (15)	2,739 ± 2,448 (29)	1,013 ± 1,419 (10)
Ac-5-ASA	40 mg/kg equivalent	1,191 ± 1,081 (12)	1,980 ± 2,198 (25)	-
	80 mg/kg equivalent	2,580 ± 1,836 (15)	2,964 ± 2,365 (29)	1,213 ± 1,389 (10)

Mean ± standard deviation (N); -, not applicable.
a) The post-dose time points for plasma concentration measurement were not standardized.

6.R Outline of the review conducted by PMDA

The applicant's explanation about the pharmacokinetics of mesalazine in Japanese[8] UC patients aged <17 years:

Figure 1 and Figure 2 show the distribution of plasma concentrations of unchanged mesalazine and Ac-5-ASA following mesalazine administration at a low dose (40 mg/kg equivalent[9]) or a high dose (80 mg/kg equivalent[10]) in the Japanese phase III studies (Studies P21 and P22) and the foreign phase III study (Study SPD476-319).[11] There were no clear differences in plasma concentration between the Japanese[8] and non-Japanese UC patients aged <17 years.

[6] Mesalazine was orally administered once daily at a dose of 900 mg in patients weighing ≥18 kg and ≤23 kg, 1,200 mg in patients weighing >23 kg and ≤35 kg, 1,800 mg in patients weighing >35 kg and ≤50 kg, and 2,400 mg in patients weighing >50 kg and ≤90 kg.
[7] Mesalazine was orally administered once daily at a dose of 1,800 mg in patients weighing ≥18 kg and ≤23 kg, 2,400 mg in patients weighing >23 kg and ≤35 kg, 3,600 mg in patients weighing >35 kg and ≤50 kg, and 4,800 mg in patients weighing >50 kg and ≤90 kg.
[8] Participants enrolled at Japanese study sites.
[9] Mean dose: 44.2 mg/kg in Study P22 and approximately 43 mg/kg in Study SPD476-319.
[10] Mean dose: 85.7 mg/kg in Study P21 and approximately 85 mg/kg in Study SPD476-319.
[11] Excluding the data of plasma concentrations below the lower limit of quantitation or measured at unknown post-dose time points.

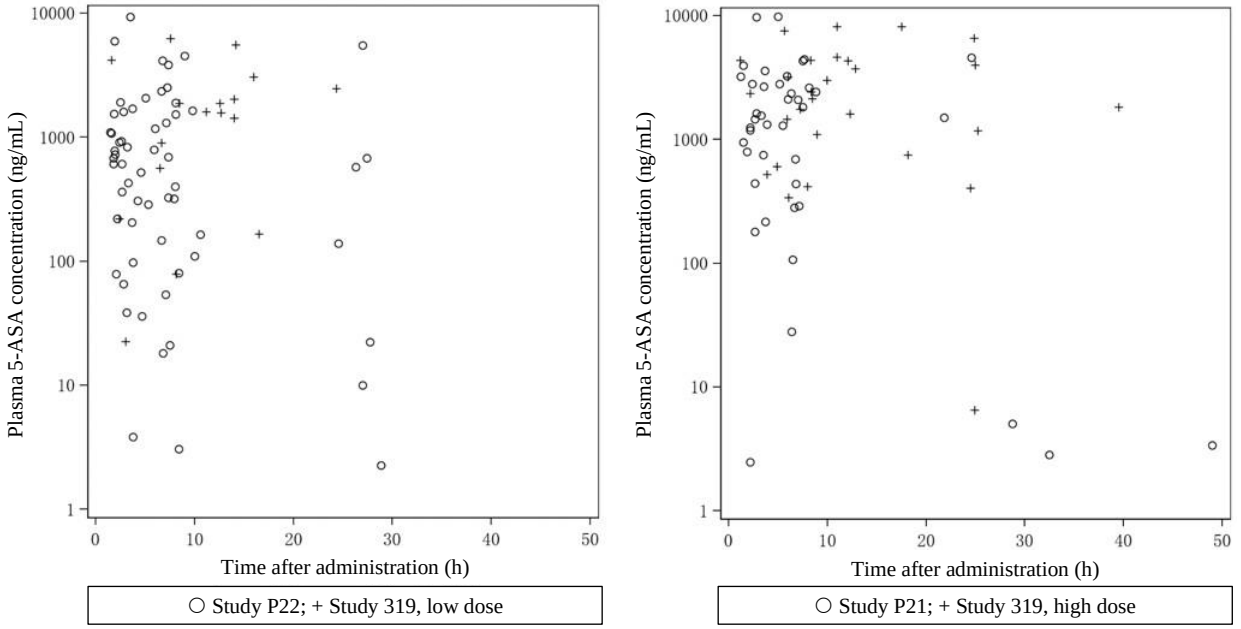

Figure 1. Plasma concentrations of unchanged mesalazine in the Japanese phase III studies (Studies P21 and P22) and the foreign phase III study (Study SPD476-319) (left, low dose; right, high dose)

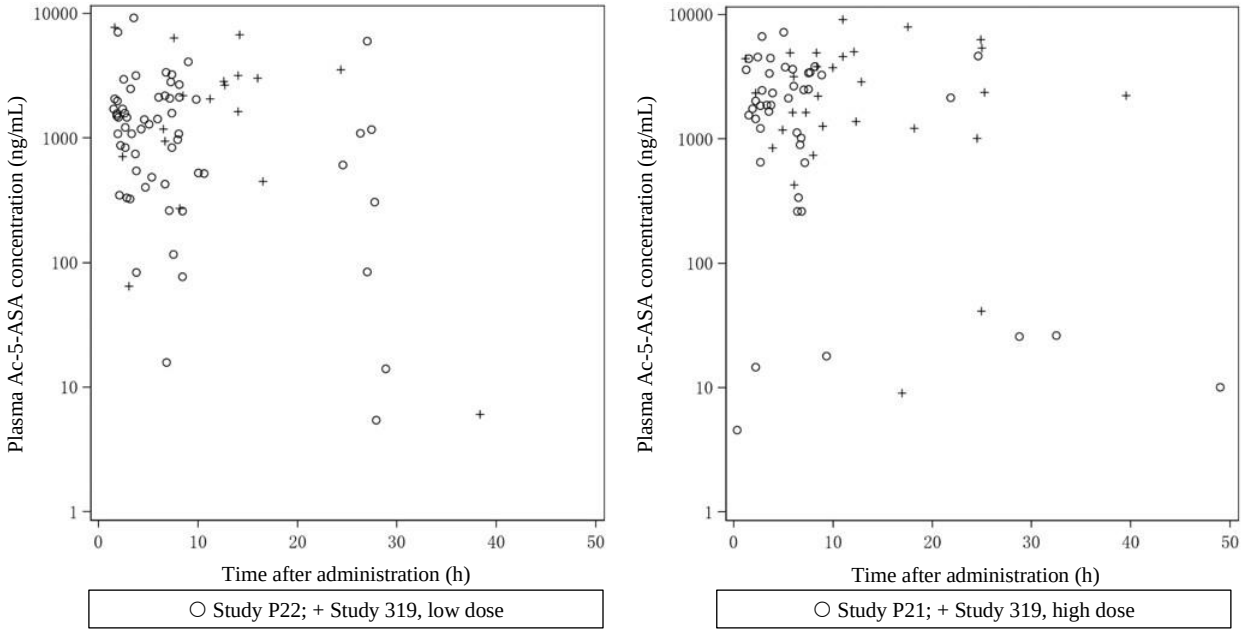

Figure 2. Plasma concentrations of Ac-5-ASA in the Japanese phase III studies (Studies P21 and P22) and the foreign phase III study (Study SPD476-319) (left, low dose; right, high dose)

Figure 3 and Figure 4 show the distribution of plasma concentrations of unchanged mesalazine and Ac-5-ASA following mesalazine administration at a low dose (dose in the remission phase, 40 mg/kg equivalent in children and 2,400 mg in adults) or a high dose (dose in the active phase, 80 mg/kg equivalent in children and 4,800 mg in adults) in the Japanese phase III studies (Studies P21 and P22) and the Japanese phase I study in Japanese[8)] healthy adults (Study MD090111N11).[11)] There were no clear differences in plasma concentration between the Japanese[8)] UC patients aged <17 years and healthy adults.

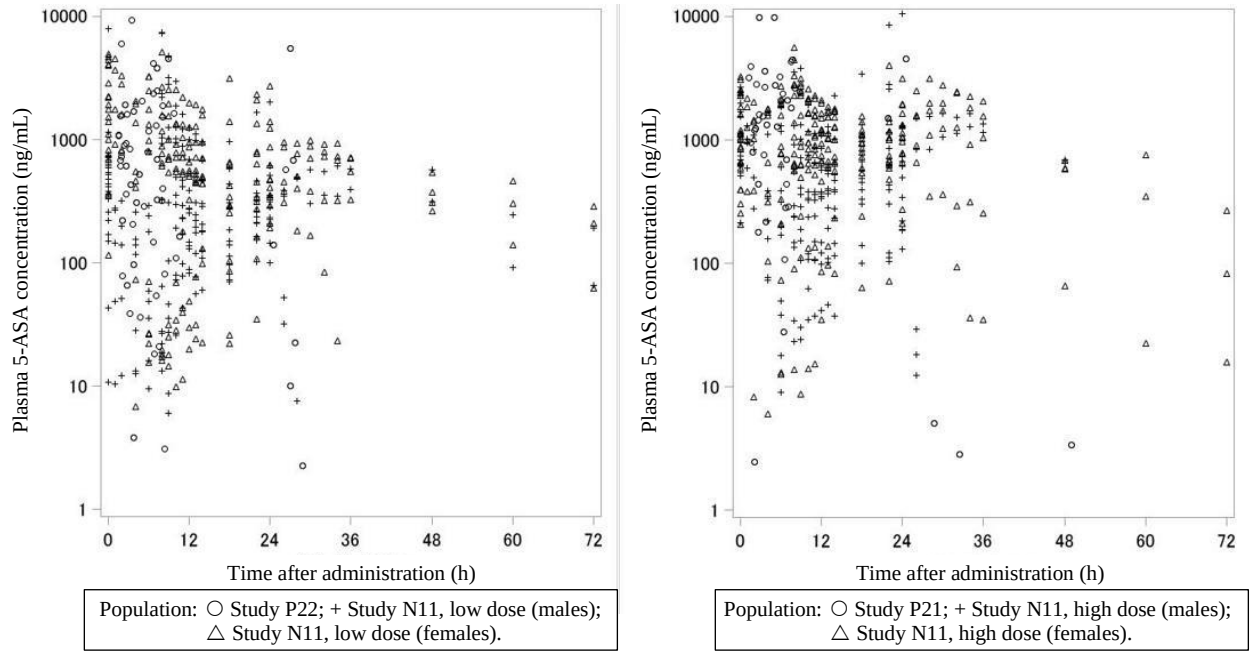

Figure 3. Plasma concentrations of unchanged mesalazine in the Japanese phase III studies (Studies P21 and P22) and the Japanese phase I study (Study MD090111N11) (left, low dose; right, high dose)

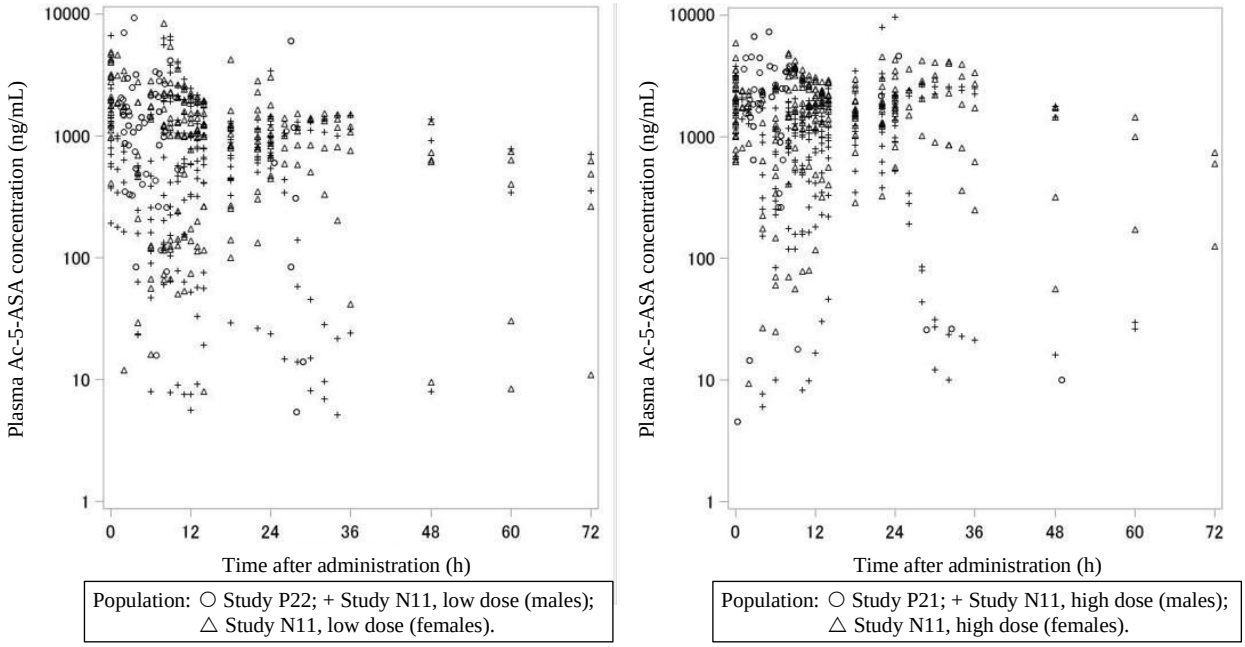

Figure 4. Plasma concentrations of Ac-5-ASA in the Japanese phase III studies (Studies P21 and P22) and the Japanese phase I study (Study MD090111N11) (left, low dose; right, high dose)

In view of the above, when mesalazine is administered at the clinical dose to Japanese UC patients aged <17 years, a higher exposure to unchanged mesalazine and Ac-5-ASA than the exposure following mesalazine administration at the clinical dose in Japanese adult UC patients or non-Japanese UC patients is unlikely to raise a safety issue in clinical practice.

On the basis of the study results submitted, PMDA has concluded that exposure to unchanged mesalazine and Ac-5-ASA is unlikely to increase with the clinical use of mesalazine in Japanese[8)] UC patients aged <17 years, compared with the exposure in adult UC patients. The dosage and administration of mesalazine in UC patients is discussed in 7.R.4.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from 3 studies shown in Table 6.

Table 6. Efficacy and safety evaluation data

Region	Phase	Study identifier	Population	Design	N	Outline of dosage regimen	Main efficacy endpoint
Japanese	III	MD090111P21	Patients with mild to moderate active UC, aged <17 years	Open-label Uncontrolled	27	Mesalazine 80 mg/kg equivalent was orally administered once daily for 8 weeks. The formulation used and the number of tablets per administration based on the body weight category were as follows: ≥18 kg and ≤23 kg: 300 mg tablet × 6 >23 kg and ≤35 kg: 600 mg tablet × 4 >35 kg and ≤50 kg: 600 mg tablet × 6 >50 kg and ≤90 kg: 1,200 mg tablet × 4	Clinical remission
Japanese	III	MD090111P22	Patients with UC in remission, aged <17 years	Open-label Uncontrolled	23	Mesalazine 40 mg/kg equivalent was orally administered once daily for 48 weeks. The formulation used and the number of tablets per administration based on the body weight category were as follows: ≥18 kg and ≤23 kg: 300 mg tablet × 3 >23 kg and ≤35 kg: 600 mg tablet × 2 >35 kg and ≤50 kg: 600 mg tablet × 3 >50 kg and ≤90 kg: 1,200 mg tablet × 2	Absence of hematochezia
Japanese	III	MD090111U21	Patients with UC in remission, aged ≥16 years	Open-label Uncontrolled	23	Evaluation period 1: Two mesalazine 1,200 mg tablets were orally administered once daily for 8 weeks. Evaluation period 2: Four mesalazine 600 mg tablets were orally administered once daily for 8 weeks.	Absence of hematochezia

Table 7 and Table 8 show the ulcerative colitis disease activity index (UC-DAI) and pediatric ulcerative colitis activity index (PUCAI) scores, respectively, that were used as indicators for efficacy evaluation in the clinical studies. Table 9 shows the response evaluation criteria for efficacy endpoints.

Table 7. UC-DAI score

Total score of the 4 items shown below. * Partial UC-DAI score is a sum of the stool frequency, rectal bleeding, and PGA scores.	
Stool frequency[a)] (Stool frequency score)	0: Normal[b)] 1: 1-2 stools >Normal 2: 3-4 stools >Normal 3: ≥5 stools >Normal
Rectal bleeding[a) c)] (Rectal bleeding score)	0: None 1: Streaks of blood in stool 2: Obvious blood in stool 3: Mostly blood in stool
Sigmoidoscopy (Sigmoidoscopy score)[d)]	0: Normal 1: Mild (erythema, reduced vascular pattern, mild friability) 2: Moderate (marked erythema, lack of vascular pattern, friability, erosion) 3: Severe (spontaneous bleeding, ulceration)
Physician's global assessment[e)] (PGA score)	0: Normal 1: Mild 2: Moderate 3: Severe

a) The investigator scored the condition on each day for 3 days before each visit based on the patient diary and used the mean score of the 3 days for the assessment.
b) Normal indicates the healthy state or maintained remission state of the participant.
c) Assessed using the most severe stool condition of the day.
d) Assessed by the investigator based on endoscopic findings. Assessment was carried out at the site with the most intense inflammatory image between the rectum to sigmoid colon at enrollment and at the same site at the end of the mesalazine treatment. If colonoscopy could not be performed due to marked worsening of symptoms at the end of the mesalazine treatment, the score was regarded as 3.
e) Assessed by the investigator based on clinical symptoms and endoscopic findings of the participant.

Table 8. PUCAI score[a)]

Total score of the 6 items shown below.	
Abdominal pain	0: No pain 5: Pain can be ignored 10: Pain cannot be ignored
Rectal bleeding	0: None 10: Small amount only, in ≤50% of stools 20: Small amount with most stools 30: Large amount (≥50% of the stool content)
Stool consistency of most stools	0: Formed 5: Partially formed 10: Completely unformed
Stool frequency per 24 hours	0: 0-2 stools 5: 3-5 stools 10: 6-8 stools 15: >8 stools
Nocturnal stools	0: No 10: Yes
Activity level	0: No limitation of activity 5: Occasional limitation of activity 10: Severely restricted activity

a) The investigator scored the condition on each day for 2 days before each visit based on history taking using the patient diary as a reference and used the mean score of the 2 days for the assessment.

Table 9. Efficacy endpoint and response evaluation criteria

Indicator	Efficacy endpoint	Criteria
UC-DAI score	Clinical remission	Both rectal bleeding score and stool frequency score = 0
	Absence of hematochezia	Rectal bleeding score = 0 at all assessment time points during the treatment period
	Duration of absence of hematochezia	Time to a rectal bleeding score of ≥1 during the treatment period
	Remission	UC-DAI score ≤2, and rectal bleeding score = 0
	Endoscopic remission	Sigmoidoscopy score = 0
	Improvement	≥2-point improvement in UC-DAI score from the start of treatment
	Relapse	UC-DAI score ≥3, and rectal bleeding score ≥1
	Change in score	(UC-DAI score at the assessment time point) - (UC-DAI score at the start of treatment)
	Change in the score of each component of UC-DAI	(Score of each component at the assessment time point) - (Score of each component at the start of treatment)
PUCAI score	Remission	PUCAI score <10
	Partial remission	PUCAI score ≥10, and ≥20-point improvement in PUCAI score from the start of treatment

7.1 Japanese phase III study (CTD 5.3.5.2.1: Study MD090111P21 [January 2018 to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted at 29 Japanese study sites[12)] to investigate the efficacy and safety of mesalazine in patients with mild to moderate active UC, aged <17 years (Table 10) (target sample size, 26 subjects[13)]).

Table 10. Main inclusion/exclusion criteria

Main inclusion criteria

- UC patients aged <17 years and weighing ≥18 kg and ≤90 kg.
- Patients with a UC-DAI score ≥3 and ≤8 and with scores of each item based on UC-DAI (sigmoidoscopy score ≥1, rectal bleeding score ≥1, and PGA score ≤2) at enrollment (Table 7).

Main exclusion criteria

- Patients with drug hypersensitivity to mesalazine-containing products or salicylic acid drugs.
- Patients with the chronic continuous or acute fulminating type of UC.
- Patients with a past history of relapse while using oral mesalazine or salazosulfapyridine at doses exceeding the dose planned in this study.
- Patients who had used oral mesalazine or salazosulfapyridine at doses exceeding the dose planned in this study within 2 weeks before enrollment.
- Patients who had used corticosteroids (oral products, suppositories, drugs for the treatment of hemorrhoidal diseases, or injections) within 4 weeks before enrollment.
- Patients who had received blood cell component removal therapy within 4 weeks before enrollment.
- Patients who had used immunomodulators (oral products or injections) within 12 weeks before enrollment.
- Patients who had used biologics for UC treatment in the past.
- Patients with a past history of colectomy (excluding appendectomy).
- Patients complicated by renal or hepatic disorder of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2.
- Patients with serious complications (CTCAE Grade ≥3 blood system, respiratory system, digestive system, cardiovascular system, neuropsychiatric system, or metabolic/electrolyte disease or hypersensitivity, etc.).
- Patients complicated by malignant tumor.

The dosage regimen was as follows: Mesalazine 80 mg/kg equivalent, by body weight as shown in Table 11, was orally administered once daily for 8 weeks.

12) Participants were enrolled at 17 sites.

13) According to the results of Japanese and foreign clinical studies of mesalazine in adult patients with active UC (Studies MD090111U31, U33, SPD476-301, and SPD476-302), the achievement rate of clinical remission with mesalazine 4,800 mg/day was 32.6% to 41.2%. Therefore, the achievement rate of clinical remission, the primary endpoint of this study, was assumed to be 40%. Based on this assumption, the target sample size was set as 26 subjects, which allows estimation of the effect with an accuracy of approximately ±20%. The target number of subjects by body weight category was set in reference to the actual results of the foreign clinical study of mesalazine in pediatric UC patients (Study SPD476-112) and foreign clinical studies of other oral 5-ASA products in pediatric UC patients, as follows: 1 or 2 subjects of ≥18 kg and ≤23 kg, 4 or 5 subjects of >23 kg and ≤35 kg, 7 to 9 subjects of >35 kg and ≤50 kg, and 10 to 13 subjects of >50 kg and ≤90 kg.

Table 11. Dose by body weight (formulation and the number of tablets)

Body weight	Dose (mg/day)	Formulation and number of tablets
≥18 kg and ≤23 kg	1,800	300 mg tablet × 6
>23 kg and ≤35 kg	2,400	600 mg tablet × 4
>35 kg and ≤50 kg	3,600	600 mg tablet × 6
>50 kg and ≤90 kg	4,800	1,200 mg tablet × 4

All of the 27 enrolled subjects received mesalazine and were included in the full analysis set (FAS) and the safety analysis set. The FAS was used as the primary efficacy analysis population. Of the subjects in the FAS, excluding a total of 7 subjects consisting of 7 with "duration of study treatment <18 days," 2 with "study drug compliance rate <75%," and 1 with "deviation from inclusion/exclusion criteria" (some subjects had >1 reason), the remaining 20 subjects were included in the per protocol set (PPS). Mesalazine treatment was discontinued in 8 subjects, and the reasons for discontinuation were "adverse events" (3 subjects), "deterioration of the primary disease" (2 subjects), and "deviation from inclusion/exclusion criteria," "inadequate response," and "difficulty to take the study drug" (1 subject each).

Table 12 shows the efficacy results in terms of the primary endpoint, "achievement rate of clinical remission based on the UC-DAI score (both rectal bleeding score and stool frequency score = 0) at Week 8" (FAS). The lower bound of the 2-sided 95% confidence interval (CI) was above the predetermined threshold of 10%.

Table 12. Results of the primary endpoint (Study P21, FAS)

N	Achievement rate of clinical remission based on the UC-DAI score at Week 8 [% (n)][a)]	2-sided 95% CI[b)]	
		Lower bound	Upper bound
27	25.9 (7)	11.1	46.3

a) Missing data of the UC-DAI score at Week 8 were imputed using the last observation carried forward (LOCF) method.
b) Calculated using the Clopper-Pearson method.

The safety results were as follows: The incidence of adverse events was 66.7% (18 of 27 subjects), and adverse events observed in ≥2 subjects were nasopharyngitis, colitis ulcerative, and constipation in 3 subjects each, and anaemia, upper respiratory tract inflammation, eczema, drug intolerance, and product residue present in 2 subjects each. The incidence of adverse drug reactions was 18.5% (5 of 27 subjects; drug intolerance and product residue present in 2 subjects each, and constipation and *β-N*-acetyl-D-glucosaminidase increased in 1 subject each [1 subject developed >1 event]). There were no deaths. The incidence of serious adverse events was 11.1% (3 of 27 subjects; herpangina, anaemia, colitis ulcerative, and drug intolerance in 1 subject each [1 subject developed >1 event]). Drug intolerance in 1 subject was assessed as a serious adverse drug reaction, but the event resolved. The incidence of adverse events leading to treatment discontinuation was 18.5% (5 of 27 subjects; drug intolerance and colitis ulcerative in 2 subjects each, and herpangina in 1 subject). Drug intolerance in 2 subjects was assessed as an adverse drug reaction leading to treatment discontinuation, but the event resolved in both subjects.

7.2 Japanese phase III study (CTD 5.3.5.2.2: Study MD090111P22 [March 2018 to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted at 30 Japanese study sites[14] to investigate the efficacy and safety of mesalazine in UC patients in remission, aged <17 years (Table 13) (target sample size, 26 subjects[15]).

Table 13. Main inclusion/exclusion criteria

Main inclusion criteria • UC patients aged <17 years and weighing ≥18 kg and ≤90 kg. • Patients with a UC-DAI score ≤2 and with a rectal bleeding score based on UC-DAI of 0 at enrollment (Table 7). **Main exclusion criteria** • Patients with drug hypersensitivity to mesalazine-containing products or salicylic acid drugs. • Patients who had used oral mesalazine or salazosulfapyridine at doses exceeding the dose planned in this study within 2 weeks before enrollment. • Patients who had used topical mesalazine or salazosulfapyridine within 4 weeks before enrollment. • Patients who had used corticosteroids (oral products, suppositories, drugs for the treatment of hemorrhoidal diseases, or injections) within 4 weeks before enrollment. • Patients who had received blood cell component removal therapy within 4 weeks before enrollment. • Patients who had used immunomodulators (oral products or injections) within 12 weeks before enrollment. • Patients who had used biologics for UC treatment in the past. • Patients with a past history of colectomy (excluding appendectomy). • Patients complicated by moderate or severe (CTCAE Grade ≥2) renal or hepatic disorder. • Patients with serious complications (CTCAE Grade ≥3 blood system, respiratory system, digestive system, cardiovascular system, neuropsychiatric system, or metabolic/electrolyte disease or hypersensitivity, etc.). • Patients complicated by malignant tumor.

The dosage regimen was as follows: Mesalazine 40 mg/kg equivalent, by body weight as shown in Table 14, was orally administered once daily for 48 weeks.

Table 14. Dose by body weight (formulation and the number of tablets)

Body weight of the participant	Dose (mg/day)	Formulation and number of tablets
≥18 kg and ≤23 kg	900	300 mg tablet × 3
>23 kg and ≤35 kg	1,200	600 mg tablet × 2
>35 kg and ≤50 kg	1,800	600 mg tablet × 3
>50 kg and ≤90 kg	2,400	1,200 mg tablet × 2

All of the 23 enrolled subjects received mesalazine and were included in the FAS and the safety analysis set. The FAS was used as the primary efficacy analysis population. Of the subjects in the FAS, excluding 3 subjects who used prohibited treatments, the remaining 20 subjects were included in the PPS. Mesalazine treatment was discontinued in 7 subjects, and the reasons for discontinuation were “deterioration of the primary disease” (5 subjects), and “adverse events” and “participant’s personal reason” (1 subject each).

Table 15 shows the efficacy results in terms of the primary endpoint, “achievement rate of absence of hematochezia based on the UC-DAI score (rectal bleeding score = 0 at all assessment time points up to Week

[14] Participants were enrolled at 16 sites.

[15] In the Japanese clinical study of mesalazine in adult UC patients in remission (Study U32), the rate of absence of hematochezia with mesalazine 2,400 mg/day was 84.8%. In the foreign clinical studies of mesalazine in adult UC patients in remission (Studies SPD476-304 and SPD476-306), the achievement rate of clinical remission with mesalazine 2,400 mg/day was 69.7% and 68.0%, respectively. Therefore, the rate of absence of hematochezia, the primary endpoint of this study, was assumed to be 80%. Based on this assumption, the target sample size was set as 26 subjects, which allows estimation of the effect with an accuracy of approximately ±20%. The target number of subjects by body weight category was set in reference to the actual results of the foreign clinical study of mesalazine in pediatric UC patients (Study SPD476-112) and foreign clinical studies of other oral 5-ASA products in pediatric UC patients, as follows: 1 or 2 subjects of ≥18 kg and ≤23 kg, 4 or 5 subjects of >23 kg and ≤35 kg, 7 to 9 subjects of >35 kg and ≤50 kg, and 10 to 13 subjects of >50 kg and ≤90 kg.

48 of the treatment period)" (FAS). The lower bound of the 2-sided 95% CI was above the predetermined threshold of 50%.

Table 15. Results of the primary endpoint (Study P22, FAS)

N	Achievement rate of absence of hematochezia based on the UC-DAI score [% (n)][a)]	2-sided 95% CI[b)]	
		Lower bound	Upper bound
23	73.9 (17)	51.6	89.8

a) Missing data of the rectal bleeding score based on the UC-DAI score were not imputed. If all of the rectal bleeding scores observed by Week 48 of the treatment period were 0, the endpoint was assessed to have been achieved.
b) Calculated using the Clopper-Pearson method.

The safety results were as follows: The incidence of adverse events was 87.0% (20 of 23 subjects), and adverse events observed in ≥2 subjects were nasopharyngitis in 9 subjects, influenza, upper respiratory tract inflammation, colitis ulcerative, and vomiting in 5 subjects each, headache and diarrhoea in 3 subjects each, and varicella, abdominal pain, dental caries, and ligament sprain in 2 subjects each. The incidence of adverse drug reactions was 13.0% (3 of 23 subjects; otitis externa, headache, ear discomfort, cough, oropharyngeal discomfort, abdominal pain, constipation, and diarrhoea in 1 subject each [some subjects developed >1 event]). There were no deaths. The incidence of serious adverse events was 8.7% (2 of 23 subjects; cerebral haemorrhage, brain herniation, and colitis ulcerative in 1 subject each [1 subject developed >1 event]). There were no serious adverse drug reactions. The incidence of adverse events leading to treatment discontinuation was 26.1% (6 of 23 subjects; colitis ulcerative in 5 subjects, and cerebral haemorrhage and brain herniation in 1 subject each [1 subject developed >1 event]). There were no adverse drug reactions leading to treatment discontinuation.

7.3 Japanese phase III study (CTD 5.3.5.2.3: Study MD090111U21 [April 2023 to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted at 11 Japanese study sites to investigate the efficacy and safety of formulation switch from mesalazine 1,200 mg tablets to 600 mg tablets in UC patients in remission, aged ≥16 years (Table 16) (target sample size, 23 subjects[16)]).

16) In reference to the results of the mesalazine 2,400 mg/day group in the Japanese clinical study of mesalazine in adult UC patients in remission (Study U32), the rates of absence of hematochezia in evaluation periods 1 and 2 were assumed to be 95% for both, and then the number of discontinued subjects in evaluation period 1 was assumed to be 1. When the target sample size in evaluation period 1 was set as 23 subjects based on the above-mentioned assumptions, the probability of meeting the criterion for determining that there was not a clear difference in efficacy between the 1,200 mg and 600 mg tablets (the difference in the rate of absence of hematochezia between evaluation period 1 and evaluation period 2 is within ±12%) would be 92.1%, which could secure a 90% probability of meeting the criterion.

Table 16. Main inclusion/exclusion criteria

Main inclusion criteria
- UC patients aged ≥16 years.
- Patients with a partial UC-DAI score ≤1 and with a rectal bleeding score based on UC-DAI of 0 at enrollment (Table 7).
- Patients who had used oral mesalazine or salazosulfapyridine at mesalazine-converted doses of ≤2,400 mg/day for ≥12 weeks.
- Patients who had maintained the absence of hematochezia attributable to UC for ≥12 weeks in the judgment of the investigator.

Main exclusion criteria
- Patients with drug hypersensitivity to mesalazine-containing products or salicylic acid drugs.
- Patients who had used topical mesalazine or salazosulfapyridine within 4 weeks before enrollment.
- Patients who had used corticosteroids (oral products, suppositories, drugs for the treatment of hemorrhoidal diseases, or injections) within 4 weeks before enrollment.
- Patients who had received blood cell component removal therapy within 4 weeks before enrollment.
- Patients who had used immunomodulators (oral products or injections), Janus kinase inhibitors, or oral α4 integrin inhibitors within 12 weeks before enrollment.
- Patients who had used biologics within 24 weeks before enrollment.

- Patients with a past history of colectomy (excluding appendectomy).
- Patients complicated by moderate or severe (CTCAE Grade ≥2) renal or hepatic disorder.
- Patients with serious complications (CTCAE Grade ≥3 blood system, respiratory system, digestive system, cardiovascular system, neuropsychiatric system, or metabolic/electrolyte disease or hypersensitivity, etc.).
- Patients complicated by malignant tumor.

This study consisted of evaluation period 1 (8 weeks) and evaluation period 2 (8 weeks). The dosage regimen was as follows: Mesalazine (1,200 mg tablet × 2 in evaluation period 1 and 600 mg tablet × 4 in evaluation period 2) was orally administered once daily.

Of 24 enrolled subjects, 23 subjects who received mesalazine completed evaluation periods 1 and 2 and were included in the FAS and the safety analysis set in each evaluation period. The FAS was used as the primary efficacy analysis population. Mesalazine treatment was discontinued in 1 subject, and the reason for discontinuation was "difficulty to take the study drug" (before the start of the study treatment).

Table 17 shows the efficacy results in terms of the primary endpoint, "achievement rate of absence of hematochezia based on the UC-DAI score (rectal bleeding score = 0 at all assessment time points in evaluation period 1 or evaluation period 2)" (FAS). The difference in the achievement rate of absence of hematochezia based on the UC-DAI score between evaluation period 1 and evaluation period 2 was within a range of ±12%, which was the predetermined efficacy criterion.[17)]

Table 17. Results of the primary endpoint (Study U21, FAS)

Time of evaluation	N	Achievement rate of absence of hematochezia based on UC-DAI [% (n)]	2-sided 95% CI[a)]		Difference in the achievement rate of absence of hematochezia based on UC-DAI (Evaluation period 2) ― (Evaluation period 1)
			Lower bound	Upper bound	
Evaluation period 1	23	100.0 (23)	85.2	100	0.0
Evaluation period 2	23	100.0 (23)	85.2	100	

a) Calculated using the Clopper-Pearson method.

The safety results were as follows: The incidence of adverse events was 30.4% (7 of 23 subjects) in evaluation period 1 and 43.5% (10 of 23 subjects) in evaluation period 2. No adverse events were observed in ≥2 subjects in evaluation period 1, but such adverse events were observed in evaluation period 2, namely, COVID-19 in 3 subjects and large intestine polyp in 2 subjects. The incidence of adverse drug reactions was 0% (0 of 23

17) Based on the predetermined criterion, if the difference in the rate of absence of hematochezia between evaluation period 1 and evaluation period 2 was within ±12%, it was determined that the efficacy of mesalazine is not clearly different between the 1,200 mg and 600 mg tablets.

subjects) in evaluation period 1 and 4.3% (1 of 23 subjects; haematuria) in evaluation period 2. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

On the basis of the data submitted and the reviews in Sections 7.R.1.1 and 7.R.1.2, PMDA has concluded that clinically meaningful efficacy of mesalazine was demonstrated in pediatric patients with mild to moderate UC in the active or remission phase enrolled in Studies P21 and P22.

7.R.1.1 Active phase

7.R.1.1.1 Design of Study P21

The applicant's explanation about the design of the Japanese phase III study in pediatric patients with mild to moderate active UC (Study P21):

Study P21 was designed as an open-label, uncontrolled study for the following reasons:

(1) Since the number of pediatric UC patients in Japan is limited, it is difficult to conduct an active-controlled study of mesalazine with a similar sample size to that of Study MD090111U33 on mesalazine in adult active UC (Study U33) (Review Report of "Lialda Tablets 1200 mg," dated August 17, 2016).

(2) In the treatment of patients with mild to moderate active UC, the first-line therapy is 5-ASA products for both adults and children ("Diagnostic Criteria and Treatment Guidelines for Ulcerative Colitis and Crohn's Disease, FY2016 Revised Edition, dated January 25, 2017" FY2016 Report "Research on Intractable Inflammatory Bowel Disease" [Suzuki group], Research on Policy Planning and Evaluation of Rare and Intractable Diseases, a project funded by the Health and Labour Sciences Research Grants; at the time of study planning), and Pentasa, an extended release formulation of mesalazine, and other drugs are used in children. It is therefore difficult to conduct a study using placebo as the comparator.

The study population was set in reference to Study U33 and "Guidelines for the Management of Ulcerative Colitis in Japan - Developed through Integration of Evidence and Consensus among Experts - (January 2006)" (First Edition), as follows: patients with a UC-DAI score corresponding to mild to moderate disease (≥3 and ≤8, with a PGA score ≤2) and evidence of active disease (sigmoidoscopy score ≥1, and rectal bleeding score ≥1), aged <17 years.

The target dose of mesalazine was set as 80 mg/kg/day in reference to the recommended dose of oral 5-ASA products for remission induction therapy, namely, 50 to 100 mg/kg/day in the Japanese pediatric UC guidelines ("Guidelines on the Treatment of Pediatric Ulcerative Colitis, revised in January 2016" FY2016 Report "Research on Intractable Inflammatory Bowel Disease" [Suzuki group], Research on Policy Planning and Evaluation of Rare and Intractable Diseases, a project funded by the Health and Labour Sciences Research Grants) (the pediatric treatment guidelines at the time of study planning) and 60 to 80 mg/kg/day in the foreign

pediatric UC guidelines.[18] Based on available formulations (300 mg, 600 mg, and 1,200 mg tablets), the dose of mesalazine (the formulation to be used and the number of tablets) was set by body weight (Table 11).

In pediatric UC patients, it is difficult to perform frequent endoscopic examinations in some cases. Therefore, the "achievement rate of clinical remission based on UC-DAI (both rectal bleeding score and stool frequency score = 0)," an indicator not involving endoscopy, was employed as the primary endpoint. This endpoint was a secondary endpoint in Study U33 in adult patients with active UC. The evaluation period was 8 weeks, as in Study U33. In view of the above, the "clinical remission based on the UC-DAI score (both rectal bleeding score and stool frequency score = 0) at Week 8" was set as the primary endpoint. The criterion to determine the efficacy was set in reference to the following Japanese placebo-controlled study results of approved mesalazine products in adults and foreign placebo-controlled study results of mesalazine or other oral 5-ASA products in adults because Study U33 was an active-controlled study and provided no placebo information:

- In the Japanese clinical study of Asacol Tablets, which contain mesalazine as the active ingredient, in adult patients with active UC, the "achievement rate of remission[19] based on the UC-DAI score at Week 8" in the placebo group was 9.4% (Review Report of "Asacol Tablets 400 mg," dated August 20, 2009).
- In the foreign placebo-controlled studies of mesalazine in adult patients with active UC (Studies SPD476-301[20] and SPD476-302[21]), the "achievement rate of clinical remission[22] based on the UC-DAI score at Week 8" in the placebo group was 18.8% and 22.1%, respectively.
- According to the meta-analysis of 16 foreign clinical studies in adult patients with active UC for which the rate of clinical remission[23] in the placebo group could be calculated, the mean clinical remission rate in the placebo group was 9.1%.[24]

The above investigations showed that, although the clinical remission rate in the placebo group was higher in the foreign studies of mesalazine (Studies SPD476-301 and SPD476-302) than in the Japanese clinical study of Asacol Tablets, the values were within a range of 0% to 39% of the clinical remission rate in the placebo group in the meta-analysis of 16 foreign clinical studies. Therefore, the achievement rate of clinical remission based on the UC-DAI score at Week 8 of placebo treatment was assumed to be approximately 10%. Based on this assumption, mesalazine was assessed to be effective if the lower bound of the 2-sided 95% CI was above 10%.

PMDA's view:

The open-label, uncontrolled design of Study P21 is inevitable from the viewpoint of feasibility because pediatric UC patients are rare. In addition, the plan of Study P21, which was developed in reference to the endpoints, time of evaluation, and results of Japanese and foreign studies in adult patients with active UC, is

[18] *J Pediatr Gastroenterol Nutr*. 2012 Sep;55(3):340-361.
[19] The UC-DAI score is ≤2 and the rectal bleeding score is 0.
[20] A foreign phase III randomized, placebo-controlled, double-blind, comparative study to evaluate the efficacy and safety of mesalazine 2,400 mg/day (1,200 mg twice daily) and mesalazine 4,800 mg/day (4,800 mg once daily) in adult patients with mild to moderate active UC.
[21] A foreign phase III randomized, placebo-controlled, double-blind, comparative study to evaluate the efficacy and safety of mesalazine 2,400 mg (2,400 mg once daily) and mesalazine 4,800 mg (4,800 mg once daily) in adult patients with mild to moderate active UC.
[22] Both the rectal bleeding score and the stool frequency score based on the UC-DAI score are 0.
[23] The definition varied among the studies. Clinical remission was determined based on clinical symptoms or endoscopic findings.
[24] *Gastroenterology*. *1997*;112:1854-1858.

justified because the pathophysiology and diagnostic criteria of UC are similar between adults and children and the treatment goal is also the same in these populations. The target dose of mesalazine in children, which was set as 80 mg/kg/day in reference to the Japanese and foreign pediatric UC guidelines, is justified, including the dose specifications by body weight based on the available formulations. The primary endpoint, which was defined as "clinical remission based on the UC-DAI score (both rectal bleeding score and stool frequency score = 0)" excluding endoscopic evaluation, is inevitable in view of the burden of endoscopy in pediatric patients. Given that the disappearance of hematochezia without an increase in stool frequency is clinically important and can be a treatment goal in UC, remission can be assessed based on such clinical symptoms in the present development plan to add a dosage for children. The time of evaluation, which was set as 8 weeks in reference to Study U33 of mesalazine, is justified. The threshold to determine efficacy, which was defined as the lower bound of the 2-sided 95% CI to be above 10% in reference to the remission rate in the placebo group in the Japanese clinical studies of similar drugs and in multiple foreign clinical studies, is justified. Since this study is an uncontrolled study, the clinical significance of the efficacy of mesalazine in pediatric patients with active UC should be comprehensively evaluated based on the results of the primary endpoint as well as other secondary endpoints.

7.R.1.1.2 Main results of Study P21

The applicant's explanation about the main results of Study P21:

Table 12 shows the results of "achievement rate of clinical remission based on the UC-DAI score at Week 8" (FAS), the primary endpoint of Study P21. The lower bound of the 2-sided 95% CI was above the predetermined threshold (10%). All participants whose missing score data at Week 8 were imputed using the LOCF method (8 subjects) did not achieve clinical remission based on the UC-DAI score.

The "achievement rate of clinical remission based on the UC-DAI score at Week 8" [2-sided 95% CI] in the PPS was 35.0% [15.4, 59.2] (7 of 20 subjects), which was similar to that of the primary analysis in the FAS.

Table 18 shows the results of the main secondary endpoints of Study P21. The results of all of these endpoints supported those of the primary endpoint.

Table 18. Results of main secondary endpoints (Study P21, FAS)

Endpoint (time of evaluation)		N	Number of achieving subjects	Change or achievement rate
UC-DAI score				
Change in score (Week 8 - start of treatment)[a) c)]		17	-	−2.2 ± 2.0
Remission (at Week 8)[a)]		27	10	37.0% [19.4, 57.6]
Endoscopic remission (at Week 8)[b)]		27	7	25.9% [11.1, 46.3]
Improvement (at Week 8)[a)]		27	11	40.7% [22.4, 61.2]
Change in the score of each component of UC-DAI (Week 8 - start of treatment)	Stool frequency score[a)]	27	-	0.0 ± 0.8
	Rectal bleeding score[a)]	27	-	−0.7 ± 0.9
	Sigmoidoscopy score[c)]	17	-	−0.7 ± 0.7
	PGA score[c)]	17	-	−0.6 ± 0.6
PUCAI score				
Remission (at Week 8)[a)]		27	11	40.7 [22.4, 61.2]
Partial remission (at Week 8)[a)]		27	3	11.1 [2.4, 29.2]

Change is expressed as mean ± standard deviation, and achievement rate is expressed as a point estimate [2-sided 95% CI] (%).

a) Missing data of stool frequency, rectal bleeding, and PUCAI scores were imputed using the LOCF method.
b) Data of subjects in whom endoscopy could not be performed at the end of this study were imputed as non-achieving subjects.
c) It was planned to assess sigmoidoscopy and PGA scores when endoscopy is performed at the end of this study. In the analysis, 10 subjects were excluded from the FAS because they had no data to impute the score at Week 8 using the LOCF method.

In view of the above, clinically meaningful efficacy of mesalazine was demonstrated in pediatric patients with mild to moderate active UC.

PMDA's view:

In Study P21, the lower bound of the 2-sided 95% CI for the primary endpoint, "achievement rate of clinical remission based on the UC-DAI score at Week 8" (FAS), was above the protocol-specified threshold, and 25.9% (7 of 27 subjects) of UC patients, including those with moderate disease, achieved clinical remission. The results of the secondary endpoints also showed that the "achievement rate of remission (UC-DAI score ≤2, and rectal bleeding score = 0) at Week 8" was 37.0% (10 of 27 subjects) and the "achievement rate of improvement (improvement in UC-DAI score by ≥2 from the start of treatment) at Week 8" was 40.7% (11 of 27 subjects). In view of these, mesalazine can be expected to have a clinically meaningful efficacy for remission induction in pediatric patients with mild to moderate active UC.

7.R.1.1.3 Efficacy by patient characteristics

The applicant's explanation about the efficacy of mesalazine against active UC by patient characteristics:

Table 19 shows the "achievement rate of clinical remission based on UC-DAI at Week 8" (FAS) by main patient characteristics in Study P21.

Table 19. Achievement rate of clinical remission based on UC-DAI at Week 8 by main patient characteristics (Study P21, FAS)

		Percentage % (n/N) [2-sided 95% CI][a)]
Body weight and daily dose (mg) (Type of formulation)	≥18 kg and ≤23 kg: 1,800 (300 mg tablets)	0.0 (0/2) [0.0, 84.2]
	>23 kg and ≤35 kg: 2,400 (600 mg tablets)	0.0 (0/2) [0.0, 84.2]
	>35 kg and ≤50 kg: 3,600 (600 mg tablets)	33.3 (6/18) [13.3, 59.0]
	>50 kg and ≤90 kg: 4,800 (1,200 mg tablets)	20.0 (1/5) [0.5, 71.6]
Age	≤10 years	0.0 (0/4) [0.0, 60.2]
	≥11 and <17 years	30.4 (7/23) [13.2, 52.9]
Sex	Male	44.4 (4/9) [13.7, 78.8]
	Female	16.7 (3/18) [3.6, 41.4]
UC-DAI score	3-5	23.5 (4/17) [6.8, 49.9]
	6-8	30.0 (3/10) [6.7, 65.2]
Disease type	First attack type	16.7 (3/18) [3.6, 41.4]
	Relapse-remitting type	44.4 (4/9) [13.7, 78.8]
Affected area	Proctitis	60.0 (3/5) [14.7, 94.7]
	Left-sided colitis	11.1 (1/9) [0.3, 48.2]
	Total colitis	23.1 (3/13) [5.0, 53.8]

a) Calculated using the Clopper-Pearson method.

The achievement rate of clinical remission based on UC-DAI tended to be low in populations weighing ≥18 kg and ≤23 kg, weighing >23 kg and ≤35 kg, aged ≤10 years, and with left-sided colitis.

In the populations weighing ≥18 kg and ≤23 kg, and >23 kg and ≤35 kg, clinical remission based on the UC-DAI score was not observed. The 2 subjects in the population weighing ≥18 kg and ≤23 kg were both discontinued subjects, and the reason for discontinuation was "adverse event (drug intolerance)" in 1 subject and "difficulty to take the study drug" in the other, not "deterioration of the primary disease." The duration of treatment in these subjects was short, namely 14 and 2 days, respectively. One of the 2 subjects in the population weighing >23 kg and ≤35 kg was a discontinued subject, and the reason for discontinuation was "violation of inclusion/exclusion criteria," not "deterioration of the primary disease." The duration of treatment in this subject was short, namely 7 days. The other subject completed the treatment period and achieved endoscopic remission based on the UC-DAI score, while the PUCAI score decreased from 17.5 to 10.0. In view of the above, although evaluation is difficult in the population weighing ≥18 kg and ≤23 kg, the efficacy of mesalazine can be expected in the population weighing >23 kg and ≤35 kg.

Subjects in the population aged ≤10 years overlapped with those in the populations weighing ≥18 kg and ≤23 kg, and >23 kg and ≤35 kg.

In the population with left-sided colitis, clinical remission based on the UC-DAI score was observed in 1 of 9 subjects, but not in the other 8 subjects. These 8 subjects included 2 discontinued subjects, and the reason for discontinuation was "violation of inclusion/exclusion criteria" in 1 subject and "adverse event (herpangina)" in the other, not "deterioration of the primary disease." The duration of treatment in these subjects was short, namely 7 and 16 days, respectively. Among the 7 other subjects than the 2 discontinued ones, remission based on the PUCAI score at the end of the treatment period was observed in 3 subjects, and endoscopic remission based on the UC-DAI score at the end of the treatment period was observed in another subject. The remaining

3 subjects also had decreased UC-DAI or PUCAI scores. These results suggest a certain level of efficacy in this population.

In view of the results of Study P21 and the applicant's explanation, PMDA has concluded that there are no patient groups that are ineligible for mesalazine treatment from the viewpoint of efficacy, except for the population weighing ≥18 kg and ≤23 kg. The appropriateness of mesalazine treatment in patients weighing ≥18 kg and ≤23 kg is discussed in Section 7.R.4.

7.R.1.2 Remission phase

7.R.1.2.1 Study design

The applicant's explanation about the design of the Japanese phase III study in pediatric UC patients in remission (Study P22):

Study P22 was designed as an open-label, uncontrolled study for the same reasons as for Study P21 [see Section 7.R.1.1.1]:

The study population was set in reference to Study U32 of mesalazine in adult UC patients in remission (Review Report of "Lialda Tablets 1200 mg," dated August 17, 2016) and "Guidelines for the Management of Ulcerative Colitis in Japan - Developed through Integration of Evidence and Consensus among Experts - (January 2006)" (First Edition), as follows: patients aged <17 years with a UC-DAI score corresponding to remission (≤2, with rectal bleeding score = 0).

The target dose of mesalazine was set as 40 mg/kg/day in reference to the recommended dose of oral 5-ASA products in remission maintenance therapy, namely, 30 to 60 mg/kg/day in the Japanese pediatric treatment guidelines and "at least 40 mg/kg/day if the patient remains in remission" in the foreign pediatric UC guidelines. Based on available formulations (300 mg, 600 mg, and 1,200 mg tablets), the dose of mesalazine (the formulation to be used and the number of tablets) was set by body weight (Table 14).

The primary endpoint and the time of evaluation were defined as "achievement rate of absence of hematochezia based on the UC-DAI score (rectal bleeding score = 0 at all assessment time points up to Week 48 of the treatment period)," an objective indicator, as in Study U32. The criterion to determine the efficacy in Study P22 was set in reference to the foreign placebo-controlled study results of mesalazine in adults because placebo-controlled studies in pediatric UC patients had not been conducted as of the time when Study P22 was planned, and Study U32 was an active-controlled study. Based on the results (remission maintenance rate 38%-59% and relapse rate 49% for 24 or 48 weeks of treatment) in the placebo group in 6 studies in adult UC patients in remission,[25)] the achievement rate of absence of hematochezia based on the UC-DAI score (rectal bleeding score = 0 at all assessment time points up to Week 48 of the treatment period) with placebo treatment was assumed to be approximately 50%. Based on this assumption, mesalazine was assessed to be effective if the lower bound of the 2-sided 95% CI was above 50% in Study P22.

[25)] *Dig Dis Sci*. 1995;40:296-304, *Aliment Pharmacol Ther*. 1999;13:373-379, *Ann Intern Med*. 1996;124:204-211, *Gastroenterology*. 1997;112:718-724, and Apriso™ extended-release capsules (US package insert).

PMDA's view:

The open-label, uncontrolled design of Study P22 is inevitable from the viewpoint of feasibility because pediatric UC patients are rare. In addition, the plan of Study P22, which was developed in reference to the endpoints, time of evaluation, and results of Japanese and foreign studies in adult UC patients in remission, is justified. The target dose of mesalazine in children, which was set as 40 mg/kg/day in reference to the Japanese and foreign pediatric UC guidelines, is justified, including the dose specifications by body weight. The primary endpoint and the time of evaluation, which were defined as "absence of hematochezia based on the UC-DAI score (rectal bleeding score = 0 at all assessment time points up to Week 48 of the treatment period)" as in Study U32, are justified. The threshold to determine efficacy, which was defined as the lower bound of the 2-sided 95% CI to be above 50% in reference to the remission maintenance rate in the placebo group in the foreign clinical studies of mesalazine, etc., is justified. Since this study is an uncontrolled study, the clinical significance of the efficacy of mesalazine in pediatric UC patients in remission should be determined comprehensively based on the results of the primary endpoint as well as other secondary endpoints.

7.R.1.2.2 Number of subjects enrolled and main results of Study P22

The applicant's explanation about the appropriateness of termination of Study P22 without achieving the target sample size of 26 subjects (actual number of subjects registered, 23):

Patient enrollment in Study P22 was continued while taking measures such as adding study sites for approximately [redacted] years until [redacted] 20[redacted]. However, the applicant encountered a difficulty in enrolling new patients partly due to coronavirus disease 2019 (COVID-19). Although the enrollment period was further extended to [redacted], 20[redacted], no additional patients were enrolled, which inevitably led to study termination after enrolling 23 patients. The statistical power with 23 subjects in the FAS is 84%. Therefore, the power of the study was ≥80%, even though the enrollment was discontinued with 23 subjects. When the termination of patient enrollment was decided ([redacted], 20[redacted]), assessment of the primary endpoint (absence of hematochezia) had not been completed in 5 subjects. Of them, 2 subjects were about to complete the 48-week observation period, whereas the remaining 3 subjects were in the early or middle stage of the observation period and the occurrence of hematochezia was unpredictable. Thus, the termination of patient enrollment was not an arbitrary decision.

The applicant's explanation about the main results of Study P22:

Table 15 shows the results of the "achievement rate of absence of hematochezia based on the UC-DAI score (rectal bleeding score = 0 at all assessment time points up to Week 48 of the treatment period)" (FAS), the primary endpoint of Study P22. The lower bound of the 2-sided 95% CI was above the predetermined threshold (50%). The "achievement rate of absence of hematochezia based on the UC-DAI score" [2-sided 95% CI] in the PPS was 80.0% [56.3, 94.3] (16 of 20 subjects), which was similar to that of the primary analysis in the FAS.

Table 20 shows the results of the main secondary endpoints of Study P22. The relapse rate (FAS) tended to be high, but the results of all other endpoints supported those of the primary endpoint. Relapse (FAS) is an endpoint involving endoscopy. In Study P22, endoscopy was not mandated in consideration of its burden on

pediatric patients, and it was specified that subjects who had not undergone endoscopy had to be handled as "relapsing subjects." As a result, 13 of the 23 subjects did not undergo endoscopy and were counted as relapsing subjects, which may have resulted in the high relapse rate.

Table 20. Results of main secondary endpoints (Study P22, FAS)

Endpoint (time of evaluation)		N	Number of subjects with relapse/ remission	Percentage or change
UC-DAI score				
Relapse (at Week 48)[a)]		23	15	65.2% [42.7, 83.6]
Change in score (Week 48 - start of treatment)[c)]		10	-	1.0 ± 2.5
Change in the score of each component of UC-DAI (Week 48 - start of treatment)	Stool frequency score[b)]	23	-	0.0 ± 0.6
	Rectal bleeding score[b)]	23	-	0.3 ± 0.7
	Sigmoidoscopy score[c)]	10	-	0.2 ± 0.6
	PGA score[c)]	10	-	0.3 ± 0.8
PUCAI score				
Remission (at Week 48)[b)]		23	18	78.3% [56.3, 92.5]

Change is expressed as mean ± standard deviation, and relapse/remission rate is expressed as a point estimate [2-sided 95% CI] (%).

a) Data of subjects in whom endoscopy could not be performed at the end of this study were imputed as relapsing subjects.
b) Missing data of stool frequency, rectal bleeding, and PUCAI scores were imputed using the LOCF method.
c) It was planned to assess sigmoidoscopy and PGA scores when endoscopy **is** performed at the end of this study. In the analysis, 13 subjects were excluded from the FAS because they had no data to impute the score at Week 48 using the LOCF method.

In the assessment of "absence of hematochezia," the primary endpoint of Study P22, subjects who had achieved a rectal bleeding score of 0 at all assessment time points during treatment had to be handled as subjects achieving "absence of hematochezia," even if they discontinued the study before Week 48, and 2[26)] (8.7%; duration of treatment, 175 and 28 days, respectively) of the participants in the FAS who had discontinued the study before Week 48 were handled as subjects achieving the primary endpoint.

The applicant's explanation about the robustness of the results on the efficacy of mesalazine in remission based on the above:

In the assessment of the primary point of Study U32 in adult UC patients in remission, subjects who had achieved the absence of hematochezia based on UC-DAI at all assessment time points during treatment had to be handled as subjects achieving "absence of hematochezia," even if they discontinued the study before Week 48. Therefore, considering the comparability with Study U32, the same specification was adopted in Study P22. Among the discontinued subjects in Study U32, 11 subjects (11.0% of the overall population of 100 subjects) were handled as subjects achieving "absence of hematochezia." The duration of treatment was <28 days in 4 of the 11 subjects (duration of treatment, 3, 5, 21, and 22 days). To evaluate the maintenance effect up to Week 48, post hoc analyses 1 and 2 were performed on the data of Studies P22 and U32, as shown in Table 21.

[26)] Female subject aged 16 years, weighing >50 kg and ≤90 kg, and treated at 2,400 mg/day (1,200 mg tablet × 2): The subject discontinued the study due to serious adverse events (cerebral haemorrhage and brain herniation) at Week 24 of the treatment period, with a duration of treatment of 175 days; since the rectal bleeding score during treatment was 0, the subject was assessed as "absence of hematochezia."
Male subject aged 14 years, weighing >50 kg and ≤90 kg, and treated at 2,400 mg/day (1,200 mg tablet × 2): The subject discontinued the study for personal reasons (difficulty to continue the monthly visits) at Week 4 of the treatment period, with a duration of treatment of 28 days; since the rectal bleeding score during treatment was 0, the subject was assessed to have achieved "absence of hematochezia."

Table 21. Analyses (FAS and PPS) and post hoc analyses on the absence of hematochezia based on UC-DAI at Week 48

Analysis method	Rate of absence of hematochezia % (n/N) [2-sided 95% CI]	
	Study P22	Study U32 (Mesalazine 2,400 mg/day group)
Analysis in the FAS	73.9 (17/23 subjects) [51.6, 89.8]	85.0 (85/100 subjects) [76.5, 91.4]
Analysis in the PPS	80.0 (16/20 subjects) [56.3, 94.3]	84.8 (84/99 subjects) [76.2, 91.3]
Post hoc analysis 1[a)]	71.4 (15/21 subjects) [47.8, 88.7]	83.1 (74/89 subjects) [73.7, 90.2]
Post hoc analysis 2[b)]	65.2 (15/23 subjects) [42.7, 83.6]	74.0 (74/100 subjects) [64.3, 82.3]

a) Post hoc analysis 1 included only "participants in the FAS who developed hematochezia or completed the treatment period." Specifically, "participants in the FAS who discontinued the study but achieved the absence of hematochezia (2 subjects in Study P22 and 11 subjects in Study U32)" were excluded from both the number of subjects evaluated and the number of subjects achieving the absence of hematochezia in the analysis in the FAS.

b) Post hoc analysis 2 was performed in the FAS and handled participants who discontinued the study as subjects not achieving the absence of hematochezia. Specifically, "participants in the FAS who discontinued the study but achieved the absence of hematochezia (2 subjects in Study P22 and 11 subjects in Study U32)" were excluded from the number of subjects achieving the absence of hematochezia in the analysis in the FAS.

The results of the analyses in the FAS and PPS in Study P22 and the post hoc analyses showed that the point estimate for the rate of absence of hematochezia in Study P22 tended to be slightly lower than that in Study U32 in adult UC patients in remission. When differences in background factors between Studies P22 and U32 were investigated, the time from UC onset showed a difference between the studies, with the median time of 2.67 and 5.95 years, respectively. There are reports on the relationship between the time from UC onset and UC relapse,[27)] stating that disease activity[28)] decreases over time in all patients with mild to severe disease, and, especially in patients with mild to moderate disease, the decrease is significant by 5 to 6 years from the initial diagnosis. Table 22 shows the rate of absence of hematochezia by time from UC onset in Studies P22 and U32. In both studies, the achievement rate was higher in the population with a time from onset of ≥5 years than in the population with a time from onset of <5 years, suggesting that the disease activity decreases with increasing time from UC onset. In view of the above, the percentage of participants with a time from UC onset of ≥5 years, which was lower in Study P22 than in Study U32, is considered to have contributed to the lower rate of absence of hematochezia in Study P22 than in Study U32.

Table 22. Rate of absence of hematochezia by time from UC onset (Studies P22 and U32)

	Study P22		Study U32	
	Percentage of participants (n)	Achievement rate of absence of hematochezia [% (n)]	Percentage of participants (n)	Achievement rate of absence of hematochezia [% (n)]
<5 years from onset	73.9 (17)	64.7 (11)	41.0 (41)	78.0 (32)
≥5 years from onset	26.1 (6)	100 (6)	59.0 (59)	89.8 (53)

In a foreign prospective pediatric IBD registry (observational study),[29)] the remission rate based on PUCAI at 1 year of treatment with a single oral 5-ASA product in pediatric UC patients was 45%. The remission rate based on the PUCAI score in Study P22 was 78.3% (18 of 23 subjects) (Table 20), which was higher than the foreign data, although the details of disease activity, etc. in the study population of the registry are unknown.

In view of the above, mesalazine can be expected to have a clinically meaningful efficacy in pediatric UC patients in remission.

27) *Journal of Japanese Society of Gastroenterology*. 1993;134-143, *Gastroenterol Jpn*. 1991;26(3):312-318.
28) In patients with active years (with diarrhea attacks accompanied by overt bleeding persisting for several days or longer on a yearly basis).
29) *Digest Liver Dis. 2015*;47S:e262.

PMDA's view:

It would be inevitable to terminate Study P22 before enrolling the targeted number of patients where there is a difficulty enrolling new patients even after study period extension. Also, in light of the applicant's explanation about the robustness of the study, the efficacy of mesalazine in pediatric UC patients in remission can be evaluated to a certain degree based on the results of Study P22. In efficacy evaluation of Study P22, the lower bound of the 2-sided 95% CI for the rate of absence of hematochezia based on the UC-DAI score, the primary endpoint, was above the predetermined threshold. Although the point estimate for the rate of absence of hematochezia in Study P22 tended to be slightly lower than in Study U32, the applicant's explanation that the difference in the time from UC onset, which was noted in the comparison of background factors between Studies P22 and U32, contributed to the lower value, is justified. The result of the main secondary endpoints did not deny the maintenance effect of mesalazine.

Thus, the result of the primary endpoint of Study P22 was above the predetermined threshold, and remission was maintained in 73.9% (17 of 23) of subjects. The results of the secondary endpoints also showed that no marked deterioration in terms of the change in UC-DAI score (including the change in each component of the UC-DAI score) was observed, and the "achievement rate of remission based on the PUCAI score at Week 48" was 78.3% (18 of 23 subjects). In view of these, mesalazine can be expected to have a clinically meaningful efficacy in pediatric UC patients in remission.

7.R.1.2.3 Efficacy by patient characteristics

The applicant's explanation about the efficacy of mesalazine in remission by patient characteristics:

Table 23 shows the "achievement rate of absence of hematochezia based on UC-DAI (rectal bleeding score = 0 at all assessment time points up to Week 48 of the treatment period)" (FAS) by main patient characteristics in Study P22.

Table 23. Achievement rate of absence of hematochezia based on UC-DAI by main patient characteristics (Study P22, FAS)

		Percentage % (n/N) [2-sided 95% CI][a)]
Body weight and daily dose (mg) (Type of formulation)	≥18 kg and ≤23 kg: 900 (300 mg tablets)	- (0/0)
	>23 kg and ≤35 kg: 1,200 (600 mg tablets)	100.0 (5/5) [47.8, 100.0]
	>35 kg and ≤50 kg: 1,800 (600 mg tablets)	20.0 (1/5) [0.5, 71.6]
	>50 kg and ≤90 kg: 2,400 (1,200 mg tablets)	84.6 (11/13) [54.6, 98.1]
Age	≤10 years	83.3 (5/6) [35.9, 99.6]
	≥11 and <17 years	70.6 (12/17) [44.0, 89.7]
Sex	Male	60.0 (6/10) [26.2, 87.8]
	Female	84.6 (11/13) [54.6, 98.1]
UC-DAI score	0	66.7 (6/9) [29.9, 92.5]
	1	50.0 (3/6) [11.8, 88.2]
	2	100.0 (8/8) [63.1, 100.0]
Time from UC onset	<1 year	33.3 (1/3) [0.8, 90.6]
	≥1 and <2 years	75.0 (3/4) [19.4, 99.4]
	≥2 and <3 years	66.7 (4/6) [22.3, 95.7]
	≥3 and <4 years	75.0 (3/4) [19.4, 99.4]
	≥4 and <5 years	- (0/0)
	≥5 years	100.0 (6/6) [54.1, 100.0]
Disease type	First attack type	60.0 (9/15) [32.3, 83.7]
	Relapse-remitting type	100.0 (8/8) [63.1, 100.0]
Affected area	Proctitis	100.0 (1/1) [2.5, 100.0]
	Left-sided colitis	80.0 (4/5) [28.4, 99.5]
	Total colitis	75.0 (12/16) [47.6, 92.7]
	Right-sided colitis	0.0 (0/1) [0.0, 97.5]

-, not calculable.
a) Calculated using the Clopper-Pearson method.

The achievement rate of absence of hematochezia based on UC-DAI tended to be low in populations weighing >35 kg and ≤50 kg, with a time from onset of <1 year, and with a baseline UC-DAI score of 1. Efficacy evaluation was difficult in the population weighing ≥18 kg and ≤23 kg because no subjects were enrolled in the population.

In the population weighing >35 kg and ≤50 kg, 3 of 5 subjects discontinued the treatment due to deterioration of the primary disease, but the rectal bleeding scores in 2 of these 3 discontinued subjects were maintained at 0 up to Week 28 and Week 36, respectively. Although 1 of 2 subjects who completed the treatment did not achieve the primary endpoint, this subject had hematochezia (rectal bleeding score = 1) only at assessment time points from Weeks 20 to 24, and the rectal bleeding score was 0 at the other assessment time points. In 3 of 5 subjects in this population, remission based on PUCAI was observed at the end of treatment.

In the population with a time from onset of <1 year, 2 of 3 subjects discontinued the treatment due to deterioration of the primary disease, but the rectal bleeding scores in these subjects were maintained at 0 up to Week 16 and Week 28, respectively.

In the population with a baseline UC-DAI score of 1, 3 of 6 subjects discontinued the treatment due to deterioration of the primary disease, but the rectal bleeding scores in 2 of these 3 discontinued subjects were maintained at 0 up to Week 16 and Week 36, respectively.

In view of the above, although evaluation is difficult in the population weighing ≥18 kg and ≤23 kg, the efficacy of mesalazine in the remission phase can be expected in other populations.

In view of the results of Study P22 and the applicant's explanation, PMDA has concluded that there are no patient groups that are ineligible for mesalazine treatment from the viewpoint of efficacy, except for the population weighing ≥18 kg and ≤23 kg. The appropriateness of mesalazine treatment in patients weighing ≥18 kg and ≤23 kg is discussed in Section 7.R.4.

7.R.1.3 Switching mesalazine from 1,200 mg tablets to 600 mg tablets

The applicant's explanation about the background and main results of the Japanese phase III study to evaluate the efficacy and safety of mesalazine before and after switching from 1,200 mg tablets to 600 mg tablets in adult UC patients in remission (Study U21):

In the US, mesalazine was developed by Shire (currently Takeda), and the equivalence of 1,200 mg tablets and 300 mg and 600 mg tablets was evaluated using the reference-scaled average bioequivalence (RSABE) approach in Studies SHP476-121 and SHP476-122. However, since these formulations of mesalazine were designed to release mesalazine in the large intestine, the site of disease, it was considered difficult to evaluate the bioequivalence of the formulations in a bioequivalence study using pharmacokinetics as the indicator. To confirm the efficacy and safety before and after switching the 1,200 mg and 600 mg tablets, a switching study was conducted.

The switching study (Study U21) was designed to evaluate the efficacy and safety of mesalazine after switching from 1,200 mg tablets to 600 mg tablets in comparison to before the switching in adult UC patients in remission with stable symptoms.

The primary endpoint was "absence of hematochezia based on the UC-DAI score," the same objective indicator as used in Studies U32 and P22 in UC patients in remission. With this setting, efficacy after formulation switch could be evaluated even in Study U21 designed as an open-label, uncontrolled study.

The time of evaluation was set as 8 weeks for both evaluation period 1 (treatment with 1,200 mg tablets) and evaluation period 2 (treatment with 600 mg tablets), because the incidence of hematochezia in the mesalazine group in Study U32, a Japanese study in UC patients in remission, did not largely differ between the periods from the start of the study treatment to Week 8 (6.0% [6 of 100 subjects]) and from Week 8 to Week 16 (3.4% [3 of 88 subjects]). With this setting, efficacy after switching from 1,200 mg tablets to 600 mg tablets could be evaluated.

In the method of efficacy evaluation, the criterion to determine that there is no clear difference in efficacy between the 1,200 mg and 600 mg tablets was set in reference to the "rate of absence of hematochezia based on the UC-DAI score" in the mesalazine group in Study U32 and the fact that the mean difference in the rate of remission maintenance or the rate of absence of relapse between the mesalazine 2,400 mg/day group and the placebo group (combined weighted average) was 23% in 4 foreign placebo-controlled studies of oral 5-

ASA products in UC patients in remission.[30] The criterion was specifically that the difference in the rate of absence of hematochezia based on the UC-DAI score between evaluation periods 1 and 2 should be within 12%, approximately half of the above mean difference of 23%.

Table 17 shows the main results of Study U21, namely, the results of the "achievement rate of absence of hematochezia based on the UC-DAI score (rectal bleeding score = 0 at all assessment time points in evaluation period 1 or evaluation period 2)" (FAS), the primary endpoint. The rate of absence of hematochezia was 100.0% in both evaluation periods 1 and 2. Therefore, the predetermined criterion to determine that there is no clear difference in efficacy before and after switching mesalazine 1,200 mg and 600 mg tablets was satisfied.

Table 24 shows the change in partial UC-DAI score in evaluation periods 1 and 2. Efficacy did not diminish, even after transition from evaluation period 1 to evaluation period 2.

Table 24. Changes in partial UC-DAI score and the score of each component of UC-DAI (Study U21, FAS)

		Evaluation period 1 (N = 23)	Evaluation period 2 (N = 23)
Change in partial UC-DAI score[a)]		0.1 ± 0.5 [−0.1, 0.3]	−0.2 ± 0.4 [−0.3, 0.0]
Change in the score of each component of partial UC-DAI score[a)]	Stool frequency score	0.1 ± 0.5 [−0.1, 0.3]	−0.2 ± 0.4 [−0.3, 0.0]
	Rectal bleeding score[b)]	0	0
	PGA score[b)]	0	0

Mean ± standard deviation [2-sided 95%CI of the mean]

a) Change from the start to Week 8 of each evaluation period.

b) Rectal bleeding and PGA scores were 0 at all time points in all participants.

On the basis of the results of Study U21, PMDA has concluded that, although the bioequivalence of 1,200 mg and 600 mg tablets has not been demonstrated, there were no changes in the state of remission before and after switching from 1,200 mg tablets to 600 mg tablets in adult UC patients in remission, suggesting no clear difference in efficacy between the 1,200 mg and 600 mg tablets. The appropriateness of switching 1,200 mg and 600 mg tablets in the post-marketing setting based on the results of Study U21 is discussed in Section 7.R.4.

7.R.2 Safety

On the basis of the data submitted and the reviews in Sections 7.R.2.1 and 7.R.2.2, PMDA has concluded that the safety of mesalazine in pediatric UC patients can be managed by issuing the same precautions as for adult patients, and that mesalazine has clinically acceptable safety in view of its efficacy.

7.R.2.1 Mild to moderate UC in the active and remission phases in children

The applicant's explanation about safety in mild to moderate UC in the active and remission phases in children: Table 25 and Table 26 show the incidences of adverse events, etc. in Studies P21 and P22, respectively.

[30] *Dig Dis Sci*. 1995;40:296-304, *Aliment Pharmacol Ther*. 1999;13:373-379, *Ann Intern Med*. 1996;124:204-211, and *Gastroenterology*. 1997;112:718-724.

Table 25. Incidences of adverse events (Study P21, active phase, safety analysis set)

	Mesalazine (N = 27)	Details of adverse events, etc.
All adverse events	66.7 (18)	Adverse events observed in ≥2 subjects: nasopharyngitis, colitis ulcerative, and constipation in 3 subjects each, and anaemia, upper respiratory tract inflammation, eczema, drug intolerance, and product residue present in 2 subjects each.
All adverse drug reactions	18.5 (5)	Drug intolerance and product residue present in 2 subjects each, and constipation and *β*-*N*-acetyl-D-glucosaminidase increased in 1 subject each (1 subject developed >1 event).
Serious adverse events	11.1 (3)	Herpangina, anaemia, colitis ulcerative, and drug intolerance in 1 subject each (1 subject developed >1 event).
Serious adverse drug reactions	3.7 (1)	Drug intolerance in 1 subject.
Death	0	-
Adverse events leading to treatment discontinuation	18.5 (5)	Drug intolerance and colitis ulcerative in 2 subjects each, and herpangina in 1 subject.
Adverse drug reactions leading to treatment discontinuation	7.4 (2)	Drug intolerance in 2 subjects.

MedDRA/J Ver.26.1; incidence % (n); -, none.

Table 26. Incidences of adverse events (Study P22, remission phase, safety analysis set)

	Mesalazine (N = 23)	Details of adverse events, etc.
All adverse events	87.0 (20)	Adverse events observed in ≥2 subjects: nasopharyngitis in 9 subjects, influenza, upper respiratory tract inflammation, colitis ulcerative, and vomiting in 5 subjects each, headache and diarrhoea in 3 subjects each, and varicella, abdominal pain, dental caries, and ligament sprain in 2 subjects each.
All adverse drug reactions	13.0 (3)	Otitis externa, headache, ear discomfort, cough, oropharyngeal discomfort, abdominal pain, constipation, and diarrhoea in 1 subject each (some subjects developed >1 event).
Serious adverse events	8.7 (2)	Cerebral haemorrhage, brain herniation, and colitis ulcerative in 1 subject each (1 subject developed >1 event).
Serious adverse drug reactions	0	-
Death	0	-
Adverse events leading to treatment discontinuation	26.1 (6)	Colitis ulcerative in 5 subjects, and cerebral haemorrhage and brain herniation in 1 subject each (1 subject developed >1 event).
Adverse drug reactions leading to treatment discontinuation	0	-

MedDRA/J Ver.26.1; incidence % (n); -, none.

Of these events, adverse drug reactions that were not observed in Study U33 or U32 in adult UC patients only included diarrhoea (1 subject, Study P22) and drug intolerance (2 subjects, both in Study P21). Diarrhoea was mild and did not lead to discontinuation of the study treatment. This event is a known adverse drug reaction. Drug intolerance was serious in 1 of the 2 subjects and non-serious in the other, and both events led to discontinuation of the study treatment. However, no new precautions are considered necessary because the package insert of mesalazine already includes the precautionary statement, “Mesalazine may cause hypersensitivity symptoms (pyrexia, abdominal pain, diarrhea, eosinophilia, etc.) or aggravate ulcerative colitis. If any abnormalities are observed, appropriate measures such as dose reduction or treatment discontinuation should be taken,” and both participants who developed drug intolerance recovered from the event after discontinuing the mesalazine treatment.

Table 27 shows the incidences of adverse events by treatment period in Study P22. The incidence of adverse events per unit of treatment duration did not tend to increase with prolonged duration of mesalazine treatment.

Table 27. Incidences of adverse events by treatment period (Study P22, remission phase, safety analysis set)

	Weeks 0-4 (N = 23)	Weeks 4-8 (N = 22)	Weeks 8-12 (N = 21)	Weeks 12-24 (N = 21)	Weeks 24-36 (N = 20)	Weeks 36-48 (N = 18)	After Week 48 (N = 16)
All adverse events	21.7 (5)	18.2 (4)	23.8 (5)	61.9 (13)	50.0 (10)	50.0 (9)	12.5 (2)
Adverse events observed in ≥2 subjects in any period							
Nasopharyngitis	4.3 (1)	4.5 (1)	9.5 (2)	19.0 (4)	15.0 (3)	16.7 (3)	0
Influenza	0	0	0	19.0 (4)	0	5.6 (1)	0
Upper respiratory tract inflammation	4.3 (1)	9.1 (2)	0	0	10.0 (2)	11.1 (2)	0
Colitis ulcerative	4.3 (1)	0	0	4.8 (1)	10.0 (2)	5.6 (1)	0
Vomiting	0	0	4.8 (1)	4.8 (1)	10.0 (2)	11.1 (2)	12.5 (2)
Abdominal pain	0	0	4.8 (1)	9.5 (2)	10.0 (2)	0	0
Headache	4.3 (1)	0	0	0	0	11.1 (2)	0

MedDRA/J Ver.26.1, incidence % (n)

PMDA's view:

The incidences of adverse events in Studies P21 and P22 did not show trends that may cause particular concerns in pediatric UC patients compared with Studies U33 and U32 in adult UC patients. In addition, the incidences of adverse events by treatment period in Study P22 suggested no particular safety concerns associated with prolonged duration of mesalazine treatment.

7.R.2.2 Switching mesalazine from 1,200 mg tablets to 600 mg tablets

The applicant's explanation about safety before and after switching mesalazine from 1,200 mg tablets to 600 mg tablets:

Table 28 shows the incidences of adverse events by evaluation period in Study U21. The incidences of adverse events did not show different trends before and after formulation switch. Therefore, switching from 1,200 mg tablets to 600 mg tablets is unlikely to cause clinical problems.

Table 28. Incidences of adverse events in Study U21 (safety analysis set)

	Evaluation period 1 (N = 23)	Evaluation period 2 (N = 23)
All adverse events	30.4% (7 subjects; COVID-19, influenza, nasopharyngitis, atrial fibrillation, oropharyngeal pain, stomatitis, nausea, vomiting, and spinal osteoarthritis in 1 subject each [some subjects developed >1 event])	43.5% (10 subjects; COVID-19 in 3 subjects, large intestine polyp in 2 subjects, and influenza, nasopharyngitis, neuropathy peripheral, rhegmatogenous retinal detachment, stomatitis, anal fissure, and haematuria in 1 subject each [some subjects developed >1 event])
All adverse drug reactions	0%	4.3% (1 subject; haematuria)
Serious adverse events	0%	0%
Death	0%	0%
Adverse events leading to treatment discontinuation	0%	0%

MedDRA/J Ver. 26.1

On the basis of the results of Study U21, PMDA has concluded that there are no differences that may cause safety concerns before and after switching from 1,200 mg tablets to 600 mg tablets, and that switching from 1,200 mg tablets to 600 mg tablets has no effects on safety.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of mesalazine:

In Japan, mesalazine has obtained marketing approval for the indication of "ulcerative colitis (non-severe cases)." Its use in pediatric UC patients was approved in the US (for UC patients weighing ≥24 kg) and Europe

(for UC patients weighing >50 kg and aged ≥10 years), both in June 2020. As of March 2025, mesalazine has been approved in 15 countries.

In the treatment of UC in children, 5-ASA products are the first-line therapy for mild to moderate disease, as in adults (the treatment guidelines).

Oral 5-ASA products (preceding products) approved in Japan include Pentasa Tablets/Granules, Asacol Tablets, and Lialda Tablets 1200 mg. Of these products, only Pentasa Tablets/Granules are approved with a dosage for pediatric UC. It is specified to administer Pentasa Tablets/Granules 3 times daily in children, with a maximum daily dose of 2,250 mg, and it can therefore not be used in children with a high body weight at high doses (equivalent to 50-100 mg/kg/day) recommended for remission induction therapy in the treatment guidelines. Lialda Tablets are administered once daily and are expected to improve the medication adherence. Lialda Tablets can be administered at high doses recommended for remission induction therapy, offering a new treatment option for pediatric patients with mild to moderate UC.

In view of the efficacy [see Section 7.R.1] and safety [see Section 7.R.2] of mesalazine confirmed in Studies P21 and P22, PMDA has concluded that Lialda Tablets can be a treatment option that provides benefits such as once daily dosage to pediatric patients with mild to moderate UC in the active and remission phases, as with the approved Pentasa Tablets/Granules.

7.R.4 Dosage and administration

The applicant's explanation about the dosage and administration of mesalazine:
In the treatment of UC, oral 5-ASA products are more effective for remission induction at high doses than at low doses. Therefore, the use of high doses is recommended for remission induction in children, as in adults (the pediatric treatment guidelines). According to the Japanese pediatric treatment guidelines and the foreign pediatric UC guidelines, the recommended dose of oral 5-ASA products for remission induction therapy is 50 to 100 mg/kg/day and 60 to 80 mg/kg/day, respectively, and that for remission maintenance therapy is 30 to 60 mg/kg/day and "at least 40 mg/kg/day if the patient remains in remission," respectively. In reference to these recommendations, the dosage regimen in Study P21 in patients in the active phase was specified as "80 mg/kg orally once daily after a meal," and that in Study P22 in patients in the remission phase as "40 mg/kg orally once daily after a meal," with dose specifications by body weight based on available formulations (300 mg, 600 mg, and 1,200 mg tablets) as shown in Table 11 and Table 14. The results of Studies P21 and P22 demonstrated the efficacy of mesalazine [see Section 7.R.1] and suggested no particular safety concerns [see Section 7.R.2]. However, its efficacy and safety in patients weighing ≥18 kg and ≤23 kg could not be fully confirmed because the 2 subjects in this body weight category enrolled in Study P21 both discontinued the study early and no subjects in the category were enrolled in Study P22. Therefore, it was considered difficult to set a dosage for this population.

In view of the above, the dosage and administration of mesalazine is set as follows: "The usual dosage for children weighing >23 kg is 40 mg/kg of mesalazine administered orally once daily after a meal. During the

active phase, the usual dosage for children weighing >23 kg is 80 mg/kg of mesalazine administered orally once daily after a meal. The dose may be reduced as necessary according to the patient's condition." Dosage by body weight category will be provided in the "Precautions Concerning Dosage and Administration" section of the package insert.

PMDA's view:
Setting the dosage regimens of mesalazine in Studies P21 and P22 in reference to the Japanese and foreign pediatric UC guidelines is justified. Since these studies demonstrated the efficacy of mesalazine [see Section 7.R.1] and suggested no particular safety concerns [see Section 7.R.2], the dosage and administration of mesalazine should be set based on the regimens in Studies P21 and P22. Evidence required for setting a dosage for patients weighing ≤23 kg could not be obtained in Study P21 or P22. In view of this as well as the dosage of mesalazine for adults, the dosage for children should be set as, "The usual dosage for children weighing >23 kg is 40 mg/kg of mesalazine administered orally once daily after a meal, which however should not exceed 2,400 mg. During the active phase, the usual dosage for children weighing >23 kg is 80 mg/kg of mesalazine administered orally once daily after a meal, which however should not exceed 4,800 mg and may be reduced as necessary according to the patient's condition." In addition, the information on dosage by body weight category should be provided in the "Precautions Concerning Dosage and Administration" section of the package insert.

The efficacy [see Section 7.R.1.3] and safety [see Section 7.R.2.2] of mesalazine before and after switching 1,200 mg and 600 mg tablets have been confirmed, but the bioequivalence of 1,200 mg and 600 mg tablets has not been demonstrated. A precaution should therefore be issued to ensure that the patient's condition should be carefully monitored after formulation switch.

7.R.5 Post-marketing investigations

The applicant's explanation about the post-marketing investigations:
No new safety concerns were identified in Study P21, P22, or U21 [see Section 7.R.2]. In Japan, mesalazine 1,200 mg tablets were approved with the indication of "ulcerative colitis (non-severe cases)" on September 28, 2016, and a specified use-results survey in adult UC patients was completed by April 2020 (the safety analysis set consisted of 1,682 patients including 6 children). The estimated cumulative exposure[31)] as of February 19, 2024 was approximately [redacted] patient-years. No findings requiring additional safety assurance measures have been observed in the spontaneous reports of adverse drug reactions/infections, research reports, report on measures, etc. obtained to date.

As described above, since there are no new safety concerns about mesalazine at present, additional pharmacovigilance activities such as post-marketing surveys are unnecessary for pediatric UC patients. However, if any new concerns arise during the routine pharmacovigilance activities, the need for actions, including post-marketing surveys, will then be assessed.

[31)] Calculated from [redacted] and [redacted].

PMDA's view:

As the applicant explains, in view of no new concerns raised about mesalazine used in pediatric UC patients [see Section 7.R.2], and based on the results of the specified use-results survey in adult UC patients and the currently available safety information, no particular information need to be collected through additional pharmacovigilance activities. Therefore, additional pharmacovigilance activities such as post-marketing surveys are unnecessary at present, and the routine pharmacovigilance activities will serve to identify new concerns. The applicant's these explanations are reasonable.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that mesalazine has efficacy in the treatment of ulcerative colitis (non-severe cases) in children, and that mesalazine has acceptable safety in view of its benefits. The drug product is not classified as a poisonous drug or a powerful drug. Mesalazine is clinically meaningful because it offers a new treatment option for ulcerative colitis.

PMDA has concluded that mesalazine may be approved if mesalazine is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

May 15, 2025

Product Submitted for Approval

Brand Name	Lialda Tablets 600 mg
	Lialda Tablets 1200 mg
Non-proprietary Name	Mesalazine
Applicant	Mochida Pharmaceutical Co., Ltd.
Date of Application	July 22, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy and safety

At the Expert Discussion, the expert advisors supported PMDA's conclusions described in "7.R.1 Efficacy" and "7.R.2 Safety" of the Review Report (1).

1.2 Dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the dosage and administration described in "7.R.4 Dosage and administration" of the Review Report (1). In view of the comments from the Expert Discussion, PMDA concluded that the dosage and administration of mesalazine and the precautions concerning dosage and administration should be as follows:

Dosage and Administration (excerpt relevant to the present application only)

The usual dosage for children weighing >23 kg is 40 mg/kg of mesalazine administered orally once daily after a meal, which however should not exceed 2,400 mg. During the active phase, the usual dosage for children weighing >23 kg is 80 mg/kg of mesalazine administered orally once daily after a meal, which however should not exceed 4,800 mg and may be reduced as necessary according to the patient's condition.

Precautions Concerning Dosage and Administration (excerpt relevant to the present application only)

- For the daily dose for children, refer to the following table.

Body weight	Active phase	Remission phase
	Dose (mg/day)	Dose (mg/day)
>23 kg and ≤35 kg	2,400	1,200
>35 kg and ≤50 kg	3,600	1,800
>50 kg	4,800	2,400

- After formulation switch, the patient's condition should be carefully monitored.

1.3 Post-marketing investigations

At the Expert Discussion, the expert advisors supported PMDA's conclusion that additional pharmacovigilance activities such as post-marketing surveys are unnecessary as described in Section "7.R.5 Post-marketing investigations" of the Review Report (1).

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below. Since the present application has been submitted for a drug with a new dosage, the re-examination period should be 4 years.

Indication

Ulcerative colitis (non-severe cases)

(No change)

Dosage and Administration

The usual adult dosage is 2,400 mg of mesalazine administered orally once daily after a meal. During the active phase, the usual adult dosage is 4,800 mg of mesalazine administered orally once daily after a meal. The dose may be reduced as necessary according to the patient's condition.

<u>The usual dosage for children weighing >23 kg is 40 mg/kg of mesalazine administered orally once daily after a meal, which however should not exceed 2,400 mg. During the active phase, the usual dosage for children weighing >23 kg is 80 mg/kg of mesalazine administered orally once daily after a meal, which however should not exceed 4,800 mg and may be reduced as necessary according to the patient's condition.</u>

(Underline denotes additions.)

Appendix

List of Abbreviations

5-ASA	5-Aminosalicylate acid
Ac-5-ASA	N-Acetyl-5-aminosalicylic acid
AUC	Area under the concentration versus time curve
CI	Confidence interval
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common technical document
DBA	Double-blind acute
DBM	Double-blind maintenance
FAS	Full analysis set
IBD	Inflammatory bowel disease
LC/MS/MS	Liquid chromatography with tandem mass spectrometry
Lialda Tablets	LIALDA Tablets
LOCF	Last observation carried forward
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
Mesalazine	Mesalazine
OLA	Open-label acute
Pediatric treatment guidelines	"Guidelines on the Treatment of Pediatric Ulcerative Colitis, dated March 2019" FY2018 Report "Research on Intractable Inflammatory Bowel Disease" [Suzuki group], Research on Policy Planning and Evaluation for Rare and Intractable Diseases, a project funded by the Health and Labour Sciences Research Grants
PGA	Physician's global assessment
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	Per protocol set
PUCAI	Pediatric ulcerative colitis activity index
Study P21	Study MD090111P21
Study P22	Study MD090111P22
Study U21	Study MD090111U21
Study U32	Study MD090111U32
Study U33	Study MD090111U33
t_{max}	Time to reach maximum concentration
Treatment guidelines	"Diagnostic Criteria and Treatment Guidelines for Ulcerative Colitis and Crohn's Disease, FY2023 Revised Edition, dated March 31, 2024" FY2023 Report "Research on Intractable Inflammatory Bowel Disease" [Hisamatsu group], Research on Policy Planning and Evaluation of Rare and Intractable Diseases, funded by the Health and Labour Sciences Research Grants
UC	Ulcerative colitis
UC-DAI	Ulcerative colitis disease activity index