NDA Multidisciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	022000/S-019
Priority or Standard	Standard
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Division/Office	Division of Gastroenterology, Office of Immunology and Inflammation
Review Completion Date	June 26, 2020
Established/Proper Name	Mesalamine
(Proposed) Trade Name	Lialda
Pharmacologic Class	5-Aminosalicylic Acid
Code Name	N/A
Applicant	Shire Development, LLC
Dosage Form	Delayed-release tablets, for oral use
Applicant Proposed Dosing Regimen	Pediatric Population (b) (4)
Applicant Proposed Indication(s)/Population(s)	(b) (4) in pediatric patients (b) (4) with mildly to moderately active ulcerative colitis (UC) (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	N/A
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if Applicable)	For the treatment of mildly to moderately active ulcerative colitis in pediatric patients weighing at least 24 kg.
Recommended SNOMED CT Indication Disease Term for Each Indication (if Applicable)	N/A
Recommended Dosing Regimen	

Weight of Pediatric Patient	Once Daily Lialda Dosage	
	Weeks 0 to 8	After Week 8
24–35 kg	2.4 g (two 1.2-g tablets)	1.2 g (one 1.2-g tablet)
>35–50 kg	3.6 g (three 1.2-g tablets)	2.4 g (two 1.2-g tablets)
>50 kg	4.8 g (four 1.2-g tablets)	2.4 g (two 1.2-g tablets)

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Glossary

5-ASA	5-aminosalicylic acid
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under plasma concentration-time curve
AUC_{SS}	area under plasma concentration-time curve at steady state
BE	bioequivalence
BLQ	below the limit of quantification
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CL	apparent total body clearance of the drug from plasma
CV	coefficient of variation
DBA	double-blind acute
DBM	double-blind maintenance
E-R	exposure-response
ECG	electrocardiogram
FDA	U.S. Food and Drug Administration
GGT	gamma-glutamyl transferase
HR	hazard ratio
IBD	inflammatory bowel disease
LC/MS/MS	liquid chromatography-mass spectrometry
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
MMX	multi-matrix system
NDA	new drug application
OCP	Office of Clinical Pharmaceuticals
OLA	open-label acute
OSIS	Office of Study Integrity and Surveillance
PGA	Physician's Global Assessment
PIBD	pediatric inflammatory bowel disease
PK	pharmacokinetic
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PUC	pediatric ulcerative colitis
PWR	Pediatric Written Request
QC	quality control
SAE	serious adverse event
SABE	scaled average bioequivalence
SAP	statistical analysis plan
SWR	intrasubject variability
TBM	to-be-marketed
TEAE	treatment-emergent adverse event
UC	ulcerative colitis
(b) (4)	(b) (4)

1 Executive Summary

1.1. Product Introduction

Lialda (5-aminosalicylic acid [5-ASA; mesalamine]) was approved for the induction of remission in adults with active, mild to moderate ulcerative colitis (UC) on January 16, 2007, and for the maintenance of remission of UC on July 14, 2011. The approved dosage for the induction of remission in adult patients with mildly to moderately active ulcerative colitis is 2.4 g to 4.8 g (two to four 1.2-g tablets) taken once daily and 2.4 g (two 1.2-g tablets) taken once daily for the maintenance of remission of UC. Lialda was issued two Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs), which this efficacy supplement addresses:

- PREA PMR 731-1, a deferred study for the treatment of UC in pediatric patients of all ages (issued with the approval of the induction of remission indication in adults).
- PREA PMR 731-2, a deferred pediatric study for the maintenance of remission of UC in pediatric patients 5 to 17 years of age (issued with the approval of the maintenance of remission indication in adults).

The recommended dosage for pediatric patients weighing at least 24 kg who can swallow tablets whole is shown below.

Table 1. Recommended Dosage for Pediatric Patients of Different Weights

	Once Daily Lialda Dosage	
Weight of Pediatric Patient	**Weeks 0 to 8**	**After Week 8**
24–35 kg	2.4 g (two 1.2-g tablets)	1.2 g (one 1.2-g tablet)
>35–50 kg	3.6 g (three 1.2-g tablets)	2.4 g (two 1.2-g tablets)
>50 kg	4.8 g (four 1.2-g tablets)	2.4 g (two 1.2-g tablets)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The data submitted in this efficacy supplement establish a clinical benefit in pediatric patients weighing at least 24 kg with mildly to moderately active ulcerative colitis. Use of Lialda in this population is supported by evidence from adequate and well-controlled trials in adults and a multicenter, randomized, double-blind, parallel group trial in 105 pediatric patients 5 to 17 years of age, as well as pharmacokinetic (PK) modeling to inform the dose recommendations. The evaluation of safety in pediatric patients was similar to that observed in adults and was adequate to support product approval and labeling.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The data submitted in this efficacy supplement establish a clinical benefit in pediatric patients weighing at least 24 kg with mildly to moderately active ulcerative colitis (UC). Use of Lialda in this population is supported by evidence from adequate and well-controlled trials in adults, a phase 3 randomized, double-blind trial in 105 pediatric patients 5 to 17 years of age (Study SPD476-319), and pharmacokinetic (PK) analyses and modeling using data from the pediatric phase 3 trial and a pediatric PK study (Study SPD476-112). The evaluation of safety in pediatric patients was similar to that observed in adults and was adequate to support product approval and labeling.

Study SPD476-319 was a multicenter, randomized, double-blind, parallel-group study that evaluated two weight-based dose levels of Lialda (low dose [900 mg to 2.4 g] and high dose [1.8 to 4.8 g]) in pediatric patients aged 5 to 17 years with mildly to moderately active UC. The trial consisted of a screening period, an 8-week double-blind acute (DBA) phase followed by a 26-week double-blind maintenance (DBM) phase. There was also an optional 8-week open-label acute (OLA) phase for patients who did not respond during the DBA phase. Patients were eligible to enter the DBA phase if they had a UC-DAI ≥4 (with a combined rectal bleeding and stool frequency score ≥1, Physician's Global Assessment [PGA] of 1 or 2, and an endoscopic score of 2 or 3).

A total of 53 patients were randomized 1:1 (stratified by body weight group) to one of two weight-based dose levels (low or high dose) in the DBA phase. Eighty-seven patients were randomized, using the same approach as the DBA phase, to one of two weight-based dose levels in the 26-week DBM phase; 27 patients enrolled into the DBM phase after completing 8 weeks of initial treatment during the DBA phase and achieving the primary endpoint of clinical response, defined as a partial UC-DAI ≤1 (with rectal bleeding =0, stool frequency ≤1, and PGA score =0); 18 patients were treated in the OLA phase with the high-dose level of mesalamine as appropriate for their weight group after completing the DBA phase and failing to achieve a clinical response/remission during the DBA phase (12 patients), or withdrawing from the DBA phase due to lack of benefit (six patients). Of these 18 patients, eight patients enrolled into the DBM phase after achieving a clinical response, as defined above; 52 patients had not participated in the DBA phase but were treated with a 5-ASA product and had a UC-DAI ≤2 (with rectal bleeding =0, stool frequency ≤1, PGA =0, and an endoscopic subscore of 0 or 1 [modified to exclude friability from a score of 1]) prior to directly enrolling in the DBM phase.

The primary efficacy endpoint for both the DBA and DBM phases was the proportion of patients with a clinical response (defined as partial UC-DAI ≤1 with rectal bleeding =0, stool frequency ≤1, and PGA =0). The study was not powered for efficacy, and there was no formal hypothesis testing planned; hence, p-values were nominal and are not reported. Efficacy was extrapolated from adequate and well-controlled trials conducted in adults with mildly to moderately active UC, based on sufficiently similar pathophysiology, disease progression, and response to treatment between adults and pediatric patients. The results of the pediatric clinical trial provide additional data to support the clinical benefit in pediatric patients and inform the dosing recommendations and safety of Lialda use in pediatric patients. At Week 8 of the DBA phase, 10/27 (37.0%) patients in the low-dose group achieved a clinical response compared to 17/26 (65.4%) patients in the high-dose group with a corresponding difference of 28.3%. While not reported in the clinical study report (CSR), the corresponding 95% confidence interval (95% CI)

from the normal approximation with a continuity correction was (-1.2, 57.9), as calculated by the review team. At Week 26 of the DBM phase, 23/42 (54.8%) patients in the low-dose group achieved clinical response compared to 24/45 (53.3%) patients in the high-dose group. The response proportion in both dose groups was similar (difference in response proportions of -1.4). While not reported in the CSR, the corresponding 95% CI from the normal approximation with a continuity correction was (-24.7, 21.8), as calculated by the review team. The Applicant's sensitivity analysis results for the primary efficacy endpoint for the DBA and DBM phases were generally consistent with the primary analysis results.

The Applicant evaluated a secondary endpoint of "clinical and endoscopic remission" in the DBA and DBM phases, defined by a UC-DAI score ≤2 with rectal bleeding subscore =0, stool frequency subscore ≤1, PGA =0, and endoscopy subscore ≤1 based on central reading. Because the endpoint definition for both the primary and secondary endpoints differed from the currently recommended endpoint definitions, the review team considered additional analyses for Weeks 8 and 26 using the recommended definition of clinical remission. The recommended definition of clinical remission is defined using the Mayo score (excluding the PGA) with a stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopic subscore of 0 or 1 (modified to exclude friability), or 0 on the UC-DAI. The recommended definition of clinical response is defined by a decrease from baseline in the Mayo Score (modified to exclude the PGA) of ≥2 points AND a 30% reduction from baseline PLUS a decrease in rectal bleeding subscore of ≥1 or an absolute rectal bleeding subscore of ≤1. In the DBA phase, only two patients in the low-dose group and three patients in the high-dose group underwent endoscopy at both Week 0 and Week 8; thus, analyses of the recommended clinical remission and clinical response endpoints were not feasible. At Week 26 of the DBM phase, 15/42 (35.7%) patients in the low-dose group achieved clinical remission compared to 12/45 (26.7%) patients in the high-dose group, which also supports the recommended low dose for continued treatment after Week 8. The difference in the proportions of patients with a clinical response (high to low dose) was -9.0% (95% CI [normal approximation with continuity correction]: -30.8, 12.7). An analysis of clinical response at Week 26 of the DBM phase (using the currently recommended endpoint definition), was not informative since this endpoint requires comparison to the pretreatment baseline disease severity score, which was not available for over half of the patients who enrolled into the DBM phase as they did not participate in the DBA phase; these patients already met the criterion of partial UC-DAI ≤1 at enrollment into the DBM phase.

The safety profile for pediatric patients was generally similar to that of adults, and to other 5-aminosalicylate products. Overall, the most common adverse event was worsening of UC, which most likely reflects lack of efficacy rather than a drug-related adverse event. Adverse events that were not related to UC were generally infrequent, mild to moderate in severity, and generally did not lead to discontinuation from the study. The most common adverse reactions reported in at least 5% of pediatric patients treated with Lialda were: abdominal pain, upper respiratory tract infection, vomiting, anemia, headache, and viral infection.

Based on extrapolation of efficacy from adult data and additional support from the efficacy results from the pediatric phase 3 trial, the review team concluded that the data support recommending the weight-based high-dose level for the initial 8 weeks of treatment and the low-dose level for continued treatment after Week 8. During the DBA phase of the pediatric trial, a higher proportion of patients achieved a clinical response at Week 8 in the high-dose level (65.4%) compared to the low-dose level (37.0%). In addition, there were fewer UC related discontinuations in the high-dose treatment arm compared to the low-dose treatment arm during the DBA phase, further supporting the recommendation of the high-dose for the initial 8 weeks of treatment. Of note, in the adult UC program, there was no dose-response observed

in remission rates between the low dose (2.4 g) and high dose (4.8 g) during the initial 8 weeks of treatment. During the DBM phase of the pediatric trial, there were no notable differences in efficacy or safety outcomes between the two dose levels; therefore, the lowest effective dose is recommended.

During the DBM phase of the trial, patients weighing >35-50 kg were administered either the low dose (1.8 g) or high dose (3.6 g); however, labeling the low dose (1.8 g) for treatment after Week 8 in this weight subgroup would not be feasible since the Applicant does not intend to manufacture the lower strength tablets that were used in the pediatric trial (i.e., 300-mg and 600-mg tablets), and the currently available marketed dose strength is a 1.2-g tablet. The 300-mg and 600-mg tablets that were used in the pediatric phase 3 study were demonstrated to be bioequivalent to the commercially available 1.2-g formulation; therefore, the review team assessed whether existing data support a dose using the 1.2-g tablet for the >35-50 kg weight group. The 2.4-g dose was identified as an appropriate dose for treatment after Week 8 in this weight group. Recommending a dose that falls between the low- (1.8 g) and high-dose (3.6 g) levels that were evaluated in patients weighing >35-50 kg during the trial was supported by the flat dose- and exposure-response relationships observed between the two dose levels (1.8 g and 3.6 g) in the DBM phase. Additionally, the safety profile of the two dose levels were similar, and the predicted systemic exposure with 2.4 g based on PK modeling was lower than the higher dose (3.6 g) studied in this weight group, thus further supporting the safety of the 2.4-g dose. Further details on the modeling are provided in the pharmacometrics section of this document. Safety data were also available for the 2.4-g dose in other body weight groups and did not raise concerns that would preclude recommending the 2.4-g dose for the patients who weigh >35-50 kg.

The initial proposed labeling was limited to patients weighing 50 to 90 kg, which would substantially limit the availability of therapy in the pediatric population since many pediatric patients weigh less than 50 kg. Although the review team leveraged existing PK modeling data to support labeling Lialda in a wider range of pediatric patients than initially proposed, there were no patients <24 kg in the DBA phase and only three patients <24 kg in the DBM phase; due to the small number of patients in the lowest weight group (18 to ≤23 kg), safety and efficacy could not be established for patients weighing less than 24 kg. Therefore, the indication will be limited to patients weighing at least 24 kg.

The recommended dosage for pediatric patients weighing at least 24 kg who can swallow tablets whole is shown below:

Recommended Dosage for Pediatric Patients of Different Weights

	Once Daily Lialda Dosage	
Weight of Pediatric Patient	**Weeks 0 to 8**	**After Week 8**
24–35 kg	2.4 g (two 1.2-g tablets)	1.2 g (one 1.2-g tablet)
>35–50 kg	3.6 g (three 1.2-g tablets)	2.4 g (two 1.2-g tablets)
>50 kg	4.8 g (four 1.2-g tablets)	2.4 g (two 1.2-g tablets)

Although labeling Lialda in patients weighing at least 24 kg does not cover the entire pediatric population who may benefit from treatment with Lialda, there is no regulatory pathway to require additional data for the treatment of pediatric patients beyond the initial 8 weeks of treatment

(b) (4). Furthermore, in light of the challenges with enrolling pediatric patients with UC in clinical trials and the wide availability of mesalamine products for the treatment of UC, the Applicant is unlikely to obtain additional, interpretable data in the subgroup of patients weighing less than 24 kg. The Applicant proposed to conduct one pediatric trial to address both Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) despite the orphan designation. The following PREA PMRs will be considered as fulfilled upon approval of this efficacy supplement:

- PMR 731-1, a deferred study for the treatment of UC in pediatric patients of all ages (issued with the approval of the induction of remission indication in adults).
- PMR 731-2, a deferred pediatric study for the maintenance of remission of UC in pediatric patients 5 to 17 years of age (issued with the approval of the maintenance of remission indication in adults).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Inflammatory bowel disease (IBD) is a chronic immune-mediated disorder characterized by relapsing and remitting intestinal inflammation. UC is a type of IBD restricted predominantly to the large intestine. Pediatric patients with UC most commonly present with abdominal pain, diarrhea, rectal bleeding, and fecal urgency. UC is also associated with extraintestinal manifestations including peripheral arthritis, aphthous stomatitis, uveitis, pyoderma gangrenosum, erythema nodosum, psoriasis, and primary sclerosing cholangitis. Severe symptoms may lead to anemia requiring blood transfusion, dehydration, weight loss, hospitalization, surgery, and death.	UC is a chronic, relapsing disease of the colonic mucosa. Patients with UC most commonly present with abdominal pain, diarrhea, rectal bleeding, and fecal urgency. If left untreated or poorly treated with residual, ongoing inflammation, patients may suffer from significant morbidity and/or mortality.
Current Treatment Options	The goals of therapy in pediatric UC include improvement in signs and symptoms, avoidance of chronic corticosteroid use, and prevention of UC-related complications such as acute severe colitis, that may require hospitalization and emergency surgery, or development of malignancy. Control of inflammation is needed to ensure appropriate nutrition to promote optimal growth and development in the pediatric population. FDA approved therapies for mildly to moderately active pediatric UC include 5-aminosalicylates (5-ASAs), which are available in several formulations and dosage regimens. In addition to FDA-approved therapies, the treatment of UC in pediatric patients frequently includes off-label treatment with therapies that are approved for use in adult patients but not pediatric patients. There are also	Additional therapies are needed for the pediatric population with mildly to moderately active UC. There remains a need for therapies approved in the pediatric population as not all patients will respond or have continued response to any given treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	a limited number of products approved for pediatric patients with moderately to severely active UC, such as infliximab.	
Benefit	Study SPD476-319 was a multicenter, randomized, double-blind, parallel-group study that evaluated two weight-based dose levels of Lialda (low dose [900 mg to 2.4 g] and high dose [1.8 to 4.8 g]) in pediatric patients aged 5 to 17 years with mildly to moderately active UC. The trial consisted of a screening period, an 8-week DBA phase followed by a 26-week DBM phase. There was also an optional 8-week OLA phase for patients who did not respond during the DBA phase. Patients were eligible to enter the DBA phase if they had a UC-DAI ≥4 (with a combined rectal bleeding and stool frequency score ≥1, PGA of 1 or 2, and an endoscopic score of 2 or 3). A total of 53 patients were randomized 1:1 (stratified by body weight group) to one of two weight-based dose levels (low and high dose) in the DBA phase. Eighty-seven patients were randomized, using the same approach as the DBA phase, to one of two weight-based dose levels in the 26-week DBM phase; 27 patients enrolled into the DBM phase after completing 8 weeks of initial treatment during the DBA phase and achieving the primary endpoint of clinical response, defined as a partial UC-DAI ≤1 (with rectal bleeding =0, stool frequency ≤1, and PGA score =0); 18 patients were treated in the OLA phase with the high-dose level of mesalamine as appropriate for their weight group after completing the DBA phase and failing to achieve a clinical response/remission during the DBA phase (12 patients), or withdrawing from the DBA phase due to lack of benefit (six patients). Of these 18 patients, eight patients enrolled into the DBM phase after achieving a clinical response, as defined above; 52 patients had not participated in the DBA phase but were treated with a 5-ASA product and had a UC-DAI ≤2 (with rectal bleeding =0, stool frequency ≤1, PGA =0, and an endoscopic subscore of 0 or 1 [modified to exclude friability from a score of 1]) prior to directly enrolling in the DBM phase.	Based on extrapolation of efficacy from adult data and additional support from the efficacy results from the pediatric phase 3 trial, the review team concluded that the data support recommending the weight-based high-dose level for the initial 8 weeks of treatment and the low-dose level for continued treatment after Week 8. The weight-based high-dose level is recommended for the initial 8 weeks of treatment and the low-dose level for continued treatment after Week 8. During the DBA phase of the pediatric trial, a higher proportion of patients achieved a clinical response at Week 8 in the high-dose level (65.4%) compared to the low-dose level (37.0%). In addition, there were fewer UC related discontinuations in the high-dose treatment arm compared to the low-dose treatment arm during the DBA phase, further supporting the recommendation of the high-dose for the initial 8 weeks of treatment. During the DBM phase, there were no notable differences in efficacy or safety outcomes between the two dose levels; therefore, the lowest effective dose is recommended. Of note, in the adult UC program, there was no dose-response observed in remission rates

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The primary efficacy endpoint for both the DBA and DBM phases was the proportion of patients with a clinical response (defined as partial UC-DAI ≤1 with rectal bleeding =0, stool frequency ≤1, and PGA =0). The study was not powered for efficacy, and there was no formal hypothesis testing planned; hence, p-values were nominal and are not reported. At Week 8 of the DBA phase, 10/27 (37.0%) patients in the low-dose group achieved a clinical response compared to 17/26 (65.4%) patients in the high-dose group with a corresponding difference of 28.3%. While not reported in the CSR, the corresponding 95% CI from the normal approximation with a continuity correction was (-1.2, 57.9), as calculated by the review team. At Week 26 of the DBM phase, 23/42 (54.8%) patients in the low-dose group achieved clinical response compared to 24/45 (53.3%) patients in the high-dose group. The response proportion in both dose groups was similar (difference in response proportions of -1.4). While not reported in the CSR, the corresponding 95% CI from the normal approximation with a continuity correction was (-24.7, 21.8), as calculated by the review team. The Applicant's sensitivity analysis results for the primary efficacy endpoint for the DBA and DBM phases were generally consistent with the primary analysis results. The Applicant evaluated a secondary endpoint of "clinical and endoscopic remission" in the DBA and DBM phases, defined by UC-DAI score ≤2 with rectal bleeding subscore =0, stool frequency subscore ≤1, PGA =0, and endoscopy subscore ≤1 based on central reading. Because the endpoint definition for both the primary and secondary endpoints differed from the currently recommended endpoint definitions, the review team requested additional analyses for Weeks 8 and 26 using the recommended definition of clinical remission. The recommended definition of clinical remission is defined using the Mayo score (excluding the PGA) with a stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopic subscore of 0 or 1 (modified to exclude friability), or 0 on the UC-DAI. The recommended definition of clinical response is defined by a decrease from baseline in the Mayo Score (modified to exclude the PGA) of ≥2 points AND a 30% reduction from baseline PLUS a decrease in rectal bleeding subscore of ≥1 or an absolute rectal bleeding subscore of ≤1. In the DBA phase, only two patients	between the low dose and high dose during the initial 8 weeks of treatment. The 2.4-g dose was identified as an appropriate dose for treatment after Week 8 in this weight group. Recommending a dose that falls between the low (1.8 g) and high-dose (3.6 g) levels that were evaluated in patients weighing >35-50 kg during the trial was supported by the flat dose- and exposure-response relationship observed between the two dose levels (1.8 g and 3.6 g) in the DBM phase. Additionally, the safety profile of the two dose levels were similar, and the predicted systemic exposure with 2.4 g was lower than the higher dose (3.6 g) studied in this weight group, thus further supporting the safety of the 2.4-g dose. Safety data were also available for the 2.4-g dose in other body weight groups and did not raise concerns that would preclude recommending the 2.4-g dose for the patients who weigh >35-50 kg. Although the review team leveraged existing PK modeling data to support labeling Lialda in a wider range of pediatric patients than initially proposed, there were no patients <24 kg in the DBA phase and only three patients <24 kg in the DBM phase; due to the small number of patients in the lowest weight group (18 to ≤23 kg), safety and efficacy could not be established for patients weighing less than

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in the low-dose group and three patients in the high-dose group underwent endoscopy at both Week 0 and Week 8; thus, analyses of the recommended clinical remission and clinical response endpoints were not feasible. At Week 26 of the DBM phase, 15/42 (35.7%) patients in the low-dose group achieved clinical remission compared to 12/45 (26.7%) patients in the high-dose group, which also supports the recommended low dose for continued treatment after Week 8. The difference in the proportions of patients with a clinical response (high to low dose) was -9.0% (95% CI [normal approximation with continuity correction]: -30.8, 12.7). An analysis of clinical response at Week 26 of the DBM phase (using the currently recommended endpoint definition), was not informative since this endpoint requires comparison to the pretreatment baseline disease severity score, which was not available for over half of the patients who enrolled into the DBM phase as they did not participate in the DBA phase; these patients already met the criterion of partial UC-DAI ≤1 at enrollment into the DBM phase. During the DBM phase of the trial, patients weighing >35-50 kg were administered either the low dose (1.8 g) or high dose (3.6 g); however, labeling the low dose (1.8 g) for treatment after Week 8 in this weight subgroup would not be feasible since the Applicant does not intend to manufacture the lower strength tablets that were used in the pediatric trial (i.e., 300-mg and 600-mg tablets), and the currently available marketed dose strength is a 1.2-g tablet. The 300-mg and 600-mg tablets that were used in the pediatric phase 3 study were demonstrated to be bioequivalent to the commercially available 1.2-g formulation; therefore, the review team performed PK modeling to help assess whether existing data support a dose using the 1.2-g tablet for the >35-50 kg weight group. Further details on the modeling are provided in the pharmacometrics section of this document. The initial proposed labeling was limited to patients weighing 50 to 90 kg which substantially limit the availability of therapy in the pediatric population since many pediatric patients weigh less than 50 kg. The data from the	24 kg. Therefore, the indication will be limited to patients weighing at least 24 kg. Although labeling Lialda in patients weighing at least 24 kg does not cover the entire pediatric population who may benefit from treatment with Lialda, there is no regulatory pathway to require additional data for the treatment of pediatric patients beyond the initial 8 weeks of treatment (b) (4) [redacted]. Furthermore, in light of the challenges with enrolling pediatric patients with UC in clinical trials and the wide availability of mesalamine products for the treatment of UC, the Applicant is unlikely to obtain additional, interpretable data in the subgroup of patients weighing less than 24 kg. Therefore, the PREA PMRs will be considered as fulfilled upon approval of this efficacy supplement.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pediatric trial, supported by extrapolation of efficacy from adult trials, provide evidence of benefit in patients weighing at least 24 kg. However, safety and efficacy could not be established for patients weighing less than 24 kg because there were no patients <24 kg in the DBA phase and three patients <24 kg in DBM phase of the clinical trial.	
Risk and Risk Management	The safety profile for pediatric patients was generally similar to that of adults, and to other 5-aminosalicylate products. Overall, the most common adverse event was worsening of UC, which most likely reflects lack of efficacy rather than a drug-related adverse event. Adverse events that were not related to UC were generally infrequent, mild to moderate in severity, and generally did not lead to discontinuation from the study. The most common adverse reactions reported in at least 5% of pediatric patients treated with Lialda were: abdominal pain, upper respiratory tract infection, vomiting, anemia, headache, and viral infection.	The evaluation of safety in pediatric patients was similar to that observed in adults and was adequate to support product approval and labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Efficacy data included patient-reported signs and symptoms
		X	Patient-reported outcome (PRO)	
		X	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	ClinRO data were collected during the study as secondary/exploratory endpoints.
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data were not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Inflammatory bowel disease (IBD) is a chronic immune-mediated disorder characterized by relapsing and remitting intestinal inflammation. UC is a type of IBD restricted predominantly to the large intestine and associated with defects in colonic epithelial cells, intestinal barrier function, and host immune responses (Ungaro et al. 2017). The principle symptoms of pediatric ulcerative colitis (PUC) include abdominal pain, diarrhea, rectal bleeding, and fecal urgency. In addition, extraintestinal manifestations may occur including peripheral arthritis, aphthous stomatitis, uveitis, pyoderma gangrenosum, erythema nodosum, psoriasis, and primary sclerosing cholangitis (Greuter et al. 2017). Clinical manifestations vary depending upon the area, extent, and severity of involvement. Patients with mild disease may have a normal stooling pattern with mild abdominal pain and/or mild rectal bleeding. Severe disease can be characterized by greater than 15 bowel movements per day with significant blood loss, protein-losing enteropathy, abdominal pain, incontinence, tenesmus, and sleep disturbance. Severe symptoms may lead to anemia requiring blood transfusion, dehydration, weight loss, hospitalization, and surgery (Ungaro et al. 2017).

The diagnosis of PUC is confirmed by a combination of clinical, endoscopic, and histologic findings. Pediatric patients presenting with the cardinal symptoms described above undergo esophagogastroduodenoscopy and colonoscopy with biopsy. Typical endoscopic findings include mucosal erythema, friability, erosions, ulcerations, and spontaneous bleeding (Schroeder et al. 1987). Histologic assessment of mucosal biopsies demonstrates chronic inflammation restricted to the mucosal layer, characterized by tissue infiltration of lymphocytes, granulocytes, and plasma cells. Other features include ulcerations, decreased goblet cells, and crypt distortion (Danese and Fiocchi 2011).

Pediatric inflammatory bowel disease (PIBD) remains a growing public health concern due to its increasing prevalence, high cost of care, and impact on the health of children. Firstly, the rates of PIBD are increasing globally (Benchimol et al. 2011). An accurate estimate of incidence rates in the United States is lacking due to the absence of a national cohort in addition to conflicting results produced by regional estimates. The annual incidence of PUC are 2.4 per 100,000 among Wisconsin children (Adamiak et al. 2013) and 4.3 per 100,000 in a Northern California health plan population (Abramson et al. 2010). Secondly, the cost of care for PIBD is not well described but there are several studies in adults that illustrate the high financial impact of IBD. For example, one adult study that evaluated direct and indirect costs, estimated a mean cost of $26,555 in the first year after diagnosis and out-of-pocket expenses averaging $2,213 per year compared to $979 in patients without IBD (Park et al. 2020). Lastly, PIBD patients may have an increased risk of all-cause mortality (adjusted hazard ratio [HR] 3.2 [confidence interval (CI): 2.8-3.7]) with the highest risk estimates in PUC (adjusted HR 4.0 [CI: 3.4-4.7]) as reported in a recent study utilizing the Swedish National Patient Registry. The increased hazard ratios of death in PIBD patients are not limited to gastrointestinal mortality, it includes deaths due to respiratory diseases, infectious disease, and cancer (Olen et al. 2019). The increased HR of death in PUC may be driven by primary sclerosing cholangitis, which significantly increases the risk of colon (Zheng and Jiang 2016) and pancreatic cancer (Razumilava et al. 2011).

2.2. Analysis of Current Treatment Options

The goals of therapy in PUC include improvement in signs and symptoms, avoidance of chronic corticosteroid use, cancer prevention, and the prevention of UC-related complications such as acute severe colitis, that may require hospitalization and emergency surgery. Unique to the pediatric population, control of inflammation is needed to ensure appropriate nutrition to promote optimal growth and development (Rufo et al. 2012). In addition to the improvement in clinical symptoms, there is a recent focus on the improvement in the endoscopic (Peyrin-Biroulet et al. 2011) and histologic (Bryant et al. 2016) appearance of the intestine, which has been associated with improved outcomes in adults.

FDA approved therapies for mildly to moderately active PUC (Table 2) include 5-aminosalicylates (5-ASAs) for the induction and maintenance of remission. 5-ASAs are available in several formulations and dosage regimens. Patients with moderate PUC may receive oral corticosteroids, such as prednisone or budesonide, either at the beginning of the disease course or in patients who do not improve with 5-ASA therapy. It is not uncommon for pediatric patients to present with moderate to severe disease that may require hospitalization. These patients may be treated with intravenous corticosteroids as a bridge to a 5-ASA or started on antitumor necrosis factor therapy, such as infliximab (Turner et al. 2012).

In addition to FDA-approved therapies, the treatment of PUC frequently includes treatment with therapies that are approved for use in adult patients but not pediatric patients. Azathioprine or mercaptopurine are often used for mildly to moderately active PUC that does not improve with 5-ASA therapy. Moderate to severe disease may be treated with anti-integrin agents (e.g., vedolizumab) (Singh et al. 2016), Janus kinase inhibitors (e.g., tofacitinib) or other immunosuppressive agents (e.g., tacrolimus) (Turner et al. 2012).

Table 2. Approved Treatments for Pediatric UC

FDA Approved Treatment	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues
Azulfidine® (sulfasalazine) Initial Approval: 1950	Adults and children 6 years of age and older: Treatment of mildly to moderately active UC and as adjunctive therapy in severely active UC Prolongation of the remission period between acute attacks of UC	<u>Pediatric dosage:</u> Induction: 40–60 mg/kg per day, divided into 3 to 6 doses Maintenance: 30 mg/kg per day, divided into 4 doses	Clinical Studies are not included in the label. An active comparator study in pediatric patients with UC showed clinical improvement in 75% at 4 weeks and 79% at 3 months (Ferry et al. 1993).	<u>Warnings and precautions:</u> Avoid in patients with hepatic or renal impairment Hypersensitivity reactions including agranulocytosis, aplastic anemia, renal, liver, pulmonary and CNS damage Oligospermia and infertility Serious infections <u>Most common adverse reactions:</u> Anorexia, headache, nausea, vomiting, abdominal pain, rash, and urticaria
Colazal® (balsalazide disodium) Approval: 2006	Adults and children 5 years of age and older: Treatment of mildly to moderately active UC Safety and effectiveness beyond 8 weeks in children and 12 weeks in adults have not been established	<u>Pediatric dosage:</u> Three 750 mg capsules 3 times a day for 8 weeks Or One 750 mg capsule 3 times a day for up to 8 weeks	One clinical trial was conducted comparing two doses in 68 pediatric patients for 8 weeks. The primary endpoint was clinical improvement.[a] In the 6.75 g/day group: 45% had a clinical improvement 64% had improved rectal bleeding 61% had improved mucosal appearance In the 2.25 g/day group 37% had a clinical improvement 54% had improved rectal bleeding 46% had improved mucosal appearance	<u>Warnings and precautions:</u> Exacerbation of symptoms of ulcerative colitis Prolonged gastric retention in patients with pyloric stenosis <u>Most common adverse reactions:</u> Headache, abdominal pain, diarrhea, nausea, vomiting, respiratory infection, and arthralgia

FDA Approved Treatment	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues
Delzicol® (mesalamine, delayed-release capsule) Approval: 2014	Adults and children 5 years of age and older: Treatment of mildly to moderately active UC	Pediatric dosage: 17–32 kg: two 400 mg capsules in AM, one 400 mg capsule in PM 33–53 kg: three 400 mg capsules in AM, two 400 mg capsules in PM 54–90 kg: three 400 mg capsules in AM, three 400 mg capsules in PM Duration: 6 weeks	One clinical trial was conducted comparing two doses in 82 pediatric patients for 6 weeks. The primary endpoint was clinical improvement.[b] In the low-dose group (1.2, 2, and 2.4 g/day based on weight) 73% had a partial response on the TM-Mayo 56% had a partial response based on the PUCAI 34% had a complete response on the TM-Mayo 46% had a complete response based on the PUCAI In the high-dose group (2, 3.6, and 4.8 g/day based on weight) 70% had a partial response on the TM-Mayo 55% had a partial response based on the PUCAI 43% had a complete response on the TM-Mayo 43% had a complete response based on the PUCAI	Warnings and precautions: Renal impairment Mesalamine-induced acute intolerance syndrome Hypersensitivity reactions, including myocarditis and pericarditis Evaluate risks and benefits of use in renal and hepatic impairment Most common adverse reactions: Nasopharyngitis, headache, abdominal pain, dizziness, sinusitis, rash, cough, and diarrhea

FDA Approved Treatment	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues
Remicade® (infliximab) Biosimilars: Avsola® (infliximab-axxq) Inflectra® (infliximab-dyyb) Ixifi® (infliximab-qbtx) Renflexis® (infliximab-abda) Approved: 2011	Adults and children 6 years of age and older: Reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderate to severely active ulcerative colitis who have had an inadequate response to conventional therapy	Pediatric dosage: Induction: 5 mg/kg IV at 0, 2, and 6 weeks Maintenance: 5 mg/kg IV every 8 weeks	One open-label safety and PK trial was performed in 60 pediatric patients with UC for 8 weeks (induction phase) and 45 pediatric patients with UC for an additional 46 or 42 weeks (maintenance phase). The primary endpoint was clinical remission.[c] 73% of patients receiving 5 mg/kg achieved a clinical response (Mayo) at Week 8 40% (Mayo) and 33% (PUCAI) of patients receiving 5 mg/kg achieved clinical remission at Week 8. 38% and 18% of patients achieved clinical remission (PUCAI) receiving every 8-week infusions and every 12-week infusions, respectively, at Week 54.	Boxed Warning: Increased risk of serious infections leading to hospitalization or death (including TB, histoplasmosis, and opportunistic pathogens) Lymphoma and other malignancies (such as lymphoma and hepatosplenic T-cell lymphoma) have been reported in children and adolescent patients treated with Remicade® Additional warnings and precautions: Hepatitis B reactivation Hepatotoxicity Hypersensitivity (including anaphylaxis or serum sickness-like reactions) Cardiovascular and cerebrovascular reactions Demyelinating disease Lupus-like syndrome Avoid giving live vaccines or therapeutic infectious agents Most common adverse reactions: Infections (upper respiratory, sinusitis, pharyngitis), infusion-related reactions, headache, and abdominal pain

[a] At least a 3-point reduction in the Modified Sutherland Ulcerative Colitis Activity Index (MUCAI) from baseline to 8 weeks.
[b] Improvement in either the TM-Mayo or the PUCAI. Success was defined as:

- Partial response
  - An improvement from baseline in stool frequency or rectal bleeding subscore with no worsening in the other (TM-Mayo)
  - A reduction of greater than or equal to 20 points from baseline to Week 6 (PUCAI)
- Complete response
  - Both stool frequency and rectal bleeding subscores equal 0 (TM-Mayo)
  - A score at Week 6 less than 10 (PUCAI)

[c] Clinical remission was defined as a Mayo Score of less than or equal to 2 points with no individual subscore greater than 1 or a PUCAI score less than 10. Clinical response was defined as a decrease from baseline in the Mayo score by greater than or equal to 30% and greater than or equal to 3 points, including a decrease in the rectal bleeding subscore by greater than or equal to 1 points or achievement of a rectal bleeding subscore of 0 or 1.
Abbreviations: CNS, central nervous system; IV, intravenous; PK, pharmacokinetic; PUCAI, Pediatric Ulcerative Colitis Activity Index; TB, tuberculosis; TM-Mayo, Truncated Mayo Score; UC, ulcerative colitis

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Approved Indications of Lialda Under NDA 022000: Ulcerative Colitis in Adults

Lialda was approved for the induction of remission in adults with active, mild to moderate UC on January 16, 2007, and for the maintenance of remission of UC on July 14, 2011. The approved dosage for the induction of remission in adult patients with mildly to moderately active ulcerative colitis is 2.4 g to 4.8 g (two to four 1.2-g tablets) taken once daily and 2.4 g (two 1.2-g tablets) taken once daily for the maintenance of remission of UC. Lialda was issued two PREA PMRs, which this supplemental NDA seeks to address. PREA PMR 731-1, a deferred study for the treatment of UC in pediatric patients of all ages, was issued with the approval of the induction of remission indication in adults. PREA PMR 731-2, a deferred pediatric study for the maintenance of remission of UC in pediatric patients 5 to 17 years of age, was issued with the approval of the maintenance of remission indication in adults.

3.2. Summary of Presubmission/Submission Regulatory Activity

Issuance of PREA PMRs and Orphan Designation for Pediatric Ulcerative Colitis

PREA PMR 731-1, a deferred study for the treatment of UC in pediatric patients of all ages, was issued at the time of the initial approval of Lialda for the induction of remission of active, mild to moderate UC in adults. (b) (4) the Applicant was reminded of prior recommendations, (b) (4) .

(b) (4) . The orphan designation (b) (4) on October 21, 2010, to include the treatment of UC in pediatric patients.

PREA PMR 731-2, a deferred pediatric study for the maintenance of remission of UC in pediatric patients 5 to 17 years of age, was issued at the time of approval of Lialda for the maintenance of remission in adults with UC. (b) (4) The Applicant proposed a single phase 3 study to evaluate the acute and maintenance treatment of UC in pediatric patients 5 to 17 years of age in order to fulfill both PREA PMRs (Pediatric Study Plan: SPD476-319, submitted June 14, 2010). Therefore, (b) (4) both PMR 731-1 and 731-2 remained in effect as postmarketing requirements that would be fulfilled with the single study.

Proposed Pediatric Study Request and Subsequent Expiration of Pediatric Written Request

The Applicant submitted a Proposed Pediatric Study Request (PPSR) on October 18, 2013, and a Pediatric Written Request (PWR) was issued on May 2, 2014. (b) (4)

(b) (4)

(b) (4)

(b) (4) Relatedly, a deferral extension was granted that extended the Final Study Report submission dates for both PREA PMRs (PMR 731-1 and 731-2) from November 2018 to September 30, 2019.

3.3. Foreign Regulatory Actions and Marketing History

Lialda was first approved in the European Union via the decentralized procedure with the Reference Member State identified as the Netherlands. The decentralized procedure was closed on December 13, 2006 and the first national license was approved in Denmark on January 12, 2007. At the time of this review, Lialda has marketing authorization in 32 countries under the trade names: Mazavant, Mazavant XL, Lialda, and Mazavant XL 1,200 mg. There are no new safety signals or ongoing postmarketing safety concerns raised by foreign regulatory agencies.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

A clinical inspection was performed at Site 356, Dr. Bartosz Korczowski because this site enrolled the highest number of study subjects. The inspection verified the reported primary efficacy measures with source data at the clinical investigator's site. Overall, the data generated by this clinical investigator's site appear to be acceptable and supportive of this sNDA.

A site inspection for the clinical study site and bioanalytical assay site for bioequivalence studies SHP476-121 and SHP476-122 were requested on January 21, 2020. The Division of New Drug Study Integrity within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection for these two study sites is not warranted at this time because the clinical site was inspected in February 2018 and the analytical site was inspected in (b) (4) which fall within the surveillance interval. The final classification for the inspections was No Action Indicated.

4.2. Product Quality

No new product quality information was submitted with the efficacy supplement.

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

N/A

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical information was submitted with the efficacy supplement.

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology review focuses on mesalamine PK characterization in the pediatric patients with UC, exposure-response analysis, and bridging between the (b) (4) formulations with lower strength (300 mg and 600 mg) that were used in the pediatric safety and efficacy study to the to-be-marketed (TBM) formulation that is the same as the already commercially available 1.2-g tablet strength.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacology

The mechanism of action of mesalamine is not fully understood, but it appears to have a topical anti-inflammatory effect on the colonic epithelial cells.

PK in Pediatric Patients With UC

PK in pediatric patients with UC were assessed with population PK analysis.

Per the Lialda label, in healthy adult subjects, approximately 21 to 22% of the administered dose is absorbed from Lialda 2.4 g or 4.8 g given once daily for 14 days. Upon oral absorption, a major metabolite N-acetyl-5-aminosalicylic acid is formed by N-acetyltransferase activity in the liver and intestinal mucosa cells. Of the approximately 21 to 22% of the dose absorbed, less than 8% of the dose was excreted unchanged in the urine after 24 hours, compared with greater than 13% for N-acetyl-5-aminosalicylic acid. The apparent terminal half-lives for mesalamine and its major metabolite after administration of Lialda 2.4 g and 4.8 g were, on average, 7 to 9 hours and 8 to 12 hours, respectively.

Following oral administration of 4.8 g mesalamine with currently marketed formulation, the overall systemic exposure of mesalamine in a limited number of pediatric patients with UC aged 5 to 17 years (area under plasma concentration-time curve [AUC] of 30,556-50,388 µg.hr/L) was in similar range to that observed in healthy adults (AUC of 49559±23780 µg.hr/L) after administration of multiple doses.

In a multiple-dose PK study in pediatric patients with mildly to moderately active UC:

- Steady state for 5-ASA appears to reach by Day 7 following daily dose in pediatric patients.
- At steady state on Day 7, systemic exposure of both the parent 5-ASA and metabolite Ac-5-ASA (measured by mean AUC_{SS} and C_{maxSS}) increased in a dose-proportional manner between 30 and 60 mg/kg/day and increased in a subproportional manner between 60 and 100 mg/kg/day dose.
- Both the AUC and C_{max} of the parent 5-ASA and metabolite Ac-5-ASA PK had moderate to high intersubject variably, with arithmetic coefficient of variation (CV) values ranging from 36 to 52% and 40 to 60%, respectively.

- The exposure in adolescents (aged 13 to 17 years) appears to be higher than that of children (aged 5 to 12 years) for this weight-based (i.e., mg/kg) dosing regimen.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The dosing used in Study SPD476-319, Applicant-proposed dosing, and the recommended dosing are shown in the table below.

Table 3. Evaluated, Applicant Proposed, and Agency-Recommended Dosing Regimens

Phase Body Weight	Studied Doses in Efficacy Study SPD476-319	Applicant Proposal (QD)	Agency Recommendation (QD)
Initial 8 weeks			
18–23 kg	900 mg vs. 1.8 g	None	
24–35 kg	1.2 g vs. 2.4 g	None	2.4 g (two 1.2-g tablets)
35–50 kg	1.8 g vs. 3.6 g	None	3.6 g (three 1.2-g tablets)
50–90 kg	2.4 g vs. 4.8 g	(b) (4) 4.8 g (b) (4) four 1.2-g tablets)	4.8 g (four 1.2-g tablets)
After Week 8			
18–23 kg	900 mg vs. 1.8 g	None	
24–35 kg	1.2 g vs. 2.4 g	None	1.2 g (one 1.2-g tablet)
35–50 kg	1.8 g vs. 3.6 g	None	2.4 g (two 1.2-g tablets)
50–90 kg	2.4 g vs. 4.8 g	2. 4 g (two 1.2-g tablets)	2.4 g (two 1.2-g tablets)

Source: Reviewer created table
Abbreviations: QD, once daily

Therapeutic Individualization

Pediatric doses will be based on body-weight tier. Per current Lialda label, no dose adjustment is recommended based on renal, hepatic function or status of concomitant medication.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PK in Pediatric Patients

Intensive PK samples were collected in pediatric PK study (SPD476-112) which was conducted with the Gen 1 formulation for 300-mg and 600-mg tablets and with 1.2-g tablet (currently marketed formulation). In addition, sparse PK samples were collected at Weeks 8 and 26 in the pediatric efficacy study (SPD476-319), which was conducted with the Gen 2 formulation for 300-mg and 600-mg strength tablets and 1.2-g tablet strength (currently marketed formulation). Pediatric PK data from Studies SPD476-112 and SPD476-319 were pooled to conduct a population PK analysis in pediatric UC population.

In the population PK analysis of pooled data of Studies SPD476-112 and SPD476-319, baseline body weight was identified to be the only covariate of clearance of 5-ASA: CL =107.17*(body weight/70)$^{0.75}$ L/h. Similarly, baseline body weight was the covariate of CL/F and Vc/F of

metabolite Ac-5-ASA (see details of pharmacometrics review (Section 15.3.2) for more information).

In pediatric PK study SPD476-112 with intensive PK samples, pediatric patients 5 to 17 years of age were dosed at 30 mg/kg, 60 mg/kg or 100 mg/kg once daily for 7 days with Gen 1 (b) (4) formulation (300-mg and 600-mg tablets strengths) and with currently marketed formulation 1.2-g tablets. On Day 7, systemic exposure of both the parent 5-ASA and metabolite Ac-5-ASA (measured by mean AUC_{SS} and C_{maxSS}) increased in a dose-proportional manner between 30 and 60 mg/kg/day and increased in a subproportional manner between 60 and 100 mg/kg/day dose. In addition, both the AUC and C_{max} of the parent 5-ASA and the major metabolite Ac-5-ASA PK had moderate to high intersubject variability, with arithmetic CV% values ranging from 36 to 52% and 40 to 60%, respectively. Please see Appendix 15.3.3.4 for further detail on PK parameters.

Because the proposed labeling will be based on fixed dose by body weight group in pediatric patients, PK parameters from study SPD476-112 were compared based on fixed dose regimen to that of adult subjects. Pediatric patients who received the 4.8 g dose in this study had only received the marketed 1.2-g tablets. The overall systemic exposure following oral administration of 4.8 g once daily for 7 days in a limited number of pediatric patients with UC (AUC of 30,556-50,388 µg.hr/L) was in similar range to that observed in healthy adults (AUC of 49559±23780 µg.hr/L) after multiple-dose administration of the 4.8 dose once daily for 14 days (Table 4). Of note, per Lialda labeling, mean AUC at steady state was only modestly greater (1.1- to 1.4-fold) than predictable from single-dose pharmacokinetics in healthy adults.

The renal clearance of mesalamine is similar in pediatric patients with UC (5.0 to 6.5 L/hr) compared to healthy adults (5.5 to 6.4 L/hr from Study SPD476-105) following multiple-dose administration. Pediatric patients who received 3.6-g, 2.4-g, and 1.2-g doses had received a combination of Gen 1 pediatric strengths (300 mg and 600 mg) and marketed 1.2-g tablets. The systemic exposure (AUC) in pediatric patients with UC following administration of 2.4 g once daily for 7 days were in a range generally overlapping with that observed in adult population after multiple-dose administration of the 2.4 g once daily dose (Table 4).

Table 4. Pharmacokinetic of Mesalamine in Healthy Adults and Pediatric Patients With UC (5 to 17 Years of Age) in Study SPD476-112 Following Multiple-Dose Administration Under Fed Condition

Population	Dose	AUC_{SS} (ug.hr/L)	C_{maxSS} (ug/L)	t_{max} (hr)
Healthy adults[a] (mean ± SD)	4.8 g (n=24)	49,559±23,780	5,280±3146	6 - 22
Pediatric patients with UC[b] (range)	4.8 g (n=3)	41,044 (30,556 -50,388)	3,293 (1,440 – 4,740)	0 - 4
Pediatric patients with UC[b] (range)	3.6 g (n=6)	54,623 (24,603-101,604)	4,166 (1,710-9,470)	0 - 24
Healthy adults[a] (mean ± SD)	2.4 g (n=28)	22,319±13,697	2,918±2,164	0 - 22
Pediatric patients with UC[b] (range)	2.4 g (n=4)	35,530 (8,252-66,818)	5,494 (888-10,400)	0 - 9.1
Pediatric patients with UC[b] (range)	1.2 g (n=3)	13,432 (9,881-19,171)	1,831 (1,560-1,940)	23.6-23.8

Source: SPD476-112 Clinical Study Report, Section 16.2.4, Listing 4.1 (Subject Demographics and Baseline Characteristics) and Section 16.2.5.1, Listing 5.7, (Individual Pharmacokinetic Parameters), SPD476-105 Clinical Study Report, Table 6
[a] PK in Healthy adults following a multiple-dose administration for 14 days under fed condition
[b] PK in Pediatric patients with UC following once daily dosing for 7 days under fed condition
Abbreviations: AUC_{SS}, area under the curve at steady state; C_{maxSS}, maximum concentration at steady state; SD, standard deviation; t_{max}, time to maximum concentration; UC, ulcerative colitis

6.3.2. Clinical Pharmacology Questions

In support of UC indication in pediatric patients and to fulfill the PMR731-1: "a deferred study under PREA for the treatment of UC in pediatric patients of all ages" and PMR 731-2 ("a deferred pediatric study under PREA for the maintenance of remission of ulcerative colitis in pediatric patients 5 to 17 years of age"), the Applicant has submitted the following four studies in this sNDA submission, a phase 1 PK study in pediatric patients with UC (5 to 17 years), two bioequivalence (BE) studies with the (b) (4) formulations in healthy adults, and a phase 3 safety and efficacy study in pediatric patients with UC.

1. SHP476-121: "A Phase 1, Randomized, Open-label, 2-sequence, 4-period Crossover, Replicate Design, Bioequivalence Study Assessing Pharmacokinetics and Safety of Two SHP476 Formulations, 1.2 g and 300 mg Administered with a Moderate Fat Meal in Healthy Volunteers"
2. SHP476-122: "A Phase 1, Randomized, Open-label, 2-Sequence, 4-period Crossover, Replicate Design, Bioequivalence Study Assessing Pharmacokinetics and Safety of Two SHP476 Formulations, 1.2 g and 600 mg Administered with a Moderate Fat Meal in Healthy Volunteers"
3. SPD476-112: "A Phase 1, Multicenter, Open-label Study to Determine the Safety and Pharmacokinetics of MMX Mesalamine Following Administration in Children and Adolescents with Ulcerative Colitis."
4. SPD476-319: "A Phase 3, Multicenter, Randomized, Double-blind Study to Determine the Safety and Efficacy of MMX Mesalamine/Mesalazine in Pediatric Subjects with Mild to Moderate Ulcerative Colitis, in both Acute and Maintenance Phases." (the pivotal study to fulfill the PMR 731-1 and PMR 731-2).

6.3.2.1. Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Efficacy of mesalamine in the treatment of mildly to moderately active UC in pediatric patients is supported by a phase 3, randomized, double-blind safety and efficacy study in 5- to 17-year-old patients with mildly to moderately active UC that includes an initial treatment duration of 8 weeks followed by continued treatment for 26 weeks (Study SPD476-319). During each phase (double-blind acute [DBA] and double-blind maintenance [DBM]), two dose levels, low dose (900 to 2,400 mg) and high dose (1,800 to 4,800 mg), were evaluated based on patient's body weight without a placebo arm.

Table 5. Pediatric Dosage Studied in Phase 3 Trial: Low Dose Vs. High Dose of Mesalamine Based on Body Weight Tier

Weight	Low Dose	High Dose
18–23 kg	900 mg	1.8 g
>23–35 kg	1.2 g	2.4 g
>35–50 kg	1.8 g	3.6 g
>50–90 kg	2.4 g	4.8 g

Source: CSR SPD476-319: The same low and high doses were studied for both DBA and DBM periods

Although Study SPD476-319 was designed to provide estimates of clinical response for the two doses of multi-matrix system (MMX) mesalamine (low and high) across a range of weight groups and was not powered to detect differences between treatment groups, a positive dose-response relationship was observed during the initial 8 weeks of treatment. During the initial

double-blinded 8-week phase, the proportion of patients who achieved the primary endpoint (proportion of patients who demonstrated a clinical response) at Week 8 was higher in the high-dose treatment arm than the low-dose treatment arm (65.4% versus 37.0%). During the double-blinded maintenance phase, the proportions of patients who achieved the primary endpoint at Week 26 were similar between the high-dose and low-dose treatment arms (53.3% versus 54.8%). Please refer to Section 8 for details of the analysis of efficacy.

Table 6. Proportion of Patients Who Achieved Primary Endpoint at Week 8 (DBA) and Week 26 (DBM)

	Adults (Remission[a])			Pediatric (Clinical Response[b])	
Phase	Placebo	Low Dose (2.4 g/day)	High Dose (4.8 g/day)	Low Dose (900 mg–2.4 g)	High Dose (1.8–4.8 g)
Initial 8 weeks	12.9%–22.1%	34.1%–40.55%	29.2%–41.2%	37%	65.4%
After Week 8		83.7%		54.8%	5.3.3%

Source: CSR SPD476-319, Table 17 and Table 20, Module 2.7.3 Summary of Clinical Efficacy, Table 4 and Table 5. Lialda Label
[a] Remission: The proportion of patients in remission after 8 weeks of treatment defined as: UC-DAI <1; rectal bleeding subscore =0, stool frequency subscore =0, and a sigmoidoscopy score reduction >1 point from baseline
[b] Clinical response: Proportion of patients who demonstrate a "clinical response" defined as partial UC-DAI** <1; rectal bleeding =0, stool frequency <1, and PGA =0.
Abbreviations: DBA, double-blind acute; DBM, double-blind maintenance

The primary endpoint in this pediatric UC study (clinical response) was different from the primary endpoint used in the adult UC program (remission). In the adult UC program, there was no dose-response in remission rate between the low dose and high dose.

6.3.2.2. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication Is Being Sought?

No, the Applicant's proposed dosing regimens are not appropriate for the pediatric patient population for which the indication is being sought.

The safety and efficacy of MMX mesalamine in pediatric patients with UC 5 to 17 years of age (body weight of 18 to 90 kg) was evaluated at two dose levels (high dose versus low dose) for the DBA phase and the DBM phase in a phase 3 trial (SPD476-319).

(b) (4)

The review team recommends the high-dose level for the initial 8 weeks of treatment (b) (4) The review team's rationale is based in-part on the higher response rate associated with high dose compared to the low dose in pediatric efficacy study during initial 8-week period. Additionally, adverse events were similar between the two doses (Section 8.2.4). For the treatment after Week 8, the Applicant's proposed low dose is acceptable based on similar response rate between low and high dose (see Section 8 for efficacy results).

In clinical trials, pediatric patients weighing <50 kg received doses with a combination of different strengths of mesalamine tablets, 300 mg, 600 mg, and 1.2 g, (b) (4) . However, the Applicant is not planning to

commercialize the lower (b) (4) strength of 300-mg and 600-mg tablets, and thus the Applicant proposes to limit the use of mesalamine in pediatric patients with >50-kg body weight.

Based on the available PK, efficacy and safety data from phase 3 pediatric Study SPD476-319, the Agency recommends the use of Lialda in pediatric patients (b) (4) with body weight down to 24 kg (Table 3) as pediatric patients may be trained to swallow the 1.2-g tablets.

For pediatric patients weighing 35 to 50 kg, the dose for continued treatment after Week 8 (b) (4) the review team proposes daily dose of 2.4 g for patients with 35 to 50 kg of body weight instead.

The dose of 2.4 g for maintenance was not studied in these patients and is in between the studied low dose (1.8 g) and high dose (3.6 g). However, the review team considers 2.4 g reasonable for maintenance treatment for patients with 35 to 50 kg of body weight based on no apparent difference in the efficacy for maintenance between two studied dose levels in general, and predicted lower systemic exposure with 2.4 g than the high dose studied in this body weight group (refer to Figure 7 of pharmacometrics review in section 15.3.2.2). In addition, 2.4 g was studied in pediatric patients in other body weight groups, i.e., >50 kg or 24 to 35 kg, for maintenance treatment; therefore, safety of 2.4 g for long-term treatment may be supported. Refer to Section 8.2 of this review.

There was very limited number of patients with body weight between 18 to <24 kg in the pediatric efficacy and safety Study SPD476-319, no patient in the DBA phase and only three patients in the DBM phase, to make any conclusive dosing recommendation in pediatric UC patients with <24 kg body weight range. Therefore, review team does not recommend the use of Lialda in patients with <24 kg body weight.

Dose Selection Rationale for Phase 3 Studies

In the pediatric safety and efficacy study (Study SPD476-319), two dose levels—low dose (900 mg to 2.4 g) and high dose (1.8 to 4.8 g)—were evaluated based on patient's weight without a placebo arm during the DBA phase (8 weeks) and DBM phase (26 weeks).

The doses for the pediatric phase 3 study were determined from PK modeling using data from the PK study in pediatric patients with UC in Study SPD476-112. The Applicants states the selection of doses in this study was based on an approximate average of 43 mg/kg for the low dose and 80 mg/kg for the high dose in the three lower weight groups (18 to ≤23 kg, >23 to ≤35 kg, and >35 to ≤50 kg). The dosing for the highest weight group (>50 to ≤90 kg) was selected based on doses approved for adult patients with UC.

6.3.2.3. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

Based on the effects of body weight on PK, body weight-based dosing is recommended for pediatric patients. No additional intrinsic factors that may necessitate alternative dosing regimen were identified. In the current approved Lialda label, there is no dose adjustment based on the hepatic or renal function. However, there are warnings for use of Lialda in patients with renal impairment or hepatic impairment in the current approved Lialda label as outlined below.

Renal Impairment

Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported in patients given products such as Lialda that contain mesalamine or are converted to mesalamine.

It is recommended that patients have an evaluation of renal function prior to initiation of Lialda therapy and periodically while on therapy. Exercise caution when using Lialda in patients with known renal dysfunction or a history of renal disease.

Hepatic Impairment

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Exercise caution when administering Lialda to patients with liver disease.

Accordingly, in both pediatric studies in patients with UC, Studies SPD476-319 and SPD476-112, subjects with any history of hepatic impairment and/or subjects with any history of moderate to severe renal impairment were excluded from the studies.

Body Weight

Based on the population PK analysis of pooled data of Studies SPD476-112 and SPD476-319, baseline body weight was identified to be the only significant covariate of clearance and volume of distribution of 5-ASA. Decreasing body weight was associated with lower clearance and volume of distribution, supporting the proposed body weight-tiered dosing regimen.

6.3.2.4. Are There Clinically Relevant Food–Drug or Drug–Drug Interactions, and What Is the Appropriate Management Strategy?

No new food effect trial or drug-drug interaction trial was submitted in this pediatric supplemental NDA. Current Lialda label recommends taking Lialda tablet once daily with meal. In pediatric efficacy and safety study (Study SPD476-319), patients were instructed to take the tablet(s) with food without crushing or chewing.

6.3.2.5. Is the To-Be-Marketed Formulation the Same as the Clinical Trial Formulation? If Not, Are There Bioequivalence Data to Support the To-Be-Marketed Formulation?

During the pediatric safety and efficacy study, (b) (4) formulation with lower strength, 300 mg and 600 mg, were used along with the commercially available 1.2-g tablet. However, the Applicant is currently not planning to manufacture the pediatric formulation with 300- and 600-mg tablet strength, but rather to offer the commercially available 1.2-g tablet formulation to pediatric patients in whom this tablet strength is appropriate. The (b) (4) formulation with 300-mg and 600-mg tablets that were used in the pediatric phase 3 safety and efficacy study were demonstrated to be bioequivalent to the formulation that is already commercially available at 1.2-g tablet under fed condition (administered with moderate fat meal) in two BE studies that compared 4×300-mg or 2×600-mg tablets with one 1.2-g tablet.

Table 7. Formulations Used in Pediatric Patients With UC and BE Bridging Studies

Study	Study Type	Strength/Formulation
SHP476-112	PK in pediatric	300-, 600-mg tablets (Gen 1 [redacted] formulation) and 1.2-g tablet
SHP476-319	Efficacy in pediatric	300-, 600-mg tablets (Gen 2 [redacted] formulation) and 1.2-g tablet
SHP476-121	BE bridging study	Test: 300-mg strength tablets used in ped efficacy study (Gen 2) Reference: 1.2-g strength tablets currently approved in adults
SHP476-122	BE bridging study	Test: 600-mg strength tablets used in ped efficacy study (Gen 2) Reference: 1.2-g strength tablets currently approved in adults

Source: 2.7.1 Summary of Biopharmaceutic Studies,
Abbreviations: BE, bioequivalence; PK, pharmacokinetic; UC, ulcerative colitis

The currently approved Lialda formulation for adult use is a delayed-release tablet containing 1.2 g mesalamine. To conduct clinical studies in pediatric patients with UC, the Applicant developed two generations (referred to as Gen 1 and Gen 2) of [redacted] formulation with lower-strength MMX mesalamine tablets (300 mg and 600 mg) with a [redacted] than the approved MMX mesalamine 1.2-g tablets [redacted].

The studies in pediatric patients with UC were conducted with the [redacted] formulations with lower strength of 300-mg and 600-mg tablets in addition to using currently approved adult strength 1.2-g tablet; Gen 1 [redacted] formulation was used in the pediatric PK Study SPD476-112 and Gen 2 [redacted] formulation was used in the phase 3 pediatric safety and efficacy Study SPD476-319 (Table 7).

While the pediatric studies were conducted with 1.2-g strength tablet as well as [redacted] formulation 300-mg and 600-mg strength tablet, the Applicant is currently not planning to manufacture the [redacted] 300-mg and 600-mg strength tablets but rather offer the commercially available 1.2-g tablet formulation to pediatric patients in whom this tablet strength is appropriate. The Gen 2 [redacted] formulation of 300-mg and 600-mg strength tablets that were used in study SPD476-319 to establish the safety and efficacy of mesalamine in pediatric patients with UC were demonstrated to be bioequivalent to the currently marketed 1.2-g strength tablet in two bioequivalence studies (SHP476-121 and SHP476-122).

No BE studies were conducted to compare the Gen 1 formulation (used in pediatric PK study) to the approved 1.2-g tablet or to Gen 2 formulation used in pediatric phase 3 trial. Gen 1 and Gen 2 [redacted]. Compared to Gen 1, [redacted] and made it easier to swallow for younger patients. Since the pediatric PK study data that used Gen 1 formulation were not used to support the efficacy of mesalamine in pediatric patients with UC, the absence of BE study to bridge between the Gen 1 [redacted] formulation to the approved 1.2-g tablet does not affect the assessment of efficacy or safety.

In vitro, according to the Applicant, both Gen 1 and Gen 2 [redacted] formulations with 300-mg and 600-mg strength achieved similar dissolution profiles compared to 1.2-g tablets suggesting that formulation changes between Gen 1 and Gen 2 were not associated with change in dissolution rate. However, the dissolution profiles were not evaluated by the Agency. There is no direct PK comparison between these two generations of formulations.

Bioequivalence Between TBM Formulation and Formulation Used in Pediatric Clinical Trial

Bioequivalence of 300-mg and 600-mg strength Gen 2 (b) (4) formulation tablets with currently marketed commercially available 1.2-g strength tablets were established in two separate phase 1, randomized, open-label, two-sequence, four-period, single-dose, crossover, replicate design BE studies in healthy subjects under fed conditions (studies SHP476-121 and SHP476-122). The four-period crossover replicate study design and statistical analysis with the scaled average bioequivalence (SABE) method were appropriate since mesalamine is considered a highly variable drug. The study design and analysis were consistent with the recommendation from the FDA draft guideline for industry, *Bioequivalence Recommendations for Mesalamine Delayed Release Tablets* (CDER, 2016).

Table 8. Drug Products Used in Two BE Studies

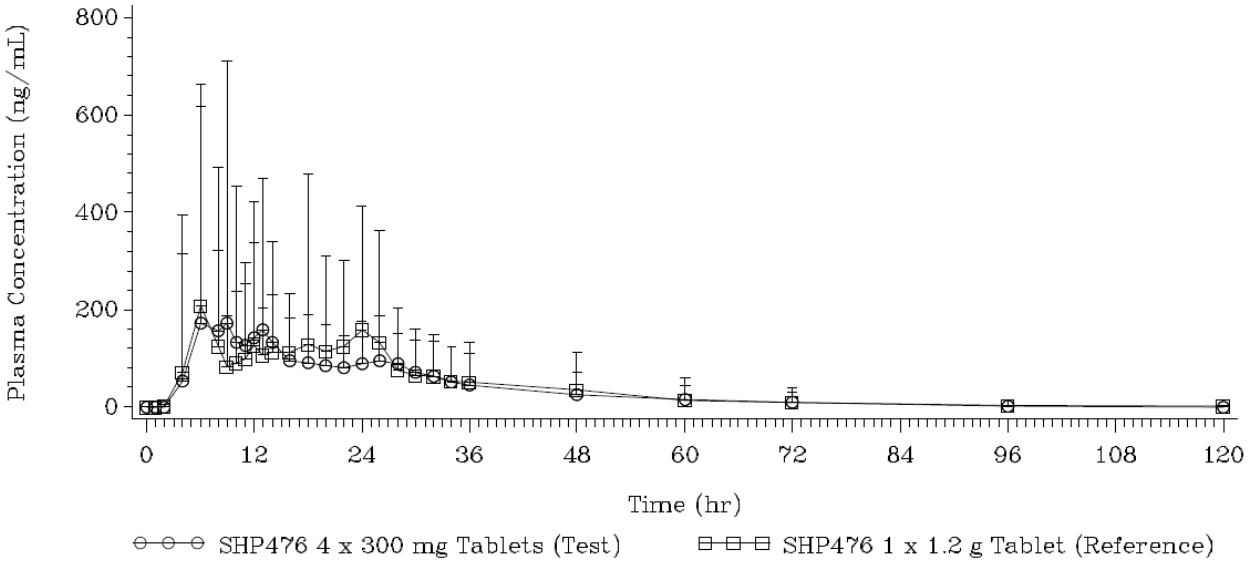
Study #	Reference Drug	Test Drug
SHP476-121	MMX mesalamine, 1.2-g strength oral tablets administered as 1×1.2-g tablet (marketed product)	MMX mesalamine, 300-mg strength oral tablets administered as 4×300-mg tablets (Gen 2)
SHP476-122	MMX mesalamine, 1.2-g strength oral tablets administered as 1×1.2-g tablet (marketed product)	MMX mesalamine, 600-mg strength oral tablets administered as 2×600-mg tablets (Gen 2)

Source: CSR SHP476-121, CSR SHP476-122 and 2.7.1 Summary of Biopharmaceutic Studies
Abbreviations: BE, bioequivalence; MMX, multi-matrix system

In both BE studies, the primary PK parameters (C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{8\text{-}48}$) met the SABE criteria for highly variable drug product demonstrating that (b) (4) formulations with 300- and 600-mg strength tablets of MMX mesalamine (Gen 2) when administered as a 1.2-g dose were bioequivalent to the marketed MMX mesalamine 1.2-g tablets.

- All three primary PK parameters, C_{max}, $AUC_{0\text{-}t}$, and $AUC_{8\text{-}48}$, met the criteria for highly variable drug product (defined as intrasubject variability [SWR] ≥0.294) in both studies. Therefore, use of SABE was appropriate for BE assessment in these studies.
- The point estimate of the geometric mean test/reference ratio was within 80% to 125%, for all three PK parameters in both BE studies.
- The 95% upper confidence limit of the SABE contrast $(\bar{Y}T\text{-}\bar{Y}R)2 - \theta \bullet S2WR$ was ≤0 for all three PK parameters in both studies.

Figure 1. Mean (±SD) Observed 5-ASA Plasma Concentrations by Treatment From 4×300-mg Mesalamine Tablets and from 1.2-g Tablets in Healthy Adults (Study SHP476-121)



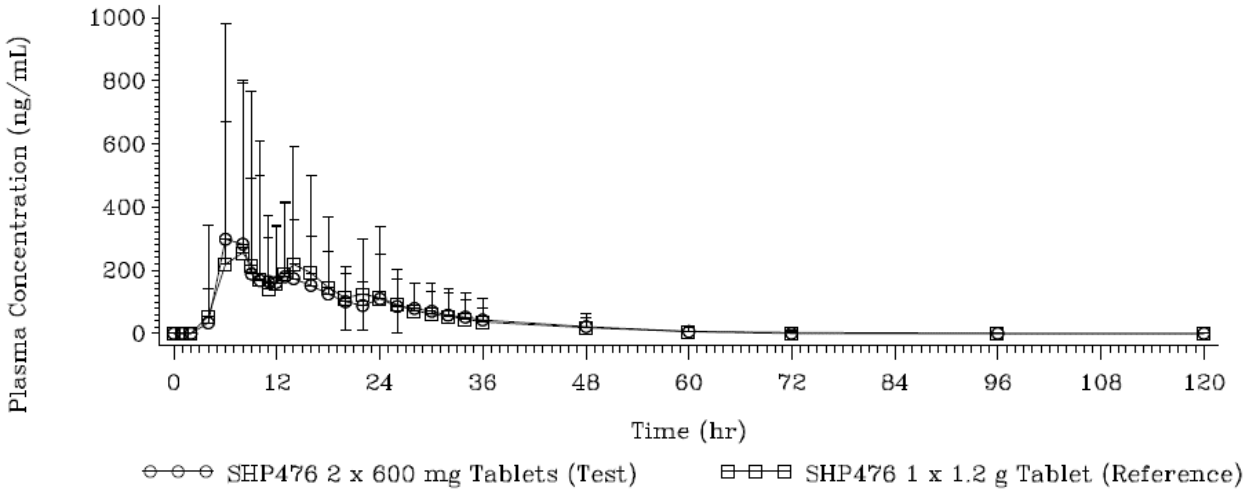
Source: CSR for Study SHP476-121, Figure 2 (page 49)
Abbreviations: 5-ASA, 5-aminosalicylic acid; SD, standard deviation

Table 9. Summary of Plasma 5-ASA Pharmacokinetic Parameters From 4×300-mg Mesalamine Tablets and From 1.2-g Tablets in Healthy Adults

Treatment	N	C_{max} (ng/mL)	t_{max} (h)	t_{lag} (h)	AUC_{0-t} (ng·h/mL)	AUC_{8-48} (ng·h/mL)
		Mean (SD) [Geometric Mean]				
4×300 mg	72	496 (732)	15.6 (7.8)	6.6 (4.2)	3975 (3270)	3038 (2473)
		[267]	[13.6]	[5.5]	[2755]	[2211]
1×1.2 g	72[a]	529 (595)	15.4 (9.3)	6.2 (5.3)	4334 (3191)	3361 (2444)
		[NC]	[12.7]	[4.7]	[NC]	[NC]
		Bioequivalence Assessment				
S_{WR}		0.9134	NC	NC	0.9392	0.6051
Geo Mean Test/Ref		0.8735	NC	NC	0.9491	0.9041
95% Upper CI $(\bar{Y}_T-\bar{Y}_R)^2-\theta\bullet S^2_{WR}$		-0.4104	NC	NC	-0.4851	-0.1810

Source: CSR for Study SHP476-121, Table 8 (page 52)
Note: Several of the 5-ASA plasma concentration versus time profiles did not exhibit a log linear decline due to low or variable plasma concentrations, and λz, $t_{1/2}$, and $AUC_{0-\infty}$ could not be estimated for these profiles. Values are presented as mean (SD) and [geometric mean]
[a] n=70 for AUC_{8-48}, t_{max}, tl_{ag}.
Abbreviations: AUC_{0-t}, area under the curve from the time of dosing to the last measurable concentration; AUC_{8-48}, area under the plasma concentration-time curve from 8 to 48 hours after administration; CI, confidence interval; C_{max}, maximum concentration occurring at t_{max}; NC, not calculated; SD, standard deviation; S_{WR}, intrasubject variability; t_{lag}, timepoint prior to the first quantifiable plasma concentration; t_{max}, time of maximum observed concentration sampled during a dosing interval

Figure 2. Mean (±SD) Observed 5-ASA Plasma Concentrations by Treatment From 2×600-mg Mesalamine Tablets and From 1.2-g Tablets in Healthy Adults



Source: CSR for Study SHP476-122, Figure 2 (page 51)
Abbreviations: 5-ASA, 5-aminosalicylic acid; SD, standard deviation

Table 10. Summary of Plasma 5-ASA Pharmacokinetic Parameters From 2×600-mg Mesalamine Tablets and From 1.2-g Tablets in Healthy Adults

Treatment	n	C_{max} (ng/mL)	t_{max} (h)	t_{lag} (h)	AUC_{0-t} (ng·h/mL)	AUC_{8-48} (ng·h/mL)
			Mean (SD) [Geometric Mean]			
2 × 600 mg tablets	71[a]	669 (794) [NC]	13.7 (8.3) [11.6]	5.9 (4.3) [4.8]	4522 (3141) [NC]	3479 (2419) [NC]
1 × 1.2 g tablet	70[b]	687 (788) [NC]	14.2 (8.3) [12.1]	5.0 (3.5) [4.2]	4621 (3346) [NC]	3697 (2806) [NC]
			Bioequivalence Assessment			
S_{WR}		0.8660	NC	NC	0.6460	0.7619
Geo Mean Test/Ref		0.9730	NC	NC	0.9036	0.8783
95% Upper CI $(\bar{Y}_T-\bar{Y}_R)^2-\theta\bullet S^2_{WR}$		-0.3878	NC	NC	-0.1841	-0.2688

Source: CSR for Study SHP476-122, Table 8 (page 54)
Note: Several of the plasma concentrations for 5-ASA versus time profiles did not exhibit a log-linear decline due to expected low or variable plasma concentration, and λz, $t_{1/2}$, and $AUC_{0-\infty}$ could not be estimated for these profiles. Values are presented as mean (SD) and [geometric mean].
Note: Two pharmacokinetic data-points were excluded from the noncompartmental analysis; 96 hours for Subject (b) (6) (Treatment Period 3) as the pharmacokinetic profile was observed to have terminated after the 16-hour time point and 26-hour time point for Subject (b) (6) (Treatment Period 1) as no actual time relative to dosing could be derived (blood sample collection date and time missing); Subject (b) (6) terminated early from the study at approximately 26 hours during Treatment Period 1 and was included in the bioequivalence analysis.
[a] n=70 for t_{max} and t_{lag}.
[b] n=67 for t_{max} and t_{lag}.
Abbreviations: AUC_{0-t}, area under the curve from the time of dosing to the last measurable concentration; AUC_{8-48}, area under the plasma concentration-time curve from 8 to 48 hours after administration; CI, confidence interval; C_{max}, maximum concentration occurring at t_{max}; NC, not calculated; SD, standard deviation; S_{WR}, intrasubject variability; t_{lag}, timepoint prior to the first quantifiable plasma concentration; t_{max}, time of maximum observed concentration sampled during a dosing interval

OSIS Inspection

The safety and efficacy in pediatric patients with UC were conducted in 5- to 17-year-old patients with >18 kg body weight with currently commercially available 1.2-g strength tablets and (b) (4) formulation 300-mg and 600-mg strength tablets. However, the Applicant is not planning to manufacture the (b) (4) 300-mg and 600-mg tablets, but rather is planning to offer the commercially available 1.2-g tablet formulation to (b) (4) pediatric patients (b) (4)

(b) (4) pediatric patients to be those who weighed >50 to ≤90 kg (N=67 out of 105), had received only multiples of the 1.2-g strength tablets of MMX mesalamine in the pediatric safety and efficacy study (Study SHP476-319), and had not received (b) (4) formulation with lower strength of 300-mg and 600-mg tablets (Table 11).

However, the review team proposes to offer mesalamine for treatment of mildly to moderately active UC in pediatric patients (b) (4) weighing more than 23 kg based on the available safety, efficacy and PK data in pediatric patients. As pediatric patients between 23 kg and 50 kg received multiples of (b) (4) formulation 600-mg tablets in safety and efficacy Study SPD476-319 (Table 11), the bioequivalence study comparing 600-mg tablets and commercially available 1.2-g tablets (Study SHP476-122) becomes a pivotal BE study. Therefore, a site inspection for the clinical study site and bioanalytical assay site for bioequivalence Studies SHP476-121 and SHP476-122 were requested on January 21, 2020. The Division of New Drug Study Integrity within the OSIS determined that an inspection for these two study sites were not warranted at this time because the clinical site was inspected in February 2018 and the analytical site was inspected in (b) (4), which falls within the surveillance interval. The final classification for the inspections was No Action Indicated.

Table 11. Tablet Strengths Used in Efficacy Study SHP476-319

Weight Category	Low-Dose MMX Mesalazine	High-Dose MMX Mesalazine
18 to ≤23 kg	900 mg (1×300-mg +1×600 mg) (n=1)	1.8 g (2×300 mg +2×600 mg) (n=2)
>23 to ≤35 kg	1.2 g (2×600-mg tablet)	2.4 g (4×600-mg tablet)
>35 to ≤50 kg	1.8 g (3×600-mg tablet)	3.6 g (6×600-mg tablet)
>50 to ≤90 kg	2.4 g (2×1.2-g tablet)	4.8 g (4×1.2-g tablet)

Source: Appendix 2 of Response to FDA Information Request, submission date October 25, 2019.
Abbreviations: MMX, multi-matrix system

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 12. Clinical Trial Relevant to NDA 022000/S-019

Trial Identity NCT No.	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration	Sample Size	Study Population	No. of Centers and Countries
Controlled studies to support efficacy and safety							
SPD476-319 02093663	Multicenter, randomized, double-blind, parallel-group study to determine the safety and efficacy of MMX mesalamine/ mesalazine in pediatric subjects with mildly to moderately active ulcerative colitis (UC), in both double-blind acute (DBA) and double-blind maintenance (DBM) phases There was an open-label acute (OLA) phase for patients who did not achieve a clinical response or who were discontinued from the DBA phase and met OLA entry criteria.	Patients were randomized 1:1 to either low or high doses of weight-based oral MMX mesalamine daily. Low-dose regimen: 18–23 kg: 900 mg >23–35 kg: 1.2 g >35–50 kg: 1.8 g >50–90 kg: 2.4 g High-dose regimen: 18–23 kg: 1.8 g >23–35 kg: 2.4 g >35–50 kg: 3.6 g >50–90 kg: 4.8 g	Primary endpoint: Clinical response defined as partial UC-DAI ≤1 with rectal bleeding subscore =0, stool frequency subscore ≤1, and PGA =0 Secondary endpoints: Clinical and endoscopic response defined as UC-DAI ≤2 with rectal bleeding subscore =0, stool frequency subscore ≤1, PGA =0, and endoscopy subscore ≤1 (based on central vs. local reading). Additionally, there must have been an at least 1-point reduction in endoscopy score from baseline. Change from baseline in DUCS score The percentage of patients with an improvement in PUCAI ≥20 points from baseline.	Patients in the DBA phase were assessed for clinical response at 8 weeks for entry into the DBM phase. Patients in the OLA phase were assessed for clinical response after an additional 8 weeks for entry into the DBM phase. Efficacy assessment occurred at 8 weeks for the DBA phase and 26 weeks for the DBM phase.	A total of 107 patients were enrolled in SPD476-319. There were 53 patients in the DBA phase, 18[a] in the OLA phase, and 87[b] in the DBM phase.	Male and female patients aged 5 to 17 years with mildly to moderately active UC.	33 centers 6 countries GBR, HUN, ISR, POL, SVK, USA

Trial Identity NCT No.	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration	Sample Size	Study Population	No. of Centers and Countries
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
SPD476-112 01130844	Multicenter, randomized, open-label, three-arm study, to determine the safety and pharmacokinetics of MMX mesalamine in children and adolescents with UC	Patients were randomized, stratified by weight, to 1 of 3 dosing regimens of oral MMX mesalamine daily. Dosing regimen: 30 mg/kg/day 60 mg/kg/day 100 mg/kg/day	Primary objective: Assess the pharmacokinetics (PK) of 5-ASA and its major metabolite Ac-5-ASA after administration of MMX mesalamine at 3 different doses after administration for 7 days. Secondary objective: Evaluate the safety and tolerability of MMX mesalamine. Evaluate the extent of absorption of 5-ASA from MMX mesalamine at steady-state, as defined by the total urinary excretion of 5-ASA and Ac-5-ASA, expressed as a percentage of the administered dose.	Patients received outpatient dosing for 4 days followed by in-clinic dosing for 3 additional days. PK parameters were measured on days 5 through 7. Additionally, one PK measurement was performed on Day 8, 1 day after completing the dosing regimen.	A total of 52 patients were enrolled. There were 21 patients in the 30 mg/kg group, 22 in the 60 mg/kg group, and 9 in the 100 mg/kg group.	Male and female patients aged 5 to 17 years with a history of ulcerative colitis.	12 centers 3 countries POL, SVK, USA

Source: Reviewer's Table.
[a] Patients were randomized to the OLA phase after enrollment in the DBA phase.
[b] The DBM phase includes 52 patients who entered directly, 27 patients who entered from the DBA phase, and eight patients who entered from the OLA phase; refer to Figure 3.
Abbreviations: 5-ASA, 5-aminosalicylic acid; DUCS, Daily Ulcerative Colitis Score; GBR, Great Britain; HUN, Hungary; ISR, Israel; MMX, multi-matrix system; PGA, Physician's Global Assessment; POL, Poland; PUCAI, Pediatric Ulcerative Colitis Activity Index; SVK, Slovakia; UC-DAI, Ulcerative colitis disease activity index with the endoscopy subscore modified to exclude friability in a score of mild disease (i.e., a score of 1), instead, friability was scored as moderate disease (i.e., a score of 2); USA, United States of America

7.2. Review Strategy

This review focused on data from a single efficacy and safety study, SPD476-319, that included a DBA phase, an open-label acute (OLA) phase, and a DBM phase. One additional PK study in pediatric patients, SPD476-112, was reviewed as described in Section 0. SPD476-112 was not considered to contribute significantly to the safety assessment of Lialda due to the short duration of exposure (i.e., 7 days of treatment); however, the safety results of the study were supportive of the safety analyses conducted on SPD476-319.

The team identified several review issues:

1. The Applicant's definition of the primary endpoint, clinical response, differed from the Division's currently recommended definition, which has evolved since SPD476-319 was designed. The team requested that the Applicant perform additional analyses utilizing the current definition for clinical response. Applicant's definition: partial UC-DAI ≤1 with rectal bleeding subscore =0, stool frequency subscore ≤1, and PGA =0. Division's currently recommended definition: a decrease from baseline in the Mayo Score (modified to exclude the PGA) of ≥2 points AND a 30% reduction from baseline PLUS a decrease in rectal bleeding subscore of ≥1 or an absolute rectal bleeding subscore of ≤1.

2. The Applicant evaluated a secondary endpoint of "clinical and endoscopic remission" (defined below) in both the DBA and DBM phases (b) (4) The Applicant's proposed endpoint definition included an assessment of both clinical signs and symptoms and endoscopic components, an approach which the Division also recommends to assess clinical remission in trials evaluating therapies for UC; however, the Applicant's definition (and terminology) differed from the currently recommended definition. The review team requested that the Applicant perform additional analyses utilizing the recommended definition for clinical remission. Applicant's definition of "clinical and endoscopic response": UC-DAI ≤2 with rectal bleeding subscore =0, stool frequency subscore ≤1,PGA =0, and endoscopy score ≤1 based on central reading. In addition, there must have been at least a 1-point reduction in endoscopy score from baseline. Division's currently recommended definition of clinical remission using the Mayo score (excluding the PGA component): stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and endoscopic subscore of 0 or 1 (modified to exclude friability), or 0 on the UC-DAI.

3. The Applicant noted that they do not intend to manufacture the lower strength tablets (b) (4) (i.e., 300-mg and 600-mg tablets). Secondary to this, the Applicant's proposed labeling was limited to patients weighing 50 to 90 kg. The review team communicated to the Applicant that this would significantly limit the indicated population as many pediatric patients weigh less than 50 kg. In an effort to increase the availability to pediatric patients who may benefit from Lialda and weigh less than 50 kg, the review team identified dosing regimens that could be accomplished with the 1.2-g tablet that the Applicant intends to manufacture. The review team requested that the Applicant perform additional safety and efficacy analyses of age and weight subgroups to support the different dosing regimens. Additionally, the review team relied on PK modeling, using data from the pediatric PK study (SPD476-112), to evaluate the appropriateness of using the 2.4-g dose in patients weighing >35 to 50 kg as treatment after Week 8 in this weight subgroup.

The review team assessed the data submitted by the Applicant to determine that the PREA PMRs were fulfilled.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study SPD476-319

Trial Design

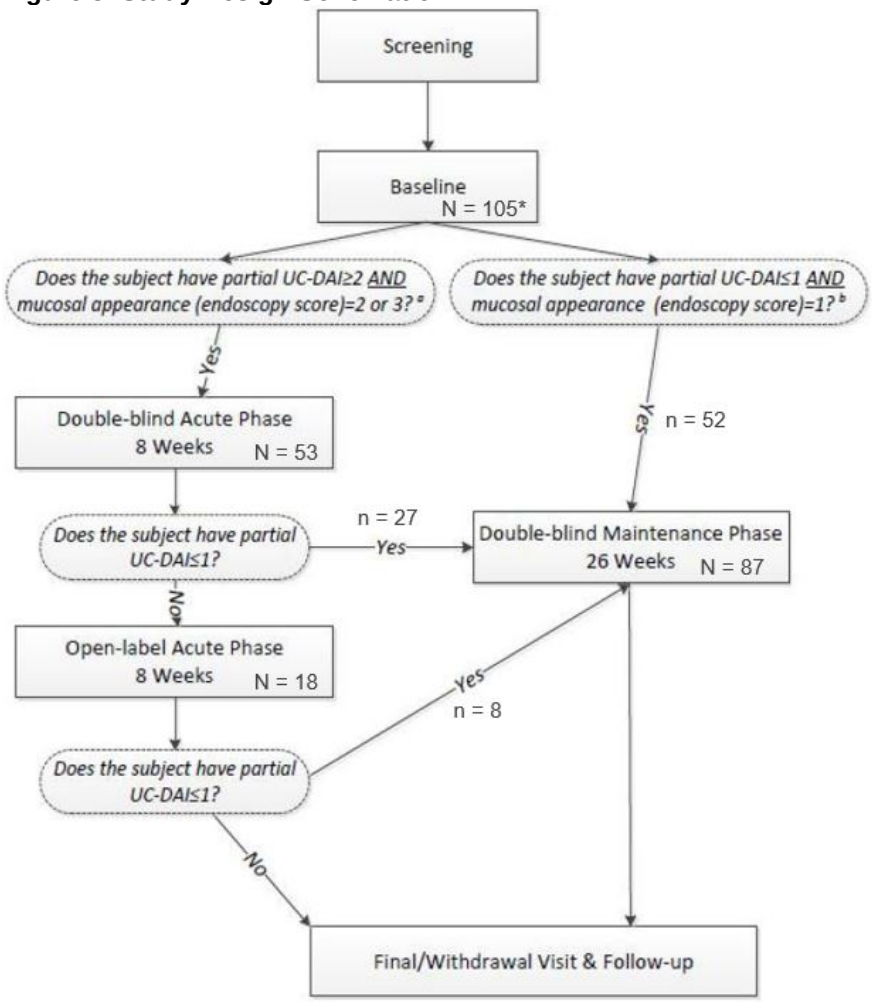
The Applicant conducted a single phase 3 study, SPD476-319, to assess two weight-based dose levels (low dose [900 to 2,400 mg] and a high dose [1,200 to 4,800 mg]) of mesalamine for the treatment of pediatric patients aged 5 to 17 years with mildly to moderately active UC.

SPD476-319 was a multicenter, randomized, double-blind, parallel-group study that consisted of a screening period, an 8-week DBA phase, a 26-week DBM phase, and an optional 8-week OLA phase (Figure 3). Patients were eligible to enter the DBA phase if they had a total UC-DAI ≥4 (with a combined rectal bleeding and stool frequency score ≥1 and PGA of 1 or 2, and with mucosal appearance [i.e., endoscopic subscore] of 2 or 3). Patients who achieved clinical response, defined as a partial UC-DAI ≤1 (with rectal bleeding =0, stool frequency ≤1, and PGA =0), after 8 weeks of initial treatment were rerandomized into the DBM phase. Patients who were treated with mesalamine but had not participated in the DBA phase were also eligible to enter the DBM phase directly if they had a UC-DAI ≤2 (with rectal bleeding =0, stool frequency ≤1, and PGA =0 and endoscopic subscore of 0 or 1; an endoscopic subscore of 1 did not include friability) at the baseline visit. Patients were randomized to one of two weight-based dose levels (low and high dose) of mesalamine at the beginning of the DBA and DBM phases. Randomization occurred in a 1:1 ratio stratified by body weight group.

There was an additional 8-week OLA phase for patients who did not achieve a clinical response after 8 weeks of treatment in the DBA phase or who withdrew from the DBA phase after a minimum of 2 weeks and, in the investigator's opinion, had not benefited from treatment. These patients were treated with the high-dose level of mesalamine as appropriate for their weight group during the OLA phase. Patients who met the definition of clinical response at the end of the OLA phase could be rerandomized into the DBM phase.

The study design is shown in Figure 3.

Figure 3. Study Design Schematic



Source: Adapted from SPD476-319 CSR Figure 1 (p. 36)
* Safety analysis set was used for safety and efficacy assessments and included randomized patients who took at least 1 dose of Lialda.
Abbreviations: UC-DAI, Ulcerative colitis disease activity index

Patients without a clinical response after completion of treatment in both the DBA phase and the OLA phase were not eligible to enter the DBM phase and were withdrawn from the study.

The main inclusion criteria that defined the study population were as follows:

- Male and female children and adolescents aged 5 to 17 years, inclusive, at baseline visit (visit 2)
- Body weight of 18 to 90 kg at screening visit (visit 1) and baseline visit (visit 2)
- Diagnosed with mildly to moderately active UC, established by sigmoidoscopy or colonoscopy with compatible histology. Screened patients may also have had an unconfirmed diagnosis of mildly to moderately active UC; however, the diagnosis of mildly to moderately active UC must have been established by sigmoidoscopy or colonoscopy with compatible histology prior to the baseline visit (visit 2)
- Patient was able to swallow Lialda whole.

Study Endpoints

In both the DBA and DBM phases, the primary efficacy endpoint was "clinical response" at the end of the study phase with clinical response defined as partial UC-DAI ≤1 with rectal bleeding =0, stool frequency ≤1, and PGA =0. The primary efficacy endpoint for the DBA phase was defined as the proportion of patients with a clinical response at Week 8. The primary efficacy endpoint for the DBM phase was defined as the proportion of patients with a clinical response at Week 26.

The Applicant's definitions for clinical remission and clinical response did not align with the Division's currently recommended endpoint definitions; however, the Division's currently recommended endpoint for clinical response could not be assessed for the DBM phase because the definition relies on change from baseline. Over half of the patients enrolled in the DBM phase did not participate in the DBA phase but were treated with mesalamine and entered the DBM phase directly. Data were not available to establish the baseline active disease status prior to treatment for these patients. In addition, analyses using the Division's recommended clinical remission and clinical response endpoints were not feasible for the DBA phase because too few patients underwent endoscopy at Week 8. Results for clinical remission, using the Division's recommended definition, at Week 26 of the DBM phase are included below.

The partial UC-DAI score includes subscores for stool frequency, rectal bleeding, and PGA (without the endoscopic component). The three components of the partial UC-DAI subscore were assessed individually on a scale from 0 to 3; the maximum partial UC-DAI score is 9.0 (most severe).

The subscores for stool frequency and rectal bleeding were reported by the patients/caregivers in an e-diary once a day for 5 days immediately prior to the evaluation time point. Symptom data were also to be reported as soon as a patient's symptoms suggested that the patient might have been experiencing an acute flare during the DBM phase. Stool frequency and rectal bleeding subscores were based on one of two versions of e-diary questions. One version was for pediatric patients aged 11 to 17 years, and the other was for caregivers of pediatric patients aged 5 to 10 years.

The PGA was performed at all visits where the partial UC-DAI score was calculated by the study site and was scored on a scale from 0 to 3, where 0 = no active disease, 1 = mild disease, 2 = moderate disease, and 3 = severe disease. The PGA was to be performed by the same investigator at all visits, if possible, for consistency in evaluation.

Statistical Analysis Plan

The primary analysis population of the DBA phase was the DBA phase safety analysis set, which consisted of randomized patients who took at least 1 dose of Lialda during the DBA phase. The primary analysis population of the DBM phase was DBM phase safety analysis set, which consisted of randomized patients who took at least 1 dose of Lialda during the DBM phase. The OLA phase safety analysis set consisted of randomized patients who took at least 1 dose of Lialda during the OLA phase. The overall safety analysis set consisted of all randomized patients who took at least 1 dose of Lialda.

Analysis for Primary Endpoint

The primary efficacy endpoint during the DBA phase, the proportion of patients who achieved a clinical response at Week 8, was compared between the low- and high-dose groups with a continuity-corrected chi-squared test.

The primary efficacy endpoint during the DBM phase, the proportion of patients who achieved a clinical response at Week 26, was compared between the low and high-dose groups with a Cochran-Mantel-Haenszel test stratified by 3 levels of Week 8 DBA phase responder status (entered DBM phase directly, responder at Week 8 of the DBA phase, or responder at Week 8 of the OLA phase).

Although not specified in the Applicant's statistical analysis plan (SAP), the analyses for both the DBA and DBM phases also included a normal approximation for the 95% confidence interval (CI) for the difference in binomial clinical response proportions between the low and high-dose groups.

The Applicant's SAP specified that in the primary analysis for the DBA phase, a continuity-corrected chi-square test would be utilized to test the primary endpoint. The Applicant's SAP did not specify whether the asymptotic 95% CIs for the difference in response proportions would be reported with or without a continuity correction.

Of the two tests (i.e., continuity corrected chi-squared test or conventional chi-squared test), the continuity corrected chi-squared test is considered more conservative, since the continuity correction reduces the chi-square statistic's magnitude. The use of a continuity correction may result in a null hypothesis not being rejected when it would have been rejected with the use of a conventional chi-square test. Concerns with the use of a continuity correction exist in the literature (Haviland 1990; Stefanescu et al. 2005; Serra et al. 2019); articles suggest that in most cases, the use of a conventional chi-square test is preferred over the use of a chi-square test with a continuity correction. In this study, the use of a conservative method to test the primary endpoint is reasonable, and results are generally consistent with those obtained from a conventional chi-square test.

For consistency, since the Applicant prespecified the use of a continuity corrected chi-square test in the primary analysis for the DBA phase, and since the method is considered as conservative, primary endpoint estimates for the DBA phase are shown in this review along with asymptotic 95% CIs with a continuity correction. Similarly, asymptotic 95% CIs for primary analysis estimates for the DBM phase are shown with a continuity correction. Corresponding 95% CIs obtained without a continuity correction are reported in the Applicant's CSR.

Multiple Testing Approach

SPD476-319 was not powered to detect differences between treatment groups. As a result, there was no planned formal hypothesis testing. P-values for primary efficacy endpoints and all other endpoints are therefore not included in this review.

Handling of Missing Data

Nonresponder imputation was the primary method specified in the protocol for handling missing binary efficacy endpoint values. With nonresponder imputation, patients with missing binary efficacy endpoint values were treated as nonresponders.

Sensitivity Analyses

The protocol specified two types of sensitivity analyses for the primary efficacy endpoints for the DBA and DBM phases: a complete-case analysis and a last observation carried forward (LOCF) analysis. In the complete-case analysis, patients who withdrew early from the study were excluded, and an analysis identical to the primary efficacy endpoint analysis was performed. In the LOCF analysis, missing values of the individual components of the partial UC-DAI score were imputed using the LOCF value, and an analysis identical to the primary efficacy endpoint analysis was performed.

Protocol Amendments

There were five amendments to the original protocol, which was finalized on September 11, 2013. Protocol amendment 5 was finalized on April 10, 2017. Pertinent changes in protocol amendment 5 include statements which clarified that SPD476-319 was an estimation study intended to provide estimates of clinical response for low and high doses of mesalamine and was not powered to detect differences between treatment groups. The sample size for the DBA phase was reduced to 53 patients due to recruitment difficulties. Also, subgroup analyses for the primary efficacy endpoint were added to explore efficacy by weight group and Week 8 responder status.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that all studies included in the submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Council for Harmonisation good clinical practice guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

Financial Disclosure

The Applicant adequately disclosed financial arrangements with the clinical investigators. These arrangements do not raise concern over the integrity of the data. See Section 15.2 for further discussion and tables detailing financial disclosures.

Patient Disposition

SPD476-319 enrolled 107 patients from 33 study sites in North America, Europe, and the Middle East. These patients comprised the overall randomized analysis set. Of the 107 patients in the overall randomized analysis set, 42 (39.3%) patients discontinued, and 65 (60.7%) patients completed the study. The reason for discontinuation with the highest percentage across all study phases was lack of efficacy (21.5%) reported by 23 patients. Two of the 107 patients never received study drug. Therefore, the overall safety analysis set contains 105 unique randomized patients who took at least one dose of Lialda (shown in the box in the table below). The safety analysis set for each phase was used for the assessment of both safety and efficacy data. Table 13 summarizes the patient disposition for the overall trial. An overview of the disposition by phase for the DBA, OLA, and DBM safety analysis sets follows the table.

Table 13. Patient Disposition (Screened Set)

	Overall n (%)
Screened set[a]	165
Enrolled set[b]	107
Overall randomized analysis set[c]	107
Double-blind acute phase randomized subjects	54
Double-blind maintenance phase randomized subjects	88
Overall safety analysis set[d]	105
Double-blind acute phase safety analysis set[e]	53
Open-label acute phase safety analysis set[f]	18
Double-blind maintenance phase safety analysis set[g]	87
Subjects who entered directly	52
Subjects who entered via the double-blind acute phase	27
Subjects who entered via the open-label acute phase	8
Completed study[h]	65 (60.7)
Did not complete study[i]	42 (39.3)
Not continued in study	2 (1.9)
Not enrolled in double-blind maintenance phase	4 (3.7)
Did not have a follow-up	1 (0.9)
Discontinued from last phase	35 (32.7)
Primary reason for discontinuation from last phase[j]	
Adverse event	7 (6.5)
Lack of efficacy	23 (21.5)
Other	4 (3.7)
Missing	1 (0.9)

Source: SPD476-319 CSR Table 10 (p. 79-80),Table 14.1.1.1 (p. 152-155)
Percentages were based on the number of patients enrolled in the study.
[a] The screened set consisted of all patients who had signed informed consent.
[b] The enrolled set included all patients who enrolled in the study.
[c] The overall randomized analysis set included all patients randomized in the study.
[d] The overall safety analysis set consisted of randomized patients who had taken at least 1 dose of Lialda.
[e] The double-blind acute phase safety analysis set consisted of randomized patients who had taken at least 1 dose of Lialda during the double-blind acute phase.
[f] The open-label acute phase safety analysis set consisted of all patients who had taken at least 1 dose of Lialda during the open-label acute phase.
[g] The double-blind maintenance phase safety analysis set consisted of randomized patients who had taken at least 1 dose of Lialda during the double-blind maintenance phase.
[h] Completed study includes patients who entered the double-blind maintenance phase from one of the acute phases, completed the Week 26 visit, and had follow-up assessment within 7 days of the last dose of Lialda, and patients who entered directly into the double-blind maintenance phase, completed the Week 26 visit, and had follow-up assessment within 7 days of the last dose of Lialda.
[i] "Not continued in study" includes patients who completed the double-blind acute phase but did not continue into the open-label acute phase or the double-blind maintenance phase. "Not enrolled in double-blind maintenance phase" includes patients who completed the open-label acute phase who did not enroll in the double-blind maintenance phase.
[j] Primary reason for discontinuation was the reason for discontinuation from the last phase that a patient was enrolled in if the patient did not complete the phase. Patient 201-0017 withdrew from the double-blind maintenance phase on October 10, 2018, but has a missing reason for withdrawal. The patient had adverse events of diarrhoea and haematochezia on September 23, 2018.

An overview of the disposition starting with patient randomization into the DBA phase is summarized below for the 105 unique patients in the overall safety analysis set.

A total of 53 patients were randomized 1:1 (stratified by body weight group) to one of two weight-based dose levels (low and high dose) in the DBA phase. Eighty-seven patients were randomized, using the same approach as the DBA phase, to one of two weight-based dose levels in the 26-week DBM phase through the following three treatment paths:

1. DBA -> DBM: 27 patients enrolled into the DBM phase after completing 8 weeks of initial treatment during the DBA phase and achieving the primary endpoint of clinical response, defined as a partial UC-DAI ≤1 (with rectal bleeding =0, stool frequency ≤1, and PGA =0)
2. DBA -> OLA -> DBM: 18 patients were treated in the OLA phase with the high-dose level of Lialda after completing the DBA phase but failing to achieve a clinical response/remission (12 patients), or withdrawing from the DBA phase, after a minimum of 2 weeks of treatment, due to lack of benefit (six patients). Of these 18 patients, eight patients enrolled into the DBM phase after achieving a clinical response, as defined above, in the OLA phase
3. Direct entry to DBM: 52 patients had not participated in the DBA phase but were receiving treatment with a 5-ASA (e.g., mesalamine, sulfasalazine, etc.) and had a partial UC-DAI ≤1 (with rectal bleeding =0, stool frequency ≤1, PGA =0), with an endoscopic subscore of 0 or 1 (modified to exclude friability from a score of 1) prior to directly enrolling in the DBM phase.

Discontinuations From the Trial (Safety Analysis Set for Each Study Phase)

DBA

Of the 12/53 (22.6%) patients who did not complete the DBA phase, eight were enrolled in the low-dose treatment group, and four were enrolled in the high-dose treatment group during the DBA phase. Six patients (two from the low-dose treatment group and four from the high-dose treatment group) left the DBA phase prior to completion and enrolled in the OLA phase (noted above). Six patients (all from the low-dose treatment group) were discontinued from the DBA phase and did not enroll in the OLA phase; five patients were discontinued due to lack of efficacy, and one patient was discontinued due to an adverse event. Two patients completed the DBA phase but did not enroll into either the OLA or DBM phases. Refer to Table 65 for further details regarding patient disposition for the DBA phase.

OLA

Of the 6/18 (33.3%) patients who did not complete the OLA phase, five patients were discontinued due to lack of efficacy, and one patient was discontinued due to an adverse event. Of note, all patients in the OLA phase received high-dose Lialda.

DBM

Of the 21/87 (24.1%) patients who did not complete the DBM phase, 10 were enrolled in the low-dose treatment group, and 11 were enrolled in the high-dose treatment group during the DBM phase. Five patients were discontinued due to an adverse event (three from the low-dose treatment group and two from the high-dose treatment group), 13 patients were discontinued due to lack of efficacy (six in the low-dose treatment group and seven from the high-dose treatment group), one patient in the high-dose treatment group was discontinued due to "randomized to incorrect weight group," one patient in the low-dose treatment group was discontinued due to "mild active disease by the endoscopy, re-elevation of faecal calprotectin," and one patient in the high-dose treatment group discontinued, but the reason was missing. Table 66 summarizes patient disposition for the DBM phase.

Protocol Violations/Deviations

Of the 105 patients in the overall safety analysis set, 82 (78.1%) patients had at least one protocol deviation. The most common deviations (occurring in >10% of patients) were “other deviations” (52 [49.5%] patients), “out of window visit” (23 [21.9%] patients), “study drug compliance” (18 [17.1%] patients), and “informed consent” and “missing safety assessment” (each with 14 [13.3%] patients).

Demographic Characteristics

Demographic characteristics of the overall safety analysis set are summarized in Table 14. In the overall safety analysis set, the median patient age was 15.0 years, ranging from 5 to 17 years. Ten (9.5%) patients were in the 5 to 10 years age category, and 95 (90.5%) patients were in the 11 to 17 years age category. There were similar proportions of male (52 [49.5%]) and female (53 [50.5%]) patients. Most patients were white (101 [96.2%]) and not-Hispanic or Latino (104 [99.0%]). The median patient weight was 53.5 kg, ranging from 19 to 86 kg. The median patient height was 164.0 cm, ranging from 111 to 185 cm.

Table 14. Demographic Characteristics (Overall Safety Analysis Set)

Demographic Characteristic	Overall N=105
Age (years)	
n	105
Mean (SD)	14.1 (2.55)
Median	15.0
Min, max	5, 17
Age category, n (%)	
5 to 10 years	10 (9.5)
11 to 17 years	95 (90.5)
Sex, n (%)	
Male	52 (49.5)
Female	53 (50.5)
Race, n (%)	
White	101 (96.2)
Black or African American	1 (1.0)
Asian	3 (2.9)
Ethnicity, n (%)	
Hispanic or Latino	1 (1.0)
Not-Hispanic or Latino	104 (99.0)
Weight (kg)	
n	105
Mean (SD)	53.2 (13.79)
Median	53.5
Min, max	19, 86
Weight group (kg) n (%)	
18 to ≤23	3 (2.9)
>23 to ≤35	9 (8.6)
>35 to ≤50	28 (26.7)
>50 to ≤90	65 (61.9)

Demographic Characteristic	Overall N=105
Height (cm)	
n	105
Mean (SD)	161.7 (14.01)
Median	164.0
Min, max	111, 185

Source: SPD476-319 CSR Table 15 (p. 84), Table 16 (p. 85), Table 14.1.4.2.1 (p. 198)
Abbreviations: SD, standard deviation

Demographic characteristics were generally similar between the low and high-dose groups in the DBA phase and DBM phase safety analysis sets. The demographic characteristics of the DBA phase and DBM phase safety analysis sets are summarized in Table 67 and Table 68, respectively.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Baseline characteristics of the overall safety analysis set are summarized in Table 15. In this set, the mean (SD) time since diagnosis of UC was 16.6 (31.54) months, and 58 (55.2%) patients were not newly diagnosed. The mean (SD) number of acute episodes of UC in the last year and since diagnosis were 0.9 (0.89) and 1.6 (1.25), respectively. The baseline mean (SD) total UC-DAI score for patients enrolled in the DBA phase was 5.8 (1.79).

Table 15. Baseline Characteristics (Overall Safety Analysis Set)

Characteristic	Overall N=105
Time since diagnosis (months)	
N	105
Mean (SD)	16.6 (31.54)
Median	3.0
Min, max	0, 160
Diagnosis state, n (%)	
Number of patients newly diagnosed	47 (44.8)
Number of patients not newly diagnosed	58 (55.2)
Number of acute episodes of UC in last year	
N	57
Mean (SD)	0.9 (0.89)
Median	1.0
Min, max	0, 4
Number of acute episodes of UC since diagnosis	
N	56
Mean (SD)	1.6 (1.25)
Median	1.0
Min, max	0, 5
Total UC-DAI score at baseline, DBA phase	
N	48[a]
Mean (SD)	5.8 (1.79)
Median	5.7
Min, max	2.0, 9.7

Source: SPD476-319 CSR Table 16 (p. 85) and Clinical Reviewer's table generated from Applicant ADSL and ADQSUC datasets
[a] Patients with endoscopic scores based on central readings; four patients did not have endoscopic scores based on central reading and were not included in the calculation of baseline total UC-DAI scores.
Abbreviations: DBA, double-blind acute; SD, standard deviation; UC-DAI, Ulcerative colitis disease activity index

Baseline characteristics were generally similar between the low and high-dose groups in the DBA phase and DBM phase safety analysis sets, except for the mean number of months since diagnosis among patients in the DBA phase (1.7 months in the low-dose group and 12.7 months in the high-dose group). Although the mean number of months since diagnosis differed between the two dose levels, the median number of months since diagnosis was similar (0.0 months in each dose group). Given that the imbalance in the mean number of months since diagnosis appears to be driven by two outliers in the high-dose group, and since the baseline UC-DAI scores were similar in both dose levels, the difference between the dose levels in the mean number of months since diagnosis was unlikely to influence the trial results. The baseline characteristics of the DBA phase and DBM phase safety analysis sets are summarized in Table 69 and Table 70, respectively.

Of note, five patients were enrolled who had more mild baseline symptoms and did not meet the enrollment criterion for a baseline total UC-DAI score ≥4; these patients' baseline UC-DAI scores ranged from 2.0 to 3.7. The disposition for these five patients is shown below:

- One patient with a baseline UC-DAI score of 2.0 was withdrawn from the DBA phase after the protocol violation was identified.
- One patient was discontinued from the DBA phase due to a lack of efficacy.
- One patient was discontinued from the OLA phase due to a lack of efficacy (i.e., did not benefit from treatment during the DBA or OLA phases).
- Two patients with a baseline UC-DAI score of 2.0 and 2.7, completed the DBA phase and continued in the DBM phase; however, one patient discontinued from the DBM phase due to an adverse event, and the other discontinued due to lack of efficacy. Of note, both patients were in the high-dose treatment group for the DBA and DBM phases.

Two of the five patients were recorded as protocol violations. Although these patients were enrolled with milder baseline disease than specified in the enrollment criterion, inclusion of these five patients did not appear to influence the outcome of the trial. All five patients discontinued from the trial and did not appear to benefit from treatment overall. For the two patients who continued from the DBA phase into the DBM phase, one patient achieved the primary endpoint in the DBA phase, but the other did not. This protocol violation did not appear in the dataset; however, the review team did not identify any other patients who were incorrectly enrolled into the DBM phase. The conclusions drawn from the results of the DBA phase remain unchanged even if this patient was considered as a treatment failure.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Lialda was administered at home by the patient and/or caregiver. The patients/caregivers were instructed to bring unused and empty/used packaging to every visit. The container/packaging was assessed for product accountability, and a selected member of the study team (e.g., a blinded pharmacist) recorded the details of the assessment on the drug accountability form. If it was determined the patient had not taken Lialda at the dose prescribed, the patient and/or caregiver was given additional instructions on the dosing requirements of the study.

The overall compliance rates during the DBA phase were generally similar between the two treatment groups: the mean (SD) percentage compliance was 95.6% (13.35) for patients in the low-dose group and 99.3% (2.32) for patients in the high-dose group. The overall compliance rates during the DBM phase were generally similar between the two treatment arms: the mean

(SD) percentage compliance was 97.0% (11.17) for patients in the low-dose group and 98.1% (7.45) for patients in the high-dose group.

Concomitant Medications

The Applicant defined concomitant medications as any medication with a start date prior to the date of the first dose of Lialda and continuing after the first dose of Lialda or with a start date between the dates of the first dose of Lialda and the end of the follow-up period.

Based on these definitions, which appear to include the day that Lialda was started or stopped, the Applicant reported 102/105 (97.1%) patients received at least one concomitant medication with mesalazine being the most common (61/105, 58.1%). Sulfasalazine (25/105, 23.8%) and paracetamol (25/105, 23.8%) were the next most common concomitant medications. To ensure that these medications were not taken during the clinical trial, the datasets were reviewed to identify the start and stop dates of the concomitant medications. Review of the data demonstrated that patients who received mesalazine, sulfasalazine, or other 5-ASAs either discontinued the concomitant medication the same day as starting Lialda or initiated the concomitant medication during the follow-up period after discontinuing Lialda.

Rescue Medication Use

The following medications were not permitted by the Applicant during the study; if a patient received any of these medications, they were withdrawn from the study:

- Systemic or rectal corticosteroids
- Other medications containing 5-ASA (e.g., sulfasalazine or mesalamine/mesalazine) including topical administration
- Immunomodulators (e.g., 6-mercaptopurine, azathioprine, cyclosporine, methotrexate)
- Biologics (e.g., anti-tumor necrosis factor agents).

According to the Applicant, administration of nonsteroidal anti-inflammatory drugs, antidiarrheals, laxatives, antibiotics, and drugs that could cause constipation were permitted for up to 10 consecutive days if taken for a condition unrelated to UC. For mild, acute pain, acetaminophen was recommended.

Efficacy Results: Primary Endpoint

The primary efficacy endpoint for the DBA phase was the proportion of patients with a clinical response (defined as partial UC-DAI ≤1 with rectal bleeding =0, stool frequency ≤1, and PGA =0) at Week 8. The primary efficacy assessment at 8 weeks did not include endoscopic evaluation. Results for the primary efficacy endpoint based on the DBA phase safety analysis set are shown in Table 16. At Week 8 of the DBA phase, 10 (37.0%) patients who received low-dose mesalamine achieved a clinical response compared to 17 (65.4%) patients who received high-dose mesalamine. The results were confirmed by the statistical reviewer. While not reported in the CSR, the corresponding 95% CI from the normal approximation with a continuity correction was (-1.2, 57.9), as calculated by the review team.

Table 16. Applicant's Primary Efficacy Endpoint Analysis for DBA Phase, Proportion of Patients With a Clinical Response at Week 8[a] (DBA Phase Safety Analysis Set)

Parameter	Low-Dose MMX Mesalamine N=27	High-Dose MMX Mesalamine N=26
Number (%) of patients with clinical response at Week 8	10 (37.0)	17 (65.4)
Difference in proportions (high to low dose) %		28.3
95% CI for difference in proportions[b] (high to low dose) %		-1.2, 57.9

Source: SPD476-319 CSR Table 17 (p. 89), statistical reviewer's analysis
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation with continuity correction for the difference in binomial proportions.
Abbreviations: CI, confidence interval; DBA, double-blind acute; MMX, multi-matrix system

The primary efficacy endpoint for the DBM phase was the proportion of patients with a clinical response (defined as partial UC-DAI ≤1 with rectal bleeding =0, stool frequency ≤1, and PGA =0) at Week 26. The primary efficacy assessment at 26 weeks did not include endoscopic evaluation. Results for the primary efficacy endpoint based on the DBM phase safety analysis set are shown in Table 17. At Week 26 of the DBM phase, 23 (54.8%) patients who received low-dose mesalamine achieved clinical response compared to 24 (53.3%) patients who received high-dose mesalamine. The response proportions in both dose groups appeared similar. These results were confirmed by the statistical reviewer. While not reported in the CSR, the corresponding 95% CI from the normal approximation with a continuity correction was (-24.7, 21.8).

Table 17. Applicant's Primary Efficacy Endpoint Analysis for DBM Phase, Proportion of Patients With a Clinical Response at Week 26[a] (DBM Phase Safety Analysis Set)

Parameter	Low-Dose MMX Mesalamine N=42	High-Dose MMX Mesalamine N=45
Number (%) of patients with clinical response at Week 26	23 (54.8)	24 (53.3)
Difference in proportions (high to low dose) %		-1.4
95% CI for difference in proportions[b] (high to low dose) %		-24.7, 21.8

Source: SPD476-319 CSR Table 20 (p. 94), statistical reviewer's analysis
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation with continuity correction for the difference in binomial proportions.
Abbreviations: CI, confidence interval; DBM, double-blind maintenance; MMX, multi-matrix system

Primary efficacy endpoint results from the DBA phase suggest a higher response rate in the high-dose group, and results from the DBM phase suggest similar response rates between both dose groups. As mentioned above, the study was not powered to detect a treatment difference between the two doses. Another limitation of the study was the reduced sample size due to study recruitment difficulties. Thus, conclusions regarding the most effective mesalamine dosing regimen must also consider the risks associated with taking the drug.

The study was not powered for efficacy, and there was no formal hypothesis testing planned; hence, p-values were nominal and are not reported. Efficacy was extrapolated from adult data, and a rigorous statistical inference was not required; however, the review team determined that the recommended pediatric dose would likely result in a similar response to treatment to support use in pediatric patients. At Week 8 of the trials that supported approval in adults, remission was defined by the UC-DAI ≤1 with scores of 0 for rectal bleeding and stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline. In the adult trials, Lialda 2.4 g and 4.8 g had similar efficacy profiles and demonstrated superiority over placebo at Week 8.

Although the endpoint definition at Week 8 of the adult trials was not identical to the definition used in the pediatric trial, both the adult and pediatric trial results demonstrated improvement in clinically relevant signs/symptoms of UC (i.e., rectal bleeding and stool frequency). Separate trials in adults evaluated the maintenance of remission, defined by a "modified UC-DAI" endoscopic subscore ≤1 (an endoscopic subscore of 0 did not include friability). At Month 6, Lialda 2.4 g and 1.6 g once daily demonstrated similar efficacy profiles in adult patients. Efficacy was established both at Week 8 and Month 6 in adult clinical trials; however, a direct comparison of results between the adult trials and pediatric trial would not be informative given the different endpoint definitions. Despite the limitations of cross-study comparison, the course of disease and effects of Lialda are expected to be sufficiently similar between adult and pediatric patients to conclude that efficacy can be extrapolated from adult data.

Sensitivity Analyses

The Applicant's sensitivity analysis results for the primary efficacy endpoint for the DBA and DBM phases were generally consistent with the primary analysis results. Results for the complete-case analyses for the DBA and DBM phases are shown in Table 71 and Table 72, respectively.

Data Quality and Integrity

In general, the data submitted by the Applicant to support the efficacy and safety of mesalamine for the proposed indication were acceptable.

Efficacy Results: Secondary and Other Relevant Endpoints

The Applicant's clinical remission and clinical response endpoints did not align with the Division's currently recommended definitions (see Section 7.2). The Division requested additional analyses for Weeks 8 and 26 using the recommended definitions of clinical remission and response. In the DBA phase, only two patients in the low-dose group and three patients in the high-dose group underwent endoscopy at both Week 0 and Week 8; thus, analyses of the recommended clinical remission and clinical response endpoints were not feasible in the absence of endoscopic data. As noted previously, an analysis of the currently recommended endpoint for clinical response for the DBM phase was not informative because the definition relies on a comparison to baseline. Pretreatment baseline disease severity scores were not available for the patients who enrolled in the DBM phase without participating in the DBA phase.

The Applicant's results for the recommended clinical remission endpoint based on the DBM phase safety analysis set are shown in Table 18. At Week 26 of the DBM phase, 15 (35.7%) patients who received low-dose mesalamine achieved clinical remission compared to 12 (26.7%) patients who received high-dose mesalamine. These results support recommending the low-dose Lialda for treatment after Week 8. The difference in the proportions of patients with clinical remission (high to low dose) was -9.0% (95% CI [normal approximation with continuity correction]: -30.8, 12.7). These results were confirmed by the statistical reviewer.

Table 18. Applicant's Analysis for DBM Phase, Proportion of Patients With Clinical Remission at Week 26[a] (DBM Phase Safety Analysis Set)

Parameter	Low-Dose MMX Mesalamine N=42	High-Dose MMX Mesalamine N=45
Number (%) of patients with clinical remission at Week 26	15 (35.7)	12 (26.7)
Difference in proportions (high to low dose) %		-9.0
95% CI for difference in proportions[b] (high to low dose) %		-30.8, 12.7

Source: SPD476-319 Table 1.1 (submitted by the Applicant as a response to the Agency's IRs), statistical reviewer's analysis
[a] Analyzed with NRI for missing data
[b] 95% CI was based on the normal approximation with continuity correction for the difference in binomial proportions.
Note: Clinical remission is defined by a stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 (modified to exclude friability) on the Mayo score, or 0 on the UCDAI.
Abbreviations: CI, confidence interval; DBM, double-blind maintenance; MMX, multi-matrix system

Dose/Dose Response

The study was not designed to detect differences between treatment arms. However, during the DBA phase a higher proportion of patients achieved the primary endpoint at Week 8 in the high-dose treatment arm than the low-dose treatment arm. During the DBM phase, the proportions of patients who achieved the primary endpoint at Week 26 were similar between the high- and low-dose treatment arms. These results suggest that there may be a positive dose-response relationship during the initial 8 weeks of treatment.

Durability of Response

Double-blinded data were available through a total of 34 weeks of treatment (double-blind acute and double-blind maintenance) in 23 patients. Additionally, five patients received a total of 42 weeks of treatment (double-blind acute, open-label acute, and double-blind maintenance). There is no planned long-term extension study, and no additional data on longer-term outcomes are anticipated to be available. Overall, the durability of response appears to be supported through 34 weeks based on limited information included in the submission (data not shown).

Persistence of Effect

Available data did not permit assessment of the persistence of effect. However, since UC is a chronic inflammatory condition that requires long-term therapy, we expect that stopping treatment would not provide useful information and would lead to disease worsening.

Efficacy Results: Secondary or Exploratory Clinical Outcome Assessment (PRO) Endpoints

N/A

Additional Analyses Conducted on the Individual Trial

Table 19 and Table 20 contain the Applicant's exploratory analyses of the primary efficacy endpoint in the DBA phase by sex and weight (>23 to ≤35 kg, >35 to ≤50 kg, >50 to ≤90 kg) subgroups. Table 21 and Table 22 contain exploratory sex and weight subgroup analyses for the DBM phase. Subgroup analyses by race are not applicable for this study since 101 of the 105 patients in the overall safety analysis set were white. The subgroup analyses are limited by small patient counts, and results should be interpreted with caution. In general, the subgroup analysis results were consistent with the primary analysis results for the DBA and DBM phases.

Table 19. Applicant's Primary Efficacy Endpoint Subgroup Analysis by Sex for DBA Phase, Proportion of Patients With a Clinical Response at Week 8[a] (DBA Phase Safety Analysis Set)

Parameter	Low-Dose MMX Mesalamine	High-Dose MMX Mesalamine
Male		
Number of patients	16	18
Number (%) of patients with clinical response at Week 8	5 (31.3)	11 (61.1)
Difference in proportions (high to low dose) %		29.9
Female		
Number of patients	11	8
Number (%) of patients with clinical response at Week 8	5 (45.5)	6 (75.0)
Difference in proportions (high to low dose) %		29.5

Source: SPD476-319 Table 14.2.1.1.1s (submitted by the Applicant as a response to the Agency's filing communication dated October 31, 2019)
[a] Analyzed with NRI for missing data
Abbreviations: DBA, double-blind acute; MMX, multi-matrix system

Table 20. Applicant's Primary Efficacy Endpoint Subgroup Analysis by Weight for DBA Phase, Proportion of Patients With a Clinical Response at Week 8[a] (DBA Phase Safety Analysis Set)

Weight Group (kg)	Low-Dose MMX Mesalamine N=27 n/N (%)	High-Dose MMX Mesalamine N=26 n/N (%)
>23 to ≤35	1/4 (25.0)	2/3 (66.7)
>35 to ≤50	1/7 (14.3)	6/7 (85.7)
>50 to ≤90	8/16 (50.0)	9/16 (56.3)

Source: SPD476-319 CSR Table 19 (p. 92)
[a] Analyzed with NRI for missing data
Abbreviations: DBA, double-blind acute; MMX, multi-matrix system

Table 21. Applicant's Primary Efficacy Endpoint Subgroup Analysis by Sex for DBM Phase, Proportion of Patients With a Clinical Response at Week 26[a] (DBM Phase Safety Analysis Set)

Parameter	Low-Dose MMX Mesalamine	High-Dose MMX Mesalamine
Male		
Number of patients	19	20
Number (%) of patients with clinical response at Week 26	8 (42.1)	10 (50.0)
Difference in proportions (high to low dose) %		7.9
Female		
Number of patients	23	25
Number (%) of patients with clinical response at Week 26	15 (65.2)	14 (56.0)
Difference in proportions (high to low dose) %		-9.2

Source: SPD476-319 Table 14.2.1.1.2s (submitted by the Applicant as a response to the Agency's filing communication dated October 31, 2019)
[a] Analyzed with NRI for missing data
Abbreviations: DBM, double-blind maintenance; MMX, multi-matrix system

Table 22. Applicant's Primary Efficacy Endpoint Subgroup Analysis by Weight for DBM Phase, Proportion of Patients With a Clinical Response at Week 26[a] (DBM Phase Safety Analysis Set)

Weight Group (kg)	Low-Dose MMX Mesalamine N=42 n/N (%)	High-Dose MMX Mesalamine N=45 n/N (%)
18 to ≤23	1/1 (100.0)	2/2 (100.0)
>23 to ≤35	1/2 (50.0)	2/2 (100.0)
>35 to ≤50	7/11 (63.6)	6/13 (46.2)
>50 to ≤90	14/28 (50.0)	14/28 (50.0)

Source: SPD476-319 CSR Table 23 (p. 97)
[a] Analyzed with NRI for missing data
Abbreviations: DBM, double-blind maintenance; MMX, multi-matrix system

8.1.3. Assessment of Efficacy Across Trials

This efficacy supplement included one clinical trial; therefore, an integrated assessment of efficacy across trials was not performed.

8.1.4. Assessment of Overall Effectiveness

The data submitted in this efficacy supplement establish a clinical benefit in pediatric patients weighing at least 24 kg with mildly to moderately active UC. Efficacy was extrapolated from adequate and well-controlled trials conducted in adults with mildly to moderately active UC, based on sufficiently similar pathophysiology of UC, disease progression, and response to treatment between adults and pediatric patients. The results of the pediatric clinical trial provide additional data to support the clinical benefit in pediatric patients and inform the dosing recommendations and safety of Lialda use in pediatric patients.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review focused on the study SPD476-319 and includes three phases: DBA, OLA, and DBM. Analyses were conducted separately for each phase due to differences in trial design, including enrollment criteria, dosing, and treatment duration. Adverse events were assessed based on the phase of the trial in which the event occurred. Only the randomized population was included in the primary assessment of safety (i.e., safety analysis set). The safety data from the pediatric PK study (SPD476-112) provided only supportive information due to its limited treatment duration of 7 days; thus, it is not discussed in detail in this section. Notably, during SPD476-112 there were no serious adverse events (SAEs) or discontinuations and reported treatment-emergent adverse events (TEAEs) were similar to those described in Section 8.2.4 for SPD476-319 (the pediatric efficacy and safety study). In addition, safety data from the OLA phase were reviewed for safety; however, due to the open-label single-dose nature of this phase, it did not contribute to the efficacy determination.

Safety information from the experience of Lialda in adults with UC identified several adverse events of special interest (AESIs) for the pediatric UC study. The AESIs are discussed in detail in Section 8.2.5.1 and include the following:

1. "Gastritis" was used as a general category to include gastritis-related events, defined by the preferred terms of dyspepsia and gastrooesophageal reflux disease
2. "Hepatic toxicity" defined by the preferred terms of alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood bilirubin increased, and gamma-glutamyl transferase (GGT) increased
3. "Pancreatitis" was used as a general category to include pancreatitis-related events defined by the preferred terms of abdominal pain, vomiting, abdominal pain upper, nausea, and blood bilirubin increased
4. Cholecystitis
5. Myocarditis
6. Pericarditis
7. Renal toxicity

In addition, the Applicant reported UC as an adverse event in the safety database if a patient experienced significant worsening of UC symptoms. If a patient's symptoms were the expected progression of the disease, the symptoms were recorded as a lack of efficacy and not as an adverse event (AE). However, patients with UC who are not responding to therapy can develop significant worsening of symptoms. Therefore, the events of ulcerative colitis that were reported as AEs were assessed in our review of the safety data, but the review team considered these events to be more representative of lack of efficacy.

During the conduct of the safety review, several terms from the Applicant were recoded by the reviewer. Table 23 lists the recoded terms used in the safety review.

Table 23. Recoded Terms for Safety Analyses From ADAE Files

Applicant's AE Code	Reviewer's Recoded Term
Abdominal pain upper	Abdominal pain
Abdominal pain lower	Abdominal pain
Haemoglobin decreased	Anemia
Hypophagia	Decreased appetite
Duodenitis	Enteritis
Viral gastroenteritis	Gastroenteritis
Anal hemorrhage	Hematochezia
Rectal hemorrhage	Hematochezia
Respiratory tract infection viral	Upper respiratory tract infection
Viral upper respiratory tract infection	Upper respiratory tract infection
Nasopharyngitis	Upper respiratory tract infection

Source: Reviewer's Table
Abbreviations: AE, adverse event

8.2.2. Review of the Safety Database

Overall Exposure

The overall safety database included 105 out of 107 patients; two patients in the low-dose treatment arm of the DBM phase never received a dose of Lialda and were not included in the safety analyses. Therefore, the labeling will reflect data from 105 patients.

The maximum duration of the study was 42 weeks (i.e., 8-week DBA phase, 8-week OLA phase, and 26-week DBM phase); five patients completed all three phases of the study and received the maximum duration of exposure of 42 weeks. Of these five patients:

- Two were in the low-dose group in the DBA phase and the low-dose group in the DBM phase
- Two were in the high-dose group in the DBA phase and the high-dose group in the DBM phase
- One patient was in the low-dose group in the DBA phase and the high-dose group in the DBM phase.

Twenty-four patients completed the DBA and DBM phases for a treatment duration of 34 weeks. Forty-two patients completed the DBM phase, without having participated in the DBA or OLA phase, for a treatment duration of 26 weeks. An overview of the exposure by study phase follows.

Exposure During the Double-Blind Acute Phase

The safety database for the DBA phase included 53 patients, including 27 patients in the low-dose treatment arm and 26 patients in the high-dose treatment arm. In the low-dose treatment arm, four patients received 1.2 g daily, seven patients received 1.8 g daily, and 16 patients received 2.4 g daily. In the high-dose treatment arm, three patients received 2.4 g daily, seven patients received 3.6 g daily, and 16 patients received 4.8 g daily. Further details of exposure during the DBA phase are provided in Table 24.

Table 24. Lialda Exposure During Double-Blind Acute Phase

	Low-dose MMX Mesalazine N=27	High-dose MMX Mesalazine N=26	Overall N=53
Average daily dose (mg/day)			
n	27	26	53
Mean (SD)	2060.1 (446.40)	4200.0 (848.53)	3109.9 (1269.71)
Median	2400.0	4800.0	2400.0
Q1, Q3	1800.0, 2400.0	3600.0, 4800.0	2400.0, 4800.0
Min, max	1200, 2400	2400, 4800	1200, 4800
Total dose (mg)			
n	27	26	53
Mean (SD)	96400.0 (45255.58)	216553.8 (65991.91)	155343.4 (82432.32)
Median	102600.0	238800.0	136800.0
Q1, Q3	66000.0, 136800.0	198000.0, 268800.0	77400.0, 223200.0
Min, max	14400, 160800	64800, 278400	14400, 278400
Length of exposure (weeks)			
n	27	26	53
Mean (SD)	6.5 (2.49)	7.4 (1.73)	6.9 (2.17)
Median	8.0	8.0	8.0
Q1, Q3	4.0, 8.1	7.7, 8.1	6.1, 8.1
Min, max	1, 10	2, 9	1, 10

Source: Applicant's submission, dated August 29, 2019, sNDA 022000, module 5.3.5.1 SPD476-319 Report Body, Table 29, page 117/1545
Note: Average daily dose (mg/day) was defined as the total dose/total exposure, where total dose (mg) is calculated as the total exposure in the double-blind acute phase (days) x the dose taken in the double-blind acute phase.
Note: Length of exposure (weeks) was calculated as (date of last dose in the double-blind acute phase – date of first dose in the double-blind acute phase +1) / 7
Abbreviations: MMX, multi-matrix system; Q1, quartile 1; Q3, quartile 3; SD, standard deviation

Exposure During the Open-Label Acute Phase

The safety database for the OLA phase included 18 patients. All of the patients in the OLA phase received high-dose treatment; three patients received 2.4 g daily, four patients received 3.6 g daily, and 12 patients received 4.8 g daily. Further details of exposure during the OLA phase are provided in Table 25.

Table 25. Lialda Exposure During Open-Label Acute Phase

	High-dose MMX Mesalazine N=18
Average daily dose (mg/day)	
n	18
Mean (SD)	4266.7 (845.75)
Median	4800.0
Q1, Q3	3600.0, 4800.0
Min, max	2400, 4800
Total dose (mg)	
n	18
Mean (SD)	194733.3 (90481.82)
Median	236400.0
Q1, Q3	134400.0, 268800.0
Min, max	43200, 288000
Length of exposure (weeks)	
n	18
Mean (SD)	6.4 (2.56)
Median	8.0
Q1, Q3	4.4, 8.0
Min, max	2, 9

Source: Applicant's submission, dated August 29, 2019, sNDA 022000, module 5.3.5.1 SPD476-319 Report Body, Table 30, page 118/1545
Note: Average daily dose (mg/day) was defined as the total dose/total exposure, where total dose (mg) is calculated as the total exposure in the open-label acute phase (days) x the dose taken in the open-label acute phase.
Note: Length of exposure (weeks) was calculated as (date of last dose in the open-label acute phase – date of first dose in the open-label acute phase +1) / 7.
Abbreviations: MMX, multi-matrix system; Q1, quartile 1; Q3, quartile 3; SD, standard deviation

Exposure During the Double-Blind Maintenance Phase

The safety database for the DBM phase included 87 patients. In the low-dose treatment arm there were 42 patients, and in the high-dose treatment arm there were 45 patients. In the low-dose treatment arm: one patient received 900 mg daily, two patients received 1.2 g daily, 11 patients received 1.8 g daily, and 28 patients received 2.4 g daily. In the high-dose treatment arm: two patients received 1.8 g daily, two patients received 2.4 g daily, 13 patients received 3.6 g daily, and 28 patients received 4.8 g daily. Further details of exposure during the DBM phase are provided in Table 26.

Table 26. Lialda Exposure During Double-Blind Maintenance Phase

	Low-dose MMX Mesalazine N=42	High-dose MMX Mesalazine N=45	Overall N=87
Average daily dose (mg/day)			
n	42	45	87
Mean (SD)	2150.0 (397.09)	4196.6 (878.70)	3208.6 (1236.25)
Median	2400.0	4800.0	2400.0
Q1, Q3	1800.0, 2400.0	3600.0, 4800.0	2400.0, 4800.0
Min, max	900, 2400	1800, 4800	900, 4800
Total dose (mg)			
n	42	45	87
Mean (SD)	325478.6 (131157.28)	649360.0 (271350.00)	493003.4 (269018.28)
Median	332100.0	763200.0	436800.0
Q1, Q3	219600.0, 436800.0	432000.0, 878400.0	327600.0, 830400.0
Min, Max	9600, 456000	9600, 907200	9600, 907200
Length of exposure (weeks)			
n	42	45	87
Mean (SD)	21.9 (7.70)	22.2 (7.60)	22.1 (7.61)
Median	26.0	25.9	25.9
Q1, Q3	21.0, 26.1	24.7, 26.1	22.7, 26.1
Min, max	1, 27	0, 27	0, 27

Source: Applicant's submission, dated August 29, 2019, sNDA 022000, module 5.3.5.1 SPD476-319 Report Body, Table 31, page 119/1545
Note: Average daily dose (mg/day) was defined as the total dose/total exposure, where total dose (mg) is calculated as the total exposure in the double-blind maintenance phase (days) x the dose taken in the double-blind maintenance phase.
Note: Length of exposure (weeks) was calculated as (date of last dose in the double-blind acute phase – date of first dose in the double-blind maintenance +1) / 7.
Abbreviations: MMX, multi-matrix system; Q1, quartile 1; Q3, quartile 3; SD, standard deviation

Adequacy of the Safety Database

Overall, the number of pediatric patients and duration of exposure appear adequate to characterize the safety of Lialda in pediatric patients with mildly to moderately active UC.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

The frequency and type of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and severe adverse events were assessed for patients in these trials. AEs and TEAEs were collected during the screening period until 7 days after the last dose of Lialda. AEs

and TEAEs were classified into preferred terms using Version 16.1 of Medical Dictionary for Regulatory Activities. The Applicant assessed severity by using the following definitions:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Section 8.2.5.1 details the AESI identified by the Applicant. Additionally, several terms from the Applicant were recoded by the reviewer (Table 23) for this safety review.

Routine Clinical Tests

The Applicant assessed clinical laboratory testing as detailed in Table 73 (Section 15.5). Investigators assessed out-of-range clinical laboratory values to determine whether or not the values were considered clinically significant. During the DBA phase hematology, chemistry, and urinalysis assessments were performed during the screening period and at Week 8 or study withdrawal. Similarly, during the OLA phase, the same assessments were performed at Week 8 or study withdrawal. During the DBM phase, assessment was performed during the screening period and at Week 26 or study withdrawal.

8.2.4. Safety Results

Deaths

No deaths occurred during the pediatric development program.

Serious Adverse Events

Overall, there were 18 SAEs in 12/105 (11.4%) patients across all phases of the study SPD476-319. In the DBA phase, a higher proportion of patients reported SAEs in the low-dose treatment arm compared to the high-dose treatment arm. This pattern was not observed in the DBM phase where there was no difference in SAEs between treatment arms. The most common SAE in all phases was ulcerative colitis, occurring in 4/12 patients who reported an SAE.

Serious Adverse Events During Double-Blind Acute Phase

There were six SAEs through Week 8 of the DBA phase reported in 4/27 (14.8%) patients in the low-dose treatment arm and 0/26 (0.0%) patients in the high-dose treatment arm. Of the four patients with at least one SAE, 3/4 (75.0%) were discontinued from the study. The most common SAE was UC, which was reported in 2/4 (50.0%) patients.

The two patients who reported an SAE of UC were hospitalized for an exacerbation of UC. The SAE occurred 2 days and 12 days after starting treatment with Lialda in a 13-year-old female weighing 66 kg and a 10-year-old male weighing 32 kg, respectively. Both patients had Lialda discontinued upon hospitalization.

Two additional patients reported SAEs. One patient, a 17-year-old female weighing 43 kg, was hospitalized for enteritis 5 days after the first dose of Lialda. During the hospitalization the patient reported two additional SAEs: dehydration and anemia. Lialda was permanently discontinued due to the SAEs. A second patient, an 11-year-old male weighing 38 kg with a history of multiple urinary tract infections, was hospitalized for pyelonephritis 34 days after starting treatment with Lialda. At the same time, a nonserious AE of an exacerbation of UC occurred. Lialda was discontinued due to the nonserious AE of UC.

Serious Adverse Events During Open-Label Acute Phase

There were three SAEs through Week 8 of the OLA phase reported in 3/18 (16.7%) patients. Of note, all patients in the OLA phase received high-dose Lialda. Of the three patients with at least one SAE, two of them (66.7%) were discontinued from the study.

The two SAEs that led to study discontinuation were UC and chest pain. One patient, a 14-year-old male weighing 65.2 kg, reported an exacerbation of UC. The patient entered the OLA phase from the DBA low-dose treatment arm. He was hospitalized for UC 13 days after starting the OLA phase. Lialda was discontinued due to the SAE.

The second SAE occurred in a 15-year-old male patient who was hospitalized 9 days after starting the OLA phase for chest pain associated with decreased appetite, torticollis, and neck pain. Laboratory results were significant for increased neutrophils, platelets, gamma-glutamyl transferase and decreased hemoglobin. The patient was discharged from the hospital with no reported treatment. Lialda was discontinued due to the SAE of chest pain.

The third reported SAE was anemia, which occurred in a 15-year-old male weighing 50 kg who required hospitalization for a blood transfusion to treat his anemia. The patient had a previous history of anemia and was on an iron supplement at the time of his enrollment in the DBA low-dose treatment arm. On the same day as he started the OLA phase he was admitted for anemia. Lialda was not discontinued due to the SAE; however, the patient was not enrolled in the DBM phase due to mild active disease and elevated calprotectin.

Of note, the greatest proportion of patients with at least one SAE occurred in the OLA phase. The patients enrolled in the OLA phase may represent a more treatment refractory population, as patients enrolled in the OLA phase did not demonstrate response at the end of the DBA phase (i.e., 8 weeks of treatment with Lialda). Additionally, only 8/18 (44.4%) patients enrolled in the OLA phase met the criteria to enter the DBM phase following 8 additional weeks of treatment with Lialda.

Serious Adverse Events During Double-Blind Maintenance Phase

There were nine SAEs through Week 26 of the DBM phase reported in 3/42 (7.1%) patients in the low-dose treatment arm and 2/45 (4.4%) patients in the high-dose treatment arm. Of the five patients with at least one SAE, one (20.0%) patient was discontinued from the study.

The patient who was discontinued from the study reported an SAE of UC. The patient was a 17-year-old male weighing 67.1 kg enrolled in the low-dose treatment arm, who was hospitalized 53 days after starting Lialda. Initially, he was treated with metronidazole and continued Lialda; however, he was hospitalized for a second exacerbation of UC, 90 days after starting Lialda. The second exacerbation led to the discontinuation of Lialda.

Two other patients in the low-dose treatment arm reported SAEs related to injuries. One patient was hospitalized following a motor vehicle accident, which led to the reporting of two SAEs: motor vehicle accident and spinal compression fractures. A second patient was admitted to the hospital following a corneal and retinal injury. Both patients were continued on Lialda and completed the study.

Lastly, two patients in the high-dose treatment arm experienced upper abdominal pain and dyspepsia. One patient, a 15-year-old female weighing 52.8 kg, had two separate hospitalizations for upper abdominal pain. She received omeprazole and trimebutine for the first episode, during which her laboratory and upper endoscopy results were normal. The second episode was treated with mebeverine and no additional evaluation was performed. Another patient, a 14-year-old male weighing 49 kg, was hospitalized for dyspepsia, which improved with paracetamol. His laboratory results were normal at the time of the SAE. Both patients were continued on Lialda and completed the study.

Dropouts and/or Discontinuations Due to Adverse Events

Overall, 28/105 (26.7%) patients were discontinued due to AEs across all phases of the study SPD476-319. The proportion of discontinuations due to AEs were similar in the individual phases; however, in the DBA phase, one-third of the patients in the low-dose treatment arm were discontinued due to AEs compared to none in the high-dose treatment arm. This increased proportion of discontinuations due to AEs in the low-dose treatment arm was not observed in the DBM phase, which suggests that pediatric patients may need a high-dose level for the initial treatment of active UC. Of note, 23/28 patients who discontinued due to an AE reported UC or hematochezia as the event leading to discontinuation. This pattern of discontinuation likely reflects a lack of efficacy in the patient population, rather than a drug-related AE.

Discontinuations During Double-Blind Acute Phase Due to Adverse Events

The proportion of patients discontinued due to AEs from the DBA phase was 9/53 (17.0%). Of note, all nine patients were in the low-dose treatment arm (9/27, 33.3%). The reason for discontinuation due to AEs in 8/9 (88.9%) patients was ulcerative colitis, including two patients determined to have severe ulcerative colitis. The ninth patient was discontinued due to an SAE of enteritis.

Discontinuations During Open-Label Acute Phase Due to Adverse Events

The proportion of patients discontinued due to AEs from the OLA phase was 2/18 (11.1%). One patient was discontinued due to a SAE of chest pain; the other patient was discontinued due to a severe exacerbation UC.

Discontinuations During Double-Blind Maintenance Phase Due to Adverse Events

The proportion of patients discontinued due to AEs from the DBM phase was 17/87 (19.5%) with 8/42 (19.0%) patients in the low-dose treatment arm and 9/45 (20.0%) patients in the high-dose treatment arm. Discontinuations due to an AE of ulcerative colitis or hematochezia were reported in 7/8 (87.5%) patients in the low-dose treatment arm and 7/9 (77.8%) patients in the high-dose treatment arm. AEs leading to discontinuation that were not due to ulcerative colitis or hematochezia included abdominal pain, increased GGT, and rash. In the low-dose treatment arm, one patient was discontinued due to an AE of moderate abdominal pain. In the high-dose treatment arm one patient was discontinued due to an AE of a severe increase in GGT and one

patient due to a mild rash. The patient with a severe increase in GGT is discussed in detail in Section 8.2.5.1.

Significant Adverse Events

Adverse events that were either severe or led to discontinuation of Lialda are included in the SAE and discontinuation analyses sections. There were no severe TEAEs that did not lead to either an SAE or a discontinuation.

Treatment-Emergent Adverse Events and Adverse Reactions

Overall, 246 TEAEs were reported in 73/105 (69.5%) patients across all phases of the study. Similar to the findings from the SAE and discontinuation analyses, in the DBA phase there was a higher proportion of patients with at least one TEAE due to ulcerative colitis in the low-dose treatment arm compared to the high-dose treatment arm. Conversely, in the DBA phase, abdominal pain and dyspepsia were more frequent in the high-dose treatment arm compared to the low-dose treatment arm. However, the TEAEs of abdominal pain and dyspepsia that were more frequent in the high-dose treatment arm were mild and did not lead to discontinuation. As stated previously, the TEAEs of ulcerative colitis reflect a lack of efficacy of the low-dose treatment regimen in this patient population rather than a drug-related AE.

In the DBM phase, a greater proportion of patients reported oropharyngeal pain, rhinorrhea, upper respiratory infection, and vomiting in the high-dose treatment arm compared to the low-dose treatment arm. These TEAEs were all mild and did not lead to discontinuation. Unlike the DBA phase, in the DBM phase the proportion of patients with TEAEs related to ulcerative colitis were similar between the low- and high-dose treatment arms.

Patients in the OLA phase reported similar TEAEs as the DBA and DBM phases and no new safety signals were identified.

Overall, the TEAE analysis supports a favorable safety profile of the high-dose treatment regimen during the initial 8 weeks of treatment, and the safety profile is comparable between the low- and high-dose treatment regimens after 8 weeks of treatment.

Treatment-Emergent Adverse Events During Double-Blind Acute Phase

In the DBA phase, 67 TEAEs were reported in 32/53 (60.4%) patients across both treatment arms. Table 27 characterizes the TEAEs reported in at least 5% of patients in the low- and high-dose treatment arms. The proportion of patients with at least one TEAE were similar between low- and high-dose treatment arms; however, eight patients in the low-dose treatment arm reported TEAEs of UC compared to no reported TEAEs of UC in the high-dose treatment arm. The proportion of patients who reported TEAEs of abdominal pain and dyspepsia was greater in the high-dose treatment arm compared to the low-dose treatment arm. These TEAEs were assessed as mild and did not lead to any discontinuations.

Table 27. Treatment-Emergent Adverse Events Reported in at Least 5% of Patients in Either Low-Dose or High-Dose MMX Mesalamine Treatment Arms of Double-Blind Acute Phase

MeDRA Preferred Term for Adverse Event	Low-Dose MMX Mesalamine (N=27) n(%)	High-Dose MMX Mesalamine (N=26) n(%)
Number of patients with at least 1 TEAE	17 (63.0)	15 (57.7)
Abdominal pain	1 (3.7)	4 (15.4)
Dyspepsia	1 (3.7)	3 (11.5)
Headache	2 (7.4)	2 (7.7)
Pharyngitis	1 (3.7)	2 (7.7)
Viral infection	1 (3.7)	2 (7.7)
Pyrexia	2 (7.4)	1 (3.8)
Vomiting	2 (7.4)	1 (3.8)
Colitis ulcerative	8 (29.6)	0 (0.0)
Cough	2 (7.4)	0 (0.0)
Oropharyngeal pain[a]	2 (7.4)	0 (0.0)

Source: Reviewer's table generated from Applicant ADAE dataset
[a] Oropharyngeal pain is reported term "sore throat"
Abbreviations: MeDRA, Medical Dictionary for Regulatory Activities; MMX, multi-matrix system; TEAE, treatment-emergent adverse event

Treatment-Emergent Adverse Events During Open-Label Acute Phase

In the OLA phase, 24 TEAEs were reported in 13/18 (72.2%) patients. Of note, patients were enrolled in the OLA phase if they did not meet the primary endpoint at the end of the DBA phase such that patients in the OLA phase may represent a more treatment refractory population. Table 28 characterizes the TEAEs reported in at least 10% of patients during the OLA phase. Due to the limited number of patients, 10% was the chosen cut-off to include TEAEs that occurred more than once. No TEAE occurred more than twice. There were no unique TEAEs reported during the OLA phase that were not reported in the DBA or DBM phases.

Table 28. Treatment-Emergent Adverse Events Reported in at Least 10% of Patients in High-Dose MMX Mesalamine Treatment Arm of Open-Label Acute Phase

MeDRA Preferred Term for Adverse Event	High-Dose MMX Mesalamine (N=18) n(%)
Number of patients with at least 1 TEAE	13 (72.2)
Anemia	2 (11.1)
Arthralgia	2 (11.1)
Colitis ulcerative	2 (11.1)
Upper respiratory tract infection	2 (11.1)

Source: Reviewer's table generated from Applicant ADAE dataset
Abbreviations: MeDRA, Medical Dictionary for Regulatory Activities; MMX, multi-matrix system; TEAE, treatment-emergent adverse event

Treatment-Emergent Adverse Events During Double-Blind Maintenance Phase

In the DBM phase, 155 TEAEs were reported in 54/87 (62.1%) patients across the low- and high-dose treatment arms. Table 29 characterizes the TEAEs reported in at least 5% of patients in the low- and high-dose treatment arms. The proportion of patients with at least one TEAE were similar between low- and high-dose treatment arms. In contrast to the DBA phase, the low-dose treatment arm of the DBM phase did not report a substantially greater proportion of UC TEAEs as compared to the high-dose treatment arm; rather, the proportion of UC TEAEs was only slightly greater in the high-dose treatment arm. A greater proportion of patients reported TEAEs of upper respiratory tract infection, oropharyngeal pain, rhinorrhea, and vomiting in the high-dose treatment arm compared to the low-dose treatment arm. These TEAEs were assessed as mild and did not lead to any discontinuations.

Table 29. Treatment-Emergent Adverse Events Reported in at Least 5% of Patients in Either Low-Dose or High-Dose MMX Mesalamine Treatment Arms of Double-Blind Maintenance Phase

MeDRA Preferred Term for Adverse Event	Low-Dose MMX Mesalamine (N=42) n(%)	High-Dose MMX Mesalamine (N=45) n(%)
Number of patients with at least 1 TEAE	27 (64.3)	27 (60.0)
Colitis ulcerative	6 (14.3)	8 (17.8)
Abdominal pain	6 (14.3)	7 (15.6)
Upper respiratory tract infection	5 (11.9)	7 (15.6)
Oropharyngeal pain[a]	1 (2.4)	3 (6.7)
Rhinorrhea	0 (0.0)	3 (6.7)
Vomiting	0 (0.0)	3 (6.7)

Source: Reviewer's table generated from Applicant ADAE dataset
[a] Oropharyngeal pain includes reported terms: "sore throat" or "throat pain"
Abbreviations: MeDRA, Medical Dictionary for Regulatory Activities; MMX, multi-matrix system; TEAE, treatment-emergent adverse event

Laboratory Findings

The specific laboratory assessments and timing of assessment were described in Section 8.2.3. During the DBA, OLA, and DBM phases, no clinically meaningful hematology or biochemistry lab parameter changes and no Hy's law cases were reported. Hepatic toxicity-related events, defined by the preferred terms: ALT increase, AST increased, blood bilirubin increased, and GGT increased; were categorized as adverse events of special interest and are described in detail below.

Vital Signs

In the DBA phase, vital signs were assessed during the screening period and Weeks 0, 2, 4, and 8 or upon study withdrawal. In the OLA phase, vital signs were assessed on Weeks 2, 4, and 8 or upon study withdrawal. In the DBM phase, vital signs were assessed during the screening period and on Weeks 0, 13, and 26 or upon study withdrawal. No clinically significant abnormal vital signs or clinically meaningful trends in vital signs were reported during the DBA, OLA, or DBM phases.

Electrocardiograms

Electrocardiograms were not performed during the study. Lialda is currently approved for the treatment of mildly to moderately active ulcerative colitis in adults and is not known to have anti-arrhythmic or pro-arrhythmic properties.

QT

QT-related studies were performed during the Lialda development program prior to approval in adults. No warning or precautions related to the QT interval are described in the currently approved label.

Immunogenicity

Immunogenicity was not evaluated during Lialda's pediatric development program as plasma concentrations of mesalamine are not considered to contribute to efficacy.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Adverse Events of Special Interest

The Applicant identified the following AEs as AESI based on the experience of Lialda in adults:

1. "Gastritis" was used as a general category to include gastritis-related events, defined by the preferred terms of dyspepsia and gastrooesophageal reflux disease.
2. "Hepatic toxicity" defined by the preferred terms of ALT increased, AST increased, blood bilirubin increased, and GGT increased
3. "Pancreatitis" was used as a general category to include pancreatitis-related events, defined by the preferred terms of abdominal pain, vomiting, abdominal pain upper, nausea, and blood bilirubin increased.
4. Cholecystitis

Additionally, the Applicant identified myocarditis, pericarditis, and renal toxicity as AESI, but there were no reported AEs of these preferred terms during the pediatric drug development program.

Gastritis

"Gastritis" was reported 8 times in seven patients, including six patients with the preferred term dyspepsia and one patient with the preferred term gastroesophageal reflux. Three patients were in the high-dose treatment arm versus one patient in the low-dose treatment arm of the DBA phase. Three patients were in the high-dose treatment arm of the DBM phase. One AESI was reported as an SAE of dyspepsia, which occurred in one patient in the high-dose treatment arm of the DBM phase. The details of the SAE were described previously. All of the AESIs of gastritis were reported as mild in severity and there were no discontinuations due to the AESI. Additionally, one patient had an upper endoscopy which was normal. The remaining patients did not have an upper endoscopy performed. Of note, the majority of the AESI occurred in the high-dose treatment arms; however, the impact of these AESIs on the determination of safety of the high-dose treatment arms is limited by the mild severity and lack of discontinuations from the study, suggesting these AEs do not raise substantial safety concerns.

Hepatic Toxicity

"Hepatic toxicity" was reported 7 times in three patients including one patient with increased ALT on two occasions (ALT: 139 U/L and 519 U/L), increased AST on one occasion (AST: 393 U/L), and increased GGT on two occasions (GGT: 163 U/L and 270 U/L); one patient with increased ALT (57 U/L) that resolved; and one patient with isolated increased bilirubin (57 µmol/L). One patient was discontinued from the study due to the elevated GGT and follow-up

information was not provided. Overall, increased liver enzymes were uncommon in pediatric patients and consistent with findings in adults.

Pancreatitis

"Pancreatitis" was reported in 31 patients including 18 patients with the preferred term abdominal pain, seven patients with the preferred term vomiting, five patients with the preferred term nausea, and one patient with the preferred term blood bilirubin increased. Five patients were in the high-dose treatment arm versus three patients in the low-dose treatment arm of the DBA phase. Three patients were in the OLA phase where all patients received high-dose treatment. Lastly, there were 12 patients in the high-dose treatment arm versus eight patients in the low-dose treatment arm of the DBM phase.

Despite the use of the term "pancreatitis" to describe patients with either abdominal pain, vomiting, nausea, or increased blood bilirubin, no abnormal amylase or lipase levels were reported during the study. Similarly, there were no abnormal abdominal ultrasounds reported during the study. Therefore, these patients probably did not have true pancreatitis in the absence of abnormal laboratory values or imaging to support the diagnosis. The pertinent SAEs, discontinuations, and TEAEs due to the preferred terms: abdominal pain, vomiting, nausea, and blood bilirubin increased; are discussed in their respective sections of the review.

Cholecystitis

Cholecystitis was reported in one patient in the low-dose treatment group of the DBA phase. The patient was a 17-year-old female weighing 43.0 kg at study entry. Five days after starting Lialda, the patient reported an SAE of enteritis requiring hospitalization. The patient received metronidazole for enteritis. During the hospitalization, the patient reported severe SAEs of dehydration and anemia. Approximately 1 week after hospitalization, the patient reported an AESI of cholecystitis that was diagnosed with abdominal ultrasound and treated with ceftriaxone and itraconazole. All AEs resolved and the patients was discharged from the hospital. Lialda was discontinued due to the SAE of enteritis. The cholecystitis was unlikely related to Lialda as the product was started shortly before the AESI. No other AESI of cholecystitis were reported during the study.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

N/A

8.2.7. Safety Analyses by Demographic Subgroups

Safety Analyses by Age and Weight Subgroups

Analyses of safety events by age and weight subgroups were performed to determine whether age or weight were associated with relevant safety findings (Section 15.5). Table 30 describes the enrollment patterns by age and weight subgroups determined by the Applicant. Of note, patients were assigned low- or high-dose treatment arms in a 1:1 ratio stratified by weight, such that the distribution of age and weight groups was similar across treatment arms.

Table 30. Safety Population by Age and Weight Category in Study SPD476-319

	Double-Blind Acute			Open-Label Acute	Double-Blind Maintenance		
Parameter	Low Dose N=27 n (%)	High Dose N=26 n (%)	Overall N=53 n (%)	High Dose N=18 n (%)	Low Dose N=42 n (%)	High Dose N=45 n (%)	Overall N=87 n (%)
Age category							
5 to 10 years	2 (7.4)	2 (7.7)	4 (7.5)	1 (5.6)	3 (7.1)	5 (11.1)	8 (9.2)
11 to 17 years	25 (92.6)	24 (92.3)	49 (92.5)	17 (94.4)	39 (92.9)	40 (88.9)	79 (55.2)
Weight category (kg)							
18 to ≤23	-	-	-	-	1 (2.4)	2 (4.4)	3 (3.4)
>23 to ≤35	4 (14.8)	3 (11.5)	7 (13.2)	2 (11.1)	2 (4.8)	2 (4.4)	4 (4.6)
>35 to ≤50	7 (25.9)	7 (26.9)	14 (26.4)	4 (22.2)	11 (26.2)	13 (28.9)	24 (27.6)
>50 to ≤90	16 (59.3)	16 (61.5)	32 (60.4)	12 (66.7)	28 (68.3)	28 (62.2)	56 (64.4)

Source: Reviewer's table created using Applicant ADAE dataset

Overall, the analyses by age and weight are limited by the small number of patients in each age and weight subgroup and the small number of AEs. No clinically meaningful relationship was found between age and AEs. Weight subgroup analyses identified that during the DBA phase lower-weight patients in the low-dose treatment arm had an increased proportion of discontinuations compared to higher-weight patients. This finding likely represents a lack of efficacy, rather than a drug-related adverse event, of the low-dose treatment regimen during the initial treatment period.

No clinically meaningful relationship between weight and AEs was found during the DBM and OLA phase. Taken together, the safety analyses by age and weight subgroups do not alter the safety profile of the high-dose treatment regimen during the initial 8 weeks of treatment and the low-dose treatment regimen following 8 weeks of treatment, and support the safety results presented in Section 8.2.4. Additional details are located in Section 15.5.

Safety Analyses by Ethnicity and Race Subgroup

Safety analyses by ethnicity and race were not performed due to the limited enrollment of Hispanic or Latino patients and Black or African American, Native Hawaiian or Other Pacific Islander, and Asian patients. Refer to Table 14, Table 67, and Table 68 for information about the demographic enrollment patterns of SPD476-319.

Safety Analyses by Sex Subgroup

Safety analyses by sex subgroup is limited by the small number of SAEs, discontinuations, and TEAEs; however, in general, male patients had a higher proportion of discontinuations and TEAEs of ulcerative colitis in the DBA phase. The clinical significance of this finding is confounded by the data presented in Section 8.2.4. that these TEAEs and discontinuations occurred exclusively in the low-dose treatment arm. Although there is likely no clinical significance to this finding, it further supports a favorable safety profile of the high-dose treatment regimen for the initial treatment period.

Table 31. Sample Size by Sex Subgroup in Study SPD476-319 (Safety Population)

	Double-Blind Acute		Open-Label Acute	Double-Blind Maintenance	
Sex	Low Dose N=27 n (%)	High Dose N=26 n (%)	High Dose N=18 n (%)	Low Dose N=42 n (%)	High Dose N=45 n (%)
Female	11 (40.7)	8 (30.8)	5 (27.8)	23 (54.8)	25 (55.6)
Male	16 (59.3)	18 (69.2)	13 (72.2)	19 (45.2)	20 (44.4)

Source: Reviewer's table created using Applicant ADAE dataset

During the DBA phase, male patients made up a greater proportion of the patients in the phase than females (Table 31). Male patients also reported a higher proportion of discontinuations (7/34, 20.6%) and TEAEs of ulcerative colitis (7/34, 20.6%), compared to females (2/19, 10.5% and 1/19, 5.3%, respectively). This finding is complicated by the overall small number of discontinuations and TEAEs. Additionally, these TEAEs occurred exclusively in the low-dose treatment group.

The sex subgroup safety analyses of the OLA and DBM phases did not identify any clinically meaningful differences between sex subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

N/A

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

N/A

Human Reproduction and Pregnancy

N/A

Pediatrics and Assessment of Effects on Growth

The short duration of the study (i.e., 36 weeks for the DBM phase) and lack of placebo arm did not permit an assessment of the effects on growth.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Reference is made to the Lialda prescribing information regarding overdosage; this was not assessed in the pediatric development program.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Postmarketing safety events are described in the currently approved labeling and include renal impairment, mesalamine-induced acute intolerance syndrome, hypersensitivity reactions, hepatic failure in patients with pre-existing liver disease, photosensitivity, and interference with laboratory tests when measuring urinary normetanephrine by liquid chromatography with electrochemical detection. Additionally, annual safety reports for the indication of mildly to moderately active ulcerative colitis in adults include the potential risks of aplastic anemia, peripheral neuropathy, pneumonia, pleurisy, anemia, and skin and subcutaneous reactions. Although the data at this time are inconclusive to establish a relationship with mesalamine use, the Applicant is monitoring these risks through routine pharmacovigilance.

Expectations on Safety in the Postmarket Setting

No postmarketing safety studies are recommended at this time.

8.2.11. Integrated Assessment of Safety

The safety analyses did not identify any new safety concerns in pediatric patients compared to adults. Similarly, the safety profile of Lialda is similar to that of other 5-aminosalicylates (i.e., Delzicol and Colazal) that are approved for the treatment of ulcerative colitis in pediatric patients. Overall, the most common adverse event reported by the Applicant was worsening of ulcerative colitis, which is most likely due to a lack of efficacy rather than a drug-related adverse event. Adverse events that were not due to ulcerative colitis were generally infrequent, mild to moderate in severity, and did not lead to discontinuation from the study.

During the DBA phase, the high-dose treatment arm had fewer discontinuations secondary to ulcerative colitis, supporting a more favorable safety profile compared to the low-dose treatment arm. During the DBM phase, there was no difference in safety outcomes between the low-dose and high-dose treatment arms, supporting the selection of the lowest effective dose.

Based on the review of the submitted safety data and clinical study reports, Lialda has a safety profile that supports a favorable risk/benefit assessment for the treatment of mildly to moderately active ulcerative colitis in pediatric patients weighing at least 24 kg. Due to the small number of patients in the lowest weight group (18 to ≤23 kg), safety and efficacy could not be established for patients weighing less than 24 kg. Patients in this weight group will not be indicated in the label.

8.3. Statistical Issues

There were no statistical issues with the safety and efficacy analyses.

8.4. Conclusions and Recommendations

The review team recommends approval of the weight-based, high-dose treatment regimen for the initial 8 weeks followed by the weight-based, low-dose treatment regimen after Week 8 for the treatment of mildly to moderately active UC in pediatric patients weighing at least 24 kg (Table 32). The high-dose treatment regimen for the initial 8 weeks of treatment is supported by efficacy data (Section 8.1.2) that demonstrated a greater number of patients achieving the

primary endpoint in the high-dose treatment arm than in the low-dose treatment arm, during the DBA phase.

The safety data (Section 8.2.4) provide additional support for the dosing recommendation since a lower proportion of patients reported TEAEs of UC that led to discontinuation in the high-dose treatment arm compared to the low-dose treatment arm, during the DBA phase. The low-dose treatment regimen for treatment after Week 8 represents the lowest effective dosage as there was no clinically meaningful difference in efficacy or safety between the high-dose and low-dose treatment regimens.

Table 32. Recommended Dosage and Administration

	Once Daily Lialda Dosage	
Weight of Pediatric Patient	**Weeks 0 to 8**	**After Week 8**
24–35 kg	2.4 g (two 1.2-g tablets)	1.2 g (one 1.2-g tablet)
>35–50 kg	3.6 g (three 1.2-g tablets)	2.4 g (two 1.2-g tablets)
>50 kg	4.8 g (four 1.2-g tablets)	2.4 g (two 1.2-g tablets)

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not held.

10 Pediatrics

Pediatric clinical trials were the focus of this efficacy supplement. Relevant regulatory history and the efficacy and safety findings are discussed in the preceding sections of this document (Sections 3 and 8). The pediatric assessment was discussed with the Pediatric Review Committee (PeRC) on May 19, 2020. Given the lack of data in patients weighing less than 24 kg, the PeRC discussed whether the PREA PMR should be fulfilled in this weight cohort. The review team and PeRC considered the challenges with enrolling pediatric patients with UC in clinical trials and the long-standing availability and established use of mesalamine products to treat pediatric patients with UC. In light of these considerations, the Applicant is unlikely to be able to obtain additional, interpretable data in patients weighing less than 24 kg. (b) (4) Although the Applicant agreed to conduct one pediatric trial to fulfill both PREA PMRs, there is no regulatory pathway to require additional data for the treatment of pediatric patients beyond the initial 8 weeks of treatment (b) (4) The PeRC agreed that the Applicant's submission fulfills PREA PMRs 731-1 and 731-2, and agreed that the product should be labeled for the treatment of pediatric patients weighing at least 24 kg with mildly to moderately active UC.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

Refer to the approved labeling for the final language. Summarized below are key changes made to the label.

Section 1 Indications and Usage

The indication statement for pediatric ulcerative colitis was added:

> Treatment of mildly to moderately active ulcerative colitis in pediatric patients weighing at least 24 kg

Rationale

- The indication statement(s) was written to align with the recommendations in the guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* https://www.fda.gov/media/114443/download.
- Information about specific endpoints and descriptions of benefit from the clinical trials that supported approval are discussed in Section 14 of the label.

Section 2 Dosage and Administration

The recommended dosage and administration for pediatric ulcerative colitis was added:

> The recommended dosage for pediatric patients weighing at least 24 kg who are able to swallow tablets whole is shown below.

Recommended Dosage of Lialda for the Treatment of Mildly to Moderately Active Ulcerative Colitis in Pediatric Patients Weighing at Least 24 kg

	Once Daily Lialda Dosage	
Weight of Pediatric Patient	**Weeks 0 to 8**	**After Week 8**
24–35 kg	2.4 g (two 1.2-g tablets)	1.2 g (one 1.2-g tablet)
>35–50 kg	3.6 g (three 1.2-g tablets)	2.4 g (two 1.2-g tablets)
>50 kg	4.8 g (four 1.2-g tablets)	2.4 g (two 1.2-g tablets)

Rationale

- The Applicant's initial proposal sought an indication for patients weighing at least 50 kg; however, this would limit accessibility of the pediatric population who may benefit from Lialda. The available data were assessed to be sufficient to support an indication in patients weighing at least 24 kg.
- The safety and effectiveness of Lialda for patients weighing less than 24 kg could not be established due to the small number of patients in the lowest weight group enrolled in the study. There were no patients <24 kg in the DBA phase and only three patients <24 kg in the DBM phase.
- There were fewer UC-related discontinuations and a greater proportion of patients who met the primary endpoint in the high-dose treatment regimen compared to the low-dose

treatment regimen during the DBA phase, supporting the selection of the high-dose regimen for the initial 8 weeks of treatment.

- The low-dose treatment regimen was the lowest-effective dose (Section 8.1.2) during the DBM phase, supporting selection of the low-dose regimen for treatment after 8 weeks.
- Additional pharmacokinetic analyses were used to support the selection of 2.4 g for the greater than 35- to 50-kg weight group. This dose is achievable with the currently marketed 1.2-g Lialda formulation.

Section 6 Clinical Trials Experience

A statement was added to describe the following most common adverse reactions reported in at least 5% of pediatric patients treated with Lialda: abdominal pain, upper respiratory tract infection, vomiting, anemia, headache, and viral infection.

Rationale

- The common adverse reactions described in the label were pooled from all phases of the trial. The adverse reactions in the pediatric clinical trial were similar to those reported in adults.

Section 8.4 Pediatric Use

The safety and effectiveness of Lialda is supported by evidence from adequate and well-controlled trials in adults, a multicenter, randomized, double-blind, parallel group trial in 105 pediatric patients 5 to 17 years of age, and additional pharmacokinetic analyses.

Rationale:

- Support for approval for pediatric ulcerative colitis includes extrapolation of efficacy from adult studies, the pediatric safety and efficacy study described in Section 8 of this review, and pharmacokinetic analyses (Section 15.3.2).

Section 12 Clinical Pharmacology

Requested to revise the label to only include the PK information of TBM formulation at the proposed dosing regimen in the pediatric patients with UC.

Rationale

- [redacted] (b) (4) the 1.2-g tablets are planned to be marketed for use in pediatric patients. The label should contain the PK information on the TBM formulation in the target population, which is the currently marketed 1.2-g strength tablet.
- Pediatric PK study SPD476-112 was conducted with weight-based dosing regimen (30 mg/kg, 60 mg/kg and 10 mg/kg) while the proposed dose in the pediatric UC population is fixed dose (1.2 g to 4.8 g) based on body weight group. (b) (4) [redacted]

Section 14 Clinical Studies

Revisions were made to Section 14.2 of the label to describe the clinical trial conducted in pediatric patients with UC, including the results from the DBA and DBM phases. (b) (4)

Rationale

- The trial design included an 8-week initial treatment phase and a second 26-week longer-term treatment phase. Endoscopy was performed on a small number of patients at Week 8, and remission could not be confirmed in the absence of endoscopic assessment. Additionally, over half of the patients who enrolled in the DBM phase entered without having participated in the DBA phase and a small number entered the DBM phase after additional treatment in the OLA phase. (b) (4) the DBA and DBM phases were described as the initial 8-week phase and 26-week treatment phase.
- Language was included to describe the lower number of discontinuations due to UC in the recommended Lialda dose compared to a lower than recommended dose, thus supporting the dosing recommendation for the initial 8-week phase.
- The limited data available for patients weighing less than 24 kg are described in this section to explain the rationale for not labeling the product in patients in this weight group.
- The analysis results according to FDA recommended definition of clinical remission were added for the 26-week maintenance phase. Clinical remission could not be assessed in the initial 8-week treatment phase because there were too few patients who underwent endoscopy. (b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not recommended.

13 Postmarketing Requirements and Commitment

There are no recommended PMR/PMCs.

14 Acting Division Director (Clinical) Comments

I concur with the recommendation of the review team to approve supplemental NDA 022000/S-019 for Lialda (mesalamine) to expand the indication to include pediatric patients weighing at

least 24 kg with mildly to moderately severe ulcerative colitis. The recommended dosage is fixed dose by body weight group (24 kg to 35 kg, >35 kg to 50 kg, and >50 kg).

Efficacy of Lialda in pediatric patients is supported, in part, by extrapolation of efficacy from adequate and well-controlled trials in adults, relying upon the similarity between adults and pediatric patients in disease progression and response to treatment. This sNDA submission included results from a multicenter, randomized, double-blind, parallel-group trial that assessed two weight-based dose levels in 105 pediatric patients; data from this trial along with PK analyses support the weight-based high-dose level during the first 8 weeks of treatment and the low-dose level for continued treatment after 8 weeks.

The safety profile of Lialda in pediatric population was similar to that seen in adults and in trials of other 5-aminosalicylates; no new safety signals were identified. The most common adverse reactions reported in pediatric patients include abdominal pain, upper respiratory tract infection, vomiting, anemia, headache, and viral infection. The existing Prescribing Information incorporating pediatric information will be adequate to communicate the potential risks to healthcare providers and patients; a REMS will not be required.

The Applicant initially proposed to limit the pediatric indication to patients weighing 50 to 90 kg based on limitation of available tablet strength only at 1.2 g; however, all available PK, efficacy and safety data were leveraged to support expanding the indication to pediatric patients weighing at least 24 kg. Due to the small number of patients in the lowest weight group (18 to ≤23 kg), safety and efficacy could not be established for patients weighing less than 24 kg.

It should also be noted that, in addition to the currently marketed 1.2 g strength tablet, the pediatric trial was conducted with 300 mg and 600 mg strength tablets, which the Applicant does not intend to manufacture. Bioequivalence was established between lower strength tablets (used in the pediatric efficacy trial) and currently marketed 1.2 g strength tablet. This 1.2 g strength tablet would provide appropriate formulation for pediatric patients weighing at least 24 kg who can swallow tablets whole, except the >35 kg to 50 kg weight group who require the 1.8 g dose for treatment beyond 8 weeks. Thus, additional population PK simulation and exposure-response analyses were conducted by the review team to explore whether available information could support labeling the 2.4 g dose (between the studied low dose [1.8 g] and high dose [3.6 g]) for this weight group. I agree with the review team's conclusion that the 2.4 g dose is reasonable for the >35 kg to 50 kg weight group for treatment beyond 8 weeks based on no apparent difference in the efficacy beyond the initial phase (i.e., after 8 weeks) between two studied dose levels (flat dose-response and exposure-response relationships), and lower predicted systemic exposure with the 2.4 g dose than the high dose (3.6 g) studied in this body weight group. Since there was no difference in safety outcomes between the low-dose and high-dose treatment arms beyond 8 weeks, the lowest effective dose is recommended.

This sNDA submission fulfilled the following two PREA PMRs:

- 731-1: A deferred study under PREA for the treatment of UC in pediatric patients of all ages
- 731-2: A deferred pediatric study under PREA for the maintenance of remission of ulcerative colitis in pediatric patients 5 to 17 years of age

No additional post-marketing studies will be required.

15 Appendices

15.1. References

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): SPD476-319

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 207		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.3.1. Summary of Bioanalytical Method Validation and Performance

15.3.1.1. How Are Parent Drug And Relevant Metabolites Identified and What Are the Analytical Methods Used to Measure Them in Plasma and Other Matrices?

The plasma concentration of mesalamine (5-aminosalicylic acid [5-ASA]) from phase 1 bioequivalence (BE) studies (SPD476-121 and SPD 476-122) in healthy subjects were analyzed at [redacted] (b) (4) using a validated liquid chromatography-mass spectrometry (LC/MS/MS) bioanalytical method titled "Validation of a Method for the Determination of 5-Aminosalicylic Acid and N-Acetyl-5-Aminosalicylic Acid in Lithium Heparin Human Plasma by LC-MS/MS."

The plasma concentration of 5-ASA and Ac-5-ASA from pediatric phase 1 pharmacokinetic (PK) study (SPD476-112) and phase 3 pediatric safety and efficacy study (SPD476-319) were analyzed at [redacted] (b) (4) using the following validated LC/MS/MS bioanalytical methods:

- Validation of an Analytical Method for the Determination of 5-Aminosalicylic Acid and N-Acetyl-5-Aminosalicylic Acid in Human Plasma Using Protein Precipitation for Sample

Preparation and Liquid Chromatography with Tandem Mass Spectrometric Detection, [redacted] study number [redacted]/064, May 15, 2006.

- Validation of an Analytical Method for the Determination of 5-Aminosalicylic Acid and N-Acetyl-5-Aminosalicylic Acid in Human Urine Using Liquid Chromatography with Tandem Mass Spectrometric Detection, [redacted] study number [redacted]/063, May 15, 2006.
- Additional Validation and Stability for a Method for the Determination of 5-Aminosalicylic Acid and N-Acetyl-5-Aminosalicylic Acid in Human Plasma Using Liquid Chromatography with Tandem Mass Spectrometric Detection, [redacted] study number [redacted]/135, August 2014.

15.3.1.2. Which Metabolites Have Been Selected for Analysis and Why?

Metabolite Ac-5-ASA was measured pediatric patients with ulcerative colitis (UC) both in plasma and urine in pediatric patients in PK study SPD476-112 and only in plasma in pediatric safety and efficacy study SPD476-319.

15.3.1.3. What Bioanalytical Methods Are Used to Assess Concentrations of the Measured Moieties?

Table 33. Validated Bioanalytical Methods for 5-ASA and Metabolite Ac-5-ASA

Protocol No.	Bioanalytical Site	Analytes	Matrix	Validation Report No.	Assay Method
SHP476-121 SHP476-122	[redacted]	5-ASA	Plasma	A8687M-SPD476	LC/MS/MS
SPD476-112 SPD476-319		5-ASA	Plasma	[redacted]/064; [redacted]135	LC/MS/MS
SPD476-112 SPD476-319		Ac-5-ASA	Plasma	[redacted]/064; [redacted]135	LC/MS/MS
SPD476-112		5-ASA	Urine	[redacted]/063; YAH/218	LC/MS/MS
SPD476-112		Ac-5-ASA	Urine	[redacted]/063; YAH/218	LC/MS/MS

Source: Module 2.7.1 Summary of Biopharmaceutic Studies, CSR and Bioanalytical Sample Analysis Report for studies SPAD476-112, SPAD476-121, SPAD476-122and SPAD476-319, Applicant's Response dated May 27, 2020 to a FDA Information Request
Abbreviations: 5-ASA, 5-aminosalicylic acid; LC/MS/MS, liquid chromatography-mass spectrometry

15.3.1.4. What Is the Range of the Standard Curve? How Does It Relate to the Requirements for Clinical Studies? What Curve Fitting Techniques Were Used? What Are the Lower and Upper Limits of Quantitation?

Table 34. Standard Curve, LLOQ, and Curve-Fitting Techniques by Study

Validation No.	Study Report	Analyte	Matrix	Standard Curve Range	LLOQ	Curve-Fitting Techniques
A8687M-SPD476	SHP476-121 SHP476-122	5-ASA	Plasma	5.0 to 5000 ng/mL	5.0 ng/mL	A linear regression with a 1/concentration^2 weighting
[redacted]064	SPD476-112 SPD476-319	5-ASA	Plasma	5.0 to 5000 ng/mL	5.0 ng/mL	A linear regression with a 1/concentration^2 weighting
[redacted]064	SPD476-112 SPD476-319	Ac-5-ASA	Plasma	5.0 to 5000 ng/mL	5.0 ng/mL	A linear regression with a 1/concentration^2 weighting
[redacted]135	SPD476-112 SPD476-319	5-ASA	Plasma	5.0 to 5000 ng/mL	5.0 ng/mL	A linear regression with a 1/concentration^2 weighting

Validation No.	Study Report	Analyte	Matrix	Standard Curve Range	LLOQ	Curve-Fitting Techniques
(b) (4)/135	SPD476-112 SPD476-319	Ac-5-ASA	Plasma	5.0 to 5000 ng/mL	5.0 ng/mL	A linear regression with a 1/concentration^2 weighting
/063 YAH/218	SPD476-112	5-ASA	Urine	5.0 to 1000 ng/mL	5.0 ng/mL	A linear regression with a 1/concentration^2 weighting
(b) (4)/063 YAH/218	SPD476-112	Ac-5-ASA	Urine	5.0 to 1000 ng/mL	5.0 ng/mL	A linear regression with a 1/concentration^2 weighting

Source: Module 2.7.1 Summary of Biopharmaceutic Studies, CSR and Bioanalytical Sample Analysis Report for studies SPAD476-112, SPAD476-121, SPAD476-122, and SPAD476-319, Bioanalytical Method Validation Reports A8687M-SPD476, (b) (4)/063, (b) (4)/064, (b) (4)/135, and YAH/218
Abbreviations: 5-ASA, 5-aminosalicylic acid; LLOQ, lower limit of quantitation

15.3.1.5. What Are the Accuracy, Precision, and Selectivity at These Limits?

The accuracy, precision and selectivity of all these bioanalytical assays were within the acceptable ranges.

Table 35. Accuracy, Precision, and Selectivity of Bioanalytical Assays

Validation No. Analyte/Matrix Parameter	Intra-Assay	Inter-Assay	Selectivity
A8687M-SPD476			
5-ASA/Plasma			
Precision (CV%)	0.8 to 9.9%	1.8 to 2.9%	≤20.0% LLOQ for analyte; ≤5.0% for IS
Accuracy	-6.8 to 10.0%	5.3 to 7.6%	
(b) (4)064			
5-ASA/Plasma			
Precision (CV%)	1.5% and 6.1%	2.4% and 7.1%	≤20.0% LLOQ for analyte; ≤2% for IS
Accuracy	-5.7% and -0.4%	-5.8% and -0.4%	
Ac-5-ASA/Plasma			
Precision (CV%)	5.8% and 10.5%	6.7% and 12.6% and 12.6%	≤20.0% LLOQ for analyte; ≤2% for IS
Accuracy	-2.9% and 4.7%	-3.2% and 4.4%	
(b) (4)135			
5-ASA/Plasma			
Precision (CV%)	1.6% to 11.7%	N/A	
Accuracy	-6.6% to 10.4%	N/A	
Ac-5-ASA/Plasma			
Precision (CV%)	1.5% to 13.8%	N/A	
Accuracy	-2.8% to 12.4%	N/A	
(b) (4)063			
5-ASA/Urine			
Precision (CV%)	2.4% and 5.7%	4.5% and 7.5%	≤20.0% LLOQ for analyte; ≤2% for IS
Accuracy	-7.6% and -2.7%	-7.6% and -2.8%	
Ac-5-ASA/Urine			
Precision (CV%)	4.0% and 7.5%	6.1% and 11.3%	≤20.0% LLOQ for analyte; ≤2% for IS
Accuracy	-8.9% and -1.9%	-9.0% and -2.0%	

Source: Module 2.7.1 Summary of Biopharmaceutic Studies, Bioanalytical Method Validation Reports A8687M-SPD476, (b) (4)063, (b) (4)064, and (b) (4)135
Abbreviations: 5-ASA, 5-aminosalicylic acid; CV, coefficient of variation; IS, Internal standard; LLOQ, lower limit of quantitation; N/A, not applicable

15.3.1.6. What Is the Sample Stability Under Conditions Used in the Study?

Plasma PK samples from study SHP476-121 and SHP476-122 were stored frozen at -70°C until analysis and plasma PK samples from Study SPD476-112 and SPD476-319 were stored at -80°C until the analysis. Urine samples from Study SPD476-112 were also stored at -80°C until the analysis. All PK plasma and urine samples were analyzed within the time-period for which the long-term stability has been established during the method validation. The long-term stability of 5-ASA and Ac-5-ASA in plasma matrix at -70°C was established for 382 days and in urine matrix at -80°C was established for 12 months.

Table 36. Sample Stability

Validation Report Analyte/Matrix	Freeze-Thaw -70°C (Cycles)	At Room Temperature	At 4°C (Autosampler)	Long-Term Stability
A8687M-PD476				
5-ASA/Plasma	5	25 hr	167 hr	382 days @ -70°C
(b) (4) 064				
5-ASA/Plasma	4	24		82 days @ -80°C
Ac-5-ASA/Plasma	4	24		82 days @ -80°C
(b) (4) 135				
5-ASA/Plasma				322 days @ -80°C
Ac-5-ASA/Plasma				322 days @ -80°C
(b) (4) 063 and YAH/218				
5-ASA/Urine	4	24		12 months @ -80°C
Ac-5-ASA/Urine	4	24		12 months @ -80°C

Source: Module 2.7.1 Summary of Biopharmaceutic Studies, Bioanalytical Method Validation Reports A8687M-SPD476, (b) (4) 063, (b) (4) 064, (b) (4) 135 and YAH/218
Abbreviations: 5-ASA, 5-aminosalicylic acid

Table 37. Sample Storage Period

Study Repot Analyte/Matrix	Sample Collection Start Date	Study End Date	Bioanalytical Analysis Start Date	Bioanalytical Analysis End Date	Maximum Storage	Samples Analyzed Within Stability Limits
SHP476-121						
5-ASA/Plasma	3/14/2017	4/19/2017	4/25/2017	5/12/2017	59	Yes
SHP476-122						
5-ASA/Plasma	5/12/2017	6/18/2017	6/21/2017	7/7/2017	56	Yes
SPD476-112						
5-ASA/Plasma	12/27/2010	6/22/2013	2/23/2011	7/5/2013	224	Yes
5-ASA/Urine	12/27/2010	6/22/2013	2/28/2011	7/5/2013	226	Yes
Ac-5-ASA/Plasma	12/27/2010	6/22/2013	2/23/2011	7/5/2013	224	Yes
Ac-5-ASA/Urine	12/27/2010	6/22/2013	2/28/2011	7/5/2013	226	Yes
SPD476-319						
5-ASA/Plasma	9/8/2015	11/28/2018	7/14/2016	1/7/2019	318	Yes
Ac-5-ASA/Plasma	9/8/2015	11/28/2018	7/14/2016	1/7/2019	318	Yes

Source: Module 2.7.1 Summary of Biopharmaceutic Studies, CSR and Bioanalytical Sample Analysis Report for studies SPAD476-112, SPAD476-121, SPAD476-122, and SPAD476-319, Bioanalytical Method Validation Reports A8687M-SPD476, (b) (4) 063, (b) (4) 064, and (b) (4) 135, Applicant's Response dated May 8, 2020 to a FDA Information Request, Applicant's Response dated May 27, 2020 to a FDA Information Request
SPD476-319: Samples were analyzed within the established storage period of 322 days at -80°C with the exception of subject b) (6) visit 5.2 (469 days), subject (b) (6) visit 5.2 (327 days), subject (b) (6) visit 5.2 (329 days), subject (b) (6) visit 5.2 (358 days) and subject (b) (6) visit 5.2 (362 days), for these samples no result was reported.
Abbreviations: 5-ASA, 5-aminosalicylic acid

15.3.1.7. What Is the Plan for QC Samples and Reanalysis of Incurred Samples?

The concentration of quality control (QC) in studies in study SHP476-121 and SHP476-122 in healthy subjects were 15, 250, 2000, and 40000 ng/mL for of 5-ASA. Concentration of QC samples in pediatric patient studies SPD476-112 and SPD476-319 were 12.5, 2500, 4000, and 10000* ng/mL for 5-ASA and Ac-5-ASA. All studies had at least 5% of the samples re-analyzed as the incurred samples reanalysis to demonstrate the reproducibility of quantification in all studies. The incurred sample reanalysis from all four studies met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20% in all studies.

Table 38. Assay Performance of 5-ASA in Plasma in Each Clinical Study

Clinical Study Analyte/Matrix	QCs Inter-Run Precision (CV%)	QCs Inter-Run Accuracy (%RE)	% of Samples for ISR	Passed ISR
SHP476-121				
5-ASA/Plasma	≤6.9%	-4.5% to 4.7%	6.3% (253/4032)	Yes
SHP476-122				
5-ASA/Plasma	≤6.6%	-0.5% to 1.3%	6.4% (251/3938)	Yes
SPD476-112				
5-ASA/Plasma	≤7.6%	-0.8% to 0%	5.0% (52/1030)	Yes
5-ASA/Urine	≤11.7%	-5.5% to -1.3%	6% (6/101)	Yes
Ac-5-ASA/Plasma	≤10.1%	2.4% to 5.2%	5.0% (52/1030)	Yes
Ac-5-ASA/Urine	≤10.2%	-1.4% to 4.0%	6% (6/101)	Yes
SPD476-319				
5-ASA/Plasma	≤9.4%	-1.6% to 2.4%	27% (26/96)	Yes
Ac-5-ASA/Plasma	≤8.0%	-0.3% to 5.6%	27% (26/96)	Yes

Source: Module 2.7.1 Summary of Biopharmaceutic Studies, CSR and Bioanalytical Sample Analysis Report for studies SPAD476-112, SPAD476-121, SPAD476-122, and SPAD476-319,
Abbreviations: 5-ASA, 5-aminosalicylic acid; CV, coefficient of variation; ISR, incurred samples reanalysis; QC, quality control; RE, relative error

15.3.2. Pharmacometrics Review

15.3.2.1. Applicant's Population Pharmacokinetics Analysis

Objectives

- Assess external predictability of the previous population pharmacokinetic model with 5-ASA/Ac-5-ASA concentration data from Study SPD476-319
- To update/refine the model using pooled pediatric data from Studies SPD476-112 and SPD476-319

Data

The pooled dataset from both pediatric studies contained 1,281 quantifiable concentrations from 110 subjects, of which 587 and 591 concentrations were for plasma 5-ASA and Ac-5-ASA, and 51 and 52 concentrations were for urinary 5-ASA and Ac-5-ASA, respectively. Study SPD476-319 contributed 144 quantifiable plasma 5-ASA/Ac-5-ASA concentrations from 58 subjects, with doses ranging from 900 to 4,800 mg (Table 39).

Table 39. Summary of Study Information Used in the Population Pharmacokinetic Analysis

Study (Phase)	Population and No. Subjects	SPD476 Dose/ Treatment Duration	Planned Pharmacokinetic Sampling[a]	
			Plasma Samples	Urine Samples
SPD476-112 (Phase 1)	Population: Children and adolescents with ulcerative colitis N=52	30, 60, or 100 mg/kg/day once daily for 7 days in the fed state, stratified by body weight	Intensive sampling at predose on Days 5, 6, and 7, and at 2, 4, 6, 9, 12 16, and 24 hours postdose on Day 7	Over 24-hour interval on Day 7
SPD476-319 (Phase 3)	Population: Children and adolescents with ulcerative colitis N=58 (N=23: low-dose arm; N=35: high-dose arm)	Double-blind acute phase (8 weeks) and double-blind maintenance phase (26 weeks): Low dose: 900; 1,200; 2,400 mg/day High dose: 1,200; 2,400; 3,600; 4,800 mg/day Stratified by body weight Open-label acute phase (8 weeks): High dose: 1,200; 2,400; 3,600; 4,800 mg/day	Sparse sampling at the end of each phase Double-blind acute phase: Week 8 Open-label acute phase: Week 8 Double-blind maintenance phase: Week 26	None

Source: Table 3-1 of Applicant's population pharmacokinetics report
[a] All pharmacokinetic analyses referred to both 5-ASA and Ac-5-ASA

The continuous and categorical covariates at baseline for subjects included in the analysis are shown in
Table 40 and Table 41.

Table 40. Continuous Covariates at Baseline for Subjects Included in Population Pharmacokinetics Analysis

Parameter	SPD476-112 (N=52)	SPD476-319 (N=58)	All Studies (N=110)
Total daily dose (mg)	2,400 [900-4,800]	3,600 [1,200-4,800]	2,550 [900-4,800]
Age (yrs)	14 [5-17]	15 [5-17]	14 [5-17]
Weight (kg)	52.8 [20.0-81.5]	53.7 [18.5-86.2]	53.2 [18.5-86.2]
Height (cm)	162 [115-190]	162 [111-185]	162 [111-190]
BSA (m^2)	1.54 [0.80-1.96]	1.56 [0.75-2.09]	1.56 [0.75-2.09]
Lean body mass (kg)	41.0 [18.1-60.8]	42.0 [15.7-65.8]	41.6 [15.7-65.8]
Total bilirubin (µmol/L)	7.65 [2.10-19.5]	6.50 [2.50-34.8]	7.00 [2.10-34.8]
Albumin (g/L)	47.0 [42.0-53.0]	45.0 [35.0-52.0]	46.0 [35.0-53.0]
Aspartate aminotransferase (IU/L)	20.5 [13.0-40.0]	20.0 [13.0-39.0]	20.0 [13.0-40.0]
Alanine aminotransferase (IU/L)	15.0 [6.00-41.0]	12.5 [6.00-62.0]	13.0 [6.00-62.0]
Serum creatinine (mg/dL)	0.617 [0.362-0.995]	0.640 [0.430-1.02]	0.640 [0.362-1.02]
Creatinine clearance (mL/min/1.73m2)	160 [107-234]	150 [99.8-230]	153 [99.8-234]

Source: Synopsis of Applicant's population pharmacokinetics report.
Abbreviations: BSA, body surface area; IU/L, international units per liter

Table 41. Categorical Covariates at Baseline for Subjects Included in Population Pharmacokinetics Analysis

Covariate	SPD476-112 (N=52) n (%)	SPD476-319 (N=58) n (%)	All Studies (N=110) n (%)
Dose			
<50 mg/kg	21 (40)	23 (40)	44 (40)
≥50 mg/kg	31 (60)	35 (60)	66 (60)
Age			
Children (5-12 years)	16 (31)	13 (22)	29 (26)
Adolescent (13-17 years)	36 (69)	45 (78)	81 (74)
Sex			
Male	22 (42)	31 (53)	53 (48)
Female	30 (58)	27 (47)	57 (52)
Race			
Caucasian	51 (98)	55 (95)	106 (96)
Black	0 (0)	1 (2)	1 (1)
Asian	1 (2)	2 (3)	3 (3)
Other	0 (0)	0 (0)	2 (2)
Ethnicity			
Non-Hispanic/Latino	51 (98)	57 (98)	108 (98)
Hispanic/Latino	1 (2)	1 (2)	2 (2)

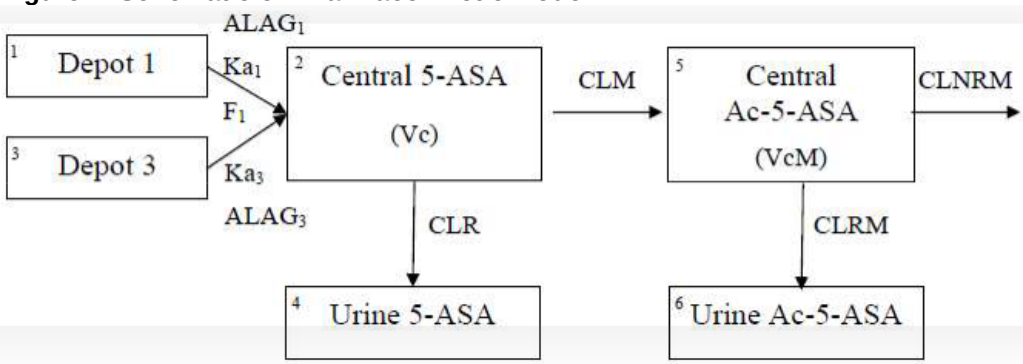
Source: Synopsis of Applicant's population pharmacokinetics report

Methodology

The population pharmacokinetic model was developed using a nonlinear mixed-effect modeling approach; the Non-linear Mixed-Effects Modeling VII software with the Monte-Carlo Importance Sampling Expectation Maximization estimation method with "Mu Referencing" was used.

The previously developed population pharmacokinetic model, including covariate effects, for 5-ASA/Ac-5-ASA in children (5 to 12 years) and adolescents (13 to 17 years) based on pharmacokinetic data from Study SPD476-112 was updated with additional pediatric data from Study SPD476-319. The structural model was consisted of first-order absorption from two depot compartments, absorption lag times, separate central compartments for 5-ASA and Ac-5-ASA with respective urine compartments for renal clearance (Figure 4). Nonrenal clearance of 5-ASA was assumed to involve only metabolism to Ac-5-ASA, and all elimination processes were based on first-order kinetics. Allometric scaling using body weight was applied to all clearance and volume parameters with the exponents fixed to the theoretical value of 0.75 for clearance and 1 for volume parameters.

Figure 4. Schematic of Pharmacokinetic Model



Source: Figure 3-1 of Applicant's population pharmacokinetics report.
Numbers on the top left-hand corner represent the compartment numbers for the population pharmacokinetic model in the NONMEM code.
Abbreviations: 5-ASA, 5-aminosalicylic acid; $ALAG_1$, absorption lag time from depot 1; $ALAG_3$, absorption lag time from depot 3 in addition the lag time from depot 1; CLM, metabolic clearance of 5-ASA; CLNRM, nonrenal clearance of Ac-5-ASA; CLR, renal clearance of 5-ASA; CLRM, renal clearance of Ac-5-ASA; F_1, fraction of dose absorbed from depot 1; Ka_1, absorption rate constant from depot 1; Ka_3, absorption rate constant from depot 3; Vc, volume of central compartment of 5-ASA; VcM, volume of central compartment of Ac-5-ASA

The performance of the final population pharmacokinetic model was evaluated using a prediction-corrected visual predictive check (pcVPC) method. Precision of the parameter estimates of the final model was also evaluated using a Markov Chain Monte Carlo Bayesian analysis.

Results

The previous model was updated using the pooled dataset, and all model parameter estimates were similar to those previous estimates from Study SPD476-112 only. The interindividual variability variance structure was modified to incorporate a full variance-covariance matrix to account for covariance between interindividual variability parameters. Allometric scaling using body weight remained a significant covariate on all clearance and volume parameters, and no additional covariates were identified in the pooled dataset. The parameter estimates of the final model are presented in Table 42.

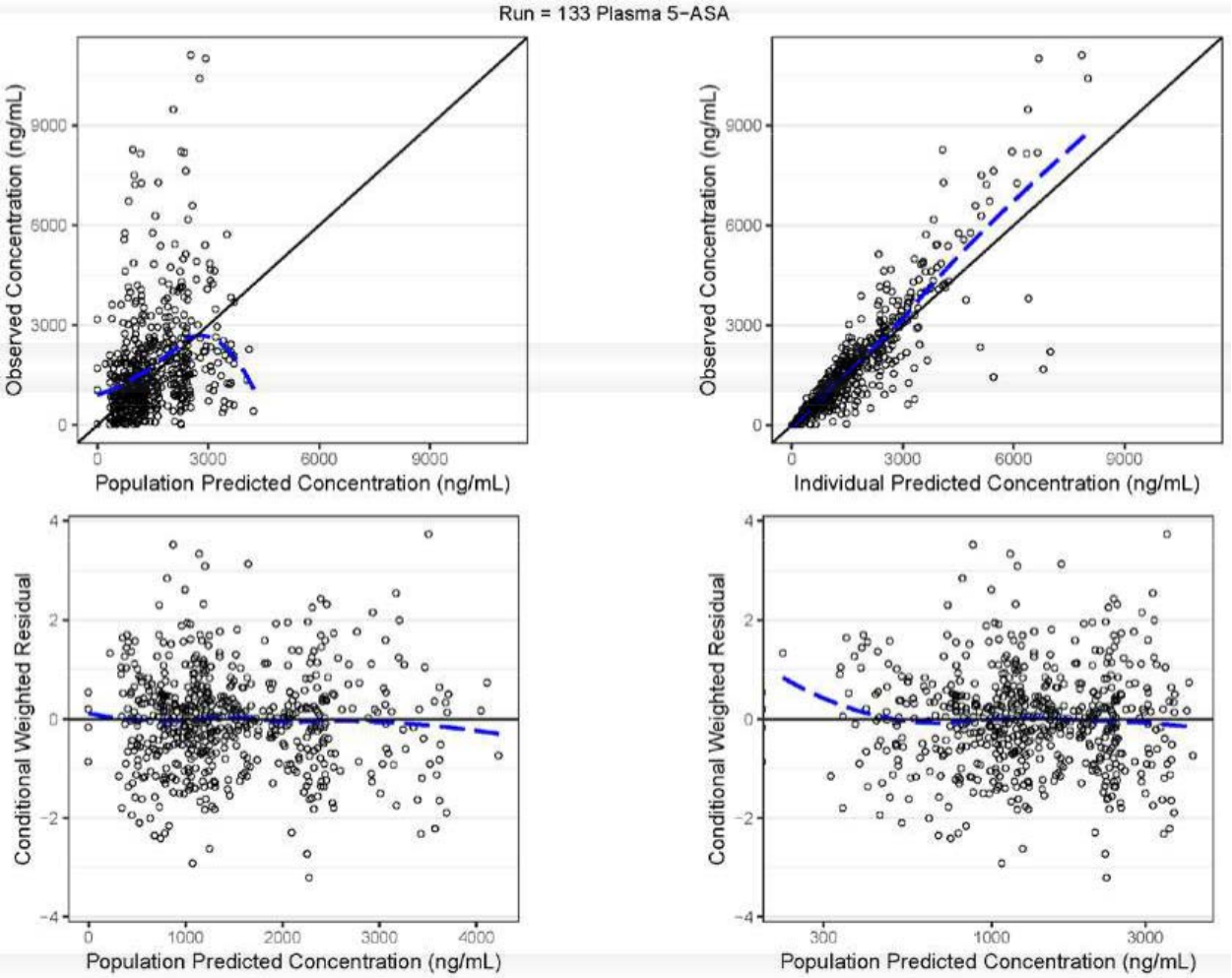
The goodness-of-fit (GoF) plots for the final population pharmacokinetic model are presented in Figure 5 for plasma 5-ASA, Figure 6 for plasma Ac-5-ASA for the overall population.

Table 42. Parameter Estimates of Final Population Pharmacokinetics Model

	NONMEM Estimates					MCMC BAYES Estimates[b]	
Parameter[a] [Units]	Point Estimate	% RSE	95% CI	Shrinkage %	CV% or R	Median	95% CI
CLR/F [L/hr]	1.17	8.67	0.987-1.39			1.22	1.03-1.41
CLM/F [L/hr]	106	7.63	91.0-123			96.8	83.0-112.
V_c/F [L]	74.7	31.4	40.4-138			50.7	19.9-102.
CLRM/F [L/hr]	2.71	6.59	2.38-3.08			2.78	2.44-3.13
CLNRM/F [L/hr]	91.3	6.26	80.8-103			82.6	72.9-93.4
V_cM/F [L]	12.1	29.9	6.76-21.8			2.83	0.643-7.80
Ka_1 [hr-1]	0.0948	21.4	0.0624-0.144			0.0582	0.03g0.106
Ka_3 [hr-1]	0.208	30.7	0.114-0.380			0.372	0.185-0.772
$ALAG_1$ [hr]	6.29	10.6	5.11-7.75			6.88	5.78-8.41
$ALAG_3$ [hr]	13.8	6.01	12.2-15.5			14.4	12.8-16.0
F_1	0.535	13.2	0.398-0.667			0.672	0.503-0.791
CLR/F~WT	0.75 FIX	-	-			-	-
CLM/F~WT	0.75 FIX	-	-			-	-
V_c/F~WT	1 FIX	-	-			-	-
CLRM/F~WT	0.75 FIX	-	-			-	-
CLNRM/F~WT	0.75 FIX	-	-			-	-
V_cM/F~WT	1 FIX	-	-			-	-
Interindividual variability							
$\omega^2_{CLR/F}$	0.332	32.2	0.123-0.541	18.9	62.7	0.316	0.206-0.502
$\omega^2_{Vc/F}$	1.63	28	0.736-2.53	35.3	203	2.36	1.25-4.20
ω^2_{Ka1}	1.18	28.9	0.511-1.84	27.7	150	3.65	2.29-5.68
ω^2_{Ka3}	3.26	26.1	1.59-4.94	20.8	502	4.59	2.78-7.32
ω^2_{ALAG1}	0.274	44.8	0.0335-0.515	28.5	56.2	0.317	0.215-0.504
ω^2_{ALAG3}	0.0720	36.4	0.0206-0.123	31.2	26.8	0.0877	0.0555-0.145
ω^2_{F1}	2.43	22.7	1.35-3.52	34.4	323	3.56	2.04-6.02
$\omega^2_{CLM/F}$	0.459	22.1	0.261-0.658	7.54	76.3	0.472	0.324-0.672
$\omega^2_{VcM/F}$	0.817	48.7	0.0366-1.60	43.4	112	1.29	0.598-2.74
$\omega^2_{CLRM/F}$	0.165	34.4	0.0536-0.276	29.9	42.3	0.179	0.117-0.283
$\omega^2_{CLNRM/F}$	0.306	23.2	0.167-0.444	7.76	59.8	0.324	0.223-0.479
Residual variability							
$\sigma^2_{prop,plasma\ 5\text{-}ASA}$	0.126	8.41	0.106-0.147	3.40	35.5	0.114	0.0965-0.133
$\sigma^2_{prop,urine\ 5\text{-}ASA}$	0.0036 fix				6.00		
$\sigma^2_{prop,plasma\ Ac5\text{-}ASA}$	0.0762	8.31	0.0638-0.0886	1E-10	27.6	0.0681	0.0586-0.0814
$\sigma^2_{prop,urine\ AC\text{-}5\text{-}ASA}$	0.0036 fix				6.00		

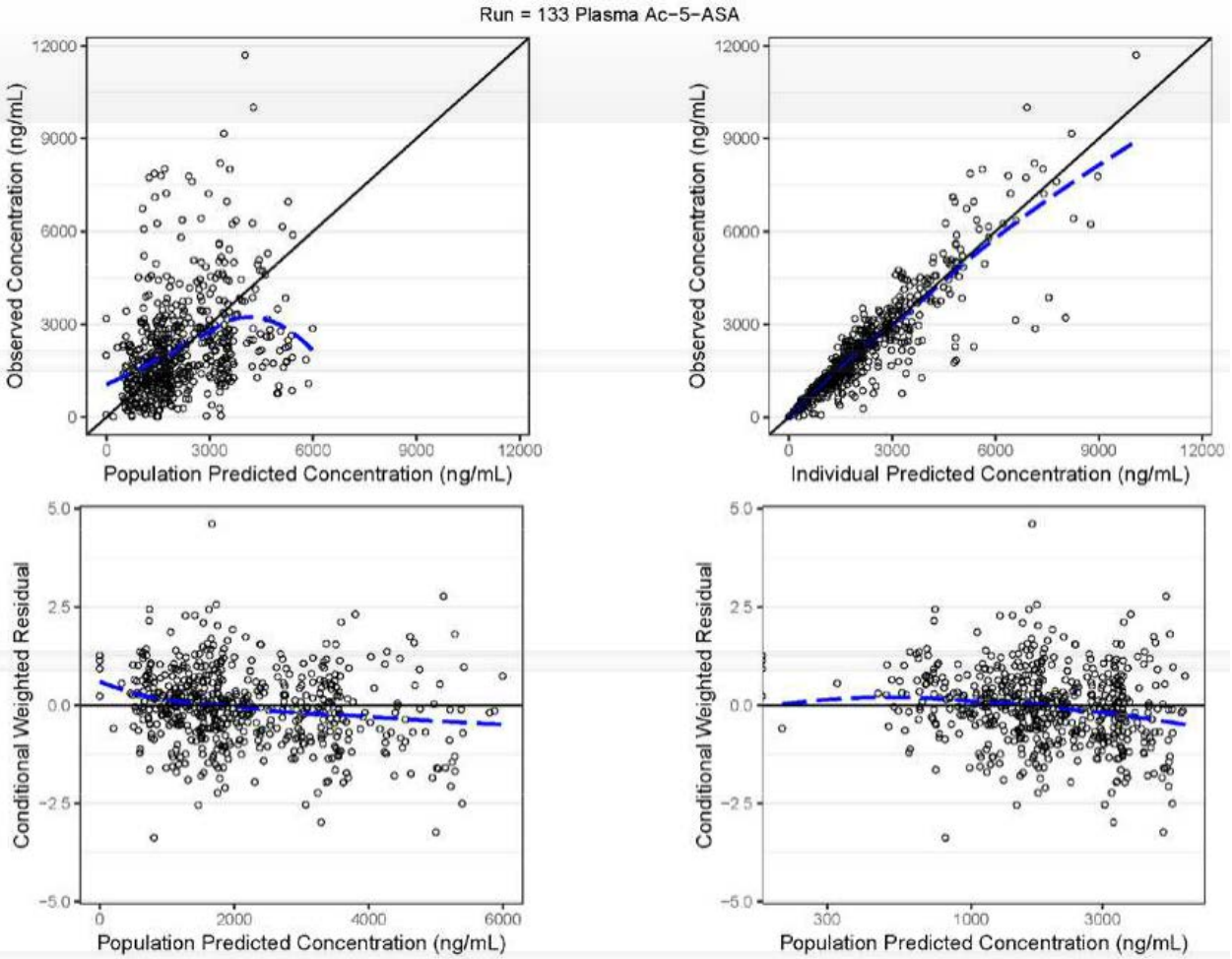
Source: Applicant's population pharmacokinetics report.
The reference population is a 70 kg individual.
[a] Estimates and 95% CI back-transformed from loge scale, except for F1 back-transformed from logistic function, and covariate untransformed.
[b] From 1,000 iterations in which every 10th iteration from a total of 10,000 was sampled.
Abbreviations: %RSE, percent relative standard error of the estimate = SE×100 for Mu referenced parameters, =SE/parameter estimate×100 for non-Mu referenced parameters, and SE×(1-parameter mean)×100 for F_1; ω_2, variance of interindividual random effect, σ^2_{prop}, proportional component of the residue error; 5-ASA, 5-aminosalicylic acid; $ALAG_1$, absorption lag time from depot 1, $ALAG_3$, absorption lag time from depot 3 in addition the lag time from depot 1; CI, confidence interval; CLM/F, apparent metabolic clearance of 5-ASA; CLR/F, apparent renal clearance of 5-ASA; CLRM/F, apparent renal clearance of Ac-5-ASA; CLNRM/F, apparent nonrenal clearance of Ac-5-ASA; CV, coefficient of variation; F_1, fraction of dose absorbed from depot 1; Ka_1, absorption rate constant from depot 1; Ka_3, absorption rate constant from depot 3, MCMC, Markov Chain Monte Carlo; V_c/F, apparent volume of central compartment of 5-ASA; V_cM/F, apparent volume of central compartment of Ac-5-ASA; WT, wildtype

Figure 5. Goodness-of-Fit Plots for Final Population Pharmacokinetic Model (Run 133), All Data, Plasma 5-ASA



Source: Figure 4-5 of Applicant's population pharmacokinetics report
Abbreviations 5-ASA, 5-aminosalicylic acid

Figure 6. Goodness-of-Fit Plots for Final Population Pharmacokinetic Model (Run 133), All Data, Plasma Ac-5-ASA



Source: Figure 4-6 of Applicant's population pharmacokinetics report
Abbreviations 5-ASA, 5-aminosalicylic acid

Reviewer's Comments on Applicant's Population PK Analysis

The final population PK model captured concentration data of parent 5-ASA and active metabolite Ac-5-ASA from 110 pediatric patients simultaneously for both plasma and urine samples. In the model, the allometric scaling by body weight was applied to all clearance and volume parameters with the exponents fixed to the theoretical value of 0.75 for clearance and 1 for volume parameters. These fixes saved modeling time during the Non-linear Mixed-Effects Modeling analysis and appears to be reasonable based on the model diagnostic plots. The reviewer conducted sensitivity analysis by analyzing plasma 5-ASA data alone, the allometric scaling coefficient for CL was estimated to be close to 1 instead of 0.75. Overall, the final model was acceptable for describing plasma PK of 5-ASA and Ac-5-ASA in pediatric patients from Study SPD476-112 and SPD476-319 and generating individual steady state AUCs for exposure-response analysis.

15.3.2.2. Reviewer's Analysis

Background

In pediatric pivotal Study SPD476-319, patients were administered with a low or high weight-based dose in 4 body weight groups. The low dose ranged from 900 mg/day to 2,400 mg/day, and the high dose ranged from 1,200 mg/day to 4,800 mg/day (Table 43). However, the Applicant states that the dosage strength for 900 mg and 1,200 mg is not available because 1,200 mg will be the only available strength in the market according to Applicant's manufacture plan. As such, they have proposed the indications to be limited to pediatric patients with body weight ≥50 kg.

Table 43. Pediatric Weight-Based Dosing in DBA and DBM Phases of Study SPD476-319

Body Weight (kg)	Low Dose (mg/day)	High Dose (mg/day)	Alternative Dose (mg/day)
18 to ≤23	900[a]	1,200[a]	1,200
>23 to ≤35	1,200	2,400	
>35 to ≤50	1,200[a]	3,600	2,400
>50 to ≤90	2,400	4,800	

Source: Reviewer's table
[a] Dosage strength not available
Abbreviations: DBA, double-blind acute; DBM, double-blind maintenance

Considering the potential benefit of Lialda in patients <50 kg, the review team had the following question: Are there potential alternative doses for patients <50 kg that may be given with the currently available dosage strength (1,200 mg)?

The reviewer's analysis is aimed to address this question using population PK simulation and exposure-response (E-R) analysis.

Method

Based on Applicant's final population PK model, typical steady state AUC (AUC_{SS}) of plasma 5-ASA were simulated for virtual subjects with body weight ranging from 18 to 90 kg, following the evaluated dosing regimens listed in Table 43. The AUC_{SS} were also simulated following alternative doses for the body weight groups of 18 to 23 kg and 35 to 50 kg (Table 43).

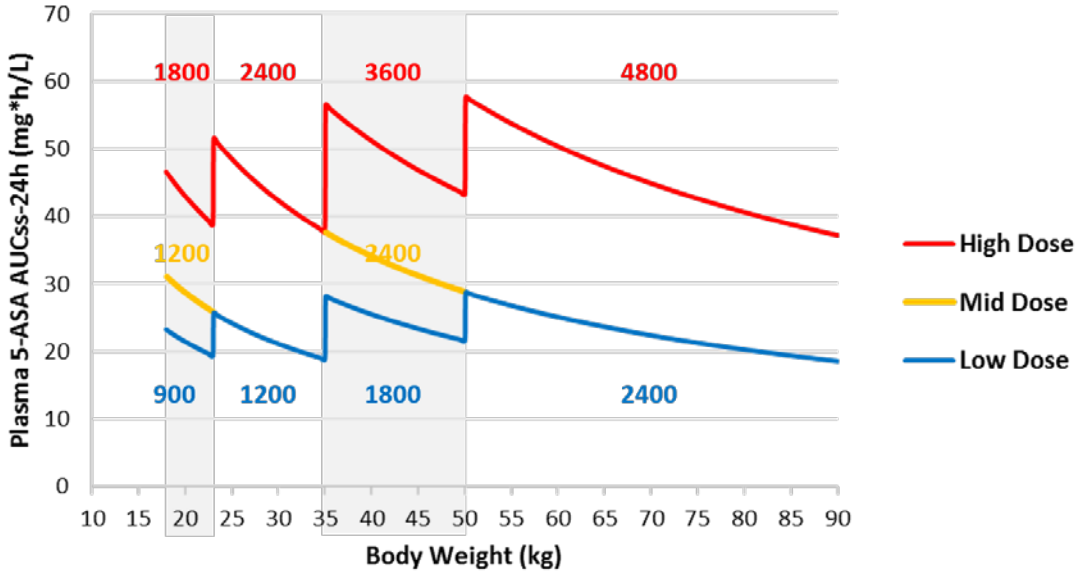
The E-R relationship between AUC_{SS} of 5-ASA and the primary efficacy endpoint defined as partial UC-DAI ≤1 (with rectal bleeding =0 and stool frequency ≤1 and Physician's Global Assessment [PGA] =0), was explored using quartile plots based on data from Study-476-319. The 5-ASA AUC_{SS} for each subject was calculated based on the empirical Bayesian individual PK parameter estimates from the Applicant's final population PK model. For subjects with no collected PK (32.7% for double-blind acute [DBA] phase and 40.5% for double-blind maintenance [DBM] phase), the AUC_{SS} was predicted based on the final population PK model. Excel was used for calculation and graphics for Figure 7 and R Version 3.6.3 (CRANcran.r-project.org) was used to conduct data manipulation and E-R analysis for Figure 8.

Results

PK Simulation

The simulated AUC_{SS} of 5-ASA across body weight are shown in Figure 7, following high (red line) and low (blue line) weight-based doses. The simulated AUC_{SS} for alternative doses in body weight groups of 18 to 23 kg and 35 to 50 kg are shown as the orange lines. In general, the AUC_{SS} of 5-ASA is proportional to doses at each given body weight and appears to be consistent across the body weight range of 18 to 90 kg at each dose level.

Figure 7. Simulated Mean Steady State 5-ASA AUC by Body Weight With Daily Dose (mg) Labeled Within Each Body Weight Group

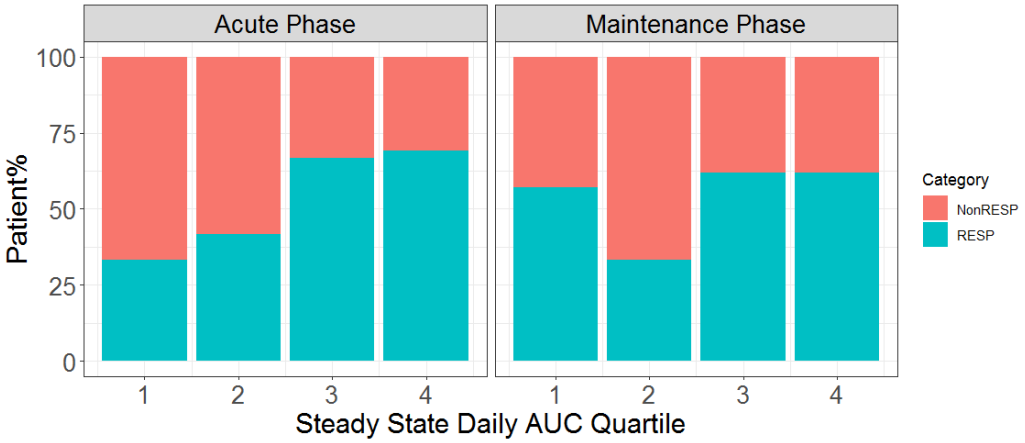


Source: FDA reviewer's analysis based on Applicant's final population PK model
Abbreviations 5-ASA, 5-aminosalicylic acid; AUC_{SS}, area under the curve at steady state

Exposure-Response Analysis for Efficacy Using Quartile Plots

Subjects in each phase of Study SPD476-319 were grouped based on predicted 5-ASA AUC_{SS} quartiles and the percent of responders per quartile were plotted in Figure 8. There appears to be a positive E-R relationship for acute phase, with increasing response rates from Q1 to Q4 (33.3%, 41.7%, 66.7%, and 69.2% for Q1-Q4, respectively) and flat E-R relationship for maintenance phase (with response rates of 57.1%, 33.3%, 61.9%, and 61.9% for Q1-Q4, respectively). The exposure (unit: mg*h/L) boundaries for the four quartiles of each phase are listed in Table 44.

Figure 8. Rate of Clinical Response Vs. Steady-State Exposure by Treatment Phase for Study 476-319



Source: FDA reviewer's analysis based on efficacy data provided by FDA statistics reviewers for Study 476-319
Abbreviations: AUC, area under the curve; RESP, response

Table 44. Exposure (mg*h/L) Boundaries for Four Quartiles of Each Phase of Study 476-319

AUC Percentile	0th	25th	50th	75th	100th
Acute phase	8.7	23.1	30.2	54.4	146.5
Maintenance phase	9.6	23.9	35.4	54.5	146.5

Source: FDA reviewer's analysis
Abbreviations: AUC, area under the curve

The E-R analysis results appear to be consistent with D-R relationships (refer to efficacy review in Section 8.1.2 for details). These results support high dose for acute phase and low dose for maintenance phase from an efficacy perspective.

Given the flat D-R and E-R relationship for the maintenance phase, replacing the low dose (blue line) with the mid dose (orange line) for the maintenance treatment is not expected to affect efficacy. Therefore, 2,400 mg and 1,200 mg appear to be reasonable alternative maintenance doses for the group of 35 to 50 kg and 18 to 23 kg, respectively. From a safety perspective, these mid-dose levels are also supported by an acceptable safety profile at the high dose (refer to safety review in Section 8.2.4 for details).

However, for the group of 18 to 23 kg, a lower alternative initial dose of 1,200 mg may not provide optimal efficacy based on the observed E-R in the DBA phase. In addition, there are only limited data available in the 18 to 23 kg group (N=0 for the DBA phase and three for the DBM phase). As such, an alternative dosing regimen is not recommended for this group.

15.3.3. Individual Study Reviews

15.3.3.1. Study SHP476-121

Title

A Phase 1, Randomized, Open-Label, 2-Sequence, 4-Period Crossover, Replicate Design, Bioequivalence Study Assessing Pharmacokinetics and Safety of Two SHP476 Formulations, 1.2 g and 300 mg Administered With a Moderate Fat Meal in Healthy Volunteers

Clinical site: Clinical Pharmacology of Miami, Inc.
Bioanalytical site: (b) (4)
Study date: February 27, 2017, to April 21, 2017

Primary Objectives

To evaluate the BE of the pediatric-friendly (smaller tablet size) 300-mg tablets of multi-matrix system (MMX) mesalamine used in the pediatric study SPD476-319 compared to the currently approved standard 1.2-g larger tablet used in adults.

Study Design

The study was a phase 1, randomized, open-label, two-sequence, four-period, single-dose, crossover, replicate design, BE study in 36 healthy adult volunteers, under fed conditions. The 4-period crossover replicate study design and statistical analysis utilized the scaled average bioequivalence (SABE) method for highly variable drugs.

- Test product (T): SHP476, MMX mesalamine, 300-mg strength oral tablets administered as 4×300-mg tablets
- Reference product (R): SHP476, MMX mesalamine, 1.2-g strength oral tablets administered as 1×1.2-g tablet

Table 45. Reference Vs. Test Product by Treatment Period for Study SHP476-121

	Treatment Period			
Sequence No.	**1**	**2**	**3**	**4**
Sequence 1	T	R	T	R
Sequence 2	R	T	R	T

Source: CSR of Study SHP476-121
Abbreviations: T, test product; R, reference product

Subjects were required to fast starting from 10 hours prior up to 1 hour prior to Lialda administration on Day 1 of each treatment period. Subjects were then fed and were to fully consume a standard moderate-fat breakfast 0.5 hours prior to Lialda administration. Subjects received a single oral dose of SHP476 1.2 g (1×1.2-g tablet or 4×300-mg tablets). There was between 10 to 14 days of washout period between each treatment. PK samples were collected for up to 120 hours postdose in each treatment period to determine the plasma concentrations of mesalamine.

Reviewer's Comments

- *The study design of single dose with fully replicated–period was consistent with the recommendation from the FDA draft guideline for industry,* Bioequivalence Recommendations for Mesalamine Delayed Release Tablets *(CDER, 2016).*
- *Administration of the drug under fed condition was acceptable as the current Lialda labels recommends taking Lialda with food.*
- *The evaluated dose of 1,200 mg is consistent with the recommendation from the FDA draft guideline for industry,* Bioequivalence Recommendations for Mesalamine Delayed Release Tablets *(CDER, 2016).*
- *The length of PK sampling scheme up to 120 hour and minimum of 10 to 14 days hours of washout period was reasonable given the half-life and t_{max} of mesalamine was 8.56 hrs (terminal) and 9 hours, respectively following a single oral dose administration of Lialda 1.2 g under fasting condition in healthy subjects.*

Study Population

The study included healthy males and nonpregnant, nonlactating females ages between 18 and 55 years with good health with a body mass index between 18 and 30. kg/m^2. This study had 36 healthy volunteers enrolled and all of them completed the study as planned by completing all four study periods.

Table 46. Pharmacokinetic Measurements by Treatment Period for Study SHP476-121

Visit	Screening	Treatment Periods 1, 2, 3, and 4[a]																																				
Study Day	-28 to -2	-1	1													2															3		4		5		6	
Study Hour (relative to dosing time)			Predose	0	1	2	4	6	8	9	10	11	12	13	14	16	18	20	22	24	26	28	30	32	34	36	48	60	72	96	120
Pharmacokinetic blood sampling			X[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Source: CSR of Study SHP476-121, Table 2
[a] There was a 10- (minimum) to 14-day (maximum) washout between administrations of Lialda in each treatment period.
[i] Pharmacokinetic samples were collected at predose (within 60 minutes prior to dosing) in each treatment period.

PK Parameters and Statistical Analysis

PK parameters were derived based on plasma concentration-time data (actual sampling times) using noncompartmental PK analysis.

The log-transformed PK parameters (C_{max}, AUC_{8-48}, and AUC_{0-t}) were compared between the two treatments using an analysis of variance model for a replicated crossover study design with fixed factors for sequence, treatment and period, and random factor for subject. The SABE analysis was performed in accordance with the FDA draft guideline for industry, *Bioequivalence Recommendations for Progesterone Oral Capsules* (CDER, 2011).

The point-estimates were evaluated by calculating the exponentiated point estimate of the geometric least squares mean difference for the log-transformed PK parameters: C_{max}, AUC_{0-t}, and AUC_{8-48} between the test product (4×300-mg tablets) and reference product (1×1.2-g tablets).

By creating a replicate design (TRTR versus RTRT), it was possible to provide an estimate of the within-subject variation of each product. That was, the variation experienced within the same subject received the same treatment on two adequately separated occasions.

If the within-subject SD of the PK parameter for the reference product (intrasubject variability [SWR]) was ≥0.294 (i.e., meets the definition for a highly variable PK parameter) then the BE assessment was made using the SABE comparison. The SABE approach utilized the scaling of BE limits based on the size of the within-subject variation of the reference product in a replicate design study. On the other hand, if SWR was <0.294 then the BE assessment was made using the standard BE assessment method using the 90% confidence intervals for the treatment comparison.

Before performing the SABE analysis, the following quantities were calculated:

- T_{ijk} = kth observation (k =1 or 2) on the test product for subject j within sequence i.
- R_{ijk} = kth observation (k =1 or 2) on the reference product for subject j within sequence i.
- I_{ij} = ½(T_{ij1}+T_{ij2})−½(R_{ij1}+R_{ij2}). The difference in means of a subject's two observations on T and the 2 observations on R.
- D_{ij} = Rij1−Rij2. The difference between a subject's two observations on R.

Bioanalytical Method (Bioanalytical Report A8736M-SPD476)

- Concentrations of 5-ASA in human plasma were measured by a validated LC/MS/MS at QPS LLC's according to the validation report A8687M-SPD476 titled "Validation of a Method for the Determination of 5-Aminosalicylic Acid and N-Acetyl-5-Aminosalicylic Acid in Lithium Heparin Human Plasma by LC-MS/MS."
- Plasma samples were stored frozen at -70ºC until analysis. Samples were collected from March 14, 2017, through April 19, 2017. Samples were analyzed between April 25, 2017, and May 12, 2017. Maximum time from sample collection to sample analysis were 59 days, and samples were assayed within the long-term stability of 95 days at -70°C.
- Calibration standard curve consisted of eight levels that ranged from 5.0 to 5000 ng/mL in human plasma and was calculated using a linear regression with (1/concentration squared weighted) algorithm. The differences of back-calculated calibration curve values from nominal values ranged from -5.2% to 4.8%.
- QC samples at four different concentrations (15, 250, 2000, and 40000 ng/mL) of 5-ASA were prepared. The inter-assay accuracy and precision data for the QC samples at four concentrations across all analytical met the predefined acceptance criteria.
- Approximately 6.3% of the (253/4032) of were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification and 95.3% met the acceptance criteria for 5-ASA. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.

Table 47. Assay Performance of Bioanalytical Quality Control Samples for 5-ASA in Plasma

	Linear Range	Low QC			Mid QCs			High QC		
Method	(ng/mL)	Value	%Bias	%CV	Value	%Bias	%CV	Value	%Bias	%CV
LC-MS/MS	5–5000	15	+4.7	4.8	250 2000	+4.4 +2.0	4.1 2.9	4000	-4.5	6.9

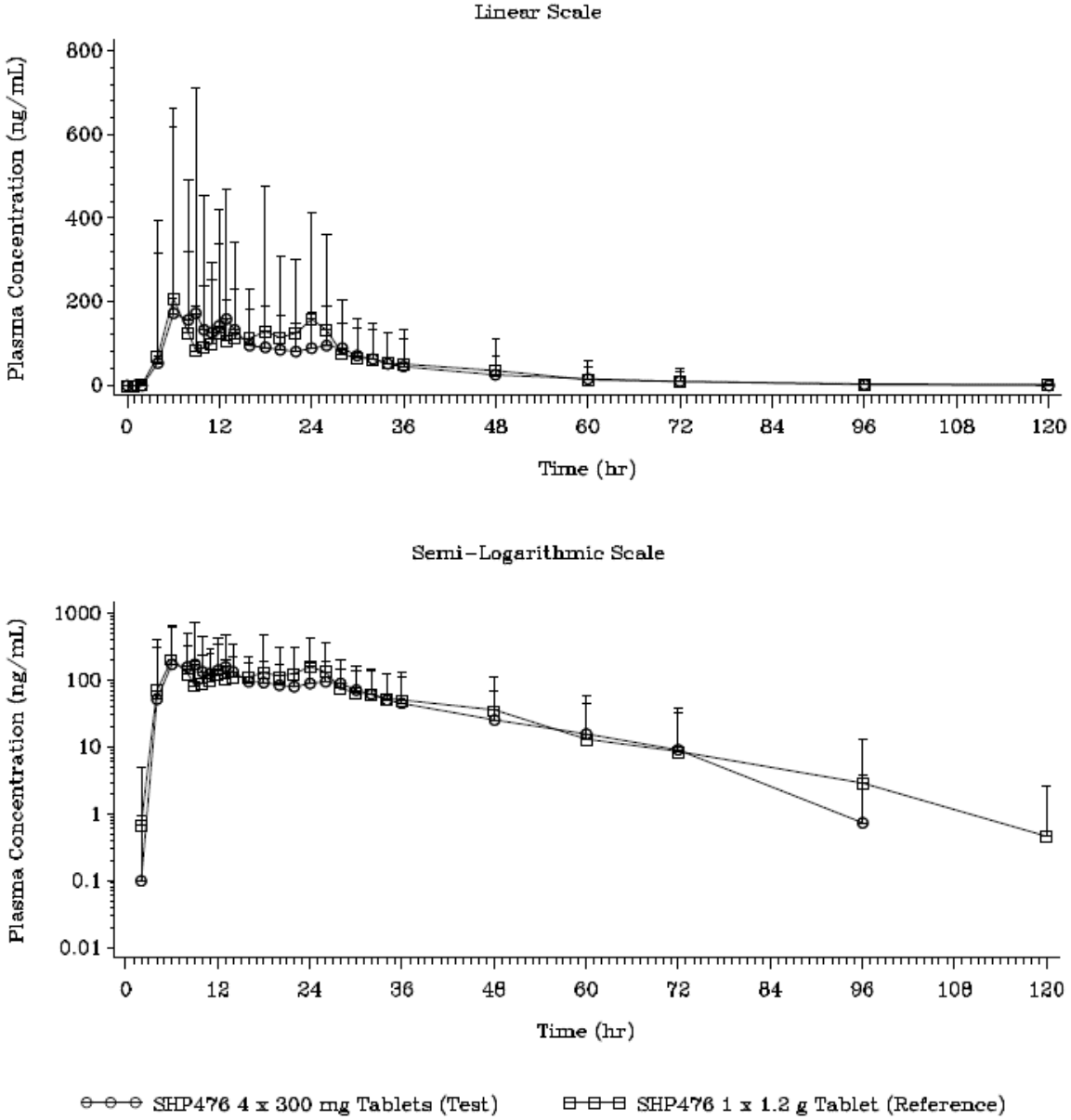
Source: Bioanalytical Report A8736M-SPD476
Abbreviations: 5-ASA, 5-aminosalicylic acid; CV, coefficient of variation; LC-MS/MS, liquid-chromatography-mass spectrometry; QC, quality control

Results

Pharmacokinetics

For two of the individual treatments (Subject [redacted], period 1, 1.2-g tablet and Subject [redacted], period 2, 1.2-g tablet), the 5-ASA plasma concentration values were below the limit of quantification of the assay (BLQ, <5 ng/mL) for all time points in the PK profile. In this case, the 5-ASA C_{max} and AUC_{0-t} were set equal to 0 and all other pharmacokinetic parameters were not calculated. Consequently, the geometric mean C_{max} and AUC_{0-t} could not be calculated for the 1.2-g tablet treatment with 0 values for these parameters.

Figure 9. Mean (±SD) Observed 5-ASA Plasma Concentrations by Treatment



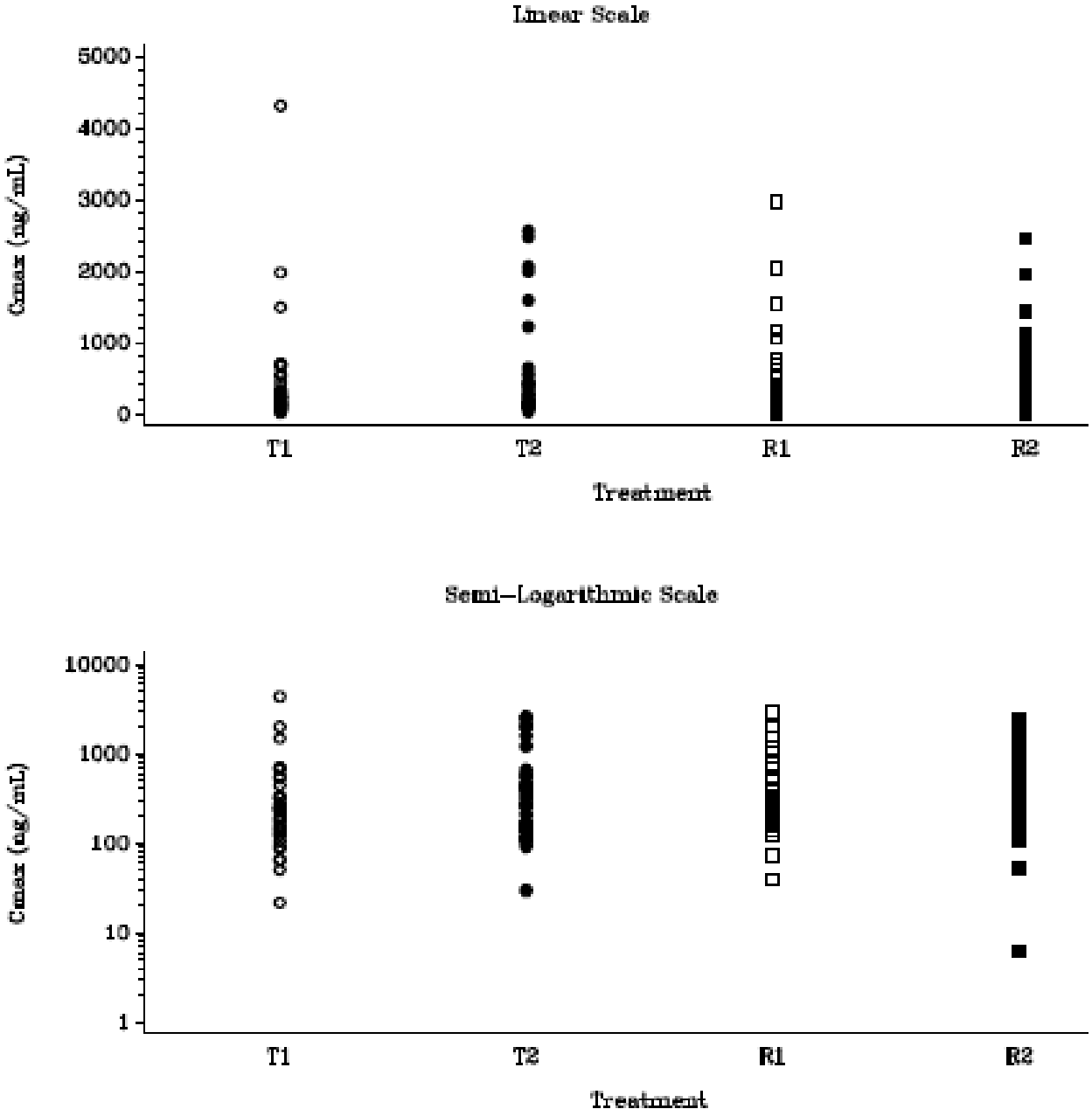
Source: CSR for Study SHP476-121, Figure 2 (page 49)
Abbreviations: 5-ASA, 5-aminosalicylic acid; SD, standard deviation

Table 48. Summary of Plasma 5-ASA Pharmacokinetic Parameters

Treatment	N	C_{max} (ng/mL)	t_{max} (h)	t_{lag} (h)	AUC_{0-t} (ng·h/mL)	AUC_{8-48} (ng·h/mL)
			Mean (SD) [Geometric Mean]			
4×300 mg	72	496 (732)	15.6 (7.8)	6.6 (4.2)	3975 (3270)	3038 (2473)
		[267]	[13.6]	[5.5]	[2755]	[2211]
1×1.2 g	72[a]	529 (595)	15.4 (9.3)	6.2 (5.3)	4334 (3191)	3361 (2444)
		[NC]	[12.7]	[4.7]	[NC]	[NC]
			Bioequivalence Assessment			
S_{WR}		0.9134	NC	NC	0.9392	0.6051
Geo Mean Test/Ref		0.8735	NC	NC	0.9491	0.9041
95% Upper CI		-0.4104	NC	NC	-0.4851	-0.1810
$(\bar{Y}_T-\bar{Y}_R)^2-\theta\bullet S^2_{WR}$						

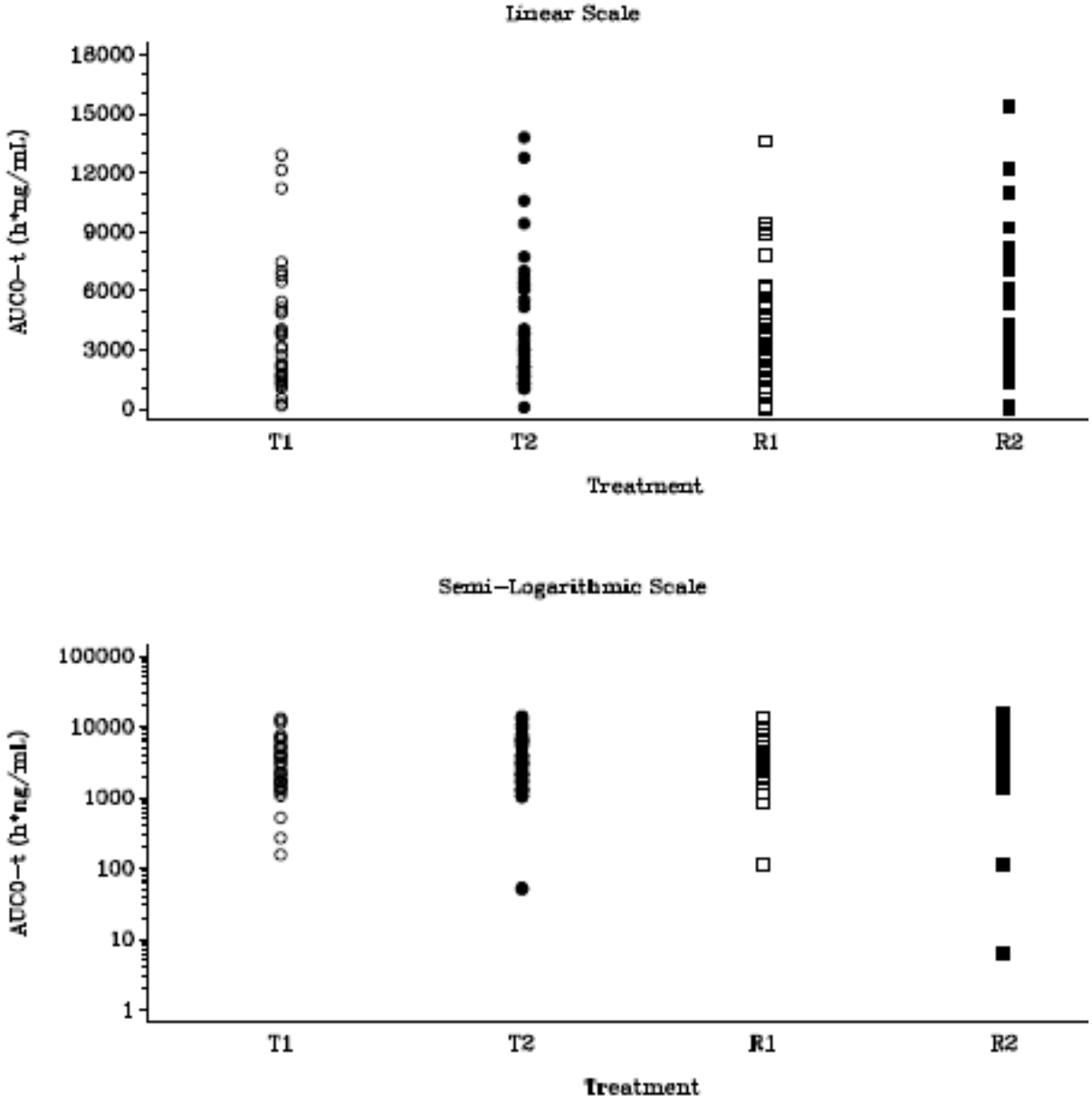
Source: CSR for Study SHP476-121, Table 8 (page 52)
Note: Several of the 5-ASA plasma concentration versus time profiles did not exhibit a log linear decline due to low or variable plasma concentrations, and λz, $t_{1/2}$, and $AUC_{0-\infty}$ could not be estimated for these profiles. Values are presented as mean (SD) and [geometric mean].
[a] n=70 for AUC_{8-48}, t_{max}, and t_{lag}.
Abbreviations: 5-ASA, 5-aminosalicylic acid; AUC_{0-t}, area under the curve from the time of dosing to the last measurable concentration; AUC_{8-48}, area under the plasma concentration-time curve from 8 to 48 hours after administration; CI, confidence interval; C_{max}, maximum concentration occurring at t_{max}; NC, not calculated; SD, standard deviation; S_{WR}, intrasubject variability; t_{lag}, timepoint prior to the first quantifiable plasma concentration; t_{max}, time of maximum observed concentration sampled during a dosing interval

Figure 10. Individual 5-ASA Plasma C_{max} Values Vs. Treatment



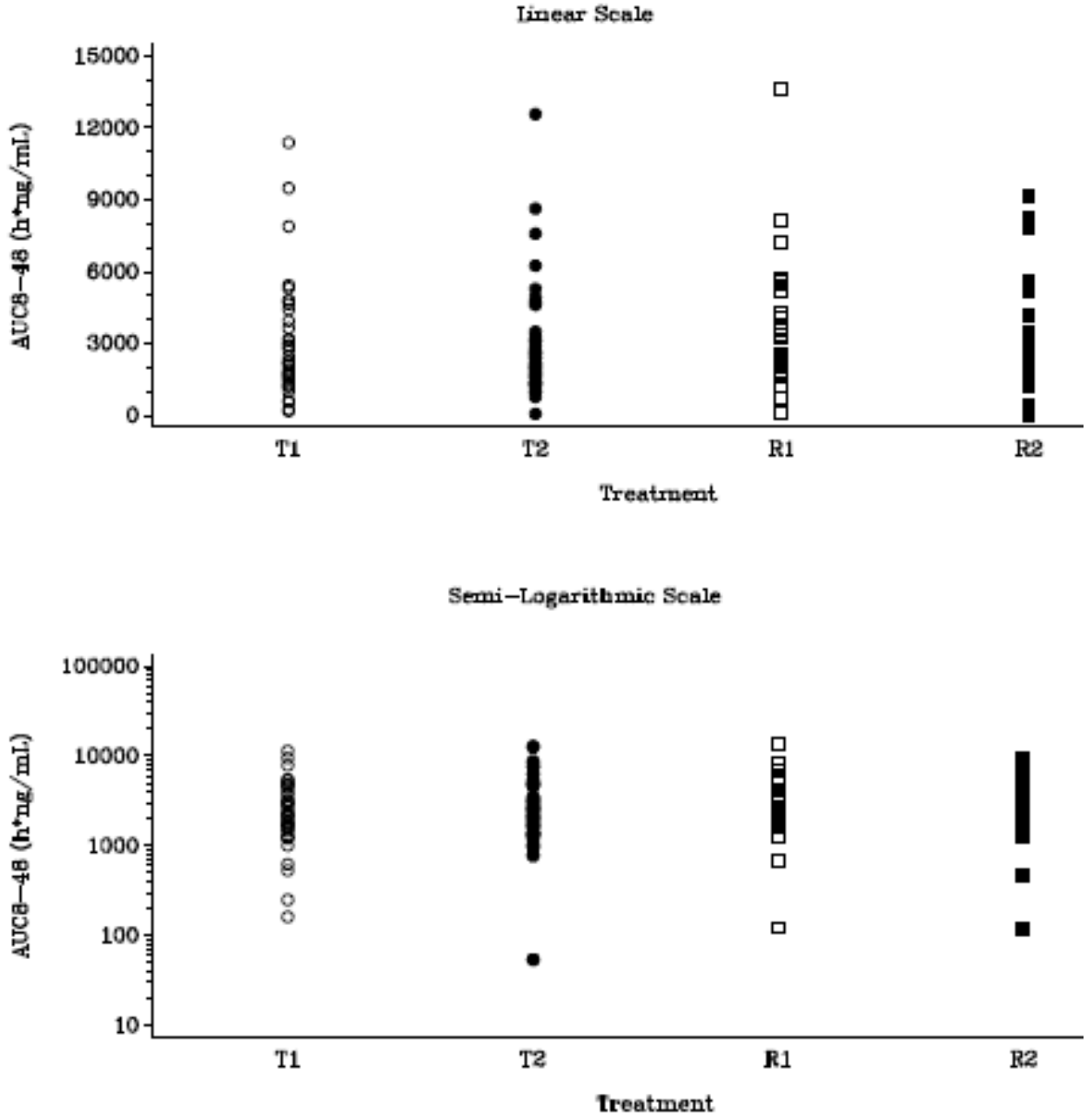
Source: CSR for Study SHP476-121, Figure 14.2.3.4 (page 461)
Treatment T: SHP476 (PO) 4 x 300-mg tablets (test); Treatment R: SHP476 (PO) 1 x 1.2-g tablet (reference); T1 and T2 are first and second administration of treatment T, respectively; R1 and R2 are first and second administration of Treatment R, respectively.
Abbreviations: 5-ASA, 5-aminosalicylic acid; C_{max}, maximum concentration; R, reference product; T, test product

Figure 11. Individual 5-ASA Plasma AUC_{0-t} Values Vs. Treatment



Source: CSR for Study SHP476-121, Figure 14.2.3.5 (page 462)
Treatment T: SHP476 (PO) 4 x 300-mg tablets (test); Treatment R: SHP476 (PO) 1 x 1.2-g tablet (reference); T1 and T2 are first and second administration of Treatment T, respectively; R1 and R2 are first and second administration of Treatment R, respectively.
Abbreviations: 5-ASA, 5-aminosalicylic acid; AUC_{0-t}, area under the curve from the time of dosing to the last measurable concentration; R, reference product; T, test product

Figure 12. Individual 5-ASA Plasma AUC_{8-48} Values Vs. Treatment



Source: CSR for Study SHP476-121, Figure 14.2.3.6 (page 463)
Treatment T: SHP476 (PO) 4 x 300-mg tablets (test); Treatment R: SHP476 (PO) 1 x 1.2-g tablet (reference); T1 and T2 are first and second administration of Treatment T, respectively; R1 and R2 are first and second administration of Treatment R, respectively.
Abbreviations: 5-ASA, 5-aminosalicylic acid; AUC_{8-48}, area under the plasma concentration-time curve from 8 to 48 hours after administration; R, reference product; T, test product

Reviewer's Comments

PK profiles

- *Both treatments had similar overall mean 5-ASA plasma concentration profiles and both treatments had multiple peaks.*
- *Similar to the previous studies, PK profile of 5-ASA were highly variable following both treatments.*
- *Following single-dose administration, t_{max} and t_{lag} (timepoint prior to the first quantifiable plasma concentration) were similar between the two treatments where t_{max} were reached around 15 hours where t_{lag} were around 6 hours postdose. t_{max} and t_{lag} in this study was more delayed compared to what was reported for Lialda 1.2 g in healthy subjects in the current label.*

BE statistical results

- *All three primary PK parameters, C_{max}, AUC_{0-t}, and AUC_{8-48}, met the criteria for highly variable drug product (defined as SWR ≥0.294) with SWR values of 0.9134, 0.9392, and 0.6051, respectively. Therefore, use of SABE was appropriate for bioequivalence assessment in this study between these two treatments.*
- *The point estimate of the geometric mean test/reference ratio was within 80% to 125%, for all three PK parameters (87.35%, 94.91%, and 90.41% for C_{max}, AUC_{0-t}, and AUC_{8-48}, respectively).*
- *The 95% upper confidence limit of the SABE contrast $(\bar{Y}T-\bar{Y}R)2-\theta \bullet S2WR$ was ≤0 for all three PK parameters (-0.41014, -0.4851, and -0.1810 for C_{max}, AUC_{0-t}, and AUC_{8-48}, respectively).*
- *Therefore, the SABE criteria were met and the two treatments, pediatric SHP476 300-mg tablets (administered as 4×300-mg tablets) and SHP476 1.2-g tablets are considered bioequivalent.*

Safety

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory test (hematology, clinical chemistry, urinalysis,) 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the Applicant, there was no death or serious adverse event (SAE) or adverse events resulting in the study drug discontinuation. Incidences of treatment-emergent adverse events (TEAEs) were comparable in both treatment groups: nine (25.0%) subjects in the SHP476 4×300 mg treatment group and six (16.7%) subjects in the SHP476 1×1.2 g treatment group.

Overall, 16 TEAEs were reported by 15 subjects (41.7%); all of them were mild in severity, considered to be related to the Lialda by the investigator, and nonserious. The most frequently reported TEAEs during the treatment period were in the system organ class of nervous system disorders (nine [25.0%] subjects). Overall, the most commonly reported TEAEs were headache and flatulence (eight [22.2%] subjects) and (three [8.3%] subjects), respectively. There were no clinically important findings noted in the physical examination, safety clinical laboratory, vital sign, or ECG data.

15.3.3.2. Study SHP476-122

Title

A Phase 1, Randomized, Open-Label, 2-Sequence, 4-Period Crossover, Replicate Design, Bioequivalence Study Assessing Pharmacokinetics and Safety of Two SHP476 Formulations, 1.2 g and 600 mg Administered With a Moderate Fat Meal in Healthy Volunteers

Clinical site: Clinical Pharmacology of Miami, Inc.
Bioanalytical site: (b) (4)
Study date: April 27, 2017, to June 20, 2017

Primary Objectives

To evaluate the BE of the pediatric-friendly (smaller tablet size) 600-mg tablets of MMX mesalamine used in the pediatric Study SPD476-319 compared to the currently approved standard 1.2-g larger tablet used in adults.

Study Design

The study was a phase 1, randomized, open-label, 2-sequence, 4-period, single-dose, crossover, replicate design, BE study in 36 healthy adult volunteers, underfed conditions. The 4-period crossover replicate study design and statistical analysis utilized the SABE method for highly variable drugs.

- Test product (T): SHP476, MMX mesalamine, 600-mg strength oral tablets administered as 2×600-mg tablets
- Reference product (R): SHP476, MMX mesalamine, 1.2-g strength oral tablets administered as 1×1.2-g tablet

Table 49. Reference Vs. Test Product by Treatment Period for Study SHP476-122

	Treatment Period			
Sequence No.	**1**	**2**	**3**	**4**
Sequence 1	T	R	T	R
Sequence 2	R	T	R	T

Source: CSR of Study SHP476-122,
Abbreviations: T, test product; R, reference product

Subjects were required to fast starting from 10 hours prior up to 1 hour prior to Lialda administration on Day 1 of each treatment period. Subjects were then fed and were to fully consume a standard moderate-fat breakfast 0.5 hours prior to Lialda administration. Subjects received a single oral dose of SHP476 1.2 g (1×1.2-g tablet or 2×600-mg tablets). There was between 10 to 14 days of washout period between each treatment. PK samples were collected for up to 120 hours postdose in each treatment period to determine the plasma concentrations of mesalamine.

Reviewer's Comments

- *The study design of single dose with fully replicated period was consistent with the recommendation from the FDA draft guideline for industry,* Bioequivalence Recommendations for Mesalamine Delayed Release Tablets *(CDER, 2016).*
- *Administration of the drug under fed condition was acceptable as the current Lialda labels recommends taking Lialda with food.*

- *The evaluated dose of 1,200 mg is consistent with the recommendation from the FDA draft guideline for industry,* Bioequivalence Recommendations for Mesalamine Delayed Release Tablets *(CDER, 2016).*
- *The length of PK sampling scheme up to 120 hour and minimum of 10 to 14 days hours of washout period was reasonable given the half-life and t_{max} of mesalamine was 8.56 hrs (terminal) and 9 hours, respectively following a single oral dose administration of Lialda 1.2 g under fasting condition in healthy subjects.*

Study Population

The study included healthy males and nonpregnant, nonlactating females ages between 18 and 55 years with good health with a body mass index between 18 and 30 kg/m^2. This study had 36 healthy volunteers enrolled and 35 of them completed the study as planned by completing all four study periods. One subject randomly assigned to treatment sequence TRTR discontinued from the study during treatment period 1 due to withdrawal by subject and did not complete the study.

Pharmacokinetic Measurements

Table 50. Pharmacokinetic Measurements for Study SHP476-122

Visit	Screening	Treatment Periods 1, 2, 3, and 4[a]																																		
Study Day	-28 to -2	-1	1												2														3		4		5		6	
Study Hour (relative to dosing time)			Predose	0	1	2	4	6	8	9	10	11	12	13	14	16	18	20	22	24	26	28	30	32	34	36	48	60	72		96		120	
Pharmacokinetic blood sampling			X[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	

Source: CSR of Study SHP476-122, Table 2
[a] There was a 10-day (minimum) to 14-day (maximum) washout between administrations of Lialda in each treatment period.
[i] Pharmacokinetic samples were collected at predose (within 60 minutes prior to dosing) in each treatment period.

PK Parameters and Statistical Analysis

PK parameters were derived based on plasma concentration-time data (actual sampling times) using noncompartmental PK analysis.

The log-transformed PK parameters (C_{max}, AUC_{8-48}, and AUC_{0-t}) were compared between the two treatments using an analysis of variance model for a replicated crossover study design with fixed factors for sequence, treatment and period, and random factor for subject. The SABE analysis was performed in accordance with the FDA draft guideline for industry, *Bioequivalence Recommendations for Progesterone Oral Capsules* (CDER, 2011).

The point-estimates were evaluated by calculating the exponentiated point estimate of the geometric least squares mean difference for the log-transformed PK parameters: C_{max}, AUC_{0-t}, and AUC_{8-48} between the test product (2×600-mg tablets) and reference product (1×1.2-g tablets).

By creating a replicate design (TRTR versus RTRT), it was possible to provide an estimate of the within-subject variation of each product. That was, the variation experienced within the same subject received the same treatment on two adequately separated occasions.

If the within-subject SD of the PK parameter for the reference product (SWR) was ≥0.294 (i.e., meets the definition for a highly variable PK parameter) then the BE assessment was made using the SABE comparison. The SABE approach utilized the scaling of BE limits based on the

size of the within-subject variation of the reference product in a replicate design study. On the other hand, if SWR was <0.294 then the BE assessment was made using the standard BE assessment method using the 90% confidence intervals for the treatment comparison.

Before performing the SABE analysis, the following quantities were calculated:

- T_{ijk} = kth observation (k =1 or 2) on the test product for subject j within sequence i.
- R_{ijk} = kth observation (k =1 or 2) on the reference product for subject j within sequence i.
- I_{ij} = ½(T_{ij1}+T_{ij2})−½(R_{ij1}+R_{ij2}). The difference in means of a subject's two observations on T and the two observations on R.
- D_{ij} = Rij1−Rij2. The difference between a subject's two observations on R.

Bioanalytical Method (Bioanalytical Report A8736M-SPD476)

- Concentrations of 5-ASA in human plasma were measured by a validated LC/MS/MS at QPS LLC's according to the validation report A8687M-SPD476 titled "Validation of a Method for the Determination of 5-Aminosalicylic Acid and N-Acetyl-5-Aminosalicylic Acid in Lithium Heparin Human Plasma by LC-MS/MS."
- Plasma samples were stored frozen at -70°C until analysis. Samples were collected from May 12, 2017, through June 18, 2017. Samples were analyzed between June 21, 2017, and July 7, 2017. Maximum time from sample collection to sample analysis were 56 days, and samples were assayed within the long-term stability of 95 days at -70°C.
- Calibration standard curve consisted of eight levels that ranged from 5.0 to 5000 ng/mL in human plasma and was calculated using a linear regression with (1/concentration squared weighted) algorithm. The differences of back-calculated calibration curve values from nominal values ranged from -2.4% to 3.0%.
- QC samples at four different concentrations (15, 250, 2000, and 40000 ng/mL) of 5-ASA were prepared. The inter-assay accuracy and precision data for the QC samples at four concentrations across all analytical met the predefined acceptance criteria.
- Approximately 6.4% of the (251/3938) of were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification and 99.63% met the acceptance criteria for 5-ASA. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.

Table 51. Assay Performance of Bioanalytical Quality Control Samples for 5-ASA in Plasma

	Linear Range	Low QC			Mid QCs			High QC		
Method	(ng/mL)	Value	%Bias	%CV	Value	%Bias	%CV	Value	%Bias	%CV
LC-MS/MS	5–5000	15	+1.3	4.5	250 2000	+1.2 +1.0	2.9 6.6	4000	-0.5	3.0

Source: A8737M-SPD476 (QPS report number: QPS 185-1623)
Abbreviations: 5-ASA, 5-aminosalicylic acid; CV, coefficient of variation; LC-MS/MS, liquid chromatography-mass spectrometry; QC, quality control

Results

Pharmacokinetics

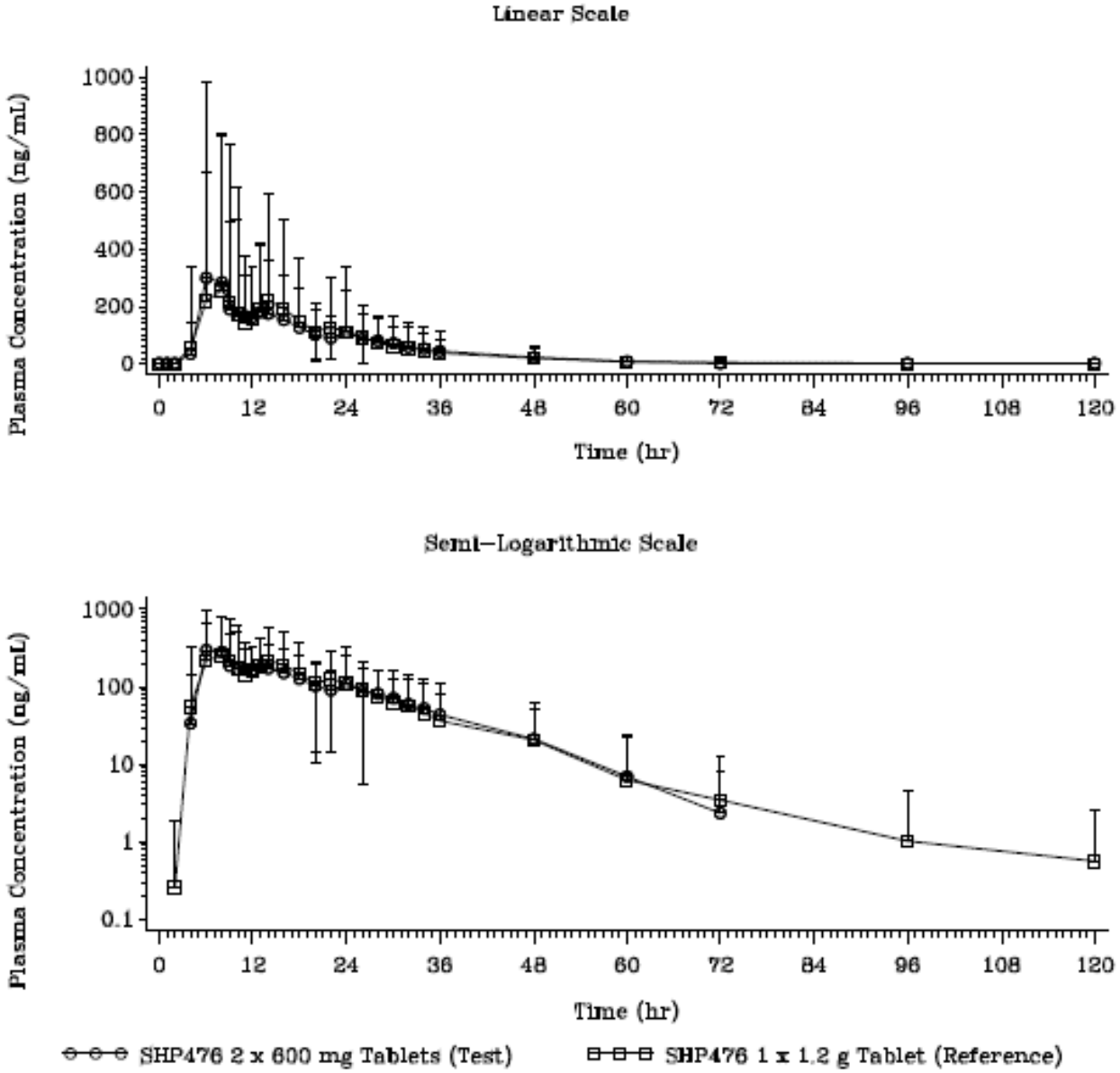
For four of the individual treatments (Subject (b) (6), treatment period 2, SHP476 2×600-mg tablets; Subject (b) (6), treatment period 2, SHP476 1×1.2-g tablet; Subject (b) (6), treatment period 1, SHP476 1×1.2-g tablet; and Subject (b) (6), treatment period 2, SHP476 1×1.2-g tablet), the 5-ASA plasma concentration values were BLQ (<5 ng/mL) for all time points in the PK profile. In this case, the 5-ASA C_{max} and AUC_{0-t} were set equal to zero and all other PK parameters were not calculated. Consequently, the geometric mean C_{max} and AUC_{0-t} could not be calculated for these treatments with zero values for these parameters.

Two PK data-points were excluded from the noncompartmental analysis; 96 hazard ratio (HR) for subject (b) (6) (treatment period 3) as the PK profile was observed to have terminated after the 16 HR time-point and 26 HR for Subject [redacted] (treatment period 1) as no actual time relative to dosing could be derived (blood sample collection date and time missing).

- The 5-ASA plasma concentration profile for Subject (b) (6), treatment period 3, SHP476 (1×1.2-g tablet), exhibited measurable 5-ASA plasma concentrations from 6 to 16 hours after administration, then BLQ values from 18 to 72 hours, with another measurable 5-ASA plasma concentration (8.79 ng/mL) at 96 hours. For this profile, the measurable 5-ASA plasma concentration at 96 hours, observed after BLQ values were observed for a few days, was excluded from the analysis in order to eliminate the bias in the calculated AUC.
- Subject (b) (6) withdrew from the study on the morning of Day 2 of treatment period 1 (SHP476, 2×600-mg tablets). Pharmacokinetic blood samples were collected through the 26-hour time point, although the time of collection for the 26-hour sample was not recorded on the electronic case report form and the actual time since dose could not be calculated for that observation. Therefore, the plasma concentration data through 24 hours after administration were used to calculate the PK parameters for this treatment.

The concentration profile for 5-ASA plasma from Subject (b) (6), treatment period 4, SHP476 2×600-mg tablets, exhibited only one measurable 5-ASA plasma concentration at 20 hours after administration (5.01 ng/mL) with BLQ values at all other time points. For this profile, only C_{max}, t_{max}, t_{lag}, AUC_{0-t}, and AUC_{8-48} were calculated; all other PK parameters were not calculated. This same subject had a plasma concentration profile of all BLQ values for SHP476, 1×1.2-g tablet in treatment period 1.

Figure 13. Mean (±SD) Observed 5-ASA Plasma Concentrations by Treatment



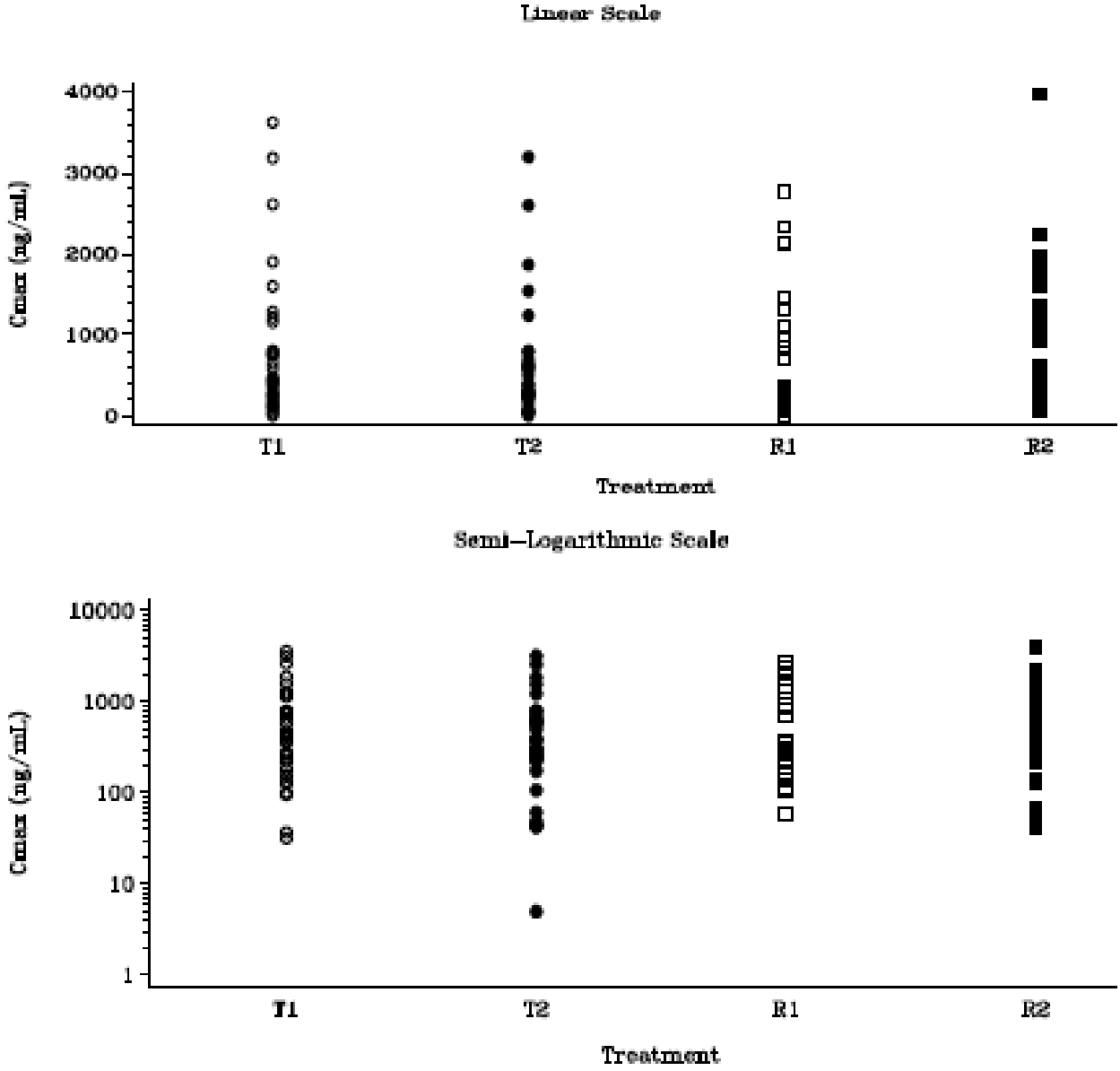
Source: CSR for Study SHP476-122, Figure 2 (page 51)
Abbreviations: 5-ASA, 5-aminosalicylic acid; SD, standard deviation

Table 52. Summary of Plasma 5-ASA Pharmacokinetic Parameters

Treatment	n	C_{max} (ng/mL)	t_{max} (h)	t_{lag} (h)	AUC_{0-t} (ng·h/mL)	AUC_{8-48} (ng·h/mL)
			Mean (SD) [Geometric Mean]			
2 × 600 mg tablets	71[a]	669 (794) [NC]	13.7 (8.3) [11.6]	5.9 (4.3) [4.8]	4522 (3141) [NC]	3479 (2419) [NC]
1 × 1.2 g tablet	70[b]	687 (788) [NC]	14.2 (8.3) [12.1]	5.0 (3.5) [4.2]	4621 (3346) [NC]	3697 (2806) [NC]
			Bioequivalence Assessment			
S_{WR}		0.8660	NC	NC	0.6460	0.7619
Geo Mean Test/Ref		0.9730	NC	NC	0.9036	0.8783
95% Upper CI $(\bar{Y}_T-\bar{Y}_R)^2-\theta\bullet S^2_{WR}$		-0.3878	NC	NC	-0.1841	-0.2688

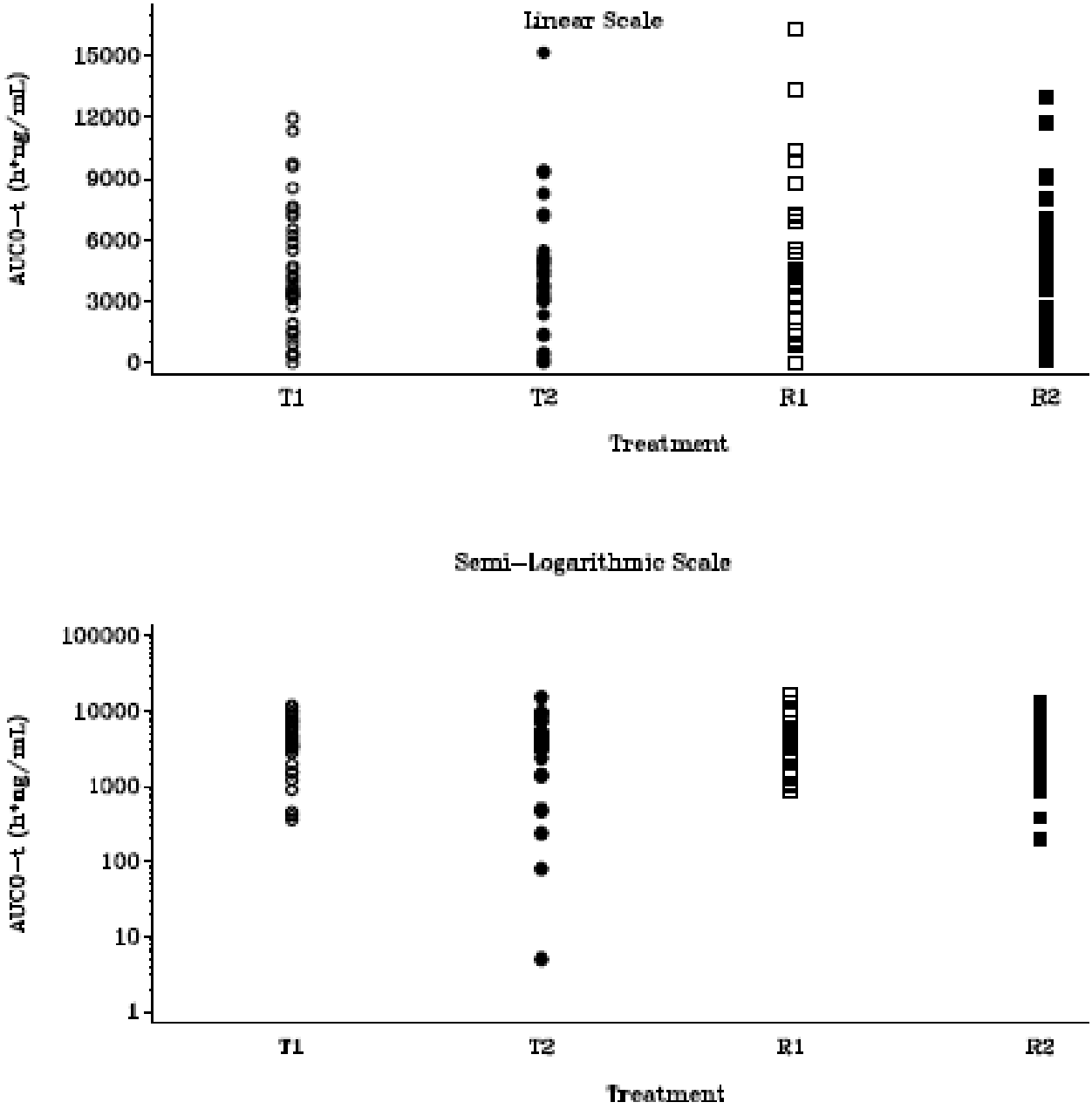
Source: CSR for Study SHP476-122, Table 8 (page 54)
Several of the plasma concentrations for 5-ASA versus time profiles did not exhibit a log-linear decline due to expected low or variable plasma concentrations, and λ_z, $t_{1/2}$, and $AUC_{0-\infty}$ could not be estimated for these profiles. Values are presented as mean (SD) and [geometric mean].
Two pharmacokinetic data-points were excluded from the noncompartmental analysis; 96 hours for Subject (b) (6) (treatment period 3) as the pharmacokinetic profile was observed to have terminated after the 16-hour time point and 26-hour time point for Subject (b) (6) (treatment period 1) as no actual time relative to dosing could be derived (blood sample collection data and time missing); Subject (b) (6) terminated early from the study at approximately 26 hours during Treatment Period 1 and was included in the bioequivalence analysis.
[a] n=70 for t_{max} and t_{lag}
[b] n=67 for t_{max} and t_{lag}
Abbreviations: 5-ASA, 5-aminosalicylic acid; AUC_{0-t}, area under the curve from the time of dosing to the last measurable concentration; AUC_{8-48}, area under the curve from 8 to 48 hours after administration; CI, confidence interval; C_{max}, maximum observed concentration occurring at t_{max}; NC, not calculated; SD, standard deviation; S_{WR}, intrasubject variability; t_{lag}, absorption lag time; t_{max}, time of maximum observed concentration sampled during a dosing interval

Figure 14. Individual 5-ASA Plasma C_{max} Values Vs. Treatment



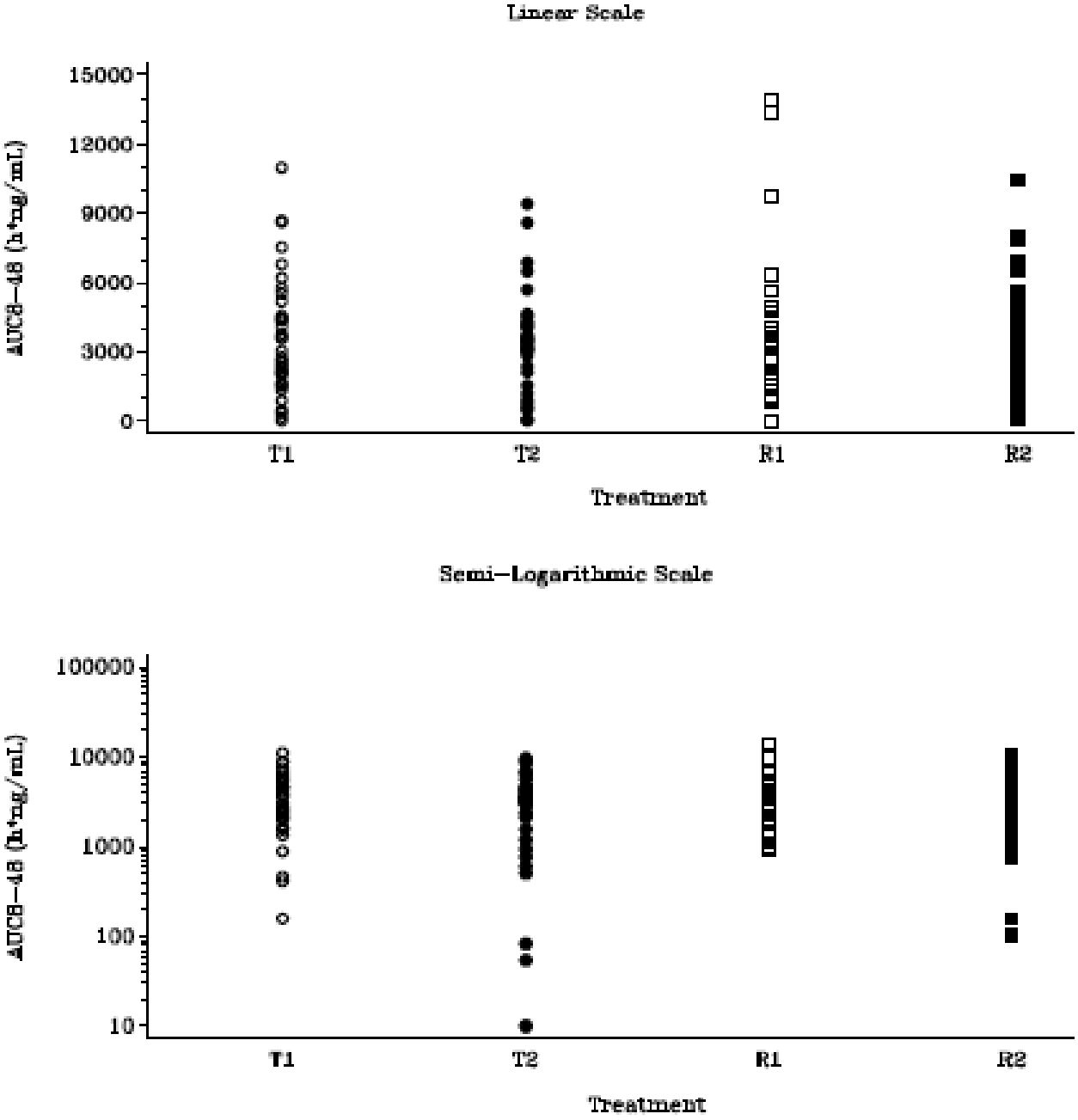
Source: CSR for Study SHP476-122, Figure 14.2.3.4 (page 452)
Treatment T: SHP476 (PO) 2 x 600-mg tablets (test); Treatment R: SHP476 (PO) 1 x 1.2-g tablet (reference); T1 and T2 are first and second administration of Treatment T, respectively; R1 and R2 are first and second administration of Treatment R, respectively.
Abbreviations: 5-ASA, 5-aminosalicylic acid; C_{max}, maximum concentration

Figure 15. Individual 5-ASA Plasma AUC_{0-t} Values Vs. Treatment



Source: CSR for Study SHP476-122, Figure 14.2.3.5 (page 453)
Treatment T: SHP476 (PO) 2 x 600-mg tablets (test); Treatment R: SHP476 (PO) 1 x 1.2-g tablet (reference); T1 and T2 are first and second administration of Treatment T, respectively; R1 and R2 are first and second administration of Treatment R, respectively.
Abbreviations: 5-ASA, 5-aminosalicylic acid; AUC_{0-t}, area under the curve from the time of dosing to the last measurable concentration

Figure 16. Individual 5-ASA Plasma AUC_{8-48} Values Vs. Treatment



Source: CSR for Study SHP476-122, Figure 14.2.3.6 (page 454)
Treatment T: SHP476 (PO) 2 x 600-mg tablets (test); Treatment R: SHP476 (PO) 1 x 1.2-g tablet (reference); T1 and T2 are first and second administration of Treatment T, respectively; R1 and R2 are first and second administration of Treatment R, respectively.
Abbreviations: 5-ASA, 5-aminosalicylic acid; AUC_{8-48}, area under the curve from 8 to 48 hours after administration

Reviewer's Comments

PK profiles

- *Both treatments had similar overall mean 5-ASA plasma concentration profiles and both treatments had multiple peaks.*
- *Similar to the previous studies, PK profile of 5-ASA were highly variable following both treatments.*
- *Following single-dose administration, t_{max} and t_{lag} (timepoint prior to the first quantifiable plasma concentration) were similar between the two treatments where t_{max} were reached around 14 hours where t_{lag} were around 5 to6 hours postdose. t_{max} and t_{lag} in this study was more delayed compared to what was reported for Lialda 1.2 g in healthy subjects in the current label.*

BE statistical results

- *All three primary PK parameters, C_{max}, AUC_{0-t}, and AUC_{8-48}, met the criteria for highly variable drug product (defined as SWR ≥0.294) with SWR values of 0.8660, 0.6460, and 0.7619, respectively. Therefore, use of SABE was appropriate for bioequivalence assessment in this study between these two treatments.*
- *The point estimate of the geometric mean test/reference ratio was within 80% to 125%, for all three PK parameters (97.30%, 90.36%, and 87.83% for C_{max}, AUC_{0-t}, and AUC_{8-48}, respectively.*
- *The 95% upper confidence limit of the SABE contrast $(\bar{Y}T-\bar{Y}R)2-\theta \bullet S2WR$ was ≤0 for all three PK parameters (−0.3878, −0.1841, and −0.2688 for C_{max}, AUC_{0-t}, and AUC_{8-48}, respectively).*
- *Therefore, the SABE criteria were met and the two treatments, pediatric SHP476 600-mg tablets (administered as 2×600-mg tablets) and SHP476 1.2-g tablets, are considered bioequivalent.*

Safety

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory test (hematology, clinical chemistry, urinalysis,) 12-lead ECG, and adverse event (AE) monitoring. According to the Applicant, there was no death or SAE or adverse events resulting in the study drug discontinuation. Incidences of TEAEs were comparable in both treatment groups: six (16.7%) subjects in the SHP476 2×600-mg treatment group and seven (20%) subjects in the SHP476 1×1.2-g treatment group).

Overall, 14 TEAEs were reported by 13 subjects (36.1%) all of which were mild in severity. One TEAE in one (2.8%) subject was of moderate severity following administration of SHP476, 2×600 mg tablets. All TEAEs reported during the treatment period were considered to be related to the Lialda by the investigator and were nonserious. The most frequently reported TEAEs during the treatment period were in the system organ class of nervous system disorders (nine [25.0%] subjects). Overall, the most commonly reported TEAEs were headache (nine [25.0%] subjects), dry mouth (three [8.3%] subjects), and flatulence (two [5.6%] subjects). There were no clinically important findings noted in the safety clinical laboratory, vital sign, or ECG data.

15.3.3.3. Study SHP476-319

Title

A Phase 3, Multicenter, Randomized, Double-Blind Study to Determine the Safety and Efficacy of MMX Mesalamine/Mesalazine in Pediatric Subjects With Mild to Moderate Ulcerative Colitis, in Both Acute and Maintenance Phases

Clinical site: Multicenter study
Bioanalytical site: (b) (4)
Study date: December 12, 2014, to November 28, 2018

Primary Objectives

The primary objective of the double-blind acute phase of the study is to assess clinical response to multi-matrix system (MMX) mesalamine/mesalazine between a low and high dose in children and adolescents aged 5 to 17 years with mildly to moderately active UC.

The primary objective of the double-blind maintenance phase of the study is to assess clinical response to MMX mesalamine/mesalazine between a low and high dose in children and adolescents aged 5 to 17 years with mildly to moderately active UC.

Study Design

This is a prospective phase 3, multicenter, randomized, double-blind, parallel-group study to determine the safety and efficacy of MMX mesalamine/mesalazine in pediatric subjects with mildly to moderately active UC with an 8-week DBA phase, and a 26-week double-blind maintenance (DBM) phase. Each phase includes two arms and subjects will be randomized to one of two doses (low or high) of MMX mesalamine/mesalazine (900 to 4,800 mg/day, given once daily) at the beginning of each phase. Randomization will be in a 1:1 ratio stratified by body weight group.

- Test product (T): MMX mesalamine/mesalazine tablets were provided in dosages of 300, 600, and 1,200 mg with matching placebos. The lower-strength 300-mg and 600-mg tablets were Gen 2 (b) (4) formulation.

Dosing Regimen

MMX mesalamine/mesalazine, administered orally, once daily with food without crushing or chewing. Patients were randomized in a 1:1 ratio stratified by body weight group to the following doses:

- 900 mg/day or 1,200 mg/day for subjects weighing 18 to ≤23 kg
- 1,200 mg/day or 2,400 mg/day for subjects weighing >23 to ≤35 kg
- 1,200 mg/day or 3,600 mg/day for subjects weighing >35 to ≤50 kg
- 2,400 mg/day or 4,800 mg/day for subjects weighing >50 to ≤90 kg

Study Population

The study enrolled 105 pediatric patients with UC aged 5 to 17 years with body weight of 18 to 90 kg at the screening visit. Subjects with any history of moderate to severe renal impairment and any history of hepatic impairment were excluded from the study.

PK Measurements

Sparse PK samples were collected at Weeks 8 and 26 determination of 5-ASA and its major metabolite acetyl-5-ASA concentrations in plasma. The PK sampling time in relation to dosing was not specified.

PK Parameters and Statistical Analysis

Due to sparse PK sampling, no formal PK analysis was conducted. The plasma concentrations of 5-ASA and Ac-5-ASA were summarized by treatment and visit using descriptive statistics.

The sparse PK plasma concentration data from this Study SPD476-319 were pooled with the plasma concentration data from Study SPD476-112 to update the original population pharmacokinetic analysis.

Bioanalytical Method

Concentrations of 5-ASA and Ac-5-ASA in human plasma were measured by a validated LC/MS/MS at (b) (4). The plasma assay range was from 5.00 to 5000 ng/mL for 5-ASA and Ac-5-ASA, and the lower limit of quantitation (LLOQ) was 5.00 ng/mL for both analytes.

Results

Pharmacokinetics

Table 53. Summary of Plasm Concentration During Double-Blind Acute Phase by Treatment Arm (Double-Blind Acute Phase Safety Analysis Set)

Parameter	Low-dose MMX (N=27)	High-dose MMX (N=26)
5-ASA (ng/mL)		
n	12	15
Mean (SD)	717.7 (795.15)	2542.9 (2961.89)
CV	110.80	116.48
Median	433.5	1450.0
Q1, Q3	56.8, 1225.0	866.0, 3140.0
Min, Max	0, 2280	0, 11100
AC-5-ASA (ng/mL)		
n	12	15
Mean (SD)	1190.5 (1080.97)	2579.7 (1836.07)
CV	90.80	71.17
Median	1001.5	2290.0
Q1, Q3	157.5, 1965.0	1230.0, 3690.0
Min, Max	0, 3510	33, 6250

Source: CRP SPD476-319, Table 14.2.3.1.1
Abbreviations: 5-ASA, 5-aminosalicylic acid; CV, coefficient of variation; MMX, multi-matrix system; Q1, quartile 1; Q3, quartile 3; SD, standard deviation

Table 54. Summary of Plasma Concentration During Double-Blind Maintenance Phase by Treatment Arm (Double-Blind Maintenance Phase Safety Analysis Set)

Parameter	Low-dose MMX (N=42)	High-dose MMX (N=45)
5-ASA (ng/mL)		
n	25	29
Mean (SD)	1445.8 (1743.85)	2738.5 (2447.57)
CV	120.61	89.38
Median	901.0	2340.0
Q1, Q3	78.7, 1880.0	569.0, 3970.0
Min, Max	0, 6280	0, 8180
AC-5-ASA (ng/mL)		
n	25	29
Mean (SD)	1980.1 (2197.50)	2964.4 (2364.53)
CV	110.98	79.76
Median	1240.0	2380.0
Q1, Q3	273.0, 2860.0	1390.0, 4440.0
Min, Max	0, 7790	0, 9150

Source: CRP SPD476-319, Table 14.2.3.1.3
Abbreviations: 5-ASA, 5-aminosalicylic acid; CV, coefficient of variation; MMX, multi-matrix system; Q1, quartile 1; Q3, quartile 3; SD, standard deviation

15.3.3.4. Study SHP476-112

Title

A Phase 1, Multicenter, Open-Label Study to Determine the Safety and Pharmacokinetics of MMX Mesalamine Following Administration in Children and Adolescents With Ulcerative Colitis

Clinical site: Multicenter study conducted in 12 sites across 3 countries (i.e., U.S., Poland, and Slovakia)
Bioanalytical site: (b) (4)
Study date: October 8, 2010, to June 27, 2013

Primary Objectives

To assess the pharmacokinetics of 5-ASA (mesalamine/mesalazine) and its major metabolite acetyl-5-aminosalicylic acid (Ac-5-ASA) after administration of MMX mesalamine at three different doses (30, 60, 100 mg/kg/day) for 7 days in children and adolescents with a history of ulcerative colitis (UC).

Study Design

This was a phase 1, multicenter, randomized, open-label, three-arm study stratified by body weight to evaluate the PK of 5-ASA and its major metabolite Ac-5-ASA after administration of SPD476 for 7 days in children and adolescents diagnosed with UC.

- Test product (T): SPD476 oral tablets containing 300 mg, 600 mg, or 1,200 mg of mesalamine SPD476 is a (b) (4) formulation of 5-ASA (30, 60, or 120 mg of mesalamine per tablet), which uses MMX technology designed to release 5-ASA throughout the colon.

Dosing Regimen

Subjects received a dose of approximately 30, 60, or 100 mg/kg per day (up to a maximum dose of 4,800 mg per day), as achievable by the nearest and most appropriate combination of the available dosage strengths (300, 600, and/or 1,200 mg). The total daily dose ranged from 900 to 4,800 mg per day.

Randomization was stratified by body weight (18 to 24 kg, 25 to 49 kg, and 50 to 82 kg).

- 18 to 24 kg were randomized to either 60 mg/kg (n=1) or 100 mg/kg (n=2)
- 25 to 49 kg were randomized to one of three doses, 30, 60, or 100 mg/kg
- 50 to 82 kg were randomized to 30 or 60 mg/kg

Subjects took a dose of Lialda every morning for 7 days and on Day 7 had blood and urine pharmacokinetic samples taken and safety assessments performed during the 24 hours postdose.

On Days 1 through 4, the Lialda dosage was taken at home. On Days 5, 6, 7 and 8, patients received standardized moderate fat meal and dosing occurred within 30 minutes after breakfast.

Study Population

The study enrolled pediatric UC patients aged 5 to 17 years. A total of 52 subjects were randomized (21 subjects in the 30 mg/kg dose group, 22 subjects in the 60 mg/kg dose group, and nine subjects in the 100 mg/kg dose group). All subjects completed the study.

Table 55. Patient Enrollment by Age Group, Study SHP476-112

Randomized subjects	SPD476 30 mg/kg	SPD476 60 mg/kg	SPD476 100 mg/kg	SPD476 All Doses
5-12 years	5	4	7	16
13-17 years	16	18	2	36

Source: CSR Study SHP476-112

Subjects with any history of moderate to severe renal impairment (glomerular filtration rate <60 mL/min/1.73m²) and any history of hepatic impairment were excluded from the study.

PK Measurements

Blood samples (2mL/sample) for measurement of plasma concentrations of 5-ASA and its major metabolite Ac-5-ASA were collected predose on treatment Days 5 and 6 and at the following time points on Day 7: predose, 2, 4, 6, 9, 12, 16, and 24 hours after dosing.

A complete 0- though 24-hour urine collection starting within 30 minutes before the morning meal on Day 7 until the final void scheduled for 30 minutes before the morning meal was collected on Day 8.

In case any subject reported an SAE, diligent efforts were to be made to collect a blood sample for quantification of 5-ASA and Ac-5-ASA, regardless of the relationship to Lialda for determination of urinary excretion of 5-ASA and Ac-5-ASA.

PK Parameters and Statistical Analysis

PK parameters of 5-ASA and Ac-5-ASA were derived based on plasma concentration-time data (actual sampling times) using noncompartmental PK analysis. Achievement of steady-state was assessed by visual inspection of predose plasma concentrations on Days 5, 6, and 7.

Additionally, the 5-ASA and Ac-5-ASA plasma concentration data were used to develop a population pharmacokinetic model to describe the relationship between the pharmacokinetic

parameters and potential explanatory covariates (e.g., age, weight, sex, etc.). This population pharmacokinetic model was used to simulate the expected 5-ASA and Ac-5-ASA plasma concentration profiles in a broader population of children and adolescents receiving 30- 60-, or 100-mg/kg doses of SPD476 for comparison with historical plasma concentration data in adults.

Bioanalytical Method (Bioanalytical Report A3046M-SPD476):

- Concentrations of 5-ASA and Ac-5-ASA in human plasma and urine were measured by a validated LC/MS/MS at [redacted] According to the validation reports:
  - Validation of an Analytical Method for the Determination of 5-Aminosalicylic Acid and N-Acetyl-5-Aminosalicylic Acid in Human Plasma Using Protein Precipitation for Sample Preparation and Liquid Chromatography with Tandem Mass Spectrometric Detection, [redacted] study number [redacted]064, May 15, 2006.
  - Validation of an Analytical Method for the Determination of 5-Aminosalicylic Acid and N-Acetyl-5-Aminosalicylic Acid in Human Urine Using Liquid Chromatography with Tandem Mass Spectrometric Detection, [redacted] study number [redacted]063, May 15, 2006.
- Plasma and urine samples were stored frozen at -80°C until analysis. Samples were collected from Dec. 27, 2010, through June 22, 2013. PK samples were analyzed between Feb. 23, 2011 and July 5, 2013. Maximum time from sample collection to sample analysis were 224 days for plasma samples and 226 days for urine samples. Both plasma and urine PK samples were assayed within the established long-term samples stability of 322 days at -80°C for plasma samples and 12 months at -80°C for urine samples.
- The plasma assay range was from 5.00 to 5000ng/mL for 5-ASA and Ac-5-ASA, and the LLOQ was 5.00ng/mL for both analytes. The urine assay range was from 5.00 to 1000 µg/mL for 5-ASA and Ac-5-ASA, and the LLOQ was 5.00 µg/mL for both analytes.
- Calibration standard curve consisted of 8 levels ranged from 5.0 to 5000 ng/mL in human plasma and ranged from 5 to 1000ug/mL in urine and was calculated using a linear regression with (1/concentration squared weighted) algorithm.
- QC samples at four different concentrations (12.5, 2500, 4000, and 100000 ng/mL in plasma and 15.0, 400, 800, and 2000 µg/mL in urine) of 5-ASA and Ac-5-ASA were prepared. The inter-assay accuracy and precision data for the QC samples at 4 concentrations across all analytical met the predefined acceptance criteria.
- The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.

Table 56. ISR by Analyte/Matrix, Study SHP476-112

Analyte Matrix	% of Samples for ISR	Passed ISR
5-ASA		
Plasma	5.0% (52/1030)	Yes
Urine	6% (6/101)	Yes
Ac-5-ASA		
Plasma	5.0% (52/1030)	Yes
Urine	6% (6/101)	Yes

Source: Appendix 16.2.5.2 Bioanalytical Report A3046M-SPD476
Abbreviations: 5-ASA, 5-aminosalicylic acid; ISR, incurred sample repeat

Table 57. Assay Performance of 5-ASA and Ac-5-ASA Bioanalytical Quality Control Samples in Human Plasma

Analyte	5-ASA and Ac-5-ASA Nominal Concentration		
Parameter	Low QC (12.5ng/mL)	Mid QC (2500ng/mL)	High QC (4000ng/mL)
5-ASA			
%CV	7.6	5.3	5.0
%Bias	0.0	1.6	-0.8
Ac-5-ASA			
%CV	10.1	4.8	7.7
%Bias	2.4	5.2	3.3

Source: CSR for Study SHP476-112, Table 9 (page 60) & Appendix 16.2.5.2 Bioanalytical Report A3046M-SPD476
Abbreviations: 5-ASA, 5-aminosalicylic acid; CV, coefficient of variation; QC, quality control

Table 58. Assay Performance of 5-ASA and Ac-5ASA Bioanalytical Quality Control Samples in Human Urine

Analyte	5-ASA and Ac-5-ASA Nominal Concentration		
Parameter	Low QC (15.0µg/mL)	Mid QC (400µg/mL)	High QC (800µg/mL)
5-ASA			
%CV	6.7	11.7	8.2
%Bias	-1.3	-5.5	-4.0
Ac-5-ASA			
%CV	10.2	9.0	7.6
%Bias	4.0	1.0	-1.4

Source: CSR for Study SHP476-112, Table 10 (page 61) & Appendix 16.2.5.2 Bioanalytical Report A3046M-SPD476
Abbreviations: 5-ASA, 5-aminosalicylic acid; CV, coefficient of variation; QC, quality control

Results

Pharmacokinetics

5-aminosalicylic acid

The mean predose concentrations on Days 5, 6, and 7 suggest that that pharmacokinetic steady-state was reached by Day 5 for all doses in pediatric patients (Table 59).

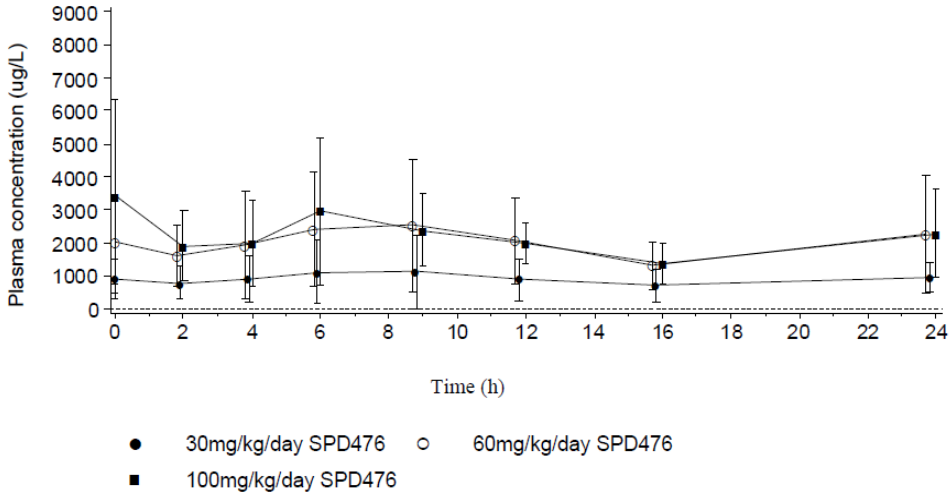
Table 59. Arithmetic Mean (%CV) of Plasma 5-ASA Concentrations (µg/L) Following Multiple Doses of SPD476 (30, 60, or 100 mg/kg Once Daily) for 7 Days in Children (5 to 12 Years) and Adolescents (13 to 17 Years) With a History of Ulcerative Colitis

Dose Age group	Day 5 Predose	Day 6 Predose	Day 7 Predose	Day 7 2 h	Day 7 4 h	Day 7 6 h	Day 7 9 h	Day 7 12 h	Day 7 16 h	Day 7 24 h
30 mg/kg										
All (n=21)	1,145 (75.2%)	999 (59.2%)	926 (66%)	784 (61%)	899 (77.4%)	1,119 (86.8%)	1,123 (98.9%)	906 (70%)	709 (68.8%)	976 (47%)
5-12 years (n=5)	1,327 (109%)	842 (921.2%)	683 (54.7%)	683 (67.7%)	888 (85.7%)	1,052 (118%)	281 (80.5%)	406 (75.5%)	306 (74.4%)	893 (59.4%)
13-17 year (n=16)	1,089 (59.2%)	1,048 (52.1%)	1,001 (65.9%)	810 (61%)	902 (78.3%)	1,140 (80.6%)	1,386 (82.9%)	1,062 (59.7%)	835 (57.8%)	1,001 (44.9%)
60 mg/kg										
All (n=22)	2,327 (75.5%)	2,344 (80.5%)	2,016 (62.7%)	1,617 (58.5%)	1,951 (84.6%)	2,144 (71.9%)	2,539 (78.7%)	2,061 (63%)	1,311 (54.8%)	2,258 (79.2%)
5-12 years (n=4)	3,082 (95.4%)	2,848 (61.7%)	1,732 (90.9%)	1,371 (109%)	1,443 (121%)	1,640 (87.7%)	1,540 (89.9%)	1,290 (70.9%)	1,011 (104%)	2,309 (62%)
13-17 years (n=18)	2,159 (67.4%)	2,232 (87.1%)	2,079 (59.2%)	1,672 (50%)	2,064 (80.4%)	2,583 (69%)	2,774 (74.9%)	2,232 (57.2%)	1,378 (46.9%)	2,247 (84.3%)
100 mg/kg										
All (n=9)	3,472 (89.9%)	2,558 (73.4%)	3,418 (86.3%)	1,907 (55.6%)	2,001 (65.8%)	2,959 (75.5%)	2,376 (46.9%)	1,976 (31.4%)	1,389 (43.3%)	2,276 (58.7%)
5-12 years (n=7)	4,206 (75.7%)	2,712 (78.9%)	3,891 (82.6%)	1,957 (61.7%)	1,780 (49.1%)	3,353 (71.3%)	2,697 (38.8%)	2,191 (23.6%)	1,517 (41.6%)	2,348 (65.2%)
13-17 years (n=2)	902	2,020	1,755	1,730	2,775	1,582	1,250	1,220	943	2,025

Source: CSR for Study SHP476-112, Section 14, Table 2.1.1
Abbreviations: 5-ASA, 5-aminosalicylic acid

On Day 7, systemic exposure of 5-ASA, as measured by mean AUC_{SS} and C_{maxSS} increased in a dose-proportional manner between 30 and 60 mg/kg/day SPD476. However, SPD476 systemic exposure increased in a subproportional manner between 60 and 100 mg/kg/day, with mean AUC_{SS} and C_{maxSS} increasing by respectively 1.07 and 1.13-fold for the 1.66-fold dose increment. Intersubject variability was high where arithmetic coefficient of variation (CV%) for AUC_{SS} and C_{maxSS}, ranging from 36 to 52% and 52 to 60%, respectively (Table 60, Figure 17).

Figure 17. Mean (SD) Plasma Concentration-Time Profiles for 5-ASA in Children (5 to 12 Years) and Adolescents (13 to 17 Years) With a History of Ulcerative Colitis Following 7 Days of Treatment With SPD476 (30, 60, or 100 mg/kg/day) by Treatment Group



Source: CSR for Study SHP476-112, Figure 2 (page 62)
Abbreviations: 5-ASA, 5-aminosalicylic acid; SD, standard deviation

Table 60. Arithmetic Mean (%CV) Pharmacokinetic Parameters of 5-ASA in Children (5 to 12 Years) and Adolescents (13 to 17 Years) With a History of Ulcerative Colitis Following 7 Days of Treatment Once-Daily Dosing With SPD476 (30, 60, or 100 mg/kg/day)

Age Group Parameter	SPD476 30 mg/kg/day	SPD476 60 mg/kg/day	SPD476 100 mg/kg/day
All (children + adolescents)			
N	N=21	N=22	N=9
AUC_{SS} (µg.h/L)	21411 (51.8%)	46173 (49.5%)	49213 (35.9%)
C_{maxSS} (µg/L)	1884 (54%))	3825 (51.8%)	4314 (60.3%)
t_{max}[a] (h)	6.00 (0.00, 24.0)	8.98 (0.00, 24.0)	1.98 (0.00, 24.0)
$Xu_{0\text{-}24\ h}$ (mg)	162 (81.4%)	298 (74.2%)	235 (51.4%)
CL_R (L/h)	6.48 (46.2%)	5.94 (50.0%)	4.95 (41.8%)
% Dose absorbed	29.4[b] (49.4%)	27.0 (50.0%)	22.1 (61.5%)
Children (5-12 years)			
N	N=5	N=4	N=7
AUC_{SS} (µg.h/L)	13575 (37.1%)	35599 (75.7%)	52882 (34.6%)
C_{maxSS} (µg/L)	1544 (63.8%)	2883 (49.9%)	4664 (58.6%)
t_{max}[a] (h)	11.5 (1.97-23.9)	14.4 (4-24)	7.70 (0-24)
$Xu_{0\text{-}24\ h}$ (mg)	74.1 (90.8%)	178 (88.8%)	226 (59.1%)
CL_R (L/h)	4.67 (61.6%)	4.06 (74.7%)	4.3 (42.9%)
% Dose Absorbed	24.3 (38.2%)	29.3 (69.4%)	23.7 (64%)

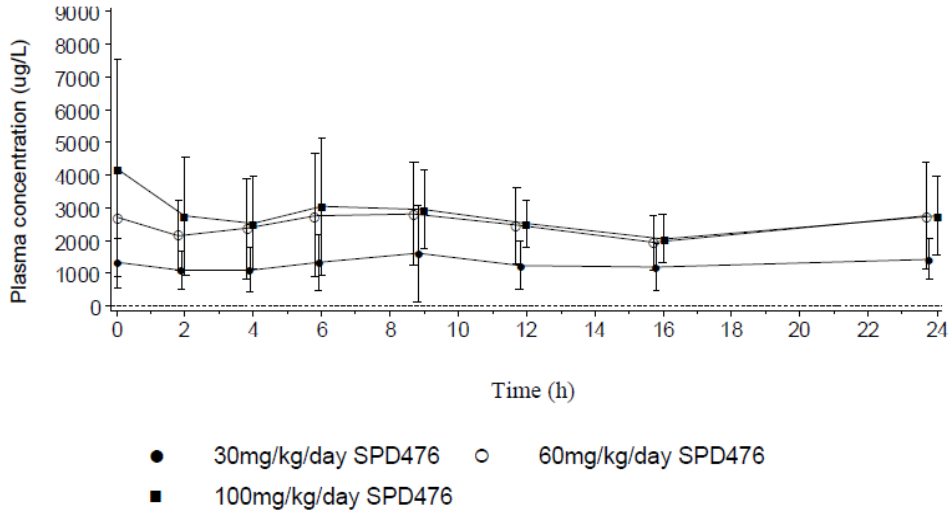
Age Group Parameter	SPD476 30 mg/kg/day	SPD476 60 mg/kg/day	SPD476 100 mg/kg/day
Adolescents (13-17 years)			
N	N=16	N=18	N=2
AUC_{SS} (µg.h/L)	23859 (47.8%)	48522 (45.4%)	36372 (NC)
C_{maxSS} (µg/L)	1990 (52.1%)	4034 (50.9%)	3090 (NC)
t_{max}[a] (h)	9.47 (0-24)	11.1 (0-24)	2.99 (1.98-4.00)
$Xu_{0\text{-}24\ h}$ (mg)	189 (72%)	325 (70.1%)	266 (NC)
CL_R (L/h)	7.04 (40.9%)	6.36 (44.7%)	7.25 (NC)
% Dose Absorbed	36.5 (72.4%)	26.5 (46.4%)	16.4 (NC)

Source: CSR for Study SHP476-112, Table 11 (page 66) and section 14, Table 2.1.3 and Table 2.1.4.
[a] Median (min, max)
[b] N=20; exclusion of outlier from summary statistics.
Abbreviations: 5-ASA, 5-aminosalicylic acid; AUC_{SS}, area under the curve for the defined interval between doses (tau =24h); C_{maxSS}, maximum concentration occurring at t_{max}; CL_R, clearance of a substance from the blood by the kidneys; NC, not calculated; t_{max}, time to reach maximum concentration; $Xu_{0\text{-}24h}$, cumulative amount recovered in urine in the time interval 0 to 24 hours

Acetyl-5-aminosalicylic acid

Similar to its parent drug, systemic exposure of Ac-5-ASA, as measured by mean AUC_{SS} and C_{maxSS} increased in a dose-proportional manner between 30 and 60 mg/kg/day SPD476, increased in a subproportional manner between 60 and 100 mg/kg/day SPD476 on Day 7. In general, Ac-5-ASA had moderate to high between-subject variability where CV% for AUC_{SS} and C_{maxSS}, ranging from 35 to 44% and 40 to 59%, respectively (Figure 18 and Table 61).

Figure 18. Mean (Standard Deviation) Plasma Concentration-Time Profiles for Ac-5-ASA in Children (5 to 12 Years) and Adolescents (13 to 17 Years) With a History of Ulcerative Colitis Following 7 Days of Treatment With SPD476 (30, 60, or 100 mg/kg/day) by Treatment Group



Source: CSR for Study SHP476-112, Figure 4 (page 67)
Abbreviations: 5-ASA, 5-aminosalicylic acid

Table 61. Arithmetic Mean (SD) Pharmacokinetic Parameters of Ac-5-ASA in Children (5 to 12 Years) and Adolescents (13 to 17 Years) With a History of Ulcerative Colitis Following 7 Days of Treatment With SPD476 (30, 60, or 100 mg/kg/day)

Parameter	SPD476 30 mg/kg/day N=21	SPD476 60 mg/kg/day N=22	SPD476 100 mg/kg/day N=9
AUC_{SS} (µg.h/L)	30942 (13743)	58119 (22729)	63067 (21752)
C_{maxSS} (µg/L)	2396 (1217)	4113 (1641)	4968 (2911)
t_{max}[a] (h)	9.00 (0.00, 24.0)	7.48 (0.00, 24.0)	1.98 (0.00, 24.0)
$Xu_{0\text{-}24\ h}$ (mg)	532 (411)	708 (341)	593 (251)
CL_R (L/h)	16.2 (6.72)	12.2 (4.43)	10.0 (4.36)
MR AUC_{SS}	1.56 (0.422)	1.34 (0.244)	1.31 (0.219)
MR C_{maxSS}	1.37 (0.409)	1.15 (0.247)	1.18 (0.223)

Source: CSR for Study SHP476-112, Table 12 (page 72)
[a] Median (min, max)
Abbreviations: 5-ASA, 5-aminosalicylic acid; AUC_{SS}, area under the curve for the defined interval between doses (tau =24h); C_{maxSS}, maximum concentration occurring at t_{max}; CL_R, clearance of a substance from the blood by the kidneys; MR AUC_{SS}, metabolic ratio (Ac-5-ASA/5-ASA) calculated using the AUC_{SS}; MR C_{maxSS}, metabolic ratio (Ac-5-ASA/5-ASA) calculated using the C_{maxSS}; SD, standard deviation; t_{max}, time to reach maximum concentration; $Xu_{0\text{-}24h}$, cumulative amount recovered in urine in the time interval 0 to 24 hours

Safety

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory test (hematology, clinical chemistry, urinalysis,) 12-lead ECG, and adverse event (AE) monitoring. According to the Applicant, there were no deaths, other serious TEAEs, or TEAEs leading to discontinuation reported during this study.

Overall, 10 subjects (19.2%) experienced at least one TEAE. The incidence was similar in the different dose groups: four subjects (19.0%), four subjects (18.2%), and two subjects (22.2%) in the 30, 60, and 100 mg/kg/day dose groups, respectively, experienced at least one TEAE. There were no serious TEAEs. No subjects experienced TEAEs leading to premature discontinuation. Two subjects (3.8%), one (4.8%) of whom was in the 30-mg/kg/day dose group and one (4.5%) in the 60-mg/kg/day dose group, experienced a TEAE that was considered related to Lialda by the investigator. The most commonly reported TEAEs were abdominal pain, musculoskeletal pain, and headache, each reported for two subjects (3.8%) overall (one subject [4.8%] in the 30-mg/kg/day dose group and one subject [4.5%] in the 60-mg/kg/day dose group). The majority of TEAEs were considered to be mild in severity (8/10 subjects with TEAEs [80.0%]). Two subjects experienced TEAEs considered moderate in intensity. There were no clinically important findings noted in the safety clinical laboratory, vital sign, or ECG data.

Overall, SPD476, administered as a 30-, 60-, or 100-mg/kg dose was generally well tolerated. The types and frequencies of TEAEs, clinical laboratory abnormalities, and other safety parameters were comparable between dose and age groups.

Reviewer's Comments and Conclusion

- *Steady state for 5-ASA appears to be reach by Day 7 following daily dose in pediatric patients.*
- *At steady state on Day 7, systemic exposure of both the parent 5-ASA and metabolite Ac-5-ASA (measured by mean AUC_{SS} and C_{maxSS}) increased in a dose-proportional manner between 30 and 60 mg/kg/day and increased in a subproportional manner between 60- and 100-mg/kg/day dose.*

- *AUC and C_{max} of parent 5-ASA and metabolite Ac-5-ASA PK had moderate to high intersubject variably, with arithmetic CV% values ranging from 36 to 52% and 40 to 60%, respectively.*
- *The exposure in adolescents (aged 13 to 17 years) appears to be higher than that of children (aged 5 to 12 years) for this weight-based (i.e., mg/kg) dosing paradigm.*

In this pediatric PK study, the doses were administered based on weight, 30, 60, or 100 mg/kg whereas the proposed dose in the label will be in fixed dose in each body weight group (1,200 mg to 4,800 mg). Because of this difference is dosing regimen, the Agency has requested the Applicant to provide PK parameters based on fixed dose in each age/body weight group.

Table 62. Steady-State 5-ASA PK Parameters for Pediatric Patients Receiving 1,200; 2,400; 3,600; or 4,800 mg/day (Study SPD476-112)

Subject #	Dose group (mg/kg)	Only 1,200 mg Tablet Formulation	BW (kg)	Age (yrs)	Age Group (yrs)	Dose (mg)	AUC_{SS} (ug.hr/L)	C_{maxSS} (ug/L)	CL_R (L/hr)	t_{max} (hr)	%Dose Abs
(b) (6)	100	Yes	48.0	12	5-12	4,800	50388	3700	5.09	0.00	20.1
	100	Yes	47.0	14	13-17	4,800	42189	4740	7.70	4.00	19
	100	Yes	50.0	15	13-17	4,800	30556	1440	6.80	1.98	13.9
	100	Yes	36.8	12	5-12	3,600	40436	2640	6.08	24.00	24.2
	100	Yes	34.9	9	5-12	3,600	24603	2530	2.85	0.00	7.4
	60	Yes	61.5	15	13-17	3,600	27336	1710	2.08	12.00	10.1
	60	Yes	59.0	14	13-17	3,600	78395	3820	7.06	5.98	38.5
	60		58.2	17	13-17	3,600	55365	4830	7.16	12.00	27.1
	60		61.0	16	13-17	3,600	101604	9470	9.14	8.98	60.4
	30	Yes	81.5	15	13-17	2,400	8252	888	6.02	9.10	12.9
	30		76.6	16	13-17	2,400	23787	1990	6.08	0.00	23.4
	100		23.0	7	5-12	2,400	43266	3310	4.48	6.03	22.3
	100		25.0	9	5-12	2,400	66818	10400	3.96	0.00	32.7
	60		21.54	6	5-12	1,200	9881	1940	0	23.8	3.61
	30		35	10	5-12	1,200	11245	1560	2.46	23.6	13.9
	30		38	13	13-17	1,200	19171	1830	7.8	23.8	43.3

Source: CSR for SPD476-112, Section 16.2.4, Listing 4.1 (Subject Demographics and Baseline Characteristics) and Section 16.2.5.1, Listing 5.7 (Individual Pharmacokinetic Parameters), Applicant's Response dated May 8, 2020 to a FDA Information Request

Abbreviations: 5-ASA, 5-aminosalicylic acid; AUC_{SS}, area under the curve for the defined interval between doses (tau =24h); BW, body weight; C_{maxSS}, maximum concentration occurring at t_{max}; CL_R, clearance of a substance from the blood by the kidneys; PK, pharmacokinetic; t_{max}, time to reach maximum concentration

This study was conducted with Gen 1 (b) (4) formulation. The phase 3 efficacy and safety studies in pediatric UC patients were conducted with Gen 2 (b) (4) formulation. However, the Applicant plans to market only the currently approved adult strength 1,200-mg tablets for the pediatric use.

No BE studies were conducted to compare the Gen 1 formulation used in this pediatric PK study to the approved 1.2-g tablet or to Gen 2 formulation. In vitro, according to the Applicant, both Gen 1 and Gen 2 (b) (4) formulations with 300-mg and 600-mg strength achieved similar dissolution profiles compared to 1.2-g tablets suggesting that formulation changes between Gen 1 and Gen 2 were not associated with change in dissolution rate. However, the dissolution profiles were not evaluated by the Agency. There is no direct PK comparison between these two generations of formulations.

In this pediatric PK study, pediatric patients who received 4,800 mg dose in this study had only received the currently marketed formulation 1.2-g tablets. Pediatric patients who received 3,600-mg; 2,400-mg; and 1,200-mg doses had received a mixture of Gen 1 (b) (4) formulation (300 mg and 600 mg) and currently marketed formulation 1.2-g tablets. Because of the difference in formulation, the Agency requested the Applicant to provide PK parameters for the pediatric patients who only received multiples of currently marketed formulation 1,200 mg tablet strength.

Table 63. Steady-State 5-ASA PK Parameters for Patients in Study SPD476-112 Receiving Multiples of the Currently Marketed Formulation 1,200-mg Tablet

TBM 1200 mg Tablets ONLY						5-ASA Pharmacokinetic Parameters				
Subj #	Dose Group (mg/kg)	BW (kg)	Age (yrs)	Age Grp (yrs)	Dose (mg)	AUCss (ug.hr/L)	Cmaxss (ug/L)	CLR (L/hr)	tmax (hr)	%Dose Abs
(b) (6)	100	36.8	12	5-12	3600	40436	2640	6.08	24.00	24.2
	100	34.9	9	5-12	3600	24603	2530	2.85	0.00	7.40
	100	48.0	12	5-12	4800	50388	3700	5.09	0.00	20.1
	100	47.0	14	13-17	4800	42189	4740	7.70	4.00	19.0
	60	61.5	15	13-17	3600	27336	1710	2.08	12.00	10.1
	60	59.0	14	13-17	3600	78395	3820	7.06	5.98	38.5
	30	81.5	15	13-17	2400	8252	888	6.02	9.10	12.9
	100	50.0	15	13-17	4800	30556	1440	6.80	1.98	13.9
MEAN		52.3				37769.4	2683.5	5.46		18.3
STDEV		14.0				19499.5	1239.8	1.89		9.2

Source: CSR SPD476-112, Section 16.2.4, Listing 4.1 (Subject Demographics and Baseline Characteristics) and Section 16.2.5.1, Listing 5.7 (Individual Pharmacokinetic Parameters), Applicant's response dated May 8, 2020, to a FDA Information Request
Abbreviations: 5-ASA, 5-aminosalicylic acid; AUC_{ss}, area under the curve for the defined interval between doses (tau =24h); BW, body weight; C_{maxss}, maximum concentration occurring at t_{max}; CLR, clearance of a substance from the blood by the kidneys; PK, pharmacokinetic; t_{max}, time to reach maximum concentration

Table 64. Steady-State Ac-5-ASA Parameters for Patients in Study SPD476-112 Receiving Multiples of Only the Currently Marketed Formulation 1,200 mg Tablet

TBM 1200 mg Tablets ONLY						Ac-5-ASA Pharmacokinetic Parameters				
Subj #	Dose Group (mg/kg)	BW (kg)	Age (yrs)	Age Grp (yrs)	5-ASA Dose (mg)	AUCss (ug.hr/L)	Cmaxss (ug/L)	Xu0-24 (mg)	CLR (L/hr)	tmax (hr)
(b) (6)	100	36.8	12	5-12	3600	51187	3160	796.0	15.60	24.00
	100	34.9	9	5-12	3600	35619	3490	250.0	7.02	0.00
	100	48.0	12	5-12	4800	87531	5880	902.0	10.30	0.00
	100	47.0	14	13-17	4800	49383	4850	745.0	15.10	4.00
	60	61.5	15	13-17	3600	37371	1970	392.0	10.50	12.00
	60	59.0	14	13-17	3600	91148	4480	1062.0	11.70	5.98
	30	81.5	15	13-17	2400	20844	2290	332.0	15.90	9.10
	100	50.0	15	13-17	4800	42572	1870	587.0	13.80	1.98
MEAN		52.3				51956.9	3498.8	633.3	12.49	
STDEV		14.0				23303.5	1370.4	272.3	2.94	

Source: CSR SPD476-112, Section 16.2.4, Listing 4.1 (Subject Demographics and Baseline Characteristics) and Section 16.2.5.1, Listing 5.7 (Individual Pharmacokinetic Parameters), Applicant's response dated May 8, 2020, to a FDA Information Request
Abbreviations: 5-ASA, 5-aminosalicylic acid; AUC_{SS}, area under the curve for the defined interval between doses (tau =24h); BW, body weight; C_{maxss}, maximum concentration occurring at t_{max}; CLR, clearance of a substance from the blood by the kidneys; PK, pharmacokinetic; t_{max}, time to reach maximum concentration; $Xu_{0\text{-}24h}$, cumulative amount recovered in urine in the time interval 0 to 24 hours

15.4. Supplemental Efficacy Tables

Table 65. Patient Disposition: DBA Phase (DBA Phase Safety Analysis Set)

Patient Disposition	Low-Dose MMX Mesalamine N=27 n (%)	High-Dose MMX Mesalamine N=26 n (%)	Overall N=53 n (%)
Completed DBA phase	19 (70.4)	22 (84.6)	41 (77.4)
Patients who did not continue in study	2 (7.4)	0	2 (3.8)
Patients who continued in study	17 (63.0)	22 (84.6)	39 (73.6)
Did not complete DBA phase	8 (29.6)	4 (15.4)	12 (22.6)
Patients who did not continue in study	6 (22.2)	0	6 (11.3)
Patients who continued in study	2 (7.4)	4 (15.4)	6 (11.3)
Primary reason for discontinuation during DBA phase			
Adverse event	1 (3.7)	0	1 (1.9)
Lack of efficacy	5 (18.5)	0	5 (9.4)

Source: SPD476-319 CSR Table 11 (p. 81)
Abbreviations: DBA, double-blind acute; MMX, multi-matrix system

Table 66. Patient Disposition: DBM Phase (DBM Phase Safety Analysis Set)

Patient Disposition	Low-Dose MMX Mesalamine N=42 n (%)	High-Dose MMX Mesalamine N=45 n (%)	Overall N=87 n (%)
Completed DBM phase	32 (76.2)	34 (75.6)	66 (75.9)
Did not complete DBM phase	10 (23.8)	11 (24.4)	21 (24.1)
Primary reason for discontinuation during DBM phase			
Adverse event	3 (7.1)	2 (4.4)	5 (5.7)
Lack of efficacy	6 (14.3)	7 (15.6)	13 (14.9)
Other	1 (2.4)	1 (2.2)	2 (2.3)
Missing	0	1 (2.2)	1 (1.1)

Source: SPD476-319 CSR Table 13 (p. 82)
Abbreviations: DBM, double-blind maintenance; MMX, multi-matrix system

Table 67. Demographic Characteristics: DBA Phase (DBA Phase Safety Analysis Set)

Demographic Characteristic	Low-Dose MMX Mesalamine N=27	High-Dose MMX Mesalamine N=26	Overall N=53
Age (years)			
n	27	26	53
Mean (SD)	13.6 (2.17)	14.4 (2.30)	14.0 (2.25)
Median	14.0	15.0	14.0
Min, max	8, 17	7, 17	7, 17
Age category, n (%)			
5 to 10 years	2 (7.4)	2 (7.7)	4 (7.5)
11 to 17 years	25 (92.6)	24 (92.3)	49 (92.5)
Sex, n (%)			
Male	16 (59.3)	18 (69.2)	34 (64.2)
Female	11 (40.7)	8 (30.8)	19 (35.8)
Race, n (%)			
White	25 (92.6)	24 (92.3)	49 (92.5)
Black or African American	1 (3.7)	0	1 (1.9)
Asian	1 (3.7)	2 (7.7)	3 (5.7)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not-Hispanic or Latino	27 (100.0)	26 (100.0)	53 (100.0)
Weight (kg)			
n	27	26	53
Mean (SD)	52.8 (12.92)	52.6 (13.09)	52.7 (12.88)
Median	53.1	53.4	53.1
Min, max	32, 74	29, 79	29, 79
Weight group (kg) n (%)			
18 to ≤23	0	0	0
>23 to ≤35	4 (14.8)	3 (11.5)	7 (13.2)
>35 to ≤50	7 (25.9)	7 (26.9)	14 (26.4)
>50 to ≤90	16 (59.3)	16 (61.5)	32 (60.4)
Height (cm)			
n	27	26	53
Mean (SD)	161.6 (12.35)	164.4 (13.73)	163.0 (13.00)
Median	165.0	164.5	165.0
Min, max	133, 182	124, 185	124, 185

Source: SPD476-319 CSR Table 14.1.4.1.2 (p. 192), Table 14.1.4.2.2 (p. 200)
Abbreviations: DBA, double-blind acute; MMX, multi-matrix system; SD, standard deviation

Table 68. Demographic Characteristics: DBM Phase (DBM Phase Safety Analysis Set)

Demographic Characteristic	Low-Dose MMX Mesalamine N=42	High-Dose MMX Mesalamine N=45	Overall N=87
Age (years)			
n	42	45	87
Mean (SD)	14.3 (2.17)	14.2 (2.88)	14.2 (2.55)
Median	15.0	15.0	15.0
Min, max	8, 17	5, 17	5, 17
Age category, n (%)			
5 to 10 years	3 (7.1)	5 (11.1)	8 (9.2)
11 to 17 years	39 (92.9)	40 (88.9)	79 (90.8)
Sex, n (%)			
Male	19 (45.2)	20 (44.4)	39 (44.8)
Female	23 (54.8)	25 (55.6)	48 (55.2)
Race, n (%)			
White	40 (95.2)	44 (97.8)	84 (96.6)
Black or African American	1 (2.4)	0	1 (1.1)
Asian	1 (2.4)	1 (2.2)	2 (2.3)
Ethnicity, n (%)			
Hispanic or Latino	1 (2.4)	0	1 (1.1)
Not-Hispanic or Latino	41 (97.6)	45 (100.0)	86 (98.9)
Weight (kg)			
n	42	45	87
Mean (SD)	54.4 (11.94)	53.7 (14.82)	54.0 (13.44)
Median	54.9	53.0	54.7
Min, max	23, 73	19, 86	19, 86
Weight group (kg) (n %)			
18 to ≤23	1 (2.4)	2 (4.4)	3 (3.4)
>23 to ≤35	2 (4.8)	2 (4.4)	4 (4.6)
>35 to ≤50	11 (26.2)	13 (28.9)	24 (27.6)
>50 to ≤90	28 (66.7)	28 (62.2)	56 (64.4)
Height (cm)			
n	42	45	87
Mean (SD)	162.7 (11.23)	161.0 (15.82)	161.8 (13.74)
Median	163.4	164.0	164.0
Min, max	128, 183	111, 182	111, 183

Source: SPD476-319 CSR Table 14.1.4.1.4 (p. 196), Table 14.1.4.2.4 (p. 204)
Abbreviations: DBM, double-blind maintenance; MMX, multi-matrix system; SD, standard deviation

Table 69. Baseline Characteristics: DBA Phase (DBA Phase Safety Analysis Set)

Characteristic	Low-Dose MMX Mesalamine N=27	High-Dose MMX Mesalamine N=26	Overall N=53
Time since diagnosis (months)			
n	27	26	53
Mean (SD)	1.7 (4.71)	12.7 (38.34)	7.1 (27.35)
Median	0.0	0.0	0.0
Min, max	0, 19	0, 160	0, 160
Diagnosis state, n (%)			
Number of patients newly diagnosed	23 (85.2)	18 (69.2)	41 (77.4)
Number of patients not newly diagnosed	4 (14.8)	8 (30.8)	12 (22.6)
Number of acute episodes of UC in last year			
n	4	8	12
Mean (SD)	1.8 (0.96)	1.1 (0.64)	1.3 (0.78)
Median	1.5	1.0	1.0
Min, max	1, 3	0, 2	0, 3
Number of acute episodes of UC since diagnosis			
n	3	8	11
Mean (SD)	2.7 (2.08)	1.8 (1.04)	2.0 (1.34)
Median	2.0	1.5	2.0
Min, max	1, 5	1, 4	1, 5

Source: SPD476-319 CSR Table 14.1.4.2.6 (p. 210)
Abbreviations: DBA, double-blind acute; MMX, multi-matrix system; SD, standard deviation; UC, ulcerative colitis

Table 70. Baseline Characteristics: DBM Phase (DBM Phase Safety Analysis Set)

Characteristic	Low-Dose MMX Mesalamine N=42	High-Dose MMX Mesalamine N=45	Overall N=87
Time since diagnosis (months)			
n	42	45	87
Mean (SD)	20.0 (32.31)	16.6 (32.07)	18.2 (32.04)
Median	6.5	3.0	5.0
Min, max	0, 132	0, 160	0, 160
Diagnosis state, n (%)			
Number of patients newly diagnosed	15 (35.7)	18 (40.0)	33 (37.9)
Number of patients not newly diagnosed	27 (64.3)	27 (60.0)	54 (62.1)
Number of acute episodes of UC in last year			
n	26	27	53
Mean (SD)	1.0 (1.04)	0.9 (0.80)	0.9 (0.92)
Median	1.0	1.0	1.0
Min, max	0, 4	0, 3	0, 4
Number of acute episodes of UC since diagnosis			
n	26	27	53
Mean (SD)	1.6 (1.27)	1.4 (1.22)	1.5 (1.23)
Median	1.0	1.0	1.0
Min, max	0, 5	0, 5	0, 5

Source: SPD476-319 CSR Table 14.1.4.2.8 (p. 218)
Abbreviations: DBM, double-blind maintenance; MMX, multi-matrix system; SD, standard deviation; UC, ulcerative colitis

Table 71. Applicant's Sensitivity Analysis for Primary Efficacy Endpoint in DBA Phase, Proportion of Patients With a Clinical Response at Week 8[a], Complete Case Analysis (DBA Phase Safety Analysis Set)

Parameter	Low-Dose MMX Mesalamine N=27	High-Dose MMX Mesalamine N=26
Number of patients, excluding patients who withdrew early from the phase	19	22
Number (%) of patients with clinical response at Week 8	10 (52.6)	17 (77.3)
Difference in proportions (high to low dose) %		24.6
95% CI for difference in proportions[b] (high to low dose) %		-3.8, 53.1

Source: SPD476-319 CSR Table 14.2.1.2.4 (p. 360)
Percentages are based on number of patients in DBA phase safety analysis set, excluding patients who withdrew early from phase.
[a] Analyzed with NRI for missing data
[b] 95% CI was based on normal approximation without continuity correction for difference in binomial proportions.
Abbreviations: DBA, double-blind acute; CI, confidence interval; MMX, multi-matrix system

Table 72. Applicant's Sensitivity Analysis for Primary Efficacy Endpoint in DBM Phase, Proportion of Patients With a Clinical Response at Week 26[a], Complete Case Analysis (DBM Phase Safety Analysis Set)

Parameter	Low-Dose MMX Mesalamine N=42	High-Dose MMX Mesalamine N=45
Number of patients, excluding patients who withdrew early from the phase	32	34
Number (%) of patients with clinical response at Week 26	23 (71.9)	24 (70.6)
Difference in proportions (high to low dose) %		-1.3
95% CI for difference in proportions[b] (high to low dose) %		-23.1, 20.6

Source: SPD476-319 CSR Table 14.2.1.2.13 (p. 374)
[a] Analyzed with NRI for missing data
Percentages are based on number of patients in DBM phase safety analysis set, excluding patients who withdrew early from phase.
[b] 95% CI was based on the normal approximation without continuity correction for the difference in binomial proportions.
Abbreviations: DBM, double-blind maintenance; CI, confidence interval; MMX, multi-matrix system

15.5. Supplemental Safety Information

Table 73. Laboratory Tests

Hematology	Chemistry	Urinalysis
Complete blood count:	Alanine aminotransferase Albumin	pH
Red blood cell count	Alkaline phosphatase	Specific gravity
White blood cell count	Aspartate aminotransferase	Protein[a]
Platelet count	Bilirubin, total	Glucose
Hemoglobin	Bicarbonate	Ketones
Hematocrit	Calcium Chloride	Bilirubin
White blood cell differential	Cholesterol, total	Blood[a]
	Creatinine, enzymatic	
	Creatine kinase	
	C-reactive protein standard	
	Direct bilirubin	
	Gamma-glutamyl transferase	
	Glucose random, serum	
	Lactate dehydrogenase	
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	Total protein	
	Triglycerides	
	Urea (blood urea nitrogen)	
	Uric acid	

Source: Adapted from Applicant's submission, dated August 29, 2019, sNDA 022000, module 5.3.5.1 SPD476-319 Report Body, Table 5, page 52/1545.
[a] Microscopic examination was conducted if protein and/or blood was/were detected during urinalysis. Microscopic examination consisted of red blood cells, white blood cells, casts, and bacteria.

Safety Analyses by Age Subgroup

Analyses by age category were limited by the small number of patients in the 5- to 10-year-old age subgroup. In general, the majority of participants in all phases were in the older, 11- to 17-year-old age subgroup. Of note, the older subgroup reported similar safety events as the overall population that was reviewed in Section 8.4.

A total of four patients aged 5 to 10 years were enrolled in the DBA phase and one patient was enrolled in the open-label acute (OLA) phase (Table 29). During the DBA and OLA phases, no more than one patient in this younger age subgroup reported an SAE or discontinuation. Similarly, specific TEAEs were not reported more than once. Analyses by age subgroup for the DBA and OLA phases are limited by the small number of patients in the younger age group; however, no association between age and safety was found.

A total of eight patients in the younger age subgroup were enrolled in the DBM phase. No reported SAEs or discontinuations occurred in these patients. Additionally, specific TEAEs were not reported more than once. Similar to the DBA and OLA phases, the analysis by age for the DBM phase is limited by the small number of AEs; however, no association between age and safety was found.

Overall, no association between age and safety was identified that would alter the benefit-risk assessment of Lialda.

Safety Analyses by Weight Subgroup

Analyses by weight subgroups are also limited by the small number of patients in the lower weight subgroups. In particular, there were no patients in the lowest weight subgroup (i.e., 18–23 kg) enrolled in the DBA and OLA phases and only three patients in the DBM phase. The limited enrollment of this weight subgroup in addition to the unavailability of the lower dosage tablets proved insurmountable when evaluating the data to support approval of Lialda for this weight subgroup. As such, it is not possible to evaluate safety signals in this lower weight subgroup and will not be presented in this section.

During the DBA phase, a greater proportion of patients in the weight subgroups of >23 to 35 kg and >35 to 50 kg reported TEAEs of UC and were discontinued from the study. All of these TEAEs and discontinuations occurred in the low-dose treatment arm. This finding suggests that lower-weight patients receiving the low-dose treatment regimen may be more susceptible to TEAEs of UC that led to discontinuation from the study. As noted previously, TEAEs of UC are likely reflective of a lack of efficacy of the low-dose treatment regimen, rather than a drug-related AE.

During the DBM phase, there were no clear differences in SAEs, discontinuations, or TEAEs due to UC based on weight subgroup. A greater proportion of patients in the >50- to 90-kg weight subgroup reported TEAEs of abdominal pain while patients in the >35- to 50-kg weight subgroup reported more TEAEs of upper respiratory tract infection. However, since the SAEs and discontinuations were similar, the small the differences in abdominal pain and upper respiratory tract infection TEAEs likely does not represent a meaningful finding.

Safety Analyses by Weight Subgroup During Double-Blind Acute Phase

As noted previously, during the DBA phase there were four patients who reports SAEs; all of whom were in the low-dose treatment arm. Table 74 describes the proportion of SAEs by weight group and each SAE is described in detail in Section 8.4. Of note, the number of patients with SAEs in the >35- to 50-kg weight group was higher than the other weight groups; however, the small number of patients makes drawing a conclusion from this observation challenging. Considering that one of the two SAEs in the >35- to 50-kg weight group was pyelonephritis in a patient with a history of urinary tract infections, there does not appear to be an association with weight group and SAEs during the DBA phase.

Table 74. Proportion of Patients With Serious Adverse Events by Weight Category in DBA Phase

Parameter	Low-Dose n (%)	High-Dose n (%)
Total patients reporting SAEs	4/27 (14.8)	0/26
Weight category (kg)		
18 to ≤23	-	-
>23 to ≤35	1/4 (25.0)	0/3
>35 to ≤50	2/7 (28.6)	0/7
>50 to ≤90	1/16 (6.3)	0/16

Source: Reviewer's table created using Applicant ADAE dataset
Abbreviations: DBA, double-blind acute; SAE, serious adverse event

Similar to SAEs, discontinuations were isolated to the low-dose treatment arm of the DBA phase. Table 75 describes the proportion of discontinuations by weight group, for further details on each discontinuation, refer to Section 8.4. The proportion of discontinuations was higher in the >23- to 35-kg and >35- to 50-kg weight groups compared to the >50- to 90-kg weight group. As discussed previously, the majority of discontinuations were due to TEAEs of ulcerative colitis.

Table 75. Proportion of Discontinuations by Weight Category in DBA Phase

Parameter	Low-Dose n (%)	High-Dose n (%)	Overall n (%)
Total patients reporting SAEs	9/27 (33.3)	0/26	9/53 (17.0)
Weight category (kg)			
18 to ≤23	-	-	-
>23 to ≤35	2/4 (50.0)	0/3	2/7 (28.6)
>35 to ≤50	4/7 (57.1)	0/7	4/14 (28.6)
>50 to ≤90	3/16 (18.8)	0/16	3/32 (9.4)

Source: Reviewer's table created using Applicant ADAE dataset
Abbreviations: DBA, double-blind acute; SAE, serious adverse event

The relationship between weight category and TEAEs was evaluated for TEAEs that occurred in more than four patients in the DBA phase as detailed in Table 76; further details regarding these TEAEs are available in Section 8.4. The cutoff of at least four patients was selected due to the overall small sample size and small number of TEAEs. Due to the small number of TEAEs of abdominal pain, dyspepsia, and headache in each weight group, it is not possible to draw conclusions about a relationship between weight groups and these TEAEs. As described previously, patients in the low-dose treatment arm reported more TEAEs of ulcerative colitis compared to patients enrolled in the high-dose treatment arm. The proportion of patients in the >23- to 35-kg and >35- to 50-kg weight groups with TEAEs of ulcerative colitis was higher than the >50- to 90-kg weight group. However, the comparison between weight groups is made difficult due to the small number of patients in the two lower weight groups.

Table 76. Proportion of TEAEs by Weight Category in DBA Phase

Adverse Event	18 to ≤23 kg n/N (%)	>23 to ≤35 kg n/N (%)	>35 to ≤50 kg n/N (%)	>50 to ≤90 kg n/N (%)
Number of patients with at least 1 TEAE	-	6/7 (85.7)	8/14 (57.1)	18/32 (56.3)
Colitis ulcerative	-	2/7 (28.6)	3/14 (21.4)	3/32 (9.4)
Abdominal pain	-	1/7 (14.3)	1/14 (7.1)	3/32 (9.4)
Dyspepsia	-	2/7 (28.6)	1/14 (7.1)	1/32 (3.1)
Headache	-	-	1/14 (7.1)	3/32 (9.4)

Source: Reviewer's table created using Applicant ADAE dataset
Abbreviations: DBA, double-blind acute; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

Safety Analyses by Weight Subgroup During Open-Label Acute Phase

During the OLA phase, SAEs and discontinuations occurred exclusively in the highest weight group. As discussed previously in Section 8.4 the small number of SAEs and discontinuations (3 and 2 respectively) combined with the small number of patients in the smaller weight groups makes interpretation of this finding challenging. Most likely, this finding is not related to a safety signal specific to the highest weight group.

Safety Analyses by Weight Subgroup During the Double-Blind Maintenance Phase

During the DBM phase there were five patients who reported an SAE; three patients in the low-dose treatment arm and two patients in the high-dose treatment arm. The proportion of SAEs by weight group is described in Table 77. No clear association between weight group and SAEs was evident. Further details regarding each SAE are available in Section 8.4.

Table 77. Proportion of Patients With Serious Adverse Events by Weight Category in DBM Phase

Parameter	Low-Dose n (%)	High-Dose n (%)	Overall n (%)
Total patients reporting SAEs	3/42 (7.1)	2/45 (4.4)	5/87 (5.7)
Weight category (kg)			
18 to ≤23	0/1	0/2	0/3
>23 to ≤35	0/2	0/2	0/4
>35 to ≤50	1/11 (9.1)	1/13 (7.7)	2/24 (8.3)
>50 to ≤90	2/28 (7.1)	1/28 (3.6)	3/56 (5.4)

Source: Reviewer's table created using Applicant ADAE dataset
Abbreviations: DBM, double-blind maintenance; SAE, serious adverse event

Overall, there were 17 patients who were discontinued from the DBM phase. Table 78 depicts the proportion of discontinuations by weight category. There is no clear association between weight category and discontinuations. For details on the specific TEAEs that led to discontinuation, refer to Section 8.4.

Table 78. Proportion of Discontinuations by Weight Category in DBM Phase

Parameter	Low-Dose n (%)	High-Dose n (%)	Overall n (%)
Total patients reporting SAEs	8/42 (19.0)	9/45 (20.0)	17/87 (19.5)
Weight category (kg)			
18 to ≤23	0/1	0/2	0/3
>23 to ≤35	0/2	0/2	0/4
>35 to ≤50	2/11 (18.2)	4/13 (30.8)	6/24 (20.8)
>50 to ≤90	6/28 (21.4)	5/28 (17.9)	11/56 (19.6)

Source: Reviewer's table created using Applicant ADAE dataset
Abbreviations: DBM, double-blind maintenance; SAE, serious adverse event

The relationship between weight category and TEAEs was evaluated for TEAEs that occurred in more than four patients in the DBM phase as detailed in Table 68; further details regarding these TEAEs are available in Section 8.4.

Overall, the comparison between the two lowest weight categories (i.e., 18 to 23 kg and >23 to 35 kg) and the two highest weight categories (i.e., >35 to 50 kg and >50 to 90 kg) is limited by the small number of patients and TEAEs in the two lowest weight categories. No TEAEs occurred in more than one patient in each of the two lowest weight categories. Additionally, several TEAEs are independently associated with age (e.g., dysmenorrhea and headache (Law et al. 2019)) and are unlikely to occur in the younger patients who constitute the majority of patients in the two lowest weight categories. Rather than an increased susceptibility to TEAEs, the higher proportion of TEAEs described in Table 79 for the two highest weight groups compared to the two lowest weight groups likely reflects the low number of patients and TEAEs.

Table 79. Proportion of TEAEs by Weight Category in DBM Phase

MeDRA Preferred Term for Adverse Event	18 to ≤23 kg n/N (%)	>23 to ≤35 kg n/N (%)	>35 to ≤50 kg n/N (%)	>50 to ≤90 kg n/N (%)
Number of patients with at least 1 TEAE	1/3 (33.3)	3/4 (75.0)	14/24 (58.3)	36/56 (64.3)
Colitis ulcerative	-	-	4/24 (13.7)	10/56 (17.9)
Abdominal pain	-	-	2/24 (8.3)	11/56 (19.6)
Upper respiratory tract infection	-	-	5/24 (20.8)	7/56 (12.5)
Dysmenorrhea	-	-	1/24 (4.2)	3/56 (5.4)
Headache	-	-	1/24 (4.2)	3/56 (5.4)
Oropharyngeal pain[a]	-	-	2/24 (8.3)	2/56 (3.6)

Source: Reviewer's table created using Applicant ADAE dataset
[a] Oropharyngeal pain includes reported terms: "sore throat" or "throat pain"
Abbreviations: DBM, double-blind maintenance; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

The proportion of patients who reported TEAEs of ulcerative colitis was similar between the >35- to 50-kg and >50- to 90-kg weight categories. Abdominal pain was reported more frequently in the >50- to 90-kg weight category whereas upper respiratory tract infection TEAEs were reported in a greater proportion of patients in the >35- to 50-kg weight category. Due to the low number of dysmenorrhea, headache, and oropharyngeal pain TEAEs in each weight group, it is not possible to draw conclusions about a relationship between weight groups and these TEAEs. Despite the differences in TEAEs between the two highest weight categories, the clinical significance is limited as analyses of SAEs and discontinuations did not identify a clear association with weight category.

Unireview Section Signatures
NDA 022000/S-019 Lialda (mesalamine) delayed-release tablets

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Dilara Jappar, Ph.D.	OTS/OCP/DIIP	Authored Section 6 and 11.1 Appendix 15.3.1 and 15.3.3	**Select one:** _X_ Authored ___ Approved
	Signature: Dilara Jappar -S Digitally signed by Dilara Jappar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Dilara Jappar -S, 0.9.2342.19200300.100.1.1=2000371317 Date: 2020.06.22 09:42:15 -04'00'			
Clinical Pharmacology Team Leader	Insook Kim, Ph.D.	OTS/OCP/DIIP	Approved Section 6 and 11.1 Appendix 15.3.1 and 15.3.3	**Select one:** __ Authored _X_ Approved
	Signature: Insook Kim -S Digitally signed by Insook Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Insook Kim -S, 0.9.2342.19200300.100.1.1=1300416436 Date: 2020.06.22 10:14:41 -04'00'			
Statistical Reviewer	Sara Jimenez, Ph.D.	OB/DBIII	Authored: Section 8.1	**Select one:** __X_ Authored __ Approved
	Signature: Sara Jimenez -S Digitally signed by Sara Jimenez -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sara Jimenez -S, 0.9.2342.19200300.100.1.1=2002241423 Date: 2020.06.19 14:07:19 -04'00'			
Statistical Team Leader	David Petullo, M.S.	OB/DBIII	Approved: Section 8.1	**Select one:** ___ Authored _X_ Approved
	Signature: David M. Petullo -S Digitally signed by David M. Petullo -S Date: 2020.06.19 14:15:22 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacometrics Reviewer	Hongshan Li, Ph.D.	OTS/OCP/DPM	Authored Section 6 and Appendix 15.3.2	**Select one:** _X_ Authored ___ Approved
	Signature: Hongshan Li -S Digitally signed by Hongshan Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hongshan Li -S, 0.9.2342.19200300.100.1.1=2001098258 Date: 2020.06.19 11:07:03 -04'00'			
Pharmacometrics Team Leader	Lian Ma, Ph.D.	OTS/OCP/DPM	Approved Section 6 and Appendix 15.3.2	**Select one:** _ _ Authored _X_ Approved
	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2020.06.19 17:08:09 -04'00'			
Clinical Reviewer	Matthew Kowalik, M.D.	OII/DG	Authored: Sections: 2, 3, 7, 8.2, 8.4, 9-13, 16.5	**Select one:** _X_ Authored __Approved
	Signature: Matthew R. Kowalik -S Digitally signed by Matthew R. Kowalik -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002780488, cn=Matthew R. Kowalik -S Date: 2020.06.25 16:07:44 -04'00'			
Clinical Team Leader/CDTL	Juli Tomaino, M.D.	OII/DG	Authored: section 1.3	**Select one:** __ Authored _X_ Approved (all sections)
	Signature: Juli A. Tomaino -S Digitally signed by Juli A. Tomaino -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001149989, cn=Juli A. Tomaino -S Date: 2020.06.25 16:27:29 -04'00'			
Director (Acting)	Jessica J. Lee, M.D., M.M.Sc.	OII/DG	Authored: Section 14 Approved: All sections	**Select one:** __ Authored _X_ Approved
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KELLY D RICHARDS
06/26/2020 10:03:35 AM

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