Clinical Pharmacology Review

NDA #:	NDA 215985/ S-002
Submission Date:	12/15/2022
Generic Name:	Roflumilast (ARQ-151)
Dosage Form:	Cream
Dosage Strength:	0.3%
Reviewer:	Rakesh Gollen, Ph.D.
Secondary Reviewer:	Chinmay Shukla, Ph.D.
Sponsor:	Arcutis Biotherapeutics, Inc.
Relevant IND(s):	135681
Submission Type:	Pediatrics Supplement

(b) (4)

1 Background: Roflumilast cream, 0.3% (ZORYVE) was approved in July 2022 for the topical treatment of plaque psoriasis in subjects 12 years of age and older. At the time of original approval following Post Marketing Requirements (PMRs) were issued as below:

- 4314-1: An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in 20 Pediatric Subjects (ages 6 to 11 years old) with Plaque Psoriasis (Study Protocol ARQ-151-215).
- 4314-2: An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in 10 Pediatric Subjects (ages 2 to 5 years old) with Plaque Psoriasis (Study Protocol ARQ-151-216).
- 4314-3: A Phase 3, multicenter, open-label extension study of the long-term safety of ARQ-151 cream 0.3% in subjects (≥ 2 years of age) with chronic plaque psoriasis (Study Protocol ARQ-151-306)

This supplement includes the final study reports of two of the above aforementioned PMRs (4314-1 and 4314-2) (b) (4)

Recommendation: From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Sponsor. Clinical Pharmacology also recommends that the Applicant has fulfilled PMR 4314-1 and PMR 4314-2 and the Applicant be released from these two PMRs.

Post marketing requirement or commitment: None.

2 Summary of the clinical study reports:

2.1 Study ARQ-151-215: (PMR 4314-1)

This was an open label, 4-Week, phase 2, maximal usage pharmacokinetics and safety study of ARQ-151 cream 0.3% administered QD in pediatric subjects (ages 6 to 11 years old) with plaque psoriasis.

Study design: Approximately 20 male and female subjects aged 6 years to 11 years with plaque psoriasis with body surface area (BSA) involvement of at least 2% (excluding the scalp, palms and soles) and mild disease (IGA -2) based on IGA at baseline were enrolled. All subjects completed the study, and 19 subjects were included in PK analysis and 10 subjects were under maximal use conditions with BSA involvement of at least 3%. Trough level PK sample was obtained in all subjects at Week 4. Subjects in the maximal use cohort had trough level PK sample at Week 2 and Week 4.
The mean treated BSA of the PK population on Week 2 and Week 4 was approximately 11% and 9.2% respectively.

Study drug was applied once daily for 28 days to all plaque psoriasis affected areas and any newly appearing plaque psoriasis lesions that arose during the study, except on the scalp. Subjects/caregivers were to maintain treatment of areas with study drug for the duration of the study regardless of whether treatable areas cleared prior to Week 4.

Identity, Packaging and Labeling of the investigational product:
Roflumilast cream 0.3% was packaged in [redacted] (b) (4) tubes. For a mean treated BSA of the PK population on Week 2 and Week 4 of approximately 11% and 9.2%, the mean ± SD of target dose on Week 2 and Week 4 are 6.61 ± 3.97 and 5.59 ± 3.43 mg respectively. The mean actual daily dose [redacted] (b) (4) is approximately 2.6 grams/day (Table 1). The tubes were packaged in kits, containing multiple tubes of IP. The number of kits dispensed to a subject was based on the BSA involvement of plaque psoriasis. The kits were labeled in an open-label manner.

Table 1: Summary of Study Medication Exposure and Compliance (Safety Population)

Variable Statistic or Category	ARQ-151 Cream 0.3% (N = 20)
Number of days study medication applied based on diary data	
Mean (SD)	28.1 (1.23)
Median	28.0
Range (Minimum, Maximum)	26, 30
Study medication used based on tube weight (g); (N = 17)	
Mean (SD)	73.7 (47.70)
Median	63.5
Range (Minimum, Maximum)	23, 181
Number of days on study medication	
Mean (SD)	28.7 (1.42)
Median	28.0
Range (Minimum, Maximum)	26, 31
Study medication application compliance; n (%)	
100%	14 (70.0)
≥80% to <100%	6 (30.0)
<80%	0
Subject compliant; n (%)	
Yes	20 (100.0)
No	0

SD = standard deviation

Source: Clinical Study Report ARQ-151-215 Table 14.2.5

Mean actual daily dose (b) (4) is approximately 2.6 grams/day

Pharmacokinetic assessment criteria:

For the analysis of all pre-dose plasma concentrations only, to allow for the calculation of geometric mean, all concentration values had 0.1 pg/mL added to their concentration value, with values below the limit of quantification (BLQ) set equal to 0.1 pg/mL.
The lower limit of quantification (LLOQ) was 0.1 ng/mL for roflumilast and the N-oxide.
For the single subject with the full PK profile, the PK analyses was performed for roflumilast and the N-oxide metabolite using non-compartmental analysis and following the Linear Trapezoidal Linear Interpolation calculation method. To complete a 24 hour interval, the pre-dose concentration was duplicated as a 24-hour value, consistent with steady state expectations. C_{max} and the corresponding T_{max} values were determined by direct assessment of the concentration versus time data. Nominal target dose values and sampling times were used for PK parameter estimations.

BSA assessment:

To calculate treated surface area, theoretical total BSA of 10,100 cm^2 was used for all subjects between 6 to 11 years of age. Treated surface area was then calculated as total

BSA * treated BSA (using the BSA determined at screening). (b) (4) [redacted] Percent change from baseline at Week 2 and Week 4 is shown below in Table 2. Mean baseline BSA was 8.8%. At the Week 2 assessment, mean BSA was 7.8%, a mean decrease of 16.2%. At the Week 4 assessment, mean BSA had reduced to 4.5%, a mean decrease of 44.4%.

Table 2: Summary of Body Surface Area (BSA) by Visit (Percent Change from Baseline at Week 2 and Week 4)

Study Visit Statistic	ARQ-151 Cream 0.3% (N = 20)
BSA - Week 2, Day 14	Percent Change from Baseline
Mean (SD)	-16.2 (21.10)
Median	-11.3
Range (Minimum, Maximum)	-67, 15
BSA - Week 4, Day 28	Percent Change from Baseline
Mean (SD)	-44.4 (36.87)
Median	-50.0
Range (Minimum, Maximum)	-100, 38

SD = standard deviation
Source: Clinical Study Report; Table 14.2.3

The BSA is changed from 8.8% at baseline to 7.8% at the Week 2 assessment, to further 4.5%, at the Week 4 assessment. This was due to resolution of disease on treatment.

Pharmacokinetic results:
Following daily topical administration for 14 days to 10 subjects in the maximal use cohort with mean BSA of 10.9% (minimum BSA = 4.0%, maximum BSA = 24.0%), the arithmetic mean of roflumilast and roflumilast N-oxide pre-dose concentrations were 3.15 and 28.9 ng/mL, respectively. At Week 4 PK assessment was conducted in all subjects including those in the maximal use cohort (n=19). In one subject, the systemic concentrations were BLQ and in the remaining 18 subjects the mean pre-dose roflumilast and roflumilast N-oxide concentrations were 1.68 ng/mL and 15.7 ng/mL, respectively.
The arithmetic mean extrapolated roflumilast AUC_{0-24} values were 75.6 and 42.8 h*ng/mL for Week 2 (n=10 and Week 4 (n=18), respectively. At Week 2, The systemic exposure in 1 subject under maximal usage conditions was higher than the average and the AUC_{0-24} values for roflumilast and the N-oxide metabolite were 170 and 863 h*ng/mL, respectively (Table 3).

PK results are summarized in Table 4. Mean treated BSA of the PK population on Week 2 and Week 4 was approximately 11% and 9.2%, respectively (Table 3).

Table 3: Plasma pharmacokinetic parameters following daily topical ARQ-151 cream 0.3% administration at week 2

Subject ID	Roflumilast			Roflumilast N-Oxide		
	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)
(b) (6)	2.0	9.40	170	4.0	40.3	863

Source: Pharmacokinetic Report; Table 1

Table 4: Summary of pre-dose concentrations and extrapolated AUC_{0-24} values following daily topical ARQ-151 cream 0.3% administration in PK Population

Day		BSA (%)	Target Dose (mg)	Roflumilast				N-Oxide			
				Conc (ng/mL)	DN Conc (ng/mL/mg)	Extra AUC_{0-24} (h*ng/mL)	DN Extra AUC_{0-24} (h*ng/mL/mg)	Conc (ng/mL)	DN Conc (ng/mL/mg)	Extra AUC_{0-24} (h*ng/mL)	DN Extra AUC_{0-24} (h*ng/mL/mg)
14	N	10	10	10	10	10	10	10	10	10	10
	Mean	10.9	6.61	3.15	0.370	75.6	8.87	28.9	3.40	693	81.5
	SD	6.56	3.97	3.54	0.304	87.3	7.29	41.1	3.51	986	84.3
	CV%	60.2	60.2	115	82.2	115	82.2	142	103	142	103
	Min	4.00	2.42	0.125	0.0487	3.00	1.17	0.855	0.328	20.5	7.87
	Median	8.50	5.15	2.00	0.340	48.1	8.15	15.4	1.96	370	47.0
	Max	24.0	14.5	11.4	0.941	274	22.6	137	11.3	3290	271
	Geometric Mean	9.36	5.67	1.36	0.240	32.7	5.75	11.1	1.96	267	47.0
28	N	18	18	18	18	17	17	18	18	17	17
	Mean	9.22	5.59	1.68	0.284	42.8	7.21	15.7	2.69	398	68.3
	SD	5.66	3.43	1.57	0.169	37.4	3.81	15.8	1.76	378	40.4
	CV%	61.4	61.4	93.3	59.7	87.5	52.8	101	65.7	94.8	59.2
	Min	2.00	1.21	0.000100	8.25E-05	6.26	1.03	0.000100	8.25E-05	41.8	6.89
	Median	8.00	4.85	1.30	0.307	31.4	7.89	13.6	2.88	331	79.7
	Max	24.0	14.5	6.75	0.558	162	13.4	67.5	5.57	1620	134
	Geometric Mean	7.76	4.70	0.758	0.161	30.8	6.04	5.83	1.24	267	52.4

Unscheduled samples were not included in summary analysis. Conc is pre-dose concentration. AUC0-24 is extrapolated from pre-dose concentration values. All values normalized by target dose applied (DN).
Source: Pharmacokinetic Report, Table 2

Mean treated BSA of the PK population on Week 2 and Week 4 was approximately 11% and 9.2%, respectively.

Following daily administration for 2 weeks the mean ± SD BSA involvement of 10.9 ± 6.56% and the mean ± SD systemic exposure (AUC_{0-24}) for roflumilast and roflumilast N-oxide was 75.6 ± 87.3% and 693 ± 986 h*ng/mL, respectively, in children aged 6 – 11 years. The systemic exposure under maximal use conditions observed in this study was comparable to adults. The systemic exposure (mean ± SD AUC_{0-24}) in adults was 72.7 ± 53.1 and 628 ± 648 h*ng/mL, respectively, for roflumilast and the N-oxide metabolite.

Subject (b) (6), where the complete PK was characterized, the AUC_{0-24} values for roflumilast and the N-oxide metabolite were 170 and 863 h*ng/mL, respectively. This value is within the range of the estimated PK parameters.

Drug interactions: No formal drug-drug interaction studies conducted with ZORYVE, but the coadministration of roflumilast with systemic CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) are known to increase roflumilast systemic exposure and may result in increased adverse reactions. There will be no change in labeling with respect to drug interactions.

Disposition of subjects: 20 subjects enrolled in this study and all subjects completed the study.

Demographic and baseline characteristics: Demographics and baseline characteristics are shown in Table 5.

Table 5: Demographic and baseline characteristics

Variable Statistic or Category	ARQ-151 Cream 0.3% (N = 20)
Age (years)	
Mean (SD)	8.8 (1.61)
Median	9.0
Range (Minimum, Maximum)	6, 11
Gender; n (%)	
Male	13 (65.0)
Female	7 (35.0)
Race; n (%)	
Black/African American	10 (50.0)
Caucasian	9 (45.0)
Asian	1 (5.0)
Ethnicity; n (%)	
Hispanic/Latino	12 (60.0)
Non-Hispanic/Latino	8 (40.0)
Height (cm)	
Mean (SD)	132.64 (10.778)
Median	130.10
Range (Minimum, Maximum)	119.1, 153.7
Weight (kg)	
Mean (SD)	38.32 (13.060)
Median	35.60
Range (Minimum, Maximum)	22.4, 71.2
Body Surface Area (BSA) at Baseline (%)	
Mean (SD)	8.80 (5.809)
Median	8.00
Range (Minimum, Maximum)	2.0, 24.0
BSA Groups; n (%)	
BSA <5%	6 (30.0)
BSA ≥5%	14 (70.0)

Source: Clinical Study Report; Table 14.1.3

Summary of Safety:
A total of 4 (20.0%) subjects experienced at least one treatment emergent adverse event (TEAE). All TEAEs were reported as Grade 1 (mild). No subjects experienced TEAEs that were considered Grade 3 (severe). Two (10.0%) subjects experienced TEAEs that were considered related to study drug. No subjects experienced serious adverse events (SAEs) or TEAEs resulting in study discontinuation. A summary of TEAEs is summarized in Table 6.

Table 6: Overview of Treatment-Emergent Adverse Events (Safety Population)

Category	ARQ-151 Cream 0.3% (N = 20) n (%)
Subjects with at least one TEAE	4 (20.0)
Subjects with at least one Grade 1 TEAE	4 (20.0)
Subjects with at least one Grade 3 TEAE	0
Subjects with at least one Related TEAE	2 (10.0)
Subjects with at least one Serious TEAE	0
Subjects with at least one TEAE leading to study discontinuation	0
Subjects with at least one TEAE leading to death	0

Source: Clinical Study Report; Table 14.3.1.1

See Clinical review for further information on safety.

Bioanalytical method validation: The bioanalytical method used was similar to the one used earlier and the range of Roflumilast and Roflumilast *N*-Oxide was 0.1 ng/mL to 100 ng/mL (the range used earlier was 0.05 ng/mL to 50 ng/mL). The method was validated, and long-term stability established earlier was adequate to support the storage stability of the PK samples in this study (Details of bioanalytical method validation with report can be found in Clinical Pharmacology review dated 07/06/2023 in DARRTS). The method validation parameters for the standard curve were acceptable and are shown in Table 7. Incurred sample reanalysis was not performed for this study. As the ISR in the original NDA passed and the sample stability in this study was within the established long term storage stability duration. Hence, although ISR assessment was preferred for this study, the ISR results from the original NDA would be supportive.

Table 7: Method validation parameters of standard curve

	Roflumilast	Roflumilast *N*-Oxide
Between-run accuracy %	-2.5 to 3.0	-1.8 to 2.0
Between-run precision %	≤7.4%	%CV: ≤4.0%

Source: BA Report # 201291AEA_ARCMC

2.2 Study ARQ-151-216: (PMR 4314-2)

This was an open label, 4-week, phase 2, maximal usage pharmacokinetics and safety study of ARQ-151 cream 0.3% administered QD in pediatric subjects (ages 2 to 5 years old) with plaque psoriasis.

Study design:

10 male and female subjects aged 2 to 5 years (inclusive) with plaque psoriasis involving at least 2% BSA (excluding the scalp, palms, soles) and an IGA of disease severity of at least Mild (2) were enrolled and treated. The PK Population comprised 9 subjects who had at least 3% BSA involvement (excluding the scalp, palms, soles) at baseline. All 10 subjects had trough level PK assessment at Week 4. The 9 subjects in the maximal use cohort, had trough level PK assessment at Week 2. The PK evaluable subjects (in the maximal usage subset) were defined as those that had PK results at Week 2.
Roflumilast cream 0.3% was applied once daily (QD) for 28 days to all plaque psoriasis affected areas and any newly appearing plaque psoriasis lesions that arose during the study, except on the scalp. Subjects/caregivers were to maintain treatment of areas with study drug for the duration of the study regardless of whether treatable areas cleared prior to Week 4. Unevaluable subjects could be replaced. All subjects were to have at least Mild ('2') psoriasis severity based on IGA at baseline.

Identity, Packaging and Labeling of the investigational product:
Roflumilast cream 0.3% was packaged in [redacted] (b) (4) tubes. For a mean treated BSA of the PK Population at Week 2 of 9.44%, the target dose was 3.9 mg. The mean actual daily dose [redacted] (b) (4) is approximately 1.4 grams/day. The tubes were packaged in kits, containing multiple tubes of IP. The number of kits dispensed to a subject was based on the BSA involvement of plaque psoriasis. The kits were labeled in an open-label manner and the lot number used in the study was lot #PMF-1C.

Table 8: Summary of Exposure to Investigational Product (Safety Population)

	Roflumilast Cream 0.3% (N = 10)
Number of days IP applied based on diary data	
Mean (SD)	28.2 (1.14)
Median (minimum, maximum)	28.0 (26, 30)
IP used based on tube weight (g)[a]	
Mean (SD)	38.5 (18.75)
Median (minimum, maximum)	32.4 (17, 73)
Number of days on IP	
Mean (SD)	28.7 (1.16)
Median (minimum, maximum)	28.5 (27, 31)

IP = investigational product; SD = standard deviation.
[a] One subject did not bring in all 4 tubes to be weighed at the last visit and is not included.

Source: Clinical Study Report ARQ-151-216 Table 14.2.5
Mean actual daily dose [redacted] (b) (4) is approximately 1.4 grams/day

Pharmacokinetic assessment criteria:
Plasma levels of circulating roflumilast and its major N-oxide metabolite were measured as follows:
Samples were analyzed using Phoenix WinNonlin (v8.3). PK parameter estimates for roflumilast, and its N-oxide metabolite were calculated using the non-compartmental analysis object (linear trapezoidal rule for area under the concentration versus time curve [AUC] calculations). The maximum plasma concentration (C_{max}) and the corresponding time to maximum plasma concentration (T_{max}) values were determined by direct assessment of the concentration versus time data. Predose plasma concentration and extrapolated area under the plasma concentration time curve from time zero to 24 hours (AUC_{0-24}) values were summarized with N, arithmetic mean, SD, percent coefficient of variation (CV%), minimum, median, maximum, and geometric mean for each analyte.

BSA assessment:
BSA affected by psoriasis was assessed at baseline, Week 2, and Week 4.
The BSA affected by plaque psoriasis was determined by the subject's hand method, where the subject's hand (including fingers) surface area is assumed to equal 1% of BSA. Percent change from baseline in BSA affected is summarized in Table 9. Mean BSA affected by psoriasis decreased (improved) 34.0% and 79.1% at Weeks 2 and 4, respectively.

Table 9: Summary of Body Surface Area Affected by Psoriasis by Study Visit (Safety Population)

Parameter	Roflumilast Cream 0.3% (N = 10)
Week 2	
Percent change from baseline	
Mean (SD)	-34.0 (24.49)
Median (minimum, maximum)	-33.3 (-73, 0)
Week 4	
Percent change from baseline	
Mean (SD)	-79.1 (19.87)
Median (minimum, maximum)	-77.3 (-100, -50)

Source: Clinical Study Report ARQ-151-216; Table 14.2.3

The decrease in BSA involvement on treatment was due to resolution of the disease.

Disposition of subjects: 10 subjects enrolled in this study and all subjects completed the study.

Demographic and baseline characteristics: Demographics and baseline characteristics are shown in Table 10.

Table 10: Demographic and baseline characteristics

Variable Statistic/Category	Roflumilast Cream 0.3% (N = 10)
Age (years)	
Mean (SD)	3.6 (1.26)
Median (minimum, maximum)	4.0 (2, 5)
Sex	
Male, n (%)	5 (50.0)
Female, n (%)	5 (50.0)
Race	
Black/African American, n (%)	9 (90.0)
White, n (%)	1 (10.0)
Ethnicity	
Hispanic or Latino, n (%)	9 (10.0)
Not Hispanic or Latino, n (%)	1 (10.0)

Source: Clinical Study Report ARQ-151-216; Table 14.1.3

Pharmacokinetic results:

Following daily administration of roflumilast cream 0.3%, evidence of systemic exposure (measurable plasma concentrations roflumilast and the N-oxide metabolite) was seen in all plasma samples assayed. Under maximal usage conditions in subjects 2 to 5 years of age (n = 9), the mean ± SD extrapolated AUC_{0-24} was 51.6 ± 29.9 and 539 ± 372 h*ng/mL for roflumilast and the N-oxide metabolite, respectively, at Week 2. One subject did not have any quantifiable systemic levels.

In this study, there was one subject who had treated BSA of 20% with a predicted target dose of 8.2 mg. In this subject, the Week 2 AUC_{0-24} values were 53.2 and 425 h*ng/mL for roflumilast and the N-oxide metabolite, respectively. The systemic exposure in this subject was generally comparable to the mean value that was extrapolated using the week 2 trough concentrations (see Table 11).

The mean treated BSA of the PK Population at Week 2 for the maximal usage evaluation (N=9) was 9.44% (minimum of 3.0%, maximum of 20.0%), with a target dose of 3.9 mg. Following daily topical administration for 2 weeks, the mean ± SD roflumilast and N-oxide pre-dose concentrations were 2.15 ± 1.25 and 22.4 ± 15.5 ng/mL, respectively (Table 11). The arithmetic mean ± SD extrapolated roflumilast AUC_{0-24} values were 51.6 ± 29.9 h*ng/mL and 539 ± 372 h*ng/mL for Week 2 roflumilast and N-oxide AUC_{0-24}, respectively.

At Week 4, the mean treated BSA for the 10 subjects was 9.6%, with a target dose of 3.9 mg. Following daily topical administration for 4 weeks, the mean (SD) roflumilast and

N-oxide pre-dose concentrations were 2.04 (1.33) and 15.8 (9.91) ng/mL, respectively. Systemic exposure was not quantifiable in one subject. The arithmetic mean (SD) extrapolated AUC_{0-24} values were 49.0 (31.9) and 379 (238) h*ng/mL for roflumilast and N-oxide, respectively, at Week 4.

Table 11: Summary of Predose Plasma Concentrations and Extrapolated AUC_{0-24} Values Following Daily Topical Roflumilast Cream 0.3% Administration (Week 2 and Week 4), PK Population

	Treated BSA (%)	Target Dose (mg)	Roflumilast				N-Oxide			
			Conc (ng/mL)	DN Conc (ng/mL/mg)	AUC0-24 (h·ng/mL)	DN AUC0-24 (h·ng/mL/mg)	Conc (ng/mL)	DN Conc (ng/mL/mg)	AUC0-24 (h·ng/mL)	DN AUC0-24 (h·ng/mL/mg)
Week 2 (maximal usage evaluation)										
N	9	9	9	9	9	9	9	9	9	9
Mean (SD)	9.44 (5.57)	3.85 (2.27)	2.15 (1.25)	0.743 (0.665)	51.6 (29.9)	17.8 (16.0)	22.4 (15.5)	7.35 (5.99)	539 (372)	176 (144)
CV%	59.0	59.0	58.0	89.5	58.0	89.5	69.1	81.4	69.1	81.4
Median	8.00	3.26	2.17	0.561	52.1	13.5	20.0	4.86	480	117
Min, max	3.00, 20.0	1.22, 8.16	0.483, 4.09	0.148, 2.22	11.6, 98.2	3.55, 53.3	4.72, 49.6	1.45, 17.4	113, 1190	34.7, 417
Geo mean	8.05	3.28	1.76	0.536	42.2	12.9	17.4	5.30	418	127
Week 4										
N	10	10	10	10	10	10	10	10	10	10
Mean (SD)	9.60 (5.27)	3.92 (2.15)	2.04 (1.33)	0.623 (0.396)	49.0 (31.9)	15.0 (9.51)	15.8 (9.91)	4.85 (3.51)	379 (238)	116 (84.2)
CV%	54.9	54.9	65.1	63.6	65.1	63.6	62.8	72.4	62.8	72.4
Median	9.00	3.67	1.86	0.528	44.6	12.7	16.2	4.59	389	110
Min, max	3.00, 20.0	1.22, 8.16	0.261, 4.63	0.0582, 1.13	6.26, 111	1.40, 27.2	2.83, 30.2	0.842, 10.8	67.9, 725	20.2, 260
Geo mean	8.31	3.39	1.58	0.467	38.0	11.2	12.3	3.62	295	87.0

AUC0-24 = area under the plasma concentration-time curve from time zero to 24 hours; BSA = body surface area; Conc = predose concentration; CV = coefficient of variation; DN = dose normalized, calculated as Value / Target Dose Applied; extra = extrapolated; Geo = geometric; PK = pharmacokinetic(s); SD = standard deviation. Note: AUC0-24 is extrapolated from predose concentration values.
Source: Clinical Study Report ARQ-151-216; Appendix 16.1.13.1, Table 3

Following daily administration for 2 weeks the mean ± SD body surface area (BSA) involvement of 9.4 ± 5.57% and the mean ± SD systemic exposure (AUC_{0-24}) was 51.6 ± 29.9 and 539 ± 372 h*ng/mL in children aged from 2-5 years. The systemic exposure in subjects 2-5 years of age was slightly lower compared the systemic exposure in children aged 6-11 years and adults. The mean ± SD AUC_{0-24} was 75.6 ± 87.3% and 693 ± 986 h*ng/mL in children aged from 6-11 years and 72.7 ± 53.1 and 628 ± 648 h· ng/mL for roflumilast and the N-oxide metabolite in adults respectively. The lower systemic exposure in the younger age is generally due to lower % BSA involvement in younger subjects.

Drug Interactions

As stated above, there was no formal drug-drug interaction studies conducted with ZORYVE, but with the coadministration of roflumilast with systemic CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) are known to increase roflumilast systemic exposure and may result in increased adverse reactions. There will be no change in labeling with respect to drug interactions.

Summary of Safety:
Overall, 1 subject (10%) experienced a TEAE. The subject experienced a single Grade 1 TEAE that was considered unrelated to investigational product (IP). No subject experienced SAEs or TEAEs resulting in study discontinuation. An overview of TEAEs is provided in Table 12.

Table 12: Overview of Treatment-emergent Adverse Events (Safety Population)

Category	Roflumilast Cream 0.3% (N = 10) n (%)
Subjects with at least one TEAE	1 (10.0)
Subjects with at least one Grade 1 TEAE	1 (10.0)
Subjects with at least one Grade 2, 3, 4, or 5 TEAE	0
Subjects with at least one related TEAE	0
Subjects with at least one serious TEAE	0
Subjects with at least one TEAE leading to study discontinuation	0
Subjects with at least one TEAE leading to death	0

TEAE = treatment-emergent adverse event
Source: Clinical Study Report ARQ-151-216; Table 14.3.1.1

See Clinical review for additional information on safety.

Bioanalytical method validation: The bioanalytical method used was similar to the one used earlier and the range of Roflumilast and Roflumilast *N*-Oxide was 0.1 ng/mL to 100 ng/mL (the range used earlier was 0.05 ng/mL to 50 ng/mL). The method was validated, and long-term stability established earlier was adequate to support the storage stability of the PK samples in this study (Details of bioanalytical method validation can be found in Clinical Pharmacology review dated 07/06/2023 in DARRTS). The method validation parameters for the standard curve are shown in Table 13. Incurred sample reanalysis was not performed for this study. As the ISR in the original NDA passed and the sample stability in this study was within the established long term storage stability duration. Hence, although ISR assessment was preferred for this study, the ISR results from the original NDA would be supportive.

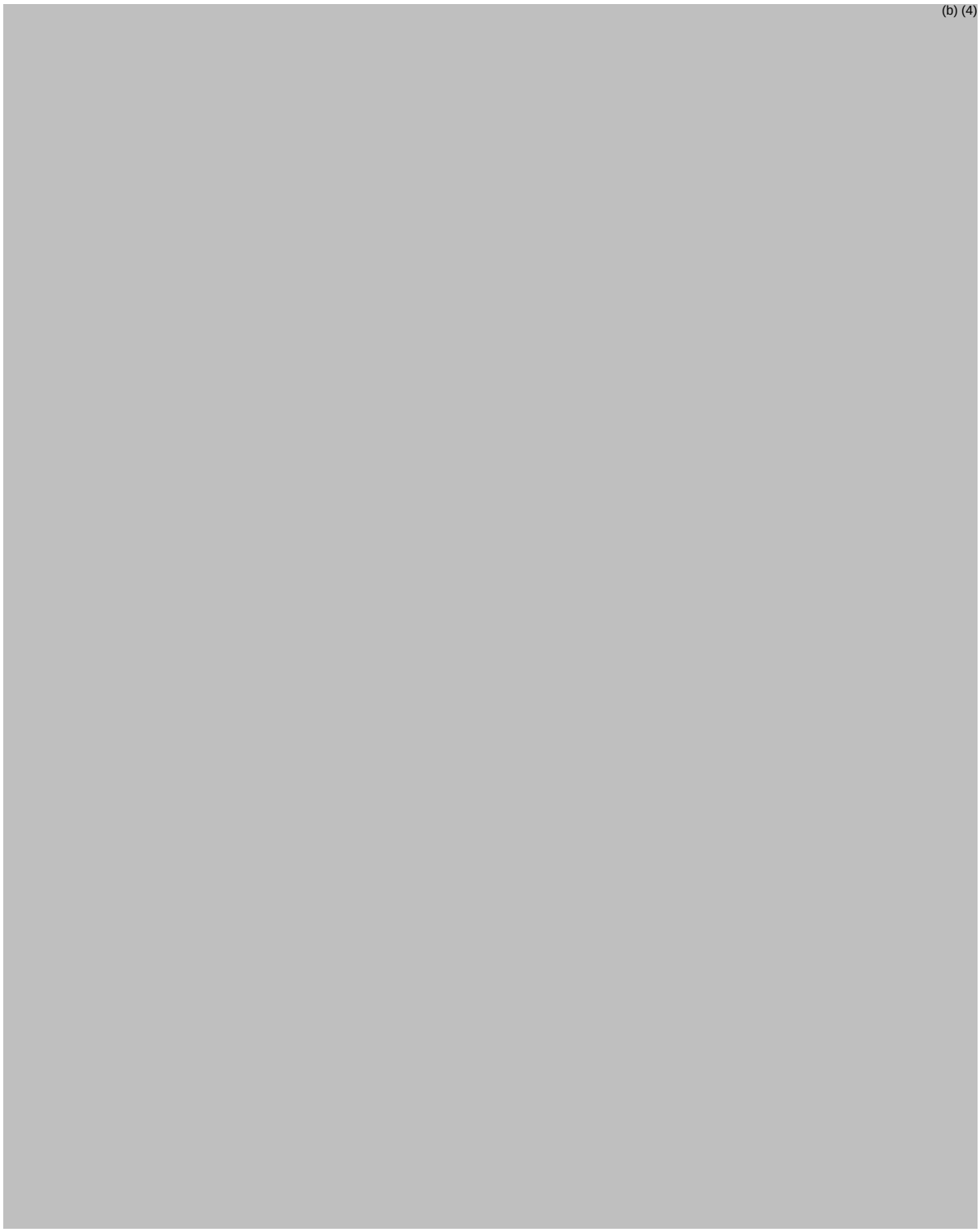
Table 13: Method validation parameters of standard curve

	Roflumilast	Roflumilast *N*-Oxide
Between-run accuracy %	-3.0 to 3.0	-1.8 to 1.2
Between-run precision %	≤10.1%	%CV: ≤7.8%

Source: Report # 201603AEA_ARCMC

Labeling: The following changes are recommended in the applicant's proposed labeling that was submitted where **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates reviewer recommended deletion.

(b) (4)



1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

RAKESH GOLLEN
09/22/2023 05:42:51 PM

CHINMAY SHUKLA
09/22/2023 05:45:12 PM