Clinical Pharmacology Review

NDA #:	204153/S-005
Submission Date:	February 27, 2017 and June 14, 2017
Generic Name:	Luliconazole cream, 1%
Dosage Form:	Cream
Dosage Strength:	1%
Reviewer:	Chinmay Shukla, Ph.D.
Secondary Reviewer:	CAPT. E. Dennis Bashaw, Pharm. D.
Sponsor:	Valent Pharmaceuticals LLC.
Relevant IND(s):	076,049
Submission Type:	Efficacy Supplement
Indication:	Topical treatment of tinea pedis, tinea cruris and tinea corporis in adults

Background: Luliconazole Cream, 1% was approved on November 14, 2013 for the topical treatment of interdigital tinea pedis, tinea cruris and tinea corporis caused by organisms *Trichophyton rubrum* and *Epidermophyton floccosum* in subjects 18 years of age and older.

At the time of original approval one of the Post Marketing Requirements (PMR) was to conduct a maximal use pharmacokinetic (PK) trial with luliconazole cream 1% for the treatment of tinea pedis and tinea cruris in pediatric patients 12 years to less than 17 years of age. This supplement includes the final report of this study and subsequent labeling revisions.

Reviewer comments: *This submission was originally submitted on 02/27/2017. However, the review clock did not start until 06/14/2017 due to delay in payment of PDUFA fees.*

Summary of the maximal use pharmacokinetic study (V01-LUZU-401, MP-1010):
This was an open-label study to assess the pharmacokinetics (PK) of Luliconazole Cream 1% in pediatric patients with moderate to severe interdigital tinea pedis or tinea cruris under maximal use conditions.

Study design: This was an open-label PK study in adolescent subjects (aged 12 to < 18 years) in which 15 subjects with moderate to severe interdigital tinea pedis and 15 subjects with moderate to severe tinea cruris were enrolled and all subjects completed this study. Approximately 3 g of Luliconazole cream was administered once daily in the morning for 15 days in subjects with tinea pedis and once daily in the morning for 8 days in subjects with tinea cruris. In subjects with tinea pedis the drug was applied to the top surface of both feet up to the ankles and in subjects with tinea cruris the drug was applied on the groin, thigh and abdomen area

PK assessment: Plasma levels of circulating luliconazole and the Z-form metabolite were measured at the following time points:

- Subjects with tinea pedis:

- Prior to study drug application on Days 1, 8, and 15
- 1, 3, 6, 9, 12, and 24 hours after study drug application on Days 1, 8, and 15

- Subjects with tinea cruris:
  - Prior to study drug application on Days 1 and 8
  - 1, 3, 6, 9, 12, and 24 hours after study drug application on Days 1 and 8

PK results: Summary of PK results of luliconazole in subjects with tinea pedis is shown in Table 1 and in subjects with tinea cruris is shown in Table 2 and the PK profile in subjects with tinea pedis is shown in Figure 1 and in subjects with tinea cruris is shown in Figure 2.

Table 1: Summary of PK parameters on Day 1, Day 8 and Day 15 in subjects with tinea pedis

	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-12} (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)	$T_{1/2}$ (h)
Day 1					
Both Genders					
N	15	15	15	15	0
Arithmetic Mean	1.80	0.00	8.61	20.47	--
SD	1.86	0.00	6.75	14.47	--
CV%	103.30	--	78.36	70.68	--
Minimum, Maximum	0.0, 7.0	0.0, 0.0	1.6, 24.9	3.3, 59.5	--
Day 8					
Both Genders					
N	15	15	15	15	1
Arithmetic Mean	3.93	1.73	32.69	64.94	20.13
SD	1.67	1.53	15.64	32.47	--
CV%	42.40	88.49	47.87	49.99	--
Minimum, Maximum	1.0, 6.0	0.0, 5.0	8.1, 58.7	15.4, 121.3	20.1, 20.1
Day 15					
Both Genders					
N	15	15	15	15	0
Arithmetic Mean	3.27	1.67	29.78	60.38	--
SD	1.71	1.54	19.08	37.92	--
CV%	52.34	92.58	64.07	62.79	--
Minimum, Maximum	1.0, 8.0	0.0, 6.0	5.8, 81.8	11.4, 159.8	--

Note: Plasma concentration values below the limit of quantitation are reported as 0.0 for calculating summary statistics.

SD = Standard Deviation; CV% = Coefficient of Variation

Table 2: Summary of PK parameters on Day 1 and Day 8 in subjects with tinea cruris

	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-12} (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)	$T_{1/2}$ (h)
Day 1					
Both Genders					
N	15	15	15	15	0
Arithmetic Mean	9.80	0.07	75.72	157.07	--
SD	5.94	0.26	48.92	92.18	--
CV%	60.64	387.30	64.61	58.68	--
Minimum, Maximum	0.0, 21.0	0.0, 1.0	0.7, 169.7	1.8, 286.8	--
Day 8					
Both Genders					
N	15	15	15	15	3
Arithmetic Mean	15.40	7.20	145.41	266.06	49.77
SD	13.62	6.99	137.08	236.07	22.74
CV%	88.42	97.11	94.27	88.73	45.70
Minimum, Maximum	0.0, 52.0	0.0, 20.0	5.0, 518.2	8.9, 888.2	34.7, 75.9

Note: Plasma concentration values below the limit of quantitation are reported as 0.0 for calculating summary statistics.

SD = Standard Deviation; CV% = Coefficient of Variation

Figure 1: Luliconazole Plasma Concentration in ng/mL (Mean ± SD) on Day 1, Day 8, and Day 15 in subjects with tinea pedis

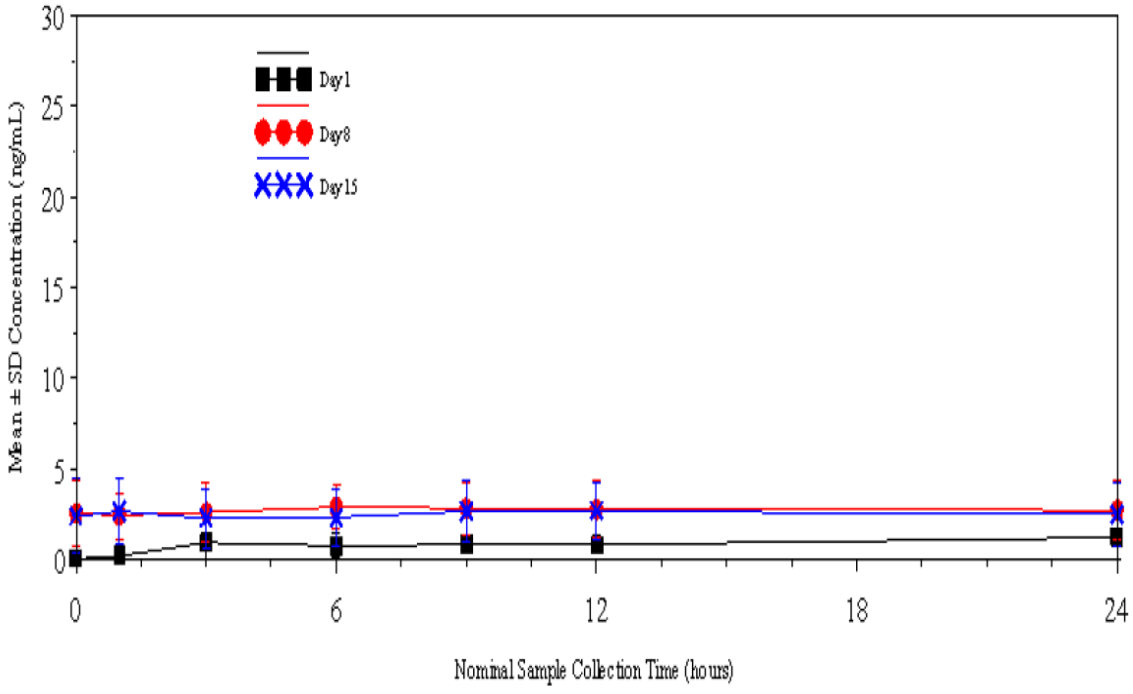
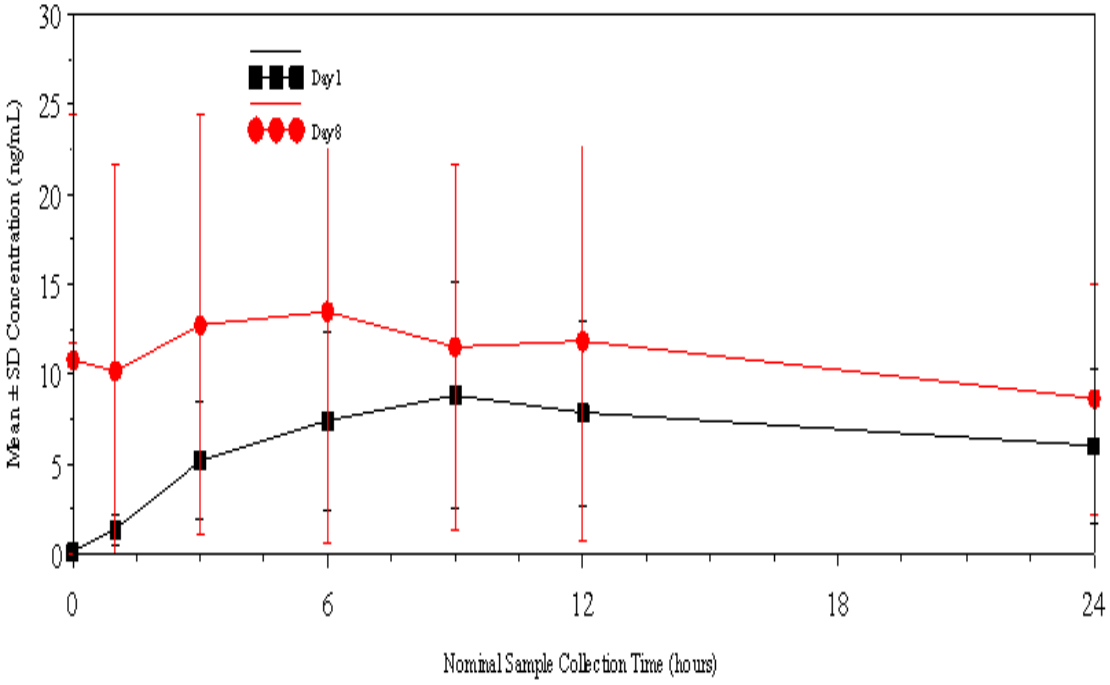


Figure 2: Luliconazole Plasma Concentration in ng/mL (Mean ± SD) on Day 1 and Day 8 in subjects with tinea cruris



Reviewer comments: *Since there were only 2 females in tinea pedis group and 5 females in tinea cruris group, effect of gender on PK will not be reported because of very few females.*

In subjects with tinea pedis, the plasma concentrations of the metabolite z-luliconazole (15 to 250 times less active than the parent) were below the limit of quantification (i.e., <0.05 ng/mL) at all time points on Day 1. On Day 8 and Day 15, the mean z-luliconazole concentrations in all subjects were less than 0.1 ng/mL (range 0.03 to 0.08 ng/mL) at all time points. In subjects with tinea cruris, the mean plasma z-luliconazole concentrations were below the limit of quantification (i.e., <0.05 ng/mL) at all time points on Day 1 and Day 8 and as such are considered to be unreliable and any parameters "calculated" using these data points would be equally unreliable hence, they will not be reported in this review.

Reviewer comments: *The applicant was asked to conduct the maximal use PK trial in subjects with both tinea pedis and tinea cruris occurring in the same subject. However, the applicant conducted the study in subjects having the two diseases separately. Comparing the PK data between Table 1 and Table 2, the C_{max} and AUC_{0-24} on Day 8 in subjects with tinea cruris was approximately 3.9 fold and 4.1 fold higher, respectively, compared to subjects with tinea pedis. Hence the overall contribution of tinea pedis to systemic exposure in subjects with both conditions would be expected to result in levels that would be essentially unchanged versus tinea cruris alone given the observed*

variability and as there are no systemic safety concerns with this product, the current study design is considered acceptable.

Identity of the investigational product: Already marketed Luliconazole Cream 1% was used in this study (Lot No. GLCR was manufactured by DPT Laboratories, Ltd., San Antonio, TX 78215).

Disposition of subjects: 30 subjects were enrolled (15 in tinea pedis group and 15 in tinea cruris group). All subjects completed the trial.

Demographics: Summary of demographic data is shown in Table 3.

Table 3: Summary of demographic data

		Tinea Pedis (N=15)	Tinea Cruris (N=15)	All (N=30)
Age (years)	Mean (SD)	14.13 (2.17)	15.27 (1.49)	14.70 (1.91)
	Minimum, Maximum	12.0, 17.0	12.0, 17.0	12.0, 17.0
Sex, n (%)	Male	13 (86.7)	10 (66.7)	23 (76.7)
	Female	2 (13.3)	5 (33.3)	7 (23.3)
Race, n (%)	White	8 (53.3)	6 (40.0)	14 (46.7)
	Black or African American	6 (40.0)	7 (46.7)	13 (43.3)
	Other	1 (6.7)	2 (13.3)	3 (10.0)
Ethnicity, n (%)	Hispanic or Latino	15 (100.0)	15 (100.0)	30 (100.0)
	Not Hispanic or Latin	0	0	0

Treatment compliance: For the tinea pedis population, Luliconazole Cream 1% was applied on-site on Days 1, 2, 8, 9, and 15. Pre-application Luliconazole study product weights were recorded on Day 1 and Day 9; post- application weights were recorded on Day 8 and Day 15. Usage in the tinea pedis group ranged from 17.6 grams up to 33.6 grams during the study. Hence the daily dose ranged from 1.17 g to 2.24 g.

For the tinea cruris population, Luliconazole Cream 1% was applied on-site on Days 1, 2, and 8. Pre-application Luliconazole study product weights were recorded on Day 1; post-application weights were recorded on Day 8. Usage in the tinea cruris group ranged from 19.4 g up to 27 g during the study. Hence the daily dose ranged from 2.43 g to 3.38 g.

How does the systemic exposure of luliconazole in adolescent subjects compare with adults in the original NDA submission?

The adult PK data following application of luliconazole cream in subjects with tinea pedis and tinea cruris is shown in Table 4. (This data is obtained from the original NDA review. See Clinical Pharmacology review in DARRTS dated 07/26/2013).

Table 4: PK data in adult subjects with tinea pedis and tinea cruris (Study MP-1007) obtained from original NDA review

Parameter	Interdigital Tinea pedis			Tinea Cruris		
	Study Day			Study Day		
	1 N=12	8 N=11	15 N=11	1 N=8	8 N=8	15 N=8
C_{max} (ng/mL)	0.396 (0.7562)	0.565 (0.4393)	0.931 (1.2321)	4.906 (2.5053)	5.633 (2.3069)	7.358 (2.6618)
T_{max} (hr)	16.9 (9.39)	12.4 (10.29)	5.8 (7.61)	21.0 (5.55)	6.3 (4.46)	6.5 (8.25)
AUC_{0-12} (ng*hr/mL)	2.82 (6.588)	5.28 (4.164)	9.32 (13.529)	32.81 (16.006)	54.40 (30.091)	64.45 (27.780)
AUC_{0-24} (ng*hr/mL)	6.88 (14.5)	10.41 (7.878)	18.74 (27.046)	85.1 (43.695)	106.93 (57.571)	121.74 (53.361)

Notes: Since BLQ were replaced with 0.05 ng/mL, C_{max} and AUC values in a subject with no measurable concentration were 0.05 ng/mL and 1.2 ng*h/mL, respectively.

Reviewer comments:

Tinea pedis:

This is 15 day treatment. Comparing the systemic exposure on Day 15 between adolescent (Table 1) and adults (Table 4), the Cmax and AUC_{0-24} in adolescent subjects were approximately 3.5 and 3.2 fold higher, respectively compared to adults.

Tinea cruris:

This is 8 day treatment. Comparing the systemic exposure on Day 8 between adolescent (Table 2) and adults (Table 4), the Cmax and AUC_{0-24} in adolescent subjects were approximately 2.7 and 2.5 fold higher, respectively compared to adults.

Drug interaction: In an information request sent to the applicant on August 22, 2017; the applicant was asked to address drug interaction potential with the higher systemic exposure of luliconazole in adolescent subjects, especially with tinea cruris.

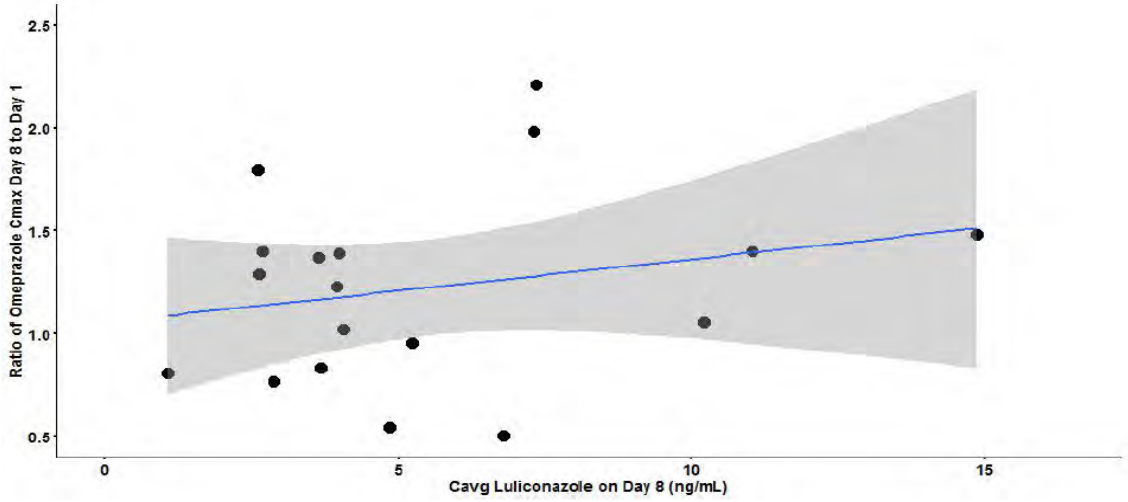
The applicant has already conducted an in-vivo drug interaction study (MP-1012) in adult subjects with tinea pedis and tinea cruris to assess the inhibition potential of luliconazole on the activity of enzyme CYP2C19 (the most sensitive enzyme). Omeprazole was used as a probe substrate and the results of the in-vivo drug interaction study suggested that luliconazole is considered a weak inhibitor of CYP2C19 based on the small increase in omeprazole systemic exposure in patients with tinea cruris and tinea pedis (See clinical pharmacology review in DARRTS dated 04/26/2016).

In order to address the drug interaction concern due to increased exposure in adolescent subjects, the applicant used the PK data from the drug interaction study (MP-1012) and performed linear regression analysis between the average plasma concentration (C_{avg}) of

luliconazole at steady state and the fold increases in exposure of omeprazole (see Figure 3 and Figure 4). The parameters of linear regression analysis are shown in Table 5.

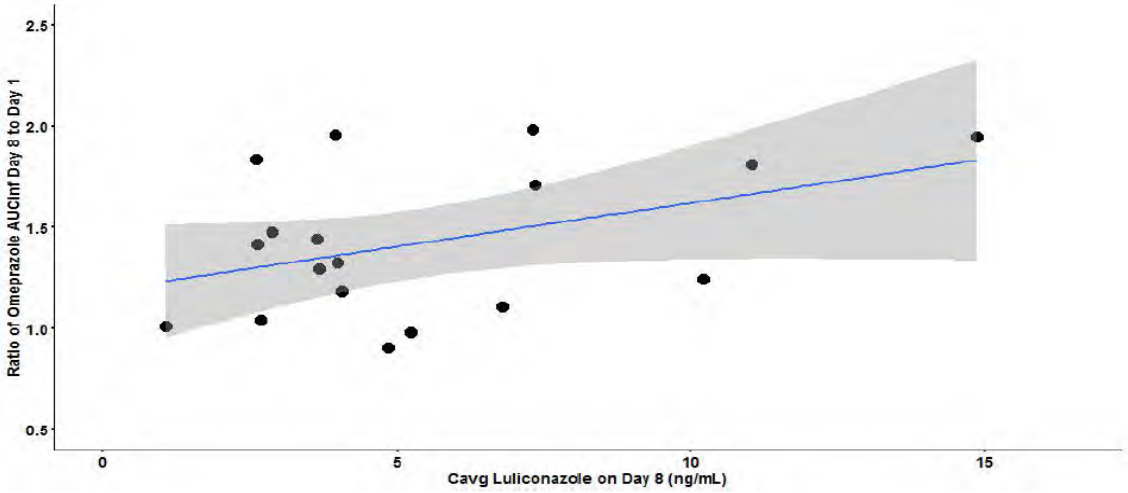
Reviewer comments: *The choice of C_{avg} instead of C_{max} is reasonable because the PK profile of luliconazole in subjects with tinea cruris on Day 8 was fairly flat in both adolescent subjects (see Figure 2) and adult subjects with tinea cruris (For adult subject PK profile, see clinical pharmacology review of the original NDA in DARRTS dated 07/26/2013).*

Figure 3: Relationship between the Fold Increase in C_{max} of Omeprazole and the C_{avg} on Day 8 of Luliconazole (Adult DDI Study MP-1012)



Blue line: Linear regression line; Grey area: 95% prediction interval (2.5th and 97.5th percentiles); Circles: Observed omeprazole exposure ratio from Day 8 to Day 1.

Figure 4: Relationship between the Fold Increase in AUC_{inf} of Omeprazole and the C_{avg} on Day 8 of Luliconazole (Adult DDI Study MP-1012)



Blue line: Linear regression line; Grey area: 95% prediction interval (2.5th and 97.5th percentiles); Circles: Observed omeprazole exposure ratio from Day 8 to Day 1.

Table 5: Summary of the Linear Regression Parameters (Study MP-1012)

Independent Variable	Dependent Variable	Number of Subjects	*Linear Relationship Coefficients
Luliconazole C_{avg} on Day 8	Day 8 to Day 1 C_{max} ratio (Omeprazole)	18	$\beta0 = 1.06$; $\beta1 = 0.0307$
	Day 8 to Day 1 AUC_{inf} ratio (Omeprazole)	18	$\beta0 = 1.19$; $\beta1 = 0.0433$

* Day 8 to Day 1 omeprazole exposure ratio = $\beta0 + \beta1 \times C_{avg}$ of luliconazole on Day 8; $\beta1$ is the slope of the linear regression, representing the increase in the ratio of omeprazole exposure with increasing luliconazole C_{avg} (ng/mL).

The parameters (β0 and β1) obtained from the linear regression analysis were used to predict the CYP2C19 drug interaction potential for relevant plasma luliconazole average concentrations on day 8 in the populations enrolled in studies MP-1012 (DDI study), MP-1007 (Original maximal use PK study in adults) and MP-1010 (Adolescent maximal use study), on an individual basis, by means of the predicted fold increases in omeprazole C_{max} and AUC_{inf} (Table 6).

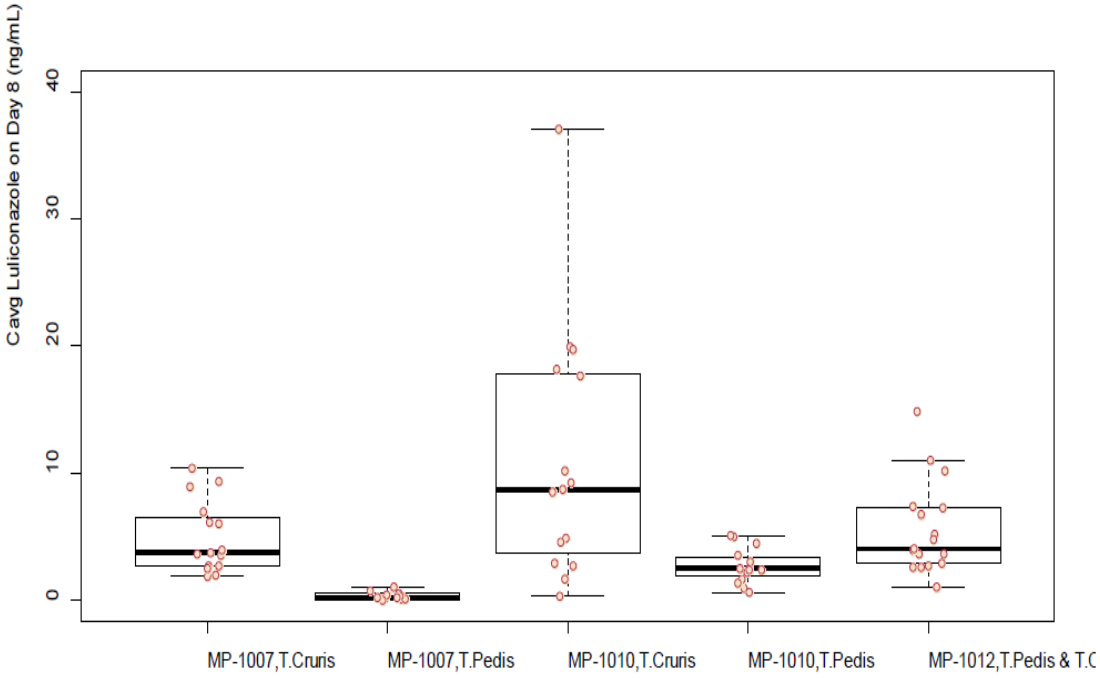
Table 6: Predicted Fold Increase in Omeprazole C_{max} and AUC_{inf} based on Observed Luliconazole Steady-State Average Concentration (C_{avg}) Under Maximal Use Conditions according to a Linear Regression Model

Study	Population	Observed Median C_{avg} (ng/mL) [5th and 95th percentile]	Predicted Median fold increases in omeprazole AUC_{inf} [5th and 95th percentile]	Predicted Median fold increases in omeprazole C_{max} [5th and 95th percentile]
MP-1012	Adults diagnosed with T. pedis and T. cruris (N=18)	4.02 [1.07, 14.9]	1.36 [1.23, 1.83]	1.18 [1.09, 1.51]
MP-1007	Adult patients diagnosed with T. pedis (N=14)	0.222 [0.0518, 1.03]	1.20 [1.19, 1.23]	1.062 [1.057, 1.087]
	Adult patients diagnosed with T. cruris (n=15)	3.80 [1.83, 10.4]	1.35 [1.27, 1.64]	1.17 [1.11, 1.37]
MP-1010	Pediatric patients diagnosed with T. pedis (N=15)	2.54 [0.641, 5.056]	1.30 [1.22, 1.41]	1.13 [1.07, 1.21]
	Pediatric patients diagnosed with T. cruris (n=15)	8.71 [0.372, 37.0]	1.57 [1.20, 2.79]	1.32 [1.07, 2.19]

From the table above, the predicted median fold increase in omeprazole AUC_{inf} and C_{max} was <2 fold in both adults and adolescent subjects. The predicted potential for inhibition of CYP2C19 indicates that luliconazole is expected to act mostly as a moderate to weak CYP2C19 inhibitor in adolescent patients under maximal use conditions (The predicted 95th percentile fold increase in omeprazole C_{max} and AUC_{inf} of 2.19 and 2.79, respectively under maximal use scenario).

It should be noted that predicted fold increases in omeprazole PK had a wider spread in the pediatric population as a reflection of more variable and higher plasma concentrations of luliconazole from Study 1010 (Figure 5). The applicant has justified this increased exposure in adolescent due to the fact that skin permeability in children could be higher than in adults due to a number of reasons such as higher ratio of total body surface area to body weight and consistency and thickness of the stratum corneum.

Figure 5: Average Plasma Concentrations (C_{avg}) of Luliconazole on Day 8 displayed by Study and Diagnosis for Studies MP-1007, MP-1010, and MP-1012



In the maximal use PK trial in adults and adolescent subjects the dose of Luliconazole Cream was approximately around 3 g. However, in the clinic the mean dose of Luliconazole Cream was approximately 1 g.

The applicant calculated luliconazole C_{avg} values for 1 g daily dose assuming linear luliconazole PK, these concentrations were used to then predict omeprazole exposure ratios during clinical use (Table 7).

Table 7: Predicted Fold Increase of Omeprazole C_{max} and AUC_{inf} based on predicted Luliconazole Steady-State Average Concentration (C_{avg}) according to a Linear Regression Model when 1 g Luliconazole Cream 1% is applied

Study Population	Predicted Median Cavg* (ng/mL) [5th and 95th percentile]	Predicted fold increases in omeprazole AUC_{inf} Median [5th and 95th percentile]	Predicted Median fold increases in omeprazole AUC_{inf} [5th and 95th percentile]
Adult patients T. pedis and T. cruris	1.34 [0.357, 4.97]	1.25 [1.20, 1.40]	1.10 [1.07,1.21]
Adult patients T. pedis	0.0740 [0.0173, 0.343]	1.189 [1.191,1.203]	1.058 [1.057, 1.066]
Adult patients T. cruris	1.27 [0.610, 3.57]	1.24 [1.21, 1.34]	1.09 [1.07, 1.16]
Pediatric patients T. pedis	0.847 [0.213, 1.69]	1.22 [1.20, 1.26]	1.08 [1.06, 1.11]
Pediatric patients T. cruris	2.90 [0.123, 12.3]	1.31 [1.19, 1.72]	1.14[1.06, 1.43]

* C_{avg} for different populations for 1 g dose was predicted from the C_{avg} when 3 g dose was given assuming dose proportionality for luliconazole in this dose range.

In this case, the applicant predicted median fold increases in omeprazole C_{max} and AUC_{inf} in all populations studied was less than 2-fold in a situation of maximal use.

Reviewer comments: *It is noted that in this study in subjects with tinea cruris, drug was applied at the clinical site only on Day 1, 2 and 8. On other days, drug was applied at home. The daily dose ranged from 2.43 g to 3.38 g. The mean amount of formulation used per day in the maximal use PK trial in adults (MP-1007) was 3.53 g and range was 2.72 g and 4.90 g and the amount of formulation used in the Phase 3 trial in tinea cruris (MP-1000-01) was 2.16 g (range 0.17 g to 4.69 g) (median ~ 2.20 g) (See Clinical Pharmacology review of the original NDA in DARRTS dated 07/26/2013).*

This information on the amount of formulation used in subjects with tinea cruris suggests that by using 1 g daily dose, the sponsor has underestimated the drug interaction potential. Hence this reviewer is of the opinion that the drug interaction potential data in Table 6 would represent a more realistic prediction and the fact that Luliconazole systemic levels are slightly above the borderline between week and moderate inhibition of CYP2C19 cannot be ignored.

Furthermore, the fact that in subjects with tinea cruris the drug application is going to be restricted to not more than 8 days provides certain level of support to the fact that drug interaction in the clinic would be less likely to be observed.

In conclusion, this reviewer opines that the labeling should indicate that in subjects with tinea cruris, luliconazole systemic concentrations suggests that it could be a moderate inhibitor of CYP2C19 in this population.

Bioanalytical method validation: The bioanalytical method used was similar to the one used earlier with the exception that the range of luliconazole and Z-luliconazole was 0.05 ng/mL to 10 ng/mL (the range used earlier was 0.05 ng/mL to 50 ng/mL). The method was validated and long term stability established was adequate to support the storage stability of the PK samples in this study (Details of original bioanalytical method validation can be found in Clinical Pharmacology review dated 07/26/2013 in DARRTS). The method validation parameters for the standard curve is shown in Table 8.

Table 8: Method validation parameters of standard curve

	Luliconazole	***Z-form metabolite***
Between-run accuracy %	-3.3 to 3.5	-3.5 to 4.2
Between-run precision %	2.8 to 5.9	2.4 to 5.8

Reviewer comment: *The inter-run % accuracy and precision for the quality control samples for luliconazole was -2.0% to 2.4% and 4.2% to 9.7% and for Z-form metabolite was -4.0 % to -2.9% and 3.3% to 7.1%, respectively. Incurred sample reanalysis was conducted for 53 out of 525 samples (~ 10 % of the samples) and approximately 68% samples were within the ± (b) (4) % acceptable limit.*

Summary of adverse events: An overall summary of adverse events (AEs) is provided in Table 9.

Table 9: Overall Summary of Adverse Events

	Tinea Pedis (N=15)		**Tinea Cruris (N=15)**		**Overall (N=30)**	
	Number of Events	Number of Subjects	Number of Events	Number of Subjects	Number of Events	Number of Subjects
Subjects with any AE	3	3 (20.0)	1	1 (6.7)	4	4 (13.3)
Subjects with any TEAE	2	2 (13.3)	1	1 (6.7)	3	3 (10.0)
Subjects with any SAE	0	0	0	0	0	0
Subjects with any TEAE leading to Withdrawal	0	0	0	0	0	0

AE = adverse event; TEAE = treatment-emergent AE; SAE = serious AE

A total of 3 AEs were reported in 3 subjects in the tinea pedis group and 1 AE was reported in 1 subject in the tinea cruris group. Treatment-emergent AEs were reported by 2 subjects in the tinea pedis group and 1 subject in the tinea cruris group (Table 10). There were no serious AEs reported. There were no subjects discontinued from the study due to an AE. No serious AEs were reported and there were no deaths in this study.

Table 10: Treatment-emergent Adverse Events by System Organ Class and Preferred Term

	Tinea Pedis n=15 n (%)	Tinea Cruris n=15 n (%)	Overall N=30 n (%)
Gastrointestinal disorders	1 (6.7)	0	1 (3.3)
Diarrhea	1 (6.7)	0	1 (3.3)
Infections and Infestations	0	1 (6.7)	1 (3.3)
Nasopharyngitis	0	1 (6.7)	1 (3.3)
Nervous system disorders	1 (6.7)	0	1 (3.3)
Headache	1 (6.7)	0	1 (3.3)

Note: Treatment-emergent adverse events were those AEs with an onset on or after the first application of study medication. Counts reflect numbers of subjects reporting one or more adverse events that map to the MedDRA preferred term.

Reviewer comments: *For additional information on drug safety, see Clinical review.*

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.

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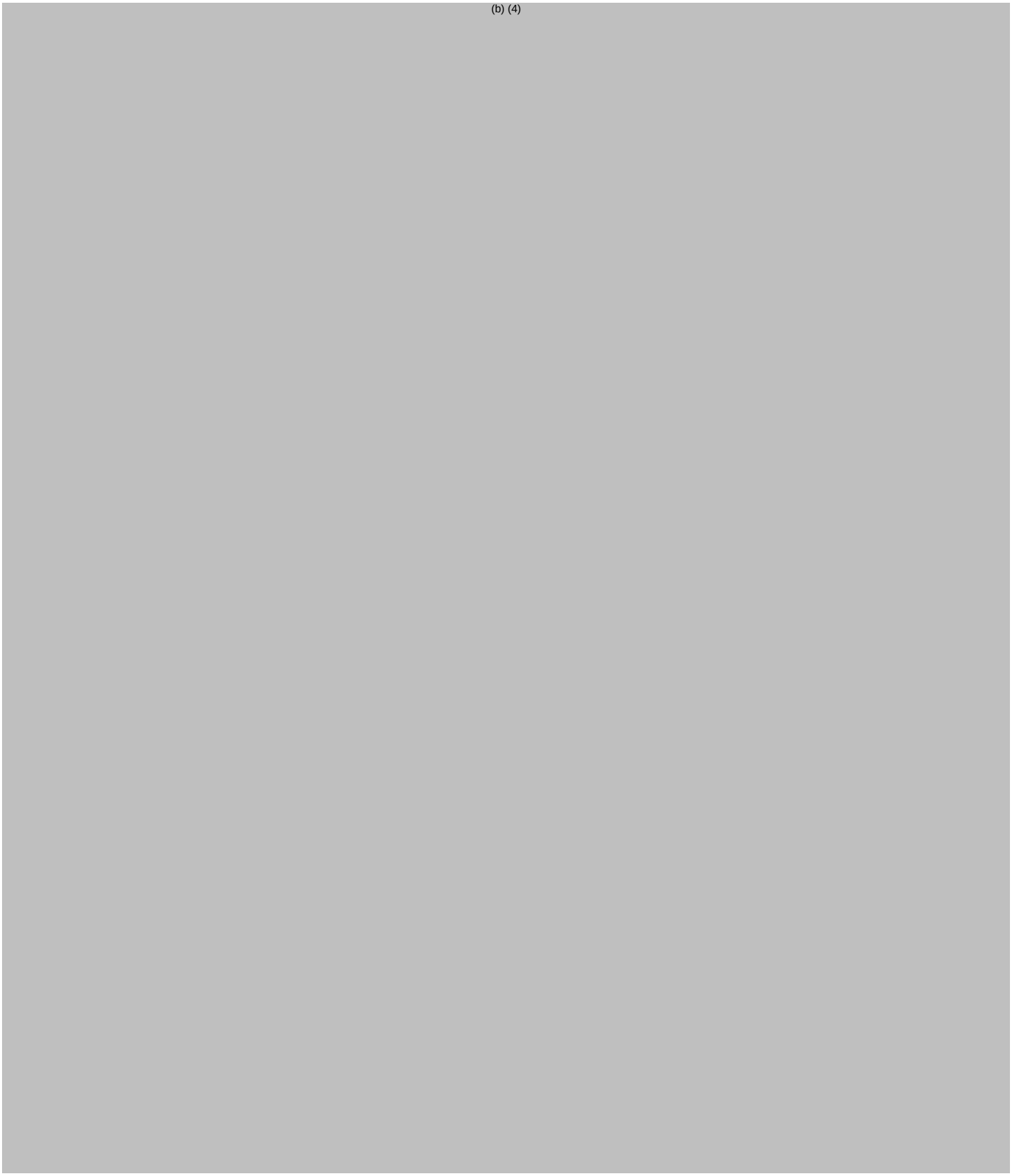

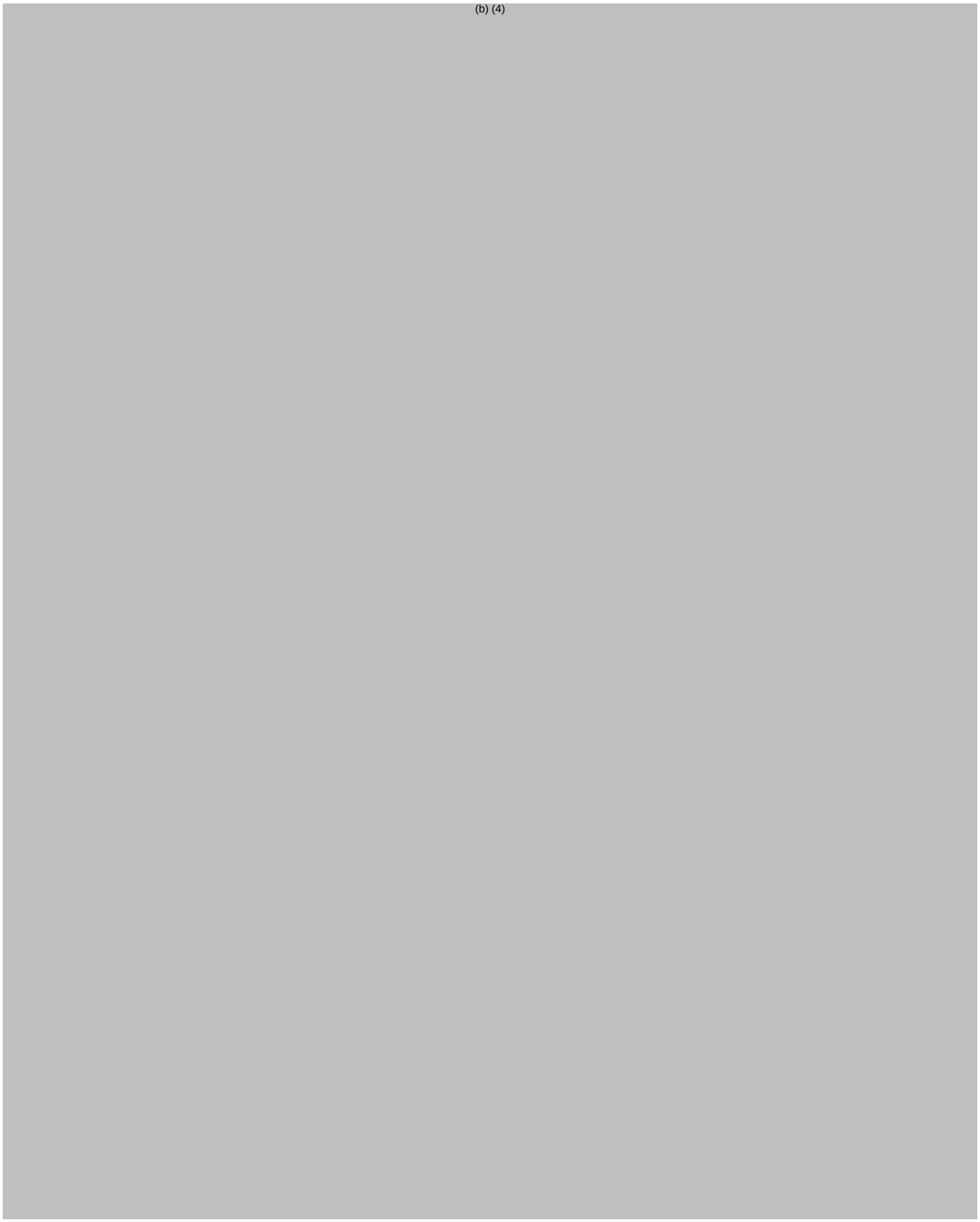
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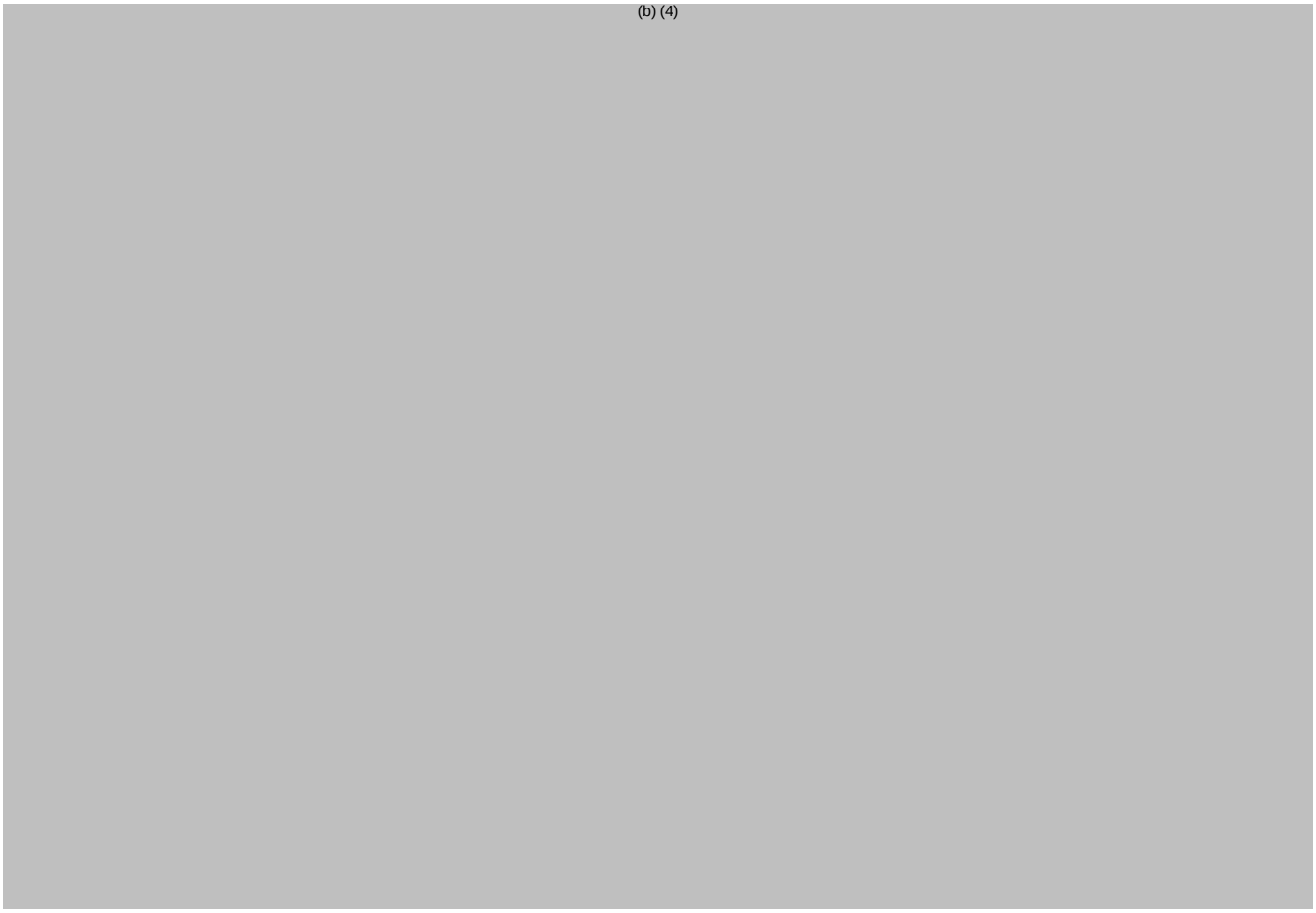
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