Office of Clinical Pharmacology Integrated Review

NDA or BLA Number	204026/S27
Link to EDR	\\CDSESUB1\evsprod\NDA204026\0230
Submission Date	5/20/2020
Submission Type	Efficacy Supplement Priority
Brand Name	Pomalyst
Generic Name	Pomalidomide
Dosage Form and Strength	Capsules: 1 mg, 2 mg, 3 mg, and 4 mg
Route of Administration	Oral
Approved Indication	For the treatment of adult patients: • in combination with dexamethasone, for patients with multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy. • with AIDS-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART) or in patients with KS who are HIV-negative.
Approved Dosing Regimen	MM: 4 mg once daily KS: 5 mg once daily With or without food on Days 1 through 21 of repeated 28-day cycles
Applicant	Celgene Corporation
OCP Division	DCP 2
OND Division	DO3
Clin Pharm Primary Reviewers	Runyan Jin, Ph.D., Youwei Bi, Ph.D.
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1. EXECUTIVE SUMMARY

Pomalidomide (Pomalyst®) has been approved for two indications, multiple myeloma (MM) and Kaposi sarcoma (KS). The approved dosage of pomalidomide is 4 mg/day for adult MM patients and 5 mg/day for adult KS patients, taken orally with or without food daily (QD) on Days 1 through 21 of repeated 28-day cycles until disease progression. The safety and effectiveness of pomalidomide had been studied in pediatric patients with brain tumors in a Phase I dose escalation study using 3 dose levels of 1.9, 2.6 and 3.4 mg/m^2 with the same dosing interval. The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of 2.6 mg/m^2 pomalidomide in pediatric patients was determined; however, the effectiveness was not established in two open-label pediatric studies. Pomalidomide exposure in 55 pediatric patients aged 4 to < 17 years old was higher than the exposure observed in adult KS patients but within the range observed in adult MM patients at the same BSA-based dose.

1.1 Recommendations

The Clinical Pharmacology and Pharmacometrics review teams have reviewed the information contained in the NDA 204026 efficacy supplement (S27). This sNDA is approvable from a clinical pharmacology perspective provided that the applicant and FDA come to a mutually satisfactory agreement regarding the labeling language.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Pomalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Pomalyst® (pomalidomide) has been approved since 2013 for the treatment of adult patients with multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy. In May 2020, it was approved under accelerated approval for the treatment of adult patients with AIDS-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART) or of adult patients with KS who are HIV-negative.

The approved dosage of pomalidomide is 4 mg/day in combination with dexamethasone for adult MM patients and 5 mg/day for adult KS patients, taken orally with or without food on Days 1 through 21 of repeated 28-day cycles until disease progression. The available commercial dosage strength is in 1 mg, 2 mg, 3 mg, and 4 mg capsules for oral administration. Per Pomalyst labeling, mean pomalidomide AUC and C_{max} at steady-state were 860 ng·h/mL and 75 ng/mL, respectively, in MM patients who received Pomalyst 4 mg QD alone or in combination with dexamethasone. In KS patients who received Pomalyst 5 mg QD, mean pomalidomide AUC and C_{max} at steady state were 462 ng·h/mL and 53 ng/mL, respectively. Refer to Pomalyst labeling for detailed PK and PD information of pomalidomide.

Pooled data from two pediatric studies (Study PBTC-043 and Study CC-4047-BRN-001) using the population PK analysis (PopPK) estimated that mean pomalidomide AUC and C_{max} at steady state were 860 ng·h/mL and 71 ng/mL, respectively following the RP2D of 2.6 mg/m^2 in 55 pediatric patients aged from 4 to < 17 years old. Comparing to pomalidomide exposure in adult patients, AUCss in pediatric patients was higher than those observed in adult KS patients, but within the range observed in adult MM patients at the same dose by body surface area.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The MTD and RP2D of pomalidomide for pediatric patients with brain tumors was determined to be 2.6 mg/m^2 orally, QD on Days 1-21 of a 28-day cycle in the dose escalation Study PBTC-043. The 2.6 mg/m^2 dose was then evaluated in the phase 2 parallel-group pediatric Study CC-4047-BRN-001; however, effectiveness was not established in pediatric patients with high-grade glioma, medulloblastoma, ependymoma, or diffuse intrinsic pontine glioma (DIPG). The efficacy, safety and PK information of pomalidomide in pediatric patients are updated in Section 8.4 Pediatric Use in the Pomalyst labeling.

2.2.2 Therapeutic individualization

NA

2.3 Outstanding Issues

None

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3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

For brevity, only QBR questions related to the current efficacy supplement submission are addressed below. For additional information, please refer to the clinical pharmacology review for MM indication in DARRTS dated 12/21/2012, the clinical pharmacology review for labeling supplement 12 and 14 regarding the effects of hepatic and renal impairment, food, CYP1A2 induction and inhibition on pomalidomide PK in DARRTS dated 6/24/2016 and the section of clinical pharmacology review in the Multidisciplinary Review and Evaluation for KS indication in DARRTS dated 5/14/2020.

3.1 Overview of the Product and Regulatory Background

Current NDA efficacy supplement is submitted to update the Pomalyst labeling Section 8.4 Pediatric Use based on the results from two completed pediatric studies PBTC-043 and CC-4047-BRN-001. The major regulatory activities regarding the pediatric written request for pomalidomide and its amendments are briefly listed in Table 1.

Table 1: Summary of Major Regulatory Activities Relating to Pediatric Written Request

Date	Description
05 Aug 2015	Celgene Proposed a Pediatric Study Request submission that was submitted to the FDA to NDA 204026, SN 0119
20 Nov 2015	The FDA extended a Written Request to Celgene
04 May 2016	Celgene proposed changes to the pomalidomide Pediatric Written Request to NDA 204026, SN 0141
13 Jul 2016	The FDA extended a revised Pediatric Written Request to Celgene – Amendment #1
22 Jul 2016	The FDA and Celgene agreed to the Written Request NDA 204026, SN 0149
06 to 20 Apr 2017	(b) (4)
25 Feb 2019	Celgene proposed a change to the FDA Written Request NDA 204026, SN 0198
08 Jul 2019	The FDA extended a revised Pediatric Written Request to Celgene – Amendment #2
30 Aug 2019	The FDA and Celgene agreed to the Written Request NDA 204026 SN 0209
(b) (4)	

FDA = Food and Drug Administration; NDA = New Drug Application; SN = serial number.

(Data source: Table 1 on page 6 in the Clinical Overview)

3.2 General Pharmacological and Pharmacokinetic Characteristics

Plasma samples of pomalidomide for PK assessment in pediatric patients were collected from 70 patients in the phase 1 Study PBTC-043 (N=29) and the phase 2 Study CC-4047-BRN-001 (N=41). The brief study design and PK parameters of pomalidomide for each study are described as below.

Study PBTC-043 was a single-arm, open-label, dose escalation study of pomalidomide for children who were ≥ 3 years and < 21 years of age at study entry with recurrent, progressive, or refractory CNS tumors. Dose levels of pomalidomide in the dose escalation part were 1.9 mg/m^2

(N=6), 2.6 mg/m^2 (N=18) and 3.4 mg/m^2 (N=5). Pomalidomide was administered orally, QD for 21 consecutive days followed by a 7-day rest period, constituting a 28-day cycle. A total of 29 patients from 5 to 20 years old were enrolled and evaluable for efficacy, safety, and PK assessments. Rich PK samples of pomalidomide were collected on Cycle 1 Day 1 (C1D1) from pre-dose to 24 hours post-dose and an additional plasma sample were collected at pre-dose between Day 3 and Day 21. The MTD and RP2D of pomalidomide was determined to be 2.6 mg/m^2 orally, QD on Days 1-21 of a 28-day cycle.

Mean plasma concentrations of pomalidomide following a single oral dose of 1.9, 2.6, or 3.4 mg/m^2 at scheduled PK sampling timepoints were shown in Table 2 and mean PK parameters with their corresponding coefficient of variations (CV%) on C1D1 are listed in Table 3. Overall, $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}inf}$ increased in a nearly dose proportional manner with the increase in pomalidomide dose while the increase in C_{max} was generally less than dose proportional. Median T_{max} occurred 2 to 4 hours with a range of 1 to 24 hours. Mean elimination half-life (t½) were in the range of approximately 5 to 7 hours which were similar among dose groups. CV% values for PK parameters were in the range of 20% to 60% for all three dose groups.

Table 2 Mean Plasma Concentrations (CV%) of Pomalidomide Following a Single Oral dose

		1.9 mg/m^2 N=6		2.6 mg/m^2 N=18		3.4 mg/m^2 N=5	
Day	Nominal Time (h)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%
Day 1	0.0	0.00	NA	0.00	NA	0.00	NA
	0.5	11.7	125	17.5	124	25.5†[4]	88.3†[4]
	1.0	41.6	111	35.8	136	50.8	68.5
	2.0	56.0	76.0	61.1	59.4	80.2	45.1
	4.0	61.2	47.3	68.6	43.5	92.0	25.6
	8.0	43.6	51.0	50.2	58.1	74.6	34.4
	24.0	7.65	76.6	7.14	85.9	16.9	73.8
Days 3-21	0.0	17.8	165	17.8†[15]	142†[15]	41.3	55.3

Where N for a specific time point differed from group N, actual number of observations presented as '†[n]'.
NA = Not applicable.

(Data Source: Table 11-5 on page 76 in the CSR PBTC-043)

Table 3 Mean (CV%) PK Parameters for Pomalidomide Following a Single Oral Dose on C1D1

	1.9 mg/m^2 N=6[c]		2.6 mg/m^2 N=18[d]		3.4 mg/m^2 N=5[e]	
PK Parameter (Units)	Geometric Mean	Geo CV%	Geometric Mean	Geo CV%	Geometric Mean	Geo CV%
Tmax (h) [a]	2.99	1.05-4.12	4.00	1.00-24.3	2.03	1.95-4.02
Cmax (ng/mL)	74.8	59.4	79.2	51.7	104	18.3
Cmax/D [b]	39.4	59.4	30.5	51.7	30.6	18.3
AUC0-24 (h·ng/mL)	704	54.4	782	45.9	1210	40.0
AUC0-24/D [b]	371	54.4	301	45.9	356	40.0
AUC0-inf (h·ng/mL)	798	55.8	766	27.8	1230	57.8
AUC0-inf/D [b]	420	55.8	295	27.8	361	57.8
λz (1/h)	0.128	22.7	0.151	19.7	0.104	54.4
t½ (h)	5.40	22.7	4.58	19.7	6.67	54.4
CL/F (L/h/m^2)	2.38	55.8	3.39	27.8	2.77	57.8
Vz/F (L/m^2)	18.5	34.9	22.4	22.3	26.6	32.2

a: Tmax presented as median and range in place of geometric mean and CV%.
b: Units for dose-normalized Cmax and AUC were (ng/mL)/(mg/m^2) and (h·ng/mL)/(mg/m^2), respectively.

(Data Source: Table 11-7 on page 80 in the CSR PBTC-043)

Study CC-4047-BRN-001 was a multicenter, open-label, parallel-group study to assess the efficacy, safety, and tolerability of pomalidomide in children and young adults < 21 years old with recurrent or progressive primary brain tumors after at least 1 prior standard therapy. The dose of pomalidomide was 2.6 mg/m^2 QD on Days 1 to 21 of a 28-day cycle. The study consisted of 4 parallel strata for each of the following primary brain tumor types: DIPG, ependymoma, high-grade glioma, and medulloblastoma. A total of 57 patients were enrolled and 41 patients aged from 4 to 18 years old who received at least 1 dose of treatment and had at least 1 measurable pomalidomide plasma concentration were included in the PK population. Sparse PK samples were collected at pre-dose and 2-hour post-dose on C1D8 and C1D15.

Mean plasma concentrations (CV%) of pomalidomide by 4 disease strata were shown in Table 4. In general, there was no significantly difference of pomalidomide exposures both at pre-dose and 2-hour post-dose between 4 different disease strata.

Table 4 Mean Plasma Concentrations of Pomalidomide (CV%) by Disease Indication and Scheduled PK Timepoints

	DIPG		Ependymoma		High-grade Glioma		Medulloblastoma	
	Cycle 1 Day 08 (N = 10)	Cycle 1 Day 15 (N = 9)	Cycle 1 Day 08 (N = 6)	Cycle 1 Day 15 (N = 8)	Cycle 1 Day 08 (N = 14)	Cycle 1 Day 15 (N = 14)	Cycle 1 Day 08 (N = 8)	Cycle 1 Day 15 (N = 8)
Predose	11.24 (220.0)	10.67 (273.2)	22.23 (105.5)	8.72 (323.7)	21.48 (95.0)	14.72 (103.2)	9.0 (144.5)	10.38 (94.3)
2-Hour Postdose	61.10 (108.6)	62.04 (106.7)	77.20 (90.0)	97.88 (9.4)	66.40 (119.2)	60.80 (61.3)	89.71 (64.1)	77.08 (61.9)

CV = coefficient of variation; DIPG = diffuse intrinsic pontine glioma.

(Data Source: Table 20 on page 101 in the CSR CC-4047-BRN-001)

In addition, population PK and exposure-response (E-R) analyses were performed to characterize the PK variability of pomalidomide in children and young adults with recurrent or progressive primary brain tumor with the data in 70 patients from the above two studies. Pomalidomide exhibited linear and time-invariant PK with moderate variability. The typical values of apparent clearance (CL/F) and apparent central volume of distribution (Vc/F) were 3.9 L/h and 43 L, respectively. The terminal elimination t½ was estimated to be 7.3 hours. Except for body surface area (BSA), none of the tested covariates, including age, sex, and race had an effect on pomalidomide PK. Refer to the pharmacometrics review in Appendix for details.

Reviewer's Analyses and Comments

A clinical pharmacology information request (IR) was sent to the applicant on 10/6/2020 to request for the clarification and justification to support the proposed labeling statement "(b) (4) " because the dose normalized AUCs in two pediatric studies are 1.7 to 2.2 times higher than those in adult KS patients as shown in Table 5 assuming the average adult BSA is 1.73 m^2 or 1.8 m^2.

Table 5 AUCs and Dose normalized AUCs of Pomalidomide in Adult Patients with KS and MM and in Pediatric Studies

	AUC (ng*h/mL)	Dose normalized AUC (ng*h/mL)/(mg/m^2)		Data Source
Adult Patients				
Dose	5 mg QD	5 mg /1.73 m^2 = 2.9 mg/m^2	5 mg /1.8 m^2 = 2.8 mg/m^2	Approved POMALYST Labeling as of 5/14/2020
KS indication	AUCss= 462	AUCss/D= 159	AUCss/D= 165	
Dose	4 mg QD	4 mg /1.73 m^2 = 2.3 mg/m^2	4mg /1.8 m^2 = 2.2 mg/m^2	
MM indication	AUCss= 860	AUCss/D= 372	AUCss/D= 387	
Pediatric Studies				
Dose	2.6 mg/m^2	2.6 mg/m^2		
Study PBTC-043	AUC_{0-24h}=782	AUC_{0-24h}/D=301		Clinical Study Report
	AUC_{0-inf}=766	AUC_{0-inf}/D=295		
	AUCss=719	AUCss/D=277		Population PK report
Study CC-4047-BRN-001	AUCss=923	AUCss/D=355		

In the applicant's response of 10/15/2020, they stated that it was more appropriate to compare pomalidomide exposures in pediatric studies to adult MM patients than to adult KS patients because pomalidomide exposures in adult KS patients were summarized from only 27 patients

with high variability (CV%=82%) from a single trial. The dose normalized AUCs for pediatric patients are 72% to 95% of those in adult MM patients as shown in Table 5.

FDA acknowledged that pomalidomide exposures in adult KS patients were summarized from a small patient sample size in a single study and the variability for PK parameters was high, while pomalidomide exposures in adult MM patients have been characterized in hundreds of patients from multiple clinical trials. It is reasonable to state that pomalidomide exposure in two pediatric studies was higher than that observed in adult KS patients but within the range observed in adult MM patients at the same dose by BSA. In addition, pomalidomide exposure was updated using PK data in pediatric patients aged < 17 years old pooled from two pediatric studies as shown in Table 6 and the conclusion of exposure comparison between pediatrics and adult patients remains the same.

Table 6 Dose normalized AUC of pomalidomide in Pediatric Patients < 17 years old

	AUC (ng*h/mL)	Dose normalized AUC (ng*h/mL)/(mg/m^2)	Data Source
Pediatric Patients (Age < 17 years old)			
Dose	2.6 mg/m^2	2.6 mg/m^2	
Pooled PK data (N=55) from Study PBTC-043 and CC-4047-BRN-001	AUCss=860	AUCss/D=331	Population PK analyses

As a result, FDA proposes the following labeling language in Section 8.4 regarding pomalidomide exposure in pediatric population: At the same dose by body surface area, pomalidomide exposure in 55 pediatric patients aged 4 to < 17 years old (4 patients aged between 17 and 18 were excluded) was higher than the exposure observed in adult patients with KS but within the range of those observed in adult patients with MM.

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

No. Effectiveness of pomalidomide was not demonstrated in Study CC-4047-BRN-001 as none of the 4 parallel disease groups in this study met the primary endpoint of objective response or long-term stable disease (SD) rate.

The E-R analysis for efficacy was not performed due to the limited number of responders in each pediatric study. For Study PBTC-043, out of the 29 treated patients, 0 patients experienced complete response (CR) or partial response (PR), 2 patients (7%) experienced long-term stable disease (SD) lasting ≥ 6 cycles, and 1 patient was not evaluable for tumor response (death prior

to first scheduled assessment). For Study CC-4047-BRN-001, out of the 46 patients who were evaluable for the primary endpoint, only 3 patients (7%) achieved objective response (OR) or long-term SD.

Refer to clinical review for details of the study design and efficacy/safety results of Study PBTC-043 and Study CC-4047-BRN-001.

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The E-R analysis for safety showed pomalidomide exposure was not associated with higher probabilities of treatment-emergent adverse events (TEAEs) or pomalidomide dose interruptions during Cycle 1. Only 2 patients (2/41 = 5%) in Study CC-4047-BRN-001 had pomalidomide dose reductions.

Refer to pharmacometrics review in the Appendix for the details.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

No. Base on the population PK analysis, none of the tested covariates including age, sex, and race except for BSA had an effect on pomalidomide PK. Although BSA was identified as a statistically significant covariate of pomalidomide CL/F and Vc/F, the impact of BSA on exposure parameters was not deemed clinically relevant given the wide pomalidomide exposure range at the clinical dose of 2.6 mg/m^2 and the lack of exposure-safety relationship.

Refer to pharmacometrics review in the Appendix for the details.

3.3.4 Is the oral suspension formulation developed for pediatric patients bioequivalent to the capsule formulation used in the adult patients? Is there clinically relevant food-drug effect for the oral suspension formulation?

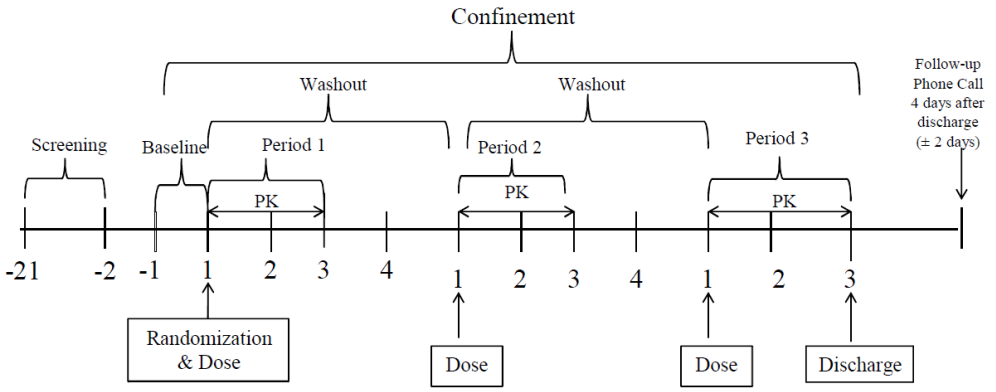
The currently approved commercial pomalidomide capsules are in dose strengths of 1, 2, 3, and 4 mg, which was used for pediatric patients in Study PBTC-043 and Study CC-4047-BRN-001 who could swallow a hard gelatin capsule. An additional 0.5 mg dose strength hard gelatin capsule currently available for clinical studies was also available for the pediatric studies. To accommodate children who were not able to swallow a hard gelatin capsule, age appropriate oral suspension formulation was developed for pediatric patients per Written Request.

Study CC-4047-CP-013

It was an open-label, randomized, three-period, two-sequence crossover study in healthy subjects. It was conducted to evaluate the bioavailability (BA) of the oral suspension formulation relative to the commercial capsule formulation and to assess the effect of food on the BA of the oral suspension formulation. The scheme of study design was shown below in Figure 1. Three treatment periods included Treatment A [Single oral dose of 4 mg pomalidomide (reference formulation, 1 × 4 mg capsule) under fasted condition], Treatment B [Single oral dose of 4 mg

pomalidomide (test formulation, 2.0 mL oral suspension) under fasted condition], and Treatment C [Single oral dose of 4 mg pomalidomide (test formulation, 2.0 mL oral suspension) under fed condition]. Washout period was 4 days between each treatment. Two crossover treatment sequences included Sequence ABC or Sequence BAC.

Figure 1 Scheme of Study Design of CC-4047-CP-013



(Data source: Figure 1 on page 15 in the CSR CC-4047-CP-013)

A total of 28 adult healthy subjects (HS) were enrolled and completed this study. All subjects were on overnight fasted state of at least 10 hours prior to dosing during treatment periods 1 and 2. During treatment period 3, all subjects were served a high-fat meal following an overnight fast. Rich plasma samples of pomalidomide were collected from pre-dose to 48 hours post-dose during each treatment period. The PK parameters of pomalidomide were derived by noncompartmental analysis.

Table 7 showed that pomalidomide systemic exposure (AUC_{0-t}, AUC_{0-inf}, and C_{max}) between the capsule and oral suspension formulation was comparable in adult HS following a single, oral 4 mg dose. The 90% confidence intervals (CI) of the means ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} between the capsule formulation (4 mg) and the oral suspension (2 mg/mL × 2 mL) formulation were within the 80% to 125% CI.

Table 7 Summary of Mean Pomalidomide PK Parameters (CV%) between Oral Suspension and Capsule Formulations

Pharmacokinetic Parameter	Treatment A (Reference, Fasted) N = 28	Treatment B (Test, Fasted) N = 28
AUC_{0-t} (ng•h/mL)	581 (31.1)	580 (31.7)
AUC_{0-inf} (ng•h/mL)	590 (31.6)	587 (32.2)
C_{max} (ng/mL)	57.3 (30.1)	63.9 (31.8)
T_{max}[a] (h)	2.00 (1.00, 6.00)	1.50 (1.00, 3.00)
$t_{1/2}$ (h)	7.33 (17.9)	7.07 (21.4)
CL/F (L/h)	6.78 (31.6)	6.81 (32.2)
Vz/F (L)	71.6 (28.6)	69.4 (21.5)

Note: [a] Median (min, max) data are presented.

(Data Source: Table 8 on page 33 in the CSR CC-4047-CP-013)

A high-fat meal following the administration of oral suspension formulation delayed median T_{max} from 1.5 to 4.5 hours, decreased mean C_{max} by approximately 35%; however, pomalidomide AUCs were similar with and without food. PK parameters of pomalidomide after a single 4 mg dose of oral suspension formulation under fasted and fed condition are listed in Table 8. The ratios of mean pomalidomide exposure between fasted and fed condition and their corresponding 90% CIs are listed in Table 9.

Table 8 Summary of Pomalidomide PK Parameters by Food Effect

PK Parameters	Treatment B (Test, Fasted) (N = 28)	Treatment C (Test, Fed) (N = 28)
AUC_{0-t} (ng•h/mL)	580 (31.7)	561 (31.4)
AUC_{0-inf} (ng•h/mL)	587 (32.2)	569 (31.9)
C_{max} (ng/mL)	63.9 (31.8)	41.8 (28.2)
T_{max}[a] (h)	1.50 (1.00, 3.00)	3.00 (2.50, 8.00)
$t_{1/2}$ (h)	7.07 (21.4)	7.21 (14.6)
CL/F (L/h)	6.81 (32.2)	7.02 (31.9)
Vz/F (L)	69.4 (21.5)	73.1 (25.0)

(Data Source: Table 11 on page 38 in the CSR CC-4047-CP-013)

Table 9 Statistical Comparison of Pomalidomide AUC and C_{max} by Food Effect

Pharmacokinetic Parameter (unit)	Treatment	N	Geometric Means	Comparison (Fed/Fasted)	Ratio (%) of Geometric Means	90% CI of Ratio of Geometric Means	Intra-subject CV%
AUC_{0-t} (h*µg/L)	B	28	579.9	C/B	96.7	(93.9, 99.7)	6.7
	C	28	561.0	-----	-----	-----	-----
$AUC_{0-\infty}$ (h*µg/L)	B	28	587.4	C/B	96.9	(94.1, 99.9)	6.6
	C	28	569.5	-----	-----	-----	-----
C_{max} (µg/L)	B	28	63.9	C/B	65.5	(61.9, 69.3)	12.4
	C	28	41.8	-----	-----	-----	-----

(Data Source: Table 12 on page 39 in the CSR CC-4047-CP-013)

However, as no clinical benefit was demonstrated in Study CC 4047 BRN-001, the oral suspension formulation will not be commercialized.

Review Comment:

PK data in Study CC-4047-CP-01 demonstrated that the oral suspension formulation is bioequivalent to the commercial capsule formulation in terms of pomalidomide exposure following a single oral dose of 4 mg. Food did not impact pomalidomide PK at a clinically meaningful level. A single oral doses of 4 mg pomalidomide for both formulations were safe and well tolerated in adult HS under either fed or fasted conditions.

Appendix

1. Population Pharmacokinetic Analyses

The goal of population PK analysis (popPK) was to apply popPK model to assess sources of variability (intrinsic and extrinsic covariates) of pomalidomide in children and young adults with recurrent or progressive brain tumors.

The popPK model for pomalidomide included 70 patients with 343 quantifiable pomalidomide concentrations pooled from 2 clinical studies PBTC-043 and CC-4047-BRN-001. A summary of the demographics and selected baseline lab assessments included in the popPK analysis is provided in Table 10 and Table 11.

The popPK analysis was conducted by the applicant and evaluated by the reviewer. The PK of pomalidomide was characterized by a one-compartment model with first-order absorption and elimination. Between-subject variability (BSV) was included on CL and Ka. Residual variability was modeled using an additive error model after the concentration was log-transformed.

Potential covariates were formally evaluated within NONMEM using a stepwise forward additive approach with a p-value of 0.01 (ΔOFV = 6.63) and a backward elimination using a p-value of 0.001 (ΔOFV = 10.83). Body surface area (BSA) was identified as a statistically significant covariate of CL/F and volume of distribution (Vc/F). Parameter estimates of final model are provided in Table 12.

The goodness of fit plots of model evaluation is presented in
Figure **2**. No bias was found in the diagnostic plots, suggesting the model fitted the data with good precision and minimal bias in general. Prediction-corrected visual predictive check also showed that the final model adequately described the observed PK profile of pomalidomide in trial PBTC-043 (Figure 3).

The effect of BSA on the pomalidomide CL was illustrated in the forest plot (
Figure 4). It suggested that BSA has a significant effect on the pomalidomide CL. Patients with BSA of 0.8 and 2 m^2 were estimated to have 41% lower and 53% higher CL compared to a typical patient with BSA of 1.33 m^2.

Exposure parameters at steady state (Cmax, Cmin and AUC) were generated based on post-hoc PK parameters from the final population PK model for each patient younger than 17 years old who took the dose of 2.6 mg/m^2. The descriptive statistics of these parameters are summarized in Table 13. The pooled geometric mean of AUCss at 2.6 mg/m^2 was estimated to be 859.8 h.ng/mL. At the same dose by BSA, pomalidomide exposure in 55 patients aged 4 to <17 years old was higher than the exposure observed in adult patients with KS but within range observed in adult patients with MM.

Table 10: Baseline Characteristics of Subjects in the PK Analysis Dataset (Continuous Variables)

Characteristics	PBTC-043 (n = 29)	CC-4047-BRN-001 (n = 41)	Overall (n = 70)
Age (years)			
Mean (SD)	12.3 (4.35)	11.4 (3.95)	11.8 (4.11)
Median [Min, Max]	12.0 [5.00, 20.0]	12.0 [4.00, 18.0]	12.0 [4.00, 20.0]
Weight (kg)			
Mean (SD)	50.7 (23.2)	44.8 (21.5)	47.3 (22.3)
Median [Min, Max]	45.1 [20.6, 103]	40.1 [17.3, 101]	41.9 [17.3, 103]
Height (cm)			
Mean (SD)	147 (18.0)	145 (21.4)	146 (19.9)
Median [Min, Max]	146 [108, 179]	147 [101, 182]	147 [101, 182]
Body Mass Index (kg/m^2)			
Mean (SD)	22.6 (6.62)	20.1 (5.43)	21.1 (6.03)
Median [Min, Max]	22.0 [12.0, 35.3]	18.6 [13.3, 35.6]	19.7 [12.0, 35.6]
Body Surface Area (m^2)			
Mean (SD)	1.42 (0.397)	1.32 (0.390)	1.36 (0.393)
Median [Min, Max]	1.41 [0.820, 2.24]	1.30 [0.690, 2.10]	1.33 [0.690, 2.24]

Source: Applicant's PopPK report, Table 5, Page 23

Table 11: Baseline Characteristics of Patients in the PK Analysis Dataset (Categorical Variables)

Characteristics	Number (%) of Subjects		
	PBTC-043 (n = 29)	CC-4047-BRN-001 (n = 41)	Overall (n = 70)
Sex			
Female	16 (55.2%)	15 (36.6%)	31 (44.3%)
Male	13 (44.8%)	26 (63.4%)	39 (55.7%)
Race			
White	23 (79.3%)	31 (75.6%)	54 (77.1%)
Black or African American	3 (10.3%)	2 (4.9%)	5 (7.1%)
Asian	0 (0%)	2 (4.9%)	2 (2.9%)
Other (Missing, not recorded)	3 (10.3%)	6 (14.6%)	9 (12.9%)

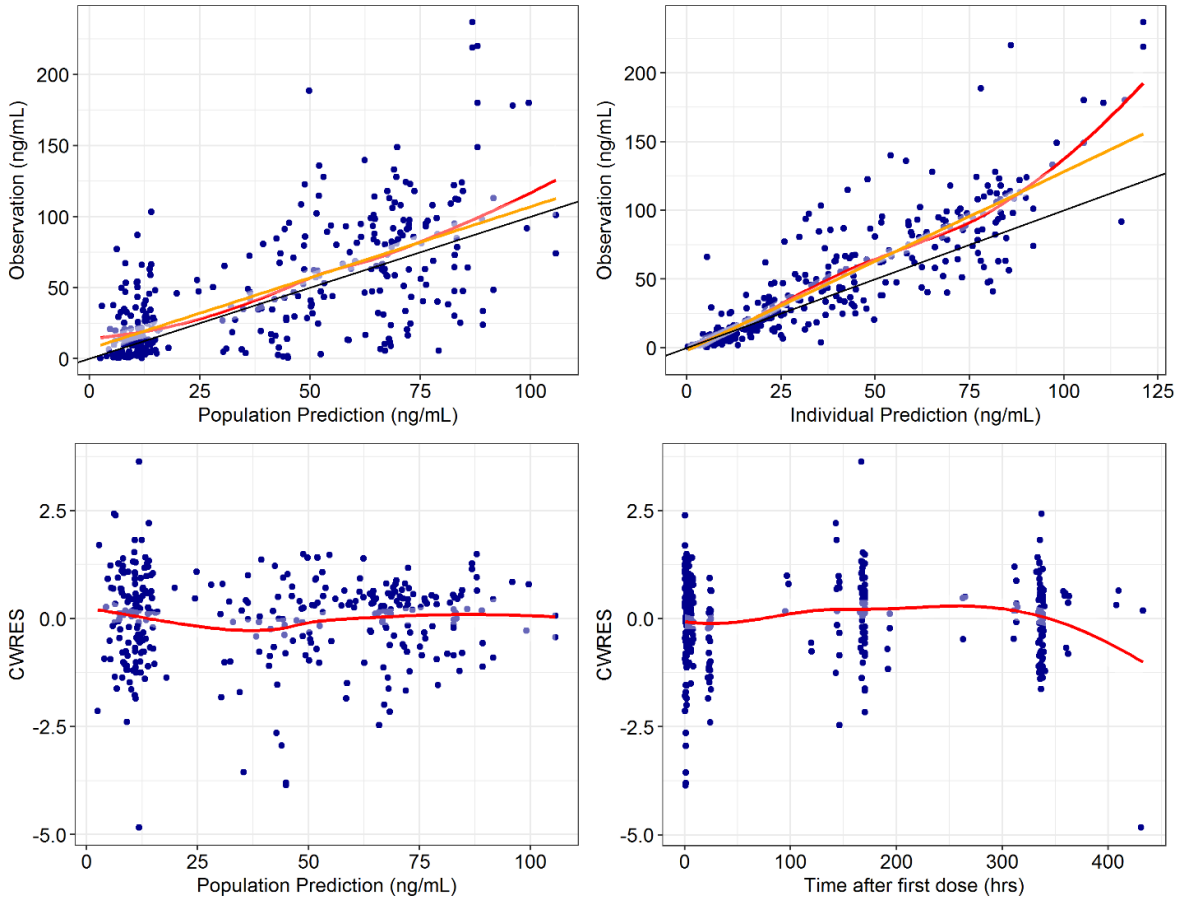
Source: Applicant's PopPK report, Table 4, Page 23

Table 12: Parameter Estimates of the Final PopPK Model for Pomalidomide

Parameter	Point estimate	RSE%	95% CI	Bootstrap	
				Median	95% CI
Typical values					
Apparent Clearance CL/F (L/h)	3.94	6.72	3.42 – 4.46	3.92	3.47 – 4.47
Apparent central volume Vc/F (L)	43.0	6.01	38.0 – 48.1	42.7	37.7 – 48.8
Absorption rate constant Ka (h^{-1})	1.45	37.8	0.378 – 2.53	1.36	0.759 – 2.83
Absorption lag time (h)	0.454	8.01	0.383 – 0.525	0.450	0.380 – 0.475
Covariate effects					
BSA on CL/F	1.04	17.9	0.676 – 1.41	1.05	0.613 – 1.40
BSA on Vc/F	1.54	12.2	1.17 – 1.90	1.54	1.16 – 1.98
Interindividual Variability					
Std. dev. of η on CL/F	0.401	11.2	0.313 – 0.488	0.394	0.300 – 0.473
Std. dev. of η on Ka	1.60	17.8	1.04 – 2.16	1.57	1.10 – 2.06
Residual Variability					
Ln-additive error (ng/mL)	0.627	10.7	0.496 – 0.758	0.616	0.502 – 0.753

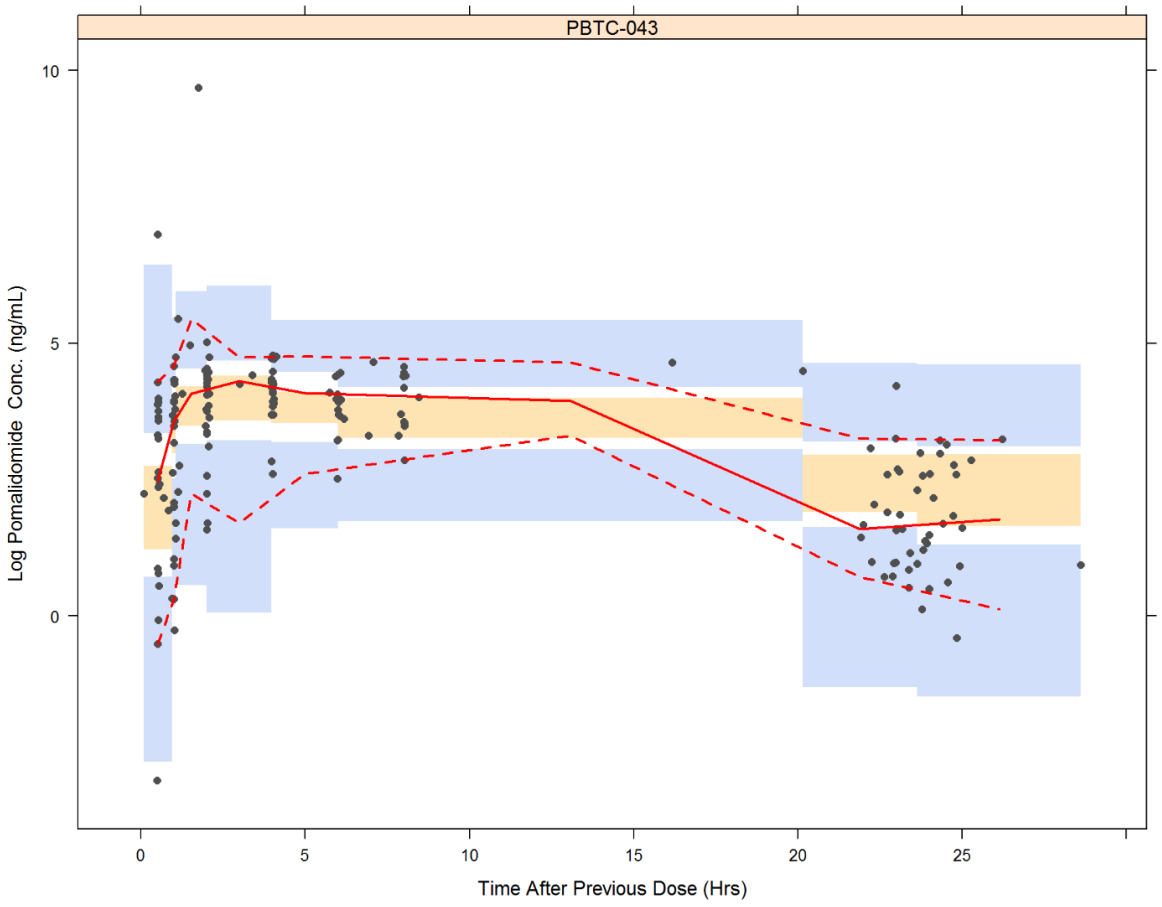
Source: Applicant's PopPK report, Page 10

Figure 2: Goodness of Fit Plots of the Final Model for Pomalidomide



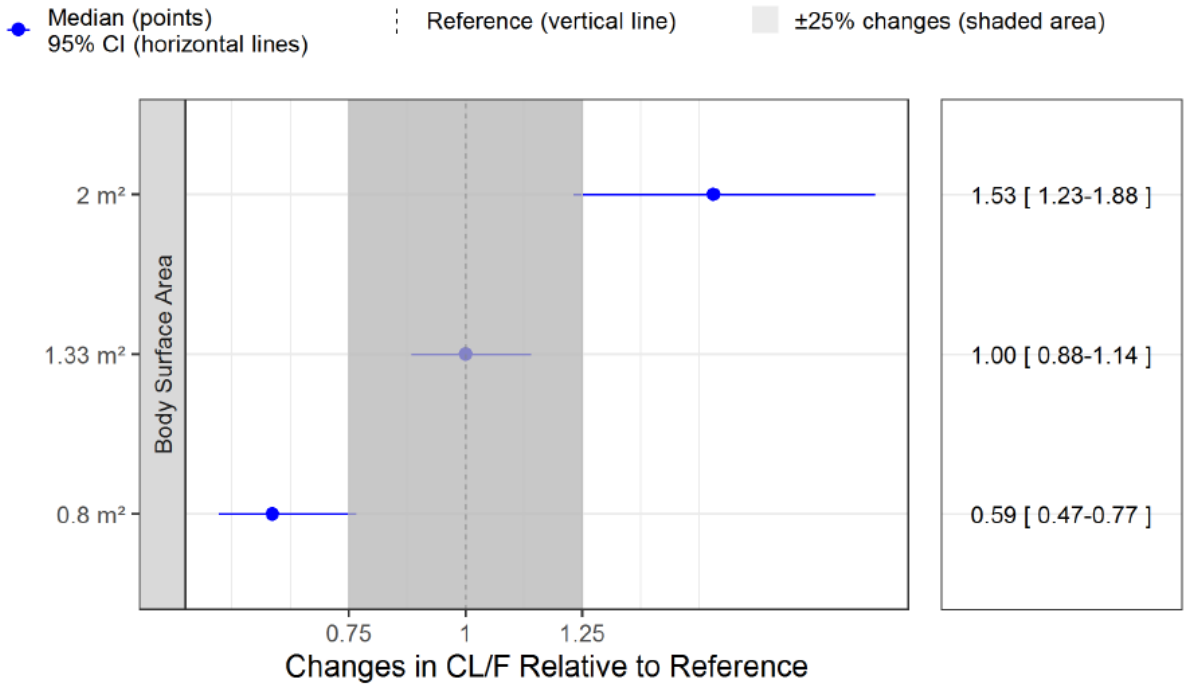
Source: Reviewer's Analysis based on data "poppkdata.xpt"

Figure 3: Visual Predictive Check of Pomalidomide Concentration-Time Data in Study PBTC-043



Source: Reviewer's Analysis based on data "poppkdata.xpt"

Figure 4: Model Predicted Effect of BSA on Fold Change in Pomalidomide Clearance



Source: Applicant poppk report, Figure 2, Page 27

Table 13: Summary of Bayesian Estimation of Pharmacokinetic and Exposure Parameters in Subjects Younger than 17 Years Old at Dose 2.6 mg/m^2.

Exposure	Geo.mean	N
AUCss (h.ng/mL)	859.8	55
Cmaxss (ng/mL)	70.5	55
Cminss (ng/mL)	10.6	55

Source: *Reviewer's Analysis based on data "poppkdata.xpt"*

2. Exposure-Response Analyses

1) Methods and Data

The exposure-efficacy analysis was not performed due to the limited number of responders in both studies.

Exposure-safety analyses were conducted by the applicant to explore the relationship between exposure of pomalidomide and safety in children and young adults with recurrent or progressive primary brain tumor. The evaluated safety endpoints include:

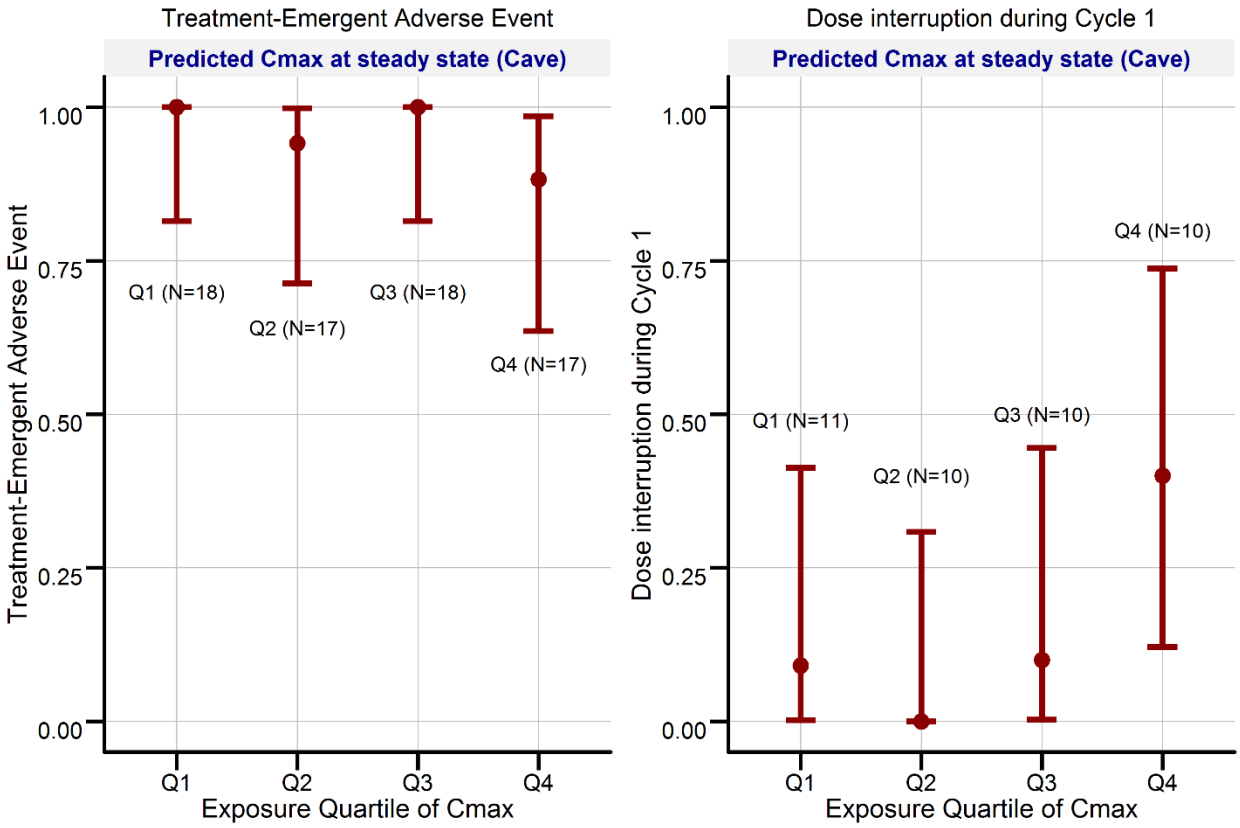
- Treatment-emergent adverse event (TEAE)
- Pomalidomide dose interruptions during Cycle 1
- Pomalidomide dose reductions during treatment period.

The ER dataset contained all patients with valid safety data and matching pomalidomide exposures. A total of 70 patients with both pomalidomide exposure and safety data from study PBTC-043 and CC-4047-BRN-001 were included in the ER analysis for TEAEs. A total of 41 patients with both pomalidomide exposure data and safety data from study CC-4047-BRN-001 were included in the ER analysis for dose interruptions during Cycle 1. The primary exposure metrics for exposure-safety assessment are individual predicted maximum plasma concentration (Cmax) at steady state.

2) Exposure-Safety Relationships

Cmax at steady state of pomalidomide were not associated with higher probabilities of TEAE. And Cmax at steady state of pomalidomide were not associated with higher probabilities of pomalidomide dose interruption during Cycle 1 (Figure 5). The patients in the higher exposure quartiles (Q3, Q4) appear to be younger with lower body weight and BSA compared to patients in the lower exposure quartiles (Q1, Q2) (Table 14). The exposure-safety analysis for pomalidomide dose reductions during treatment period was not performed because only 2 patients (2/41 = 5%) in Study CC-4047-BRN-001 had the event.

Figure 5: Relationship between Pomalidomide Cmax and Probability of Treatment-Emergent Adverse Event or Dose Interruption during Cycle 1



Source: Reviewer's Analysis based on data "safetydata.xpt"

Table 14: Baseline Covariates across 4 Exposure Quartiles in the Exposure-Safety Analyses.

Covariate	Value	Q1	Q2	Q3	Q4
Number of Subjects		18	17	18	17
Age		13 (4.3)	14 (3.9)	10.5 (3.9)	10 (4.2)
BSA		1.5 (0.4)	1.4 (0.4)	1.2 (0.4)	1.1 (0.4)
Weight		53.9 (23.1)	47.5 (21.4)	36.5 (21.8)	32 (21.5)
Race	Asian	NA	NA	1 (5.6%)	1 (5.9%)
Race	Black or African American	3 (16.7%)	1 (5.9%)	1 (5.6%)	NA
Race	Other	2 (11.1%)	3 (17.6%)	2 (11.1%)	2 (11.8%)
Race	White	13 (72.2%)	13 (76.5%)	14 (77.8%)	14 (82.4%)
Sex	Female	7 (38.9%)	4 (23.5%)	11 (61.1%)	9 (52.9%)
Sex	Male	11 (61.1%)	13 (76.5%)	7 (38.9%)	8 (47.1%)

Source: Reviewer's Analysis based on data "safetydata.xpt"

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/s/

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I concur.