OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW:

Application Number (SDN)	202192 (726), Supplement-15 Efficacy
Submission Date	06/15/17
Compound	Ruxolitinib (JAKAFI®)
Sponsor	Incyte Corporation
Indications and Dosing	▪ **Intermediate or high-risk myelofibrosis (MF)**, including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF o Starting dose, based on patient's baseline platelet count: ▪ > 200 x 10^9/L: **20 mg BID** ▪ 100 – 200 x 10^9/L: **15 mg BID** ▪ 50 – < 100 x 10^9/L: **5 mg BID** ▪ **Polycythemia Vera (PV)** who have had an inadequate response to or are intolerant of HU o Starting dose: **10 mg BID**
Dosage Forms	Tablets (5, 10, 15, 20, 25 mg)
Clinical Division	Division of Hematology Products
OCP Division	Division of Clinical Pharmacology V
Primary Reviewer	Vicky Hsu, Ph.D.
Team Leader	Gene Williams, Ph.D.

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1.0 Executive Summary

Ruxolitinib is an inhibitor of Janus Associated Kinases 1 and 2 (JAK1/2) currently approved for the treatment of patients with 1) intermediate or high-risk myelofibrosis, or 2) polycythemia vera who have had inadequate response to or are intolerant of hydroxyurea.

In the current sNDA, the Applicant proposes to update labeling based on the results of **Study 1 (ADVL1011)** from their Written Request. **Study 1** was a dose-escalation study to determine the MTD and/or RP2D of ruxolitinib BID in children with R/R solid tumors (Part A) and R/R leukemias or myeloproliferative neoplasms (MPNs) (Part B). It evaluated 15, 21, 29, 39, and 50 mg/m^2 ruxolitinib BID in 28-day cycles. The safety and efficacy results were not sufficient to establish the safety and effectiveness of ruxolitinib in pediatric patients. In regards to PK, clearance, volume of distributions, and half-life appeared to be similar across the dose levels evaluated.

1.1 Recommendation(s)

The Office of Clinical Pharmacology has determined that **Study 1** from Applicant's Written Request may be considered as fulfilled. Additionally, the pediatric findings from this sNDA submission should be included in the labeling.

1.2 Signatures

Vicky Hsu, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology V

Gene Williams, Ph.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology V

1.3 Clinical Pharmacology Summary

Ruxolitinib (JAKAFI®, Incyte Corporation) is JAK1/2 inhibitor that is currently approved for the following indications:

- Intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF
- Polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea

Clinical pharmacology properties of ruxolitinib are as follows:

- PK and PD
  - Rapid, near-complete absorption (T_{MAX} ~ 1-2 h)
  - Mean half-life is approximately 3 hours
  - Dose proportional exposure increase from 5 to 200 mg
  - Primarily metabolized by CYP3A4 and to a lesser extent by CYP2C9
  - Active metabolites contribute approximately 18% of overall pharmacodynamics of ruxolitinib
- Drug Interactions
  - **> 200 mg Fluconazole:** Avoid use
  - **Strong CYP3A4 inhibitors or ≤ 200 mg Fluconazole:** Reduce, interrupt or discontinue dose
- Hepatic Impairment (HI)
  - **Mild, Moderate or Severe HI:** Reduce dose or avoid use
- Renal Impairment (RI)
  - **Moderate or Severe RI:** Reduce dose or avoid use

In the current submission, the Applicant submitted results from **Study 1 (ADVL1011)** of their Written Request.

Study 1 was a Phase 1, single-arm, open-label, dose-escalation study to determine the MTD and/or RP2D of ruxolitinib BID in children (12 months < age ≤ 21 years) with R/R solid tumors (Part A) and R/R leukemias or MPNs (Part B). The study evaluated ruxolitinib dose levels of 15, 21, 29, 39, and 50 mg/m^2 BID in 28-day cycles. Based on limited treatment exposures and TEAEs including death, the safety of ruxolitinib in pediatric patients could not be established. Likewise, based on limited objective response observed (only n=1/37 evaluable achieved a PR), the effectiveness of ruxolitinib in pediatric patients could not be established either. In regards to PK, clearance, volume of distributions, and half-life appeared to be similar across the dose levels evaluated. Additionally, the overall PK profile of ruxolitinib in pediatric patients appeared similar as that observed in adults.

2.0 Question-Based Review

What are the results of Applicant's pediatric Study ADVL1011?
The FDA issued a Written Request (WR) for ruxolitinib pediatric studies (dated 12-11-15, timeline revised 09-15-16). The WR consists of 2 Studies (**"Study 1"** and "**Study 2"**). In this sNDA, the Applicant submitted CSR for **Study 1** (CSR for **Study 2** is due in July 2022). **Study 1** is summarized below:

Study 1 (ADVL1011)—*conducted by the Children's Oncology Group*
Title
A Phase 1 Study of ruxolitinib in children with R/R solid tumors, leukemias, and myeloproliferative neoplasms (MPNs)

Design
This was a Phase 1, single-arm, open-label, dose-escalation study to determine the MTD and/or RP2D of ruxolitinib BID in children (12 months < age ≤ 21 years) with R/R solid tumors (Part A) and R/R leukemias or MPNs (Part B, including preferential enrollment of those with confirmed CRLF2 and/or JAK mutations). The starting dose was 15 mg/m^2 ruxolitinib BID, which was selected to achieve similar exposures as the adult MTD (1 cycle = 28 d). In Part A, a rolling 6 design was used for dose-escalation (n=2-6/dose level, n=up to 12 may be enrolled at the RP2D to acquire PK data). In Part B, patients were treated at 1 dose level below that was currently evaluated in Part A, or at a starting dose of 15 mg/m^2 BID if dose-escalation had not occurred in Part A. If all dose levels from Part A were tolerable, then n=up to 6 may be enrolled in Part B at the RP2D determined from Part A.

Ruxolitinib was administered as tablets for oral administration (5, 25 mg). Patients who could not swallow crushed or whole tablets were not eligible for the study. Tablets may be crushed and dispensed with Ora-Sweet, apple sauce, apple juice, or orange juice (grapefruit juice was not allowed). Detailed instructions for crushing tablet and administering the suspension were provided.

Reviewer Note: The use of crushed tablets and administration with the listed foods was previously reviewed by CMC Team ((b) (4) *).*

The primary objectives were to estimate the MTD and/or RP2D, define/describe the toxicities, and characterize the PK of ruxolitinib BID in children with R/R solid tumors, leukemias or MPNs. Secondary objectives included the assessment of preliminary anti-tumor activity, JAK-STAT signaling activity, and activity in children whose leukemias or MPNs have known JAK and/or CRLF2 mutations.

PK samples for ruxolitinib were collected from all patients at the following time points:
- Cycle 1, Day 1: pre-dose, then post-dose 1, 2, 4, 8, 12, 24 h
- Cycle 1, Day 15: pre-dose
- Cycle ≥2, Day 1: pre-dose

Overall patient demographics and dose levels evaluated are shown in **Table 1** and **Table 2**, respectively. Note that no infants were enrolled in the study.

Table 1. Summary of patient demographic (safety population)

Baseline Characteristics	Number (%) of Subjects in Each Ruxolitinib BID Dose Group					Total (N=47)
	15 mg/m^2 (N=9)	21 mg/m^2 (N=9)	29 mg/m^2 (N=12)	39 mg/m^2 (N=11)	50 mg/m^2 (N=6)	
Age (years)						
n	9	9	12	11	6	47
Mean (SD)	13.2 (5.29)	13.4 (5.73)	10.8 (6.90)	11.8 (6.16)	16.2 (4.88)	12.7 (5.97)
Median	15.0	14.0	12.0	10.0	17.0	14.0
Range	2, 21	5, 20	2, 20	3, 20	8, 21	2, 21
Age group (n [%])						
2-6 years	1 (11.1)	1 (11.1)	5 (41.7)	3 (27.3)	0 (0.0)	10 (21.3)
7-11 years	1 (11.1)	2 (22.2)	1 (8.3)	3 (27.3)	1 (16.7)	8 (17.0)
12-17 years	6 (66.7)	3 (33.3)	3 (25.0)	2 (18.2)	2 (33.3)	16 (34.0)
≥ 18 years	1 (11.1)	3 (33.3)	3 (25.0)	3 (27.3)	3 (50.0)	13 (27.7)
Gender (n [%])						
Male	5 (55.6)	5 (55.6)	10 (83.3)	6 (54.5)	4 (66.7)	30 (63.8)
Female	4 (44.4)	4 (44.4)	2 (16.7)	5 (45.5)	2 (33.3)	17 (36.2)
Race (n [%])						
American Indian or Alaska Native	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Asian	1 (11.1)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	2 (4.3)
Black	1 (11.1)	1 (11.1)	2 (16.7)	3 (27.3)	1 (16.7)	8 (17.0)
White	6 (66.7)	4 (44.4)	8 (66.7)	5 (45.5)	4 (66.7)	27 (57.4)
Unknown	1 (11.1)	3 (33.3)	1 (8.3)	3 (27.3)	1 (16.7)	9 (19.1)

Source: Table 8 of Applicant's Study ADVL1011 CSR

Table 2. Dose levels evaluated per population

Subject Population	Number (%) of subjects in each ruxolitinib BID dose group					Total
	15 mg/m^2	21 mg/m^2	29 mg/m^2	39 mg/m^2	50 mg/m^2	
Safety Population	9 (100)	9 (100)	12 (100)	11 (100)	6 (100)	47 (100)
Subjects with solid tumors	3 (33)	6 (67)	6 (50)	6 (55)	6 (100)	27 (57)
Subjects with leukemia or MPNs	6 (67)	3 (33)	6 (50)	5 (45)	0	20 (43)
DLT-Evaluable Population	7 (100)	7 (100)	9 (100)	8 (100)	6 (100)	37 (100)
Subjects with solid tumors	3 (43)	6 (86)	6 (67)	6 (75)	6 (100)	27 (73)
Subjects with leukemia or MPNs	4 (57)	1 (14)	3 (33)	2 (25)	0	10 (27)

Source: Table 5 of Applicant's Study ADVL1011 CSR

Results

PK

PK profiles following a single-dose of ruxolitinib per dose level are shown in **Figure 1.** Ruxolitinib was rapidly absorbed with a median T_{MAX} ~ 1-2 h and appeared to decrease in a monophasic manner with a mean elimination half-life of 2-3 h, similar to that observed in adult patients. Summary of PK parameters is provided in **Table 3.** Ruxolitinib PK appeared linear over the dose range studied based on similar CL/F observed across dose levels. Half-lives were also similar across the dose levels. While patients with R/R leukemia or MPN (Part B) appeared to have lower CL/F than patients with R/R solid tumors (Part A) (12 ± 5.3 L/h vs. 16 ± 6.6 L/h), this effect was due to lower BW and BSA in patients from Part B—no significant difference was observed with BW- or BSA-normalized CL/F between the 2 populations **(Figure 2)**. Age, BW and BSA were potential predictors for CL and V. Age, BW and BSA were also highly correlated, which suggest that BW- or BSA-based dosing is appropriate in the pediatric population.

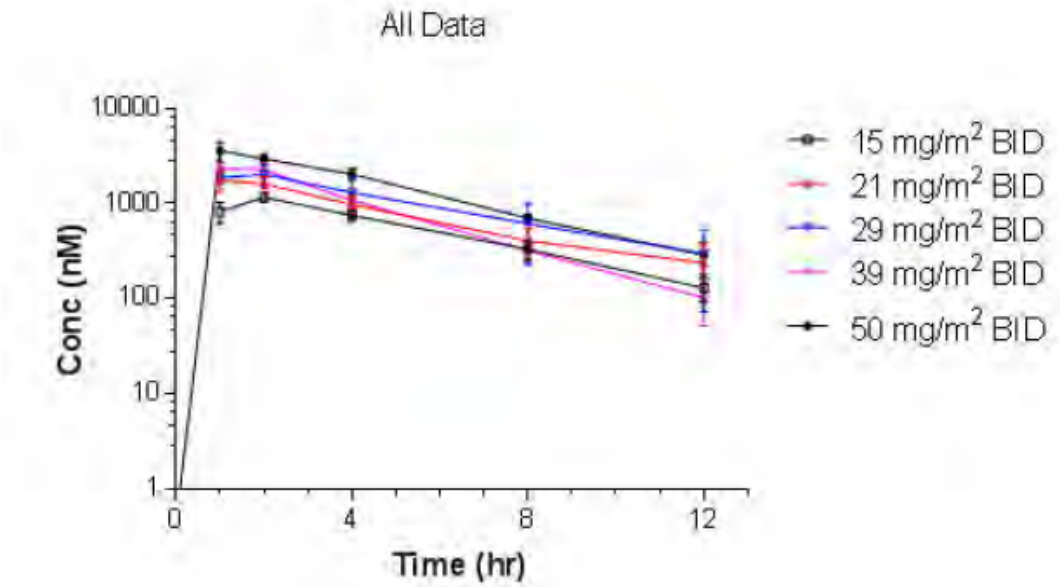

Figure 1. Ruxolitinib PK profiles per dose level following single-dose (concentrations shown as mean ± SE)
Source: Figure 1 of Applicant's INCYTE-DMB-17.16. Report

Table 3. Summary of ruxolitinib PK parameters following single-dose

Part	Dose Level (mg/m^2)	N	C_{max} (nM)	t_{max} (h)	AUC_{0-t} (nM*h)	AUC_{0-inf} (nM*h)	$t_{½}$ (h)	CL/F (L/h)	Vz/F (L/h)
A1	15	3	1030 ± 145 1020	2.0 (1.0,4.0)	5020 ± 1100 4940	5460 ± 1820 5270	3.23 ± 0.709 3.18	15.5 ± 3.72 15.3	70.3 ± 7.44 70.0
	21	5	1560 ± 512 1470	1.0 (1.0,4.0)	6250 ± 1960 6020	6580 ± 1990 6350	2.51 ± 0.492 2.47	18.2 ± 6.53 17.2	65.7 ± 28.6 61.3
	29	5	2990 ± 2320 2470	2.0 (1.0,4.0)	18000 ± 21700 11900	22400 ± 30600 13100	3.02 ± 1.47 2.79	14.0 ± 8.09 10.5	50.9 ± 29.4 42.1
	39	4	2500 ± 859 2380	1.0 (1.0,2.0)	7630 ± 3270 7170	8160 ± 3450 7640	2.03 ± 0.871 1.91	18.9 ± 2.77 18.7	56.1 ± 29.1 51.6
	50	5	4050 ± 1880 3730	1.0 (1.0,4.0)	16900 ± 5950 16000	18100 ± 4910 17500	2.79 ± 0.808 2.71	18.4 ± 5.04 17.8	75.9 ± 38.8 69.6
B	15	6	1370 ± 454 1310	2.0 (1.0,2.0)	7350 ± 3620 6690	7450 ± 3710 6780	2.66 ± 0.876 2.56	9.21 ± 3.72 8.57	33.2 ±10.8 31.7
	21	3	2950 ± 1610 2550	1.0 (1.0, 2.0)	14200 ± 10300 10500	17500 ± 14600 12000	2.83 ± 1.71 2.41	9.09 ± 10.2 5.97	22.3 ± 9.79 20.8
	29	5	1610 ± 644 1520	1.0 (1.0,1.0)	4820 ± 2200 4430	5010 ± 2360 4560	1.94 ± 1.20 1.68	15.4 ± 6.86 14.2	47.0 ± 47.8 34.3
	39	4	3690 ± 752 3630	1.5 (1.0,2.0)	12700 ± 4330 12200	13400 ± 4980 12700	1.50 ± 0.577 1.41	13.0 ± 6.27 12.0	41.4 ± 22.3 36.5
All Data	15	9	1260 ± 404 1210	2.0 (1.0,4.0)	6570 ± 3140 6050	6790 ± 3230 6240	2.85 ± 0.828 2.75	11.3 ± 4.71 10.4	45.6 ± 20.7 41.2
	21	9	1970 ± 1160 1710	1.0 (1.0,4.0)	8880 ± 6630 7270	10200 ± 9230 7820	2.65 ± 0.935 2.48	14.9 ± 8.17 12.0	51.1 ± 30.0 42.9
	29	11	2370 ± 1690 2020	1.0 (1.0,4.0)	11400 ± 15300 7560	13500 ± 21300 8030	2.46 ± 1.32 2.18	14.6 ± 6.75 12.3	48.7 ± 35.6 38.7
	39	9	2880 ± 1120 2650	1.0 (1.0,2.0)	9880 ± 4290 9110	10400 ± 4650 9570	2.43 ± 1.1.8 2.21	15.6 ± 5.24 14.7	53.1 ± 26.9 46.9
	50	6	3820 ± 1770 3520	1.0 (1.0,4.0)	17600 ± 5550 16700	18700 ± 4680 18200	3.25 ± 1.34 3.05	16.6 ± 6.36 15.4	73.2 ± 35.4 67.8

Values are mean ± SD, except T_{MAX} is median (min, max)
Source: Table 2 of Applicant's INCYTE-DMB-17.16. Report

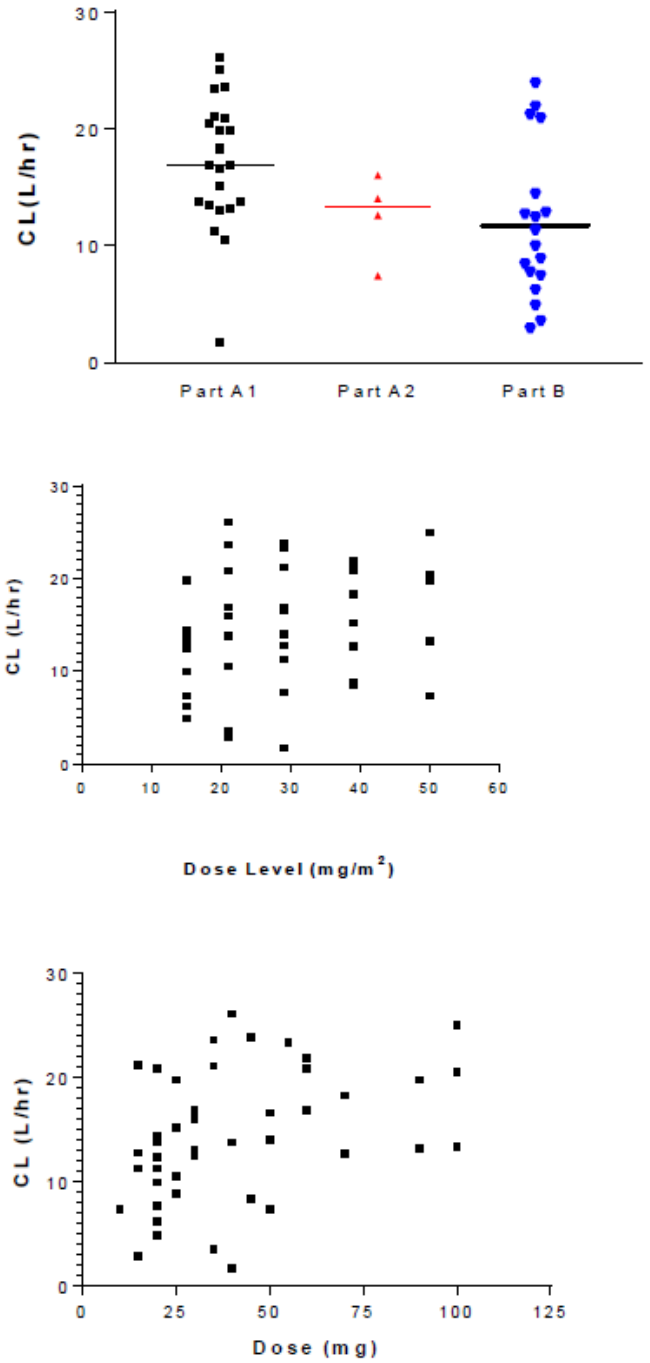

Figure 2. Ruxolitinib clearance per part (top), dose level (middle), or actual dose (bottom)
Part A1 =R/R solid tumors, without bone marrow involvement (n=22)
Part A2 = R/R solid tumors, with or without bone marrow involvement (n=4)
Part B = R/R leukemias or MPNs (n=18)
Source: Figure 5 of Applicant's INCYTE-DMB-17.16. Report

Safety

The mean and median duration of dosing for all dose levels combined were 45 and 28 d, respectively (interquartile range = 24 – 28 d). Overall summary of TEAEs in the **Table 4** below. Of note, 40 patients (85%) experienced a Grade ≥ 3 TEAE. Additionally, 9 patients (19%) experienced a TEAE with a fatal outcome, not including 2 patients who passed during the follow-up period and were therefore not captured as having a fatal TEAE. As seen in **Table 5**, most commonly reported TEAEs included anemia (77%), decreased platelet count (66%), decreased lymphocyte count (62%), decreased neutrophil count (55%), and decreased white blood cell count (55%).

Table 4. Overall summary of TEAEs (safety population)

Adverse Event Category	Number (%) of Subjects in Each Ruxolitinib BID Dose Group					Total (N=47)
	15 mg/m^2 (N=9)	21 mg/m^2 (N=9)	29 mg/m^2 (N=12)	39 mg/m^2 (N=11)	50 mg/m^2 (N=6)	
Any TEAE	9 (100.0)	9 (100.0)	12 (100.0)	11 (100.0)	6 (100.0)	47 (100.0)
Any treatment-related TEAE	9 (100.0)	9 (100.0)	10 (83.3)	10 (90.9)	6 (100.0)	44 (93.6)
Any TEAE ≥ Grade 3	7 (77.8)	7 (77.8)	12 (100.0)	9 (81.8)	5 (83.3)	40 (85.1)
Any fatal TEAE	1 (11.1)	2 (22.2)	1 (8.3)	5 (45.5)	0 (0.0)	9 (19.1)

Source: Table 14 of Applicant's Study ADVL1011 CSR

Table 5. Summary of TEAEs reported in ≥ 10% of subjects overall by dose level and preferred term (safety population)

Preferred Term	Number (%) of Subjects in Each Ruxolitinib BID Dose Group					Total (N=47)
	15 mg/m^2 (N=9)	21 mg/m^2 (N=9)	29 mg/m^2 (N=12)	39 mg/m^2 (N=11)	50 mg/m^2 (N=6)	
Subjects with any TEAEs, n (%)	9 (100.0)	9 (100.0)	12 (100.0)	11 (100.0)	6 (100.0)	47 (100.0)
Anaemia	4 (44.4)	6 (66.7)	9 (75.0)	11 (100.0)	6 (100.0)	36 (76.6)
Platelet count decreased	7 (77.8)	5 (55.6)	7 (58.3)	8 (72.7)	4 (66.7)	31 (66.0)
Lymphocyte count decreased	3 (33.3)	5 (55.6)	10 (83.3)	6 (54.5)	5 (83.3)	29 (61.7)
Neutrophil count decreased	3 (33.3)	2 (22.2)	9 (75.0)	7 (63.6)	5 (83.3)	26 (55.3)
White blood cell count decreased	5 (55.6)	5 (55.6)	7 (58.3)	4 (36.4)	5 (83.3)	26 (55.3)
Hypocalcaemia	7 (77.8)	3 (33.3)	7 (58.3)	3 (27.3)	3 (50.0)	23 (48.9)
Aspartate aminotransferase increased	5 (55.6)	3 (33.3)	6 (50.0)	3 (27.3)	4 (66.7)	21 (44.7)
Hypokalemia	7 (77.8)	3 (33.3)	6 (50.0)	2 (18.2)	3 (50.0)	21 (44.7)
Fatigue	3 (33.3)	2 (22.2)	6 (50.0)	5 (45.5)	4 (66.7)	20 (42.6)
Alanine aminotransferase increased	4 (44.4)	3 (33.3)	7 (58.3)	2 (18.2)	3 (50.0)	19 (40.4)
Nausea	5 (55.6)	3 (33.3)	5 (41.7)	4 (36.4)	2 (33.3)	19 (40.4)
Hyperglycemia	3 (33.3)	2 (22.2)	7 (58.3)	4 (36.4)	2 (33.3)	18 (38.3)

Source: Table 16 of Applicant's Study ADVL1011 CSR

The MTD was not reached in this study. The Applicant stated that 50 mg/m^2 BID (highest dose evaluated in Part A) was determined to be the RP2D for ruxolitinib. Summary of DLTs in patients with solid tumors (Part A) is shown in **Table 6**. Based on their determination of the RP2D of 50 mg/m^2 BID from Part A, the study closed enrollment to proceed to Phase 2 study prior to the administration of 50 mg/m^2 in Part B.

Table 6. Summary of DLTs by MedDRA SOC and preferred term in subjects with solid tumors (DLT-evaluable population)

MedDRA System Organ Class Preferred Term	Number (%) of Subjects With Solid Tumors in Each Ruxolitinib BID Dose Group					Total (N=27)
	15 mg/m^2 (N=3)	21 mg/m^2 (N=6)	29 mg/m^2 (N=6)	39 mg/m^2 (N=6)	50 mg/m^2 (N=6)	
Subjects with any DLTs, n (%)	0 (0.0)	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	5 (18.5)
Gastrointestinal disorders	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Nausea	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Vomiting	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
General disorders conditions	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Multiple organ dysfunction syndrome	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Investigations	0 (0.0)	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	5 (18.5)
Alanine aminotransferase increased	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (3.7)
Neutrophil count decreased	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	2 (7.4)
Platelet count decreased	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.7)
Metabolism and nutrition disorders	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Dehydration	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Vascular disorders	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Hypotension	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)

Source: Table 19 of Applicant's Study ADVL1011 CSR

Reviewer Note: Per Clinical review, the results of this study are not sufficient to demonstrate safety of ruxolitinib in pediatric patients, thus no claim will be provided in the labeling. Additionally, an insufficient number of patients have been exposed to establish a RP2D for continuous administration.

Efficacy

In patients with solid tumors, no objective responses were achieved. The majority of patients had progressive disease (67%) or stable disease (30%), as indicated in **Table 7** below:

Table 7. Best response in subjects with solid tumors (DLT-evaluable population)

Best Response	Number (%) Of Subjects With Solid Tumors In Each Ruxolitinib BID Dose Group					Total (N=27)
	15 mg/m^2 (N=3)	21 mg/m^2 (N=6)	29 mg/m^2 (N=6)	39 mg/m^2 (N=6)	50 mg/m^2 (N=6)	
Overall response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease	1 (33.3)	3 (50.0)	1 (16.7)	2 (33.3)	1 (16.7)	8 (29.6)
Progressive disease	2 (66.7)	2 (33.3)	5 (83.3)	4 (66.7)	5 (83.3)	18 (66.7)
Unable to evaluate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)

Source: Table 11 of Applicant's Study ADVL1011 CSR

In patients with hematological malignancies, 1 patient with JAK2-mutant PV in the 15 mg/m^2 dose level achieved a partial remission with 17 complete cycles before discontinuing due to her physician's decision. The remaining patients had stable disease (40%), progressive disease (30%), or missing data (20%), as seen in **Table 8** below.

Table 8. Best response in subjects with leukemia or MPNs (DLT-evaluable population)

Best Response	Number (%) of Subjects With Leukemia or an MPN in Each Ruxolitinib BID Dose Group				Total (N=10)
	15 mg/m^2 (N=4)	21 mg/m^2 (N=1)	29 mg/m^2 (N=3)	39 mg/m^2 (N=2)	
Overall response	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)
Complete remission	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial remission	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)
Stable disease	2 (50.0)	0 (0.0)	2 (66.7)	0 (0.0)	4 (40.0)
Progressive disease	1 (25.0)	1 (100.0)	1 (33.3)	0 (0.0)	3 (30.0)
Unable to evaluate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	2 (20.0)

Source: Table 12 of Applicant's Study ADVL1011 CSR

Note that the was insufficient to conduct survival analysis.

Reviewer Note: Per Clinical review, the results of this study are not sufficient to demonstrate effectiveness of ruxolitinib in pediatric patients, thus no claim will be provided in the labeling.

3.0 Labeling Recommendations

The Applicant proposes to add the following text in Section 8.4 of the labeling:

(b) (4)

.

Reviewer Note: Based on the Pediatric Labeling Guidance and in consultation with OCP's Labeling and Health Communication Group, the above PK labeling language should not be included in the labeling. The Guidance reads, "PK data, in the absence of efficacy data, should only be included in this subsection when the data reflect a safety concern related to dosing."

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/s/

WENCHI HSU
11/16/2017

GENE M WILLIAMS
11/16/2017
I concur with the recommendations