Division of Hematology Products
Clinical Review of NDA
Written Request / Labeling Supplement

NDA/BLA Number(s): 202192 015
Supporting Document Number:
Drug Name: Ruxolitinib (Jakafi)
Sponsor: Incyte Corporation
Type of Submission: Efficacy Supplement with Labeling Component of Written Request
Date Received: 6/15/17
Date Completed: 10/31/17

Reviewer: Patricia Dinndorf, MD
Team Leader: Donna Przepiorka, MD, PhD

EXECUTIVE SUMMARY
Purpose of Submission:
The purpose of this submission is to fulfill the requirements for Study 1 of the FDA Pediatric Written Request, dated 12/11/15, for ruxolitinib by reporting the results of Study ADVL1011 and to provide information to support updates to the Pediatric Use section of labeling.

> WRITTEN REQUEST – AMENDMENT 1 dated 9/15/16
> Study 1: Protocol ADVL1001 "A Phase 1 Study of JAK Inhibition (INCB018424) in Children with Relapsed or Refractory Solid Tumors, Leukemias, and Myeloproliferative Neoplasms" is an open-label, single-arm, Phase 1 trial of ruxolitinib monotherapy for pediatric patients with malignancies. The primary objective is to determine the maximal tolerated dose and/or recommended Phase 2 dose in children with solid tumors and to describe the toxicities in children with solid tumors or hematological neoplasms. Up to 106 children may be treated on this protocol. Follow-up will be through 30 days after the last dose of ruxolitinib.

The final study report of ADVL1011 (study 1) adequately addresses the requirements of the written request. Analysis of the study report to address the requirements of study 1 of the WR are summarized in the table in Appendix 2. The final assessment regarding the fulfilment of the written request will be determined on review of study 2 due on or before 7/1/22.

The revision to label section 8.4 are summarized in the table in Appendix1.

STUDY INFORMATION:

- **Title:** ADVL1011 "A Phase 1 Study Of JAK Inhibition (INCB018424) In Children With Relapsed or Refractory Solid Tumors, Leukemias, And Myeloproliferative Neoplasms"
- **IND:** Conducted under IND 109051
- **Agent:** INCB018424 (ruxilitinib, Jakafi™)
- **Phase:** 1
- **Design:** Open-label, single-arm, Phase 1 trial of ruxolitinib monotherapy for pediatric patients with malignancies
- **Study Sites:** Children's Oncology Group Phase 1 Institutions
- **Proposed Sample Size:** Up to 106 patients
- **Gender:** M:F
- **Age Range:** 2 to 21

Trial Opened: 9/7/10
Trial Closed: 3/28/14

Planned Dose Levels: 15 mg/m^2, 21 mg/m^2, 29 mg/m^2, 39 mg/m^2, and 50 mg/m^2 BID.
Route: Oral
Planned enrollment: Up to 106
Actual enrollment: 49

Objectives (copied from WRITTEN REQUEST – AMENDMENT 1 dated 9/15/16)
Primary objectives

- To define the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of oral ruxolitinib administered twice daily to children with relapsed or refractory solid tumors and leukemias.
- To define and describe the toxicities of ruxolitinib administered on this schedule in patients with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms (MPNs).
- To characterize the pharmacokinetics of ruxolitinib in children with relapsed or refractory solid tumors, leukemias, or MPNs.

Secondary objectives

- To assess the antitumor activity of ruxolitinib within the context of a phase 1 study.
- To assess the biologic activity of ruxolitinib upon JAK-STAT signaling in patients with relapsed or refractory solid tumors, leukemia or MPNs.
- To assess the biologic activity of ruxolitinib upon phosphosignaling and mutation burden in patients whose leukemias or MPNs have known CRLF2 and/or JAK mutations.

Study Endpoints (copied from WRITTEN REQUEST – AMENDMENT 1 dated 9/15/16)

- Determination of the RP2D of ruxolitinib in patients with solid tumors.

- Safety and tolerability of ruxolitinib
- Pharmacokinetic endpoints for the study drug will include maximum observed plasma drug concentration (C_{max}), time to maximum concentration (T_{max}), and study drug exposure (AUC_{0-t}) measured as the area under the single-dose plasma concentration-time curve

Eligibility Criteria (copied from protocol ADVL1011)
Inclusion Criteria:

- Age: Patients must be > 12 months and 21 years of age at the time of study enrollment.
- Body Surface Area (Dose Level -1, 1 and 2): Patients must have a BSA ≥ 0.65m^2 at the time of study enrollment.
- Diagnosis: Patients must have had histologic verification of an extracranial solid tumor, leukemia or MPN at original diagnosis or relapse.
    - Part A: Patients with relapsed or refractory solid tumor
    - Part B: Patients with relapsed or refractory leukemia or MPN
    - Part C: Patients with relapsed or refractory leukemia or MPN that have confirmed JAK alterations or mutations in genes that would predict enhanced sensitivity to ruxolitinib
- Patients with leukemia must have ≥ 25% blasts in the bone marrow (M3), with the exception of patients with AML, who must have > 20% blasts in the bone marrow.
- Patients with solid tumors must have either measurable or evaluable disease
- Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.
- Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients 16 years of age
- Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy prior to enrolling on this study.
- Adequate organ function [specifics enumerated]

Exclusion Criteria:

- Pregnancy / Breastfeeding
- Medications
    - Investigational agents
    - Anti-cancer agents
    - List of prohibited medications [specifics enumerated (CYP3A4)]
    - Anti-GVHD therapy
- Infections
- CNS involevement
- Not able to swallow tablets (crushed allowed)

Statistical Considerations: (copied from sponsor's report)
The analyses will utilize only descriptive statistics.

Treatment Plan: (copied from sponsor's report)
Part A - relapsed or refractory solid tumors
In Part A of the study, a rolling 6 design was used to determine the MTD of ruxolitinib in children with relapsed or refractory solid tumors.

Treatment Schedule Table	
Days 1-28	INCB018424 orally, twice daily
Day 28	End of Cycle

Dose levels:

Dose Level	Dose (mg/m^2/dose p.o. BID)
-1	12
1	**15**
2	21
3	29
4	39
5	50

Definition of DLT
The observation for DLT was the first 28 days of cycle 1.
Non- Hematologic DLT

- Any Grade 4 non-hematological toxicity
- Any Grade 3 non-hematological toxicity with the specific exclusion of
  - Grade 3 nausea and vomiting of < 3 days duration
  - Grade 3 ALT/AST that return to levels that meet initial eligibility criteria within 7 days.
  - Grade 3 fever or infection < 5 days duration.
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation
- Grade 2 allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.
- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption

Hematological DLT in patients with solid tumors
Solid tumor patients evaluable for hematologic toxicity were patients without bone marrow involvement and ANC ≥ $1000/mm^3$, platelet count ≥ $100,000/mm^3$, and Hgb ≥ 8g/dL. Solid tumor patients with bone marrow involvement could be entered but were not evaluable for hematologic toxicity.

In patients evaluable for hematological DLT

- Grade 4 thrombocytopenia (platelet count < 25,000/mm3) or
- Grade 4 neutropenia

Part B - relapsed or refractory leukemias and MPNs
Subjects enrolled in Parts B of the study were to be treated at 1 dose level below that currently being administered in Part A.

Non- Hematologic DLT (see Part A definition)

Hematological DLT in patients with leukemias and MPNs

- failure to recover a peripheral ANC > 500/mm^3 and platelets > 20,000/mm^3 by 42 days after the first treatment day, not due to malignant infiltration.

Part C – relapsed or refractory leukemias and MPNs that have confirmed JAK alterations or mutations in genes that would predict enhanced sensitivity to ruxolitinib

- Patients were not enrolled on this part because a CLIA-approved CRLF-R and JAK mutation test was not available.

Definition MTD
The MTD will be the maximum dose at which fewer than one-third of patients experience DLT during cycle 1.

Results:
Disposition: (copied from sponsor's report)
All subjects in both Part A and Part B were considered to have discontinued study drug; however, the majority of subjects completed Cycle 1. Across all dose levels, disease progression was the most common reason for discontinuation of study drug (34 [72.3%] of subjects overall).

Diagnoses

Diagnosis	n=47
Part A – Solid Tumors	27
Sarcoma	9
Osteosarcoma	9
Neuroblastoma	4
Miscellaneous	5
Part B – Hematologic Malignancies	20
ALL	6
Myeloid	13
AML	9
AML –M7	1
JMML	3
Polycythemia Vera	1

Demographics and Patient Characteristics:

Demographics and Patient Characteristics ADVL-1011			
	Solid Tumor	**Hematologic Malignancies**	**Total**
	n=27	**n=20**	**n=47**
Gender, n			
Male	19	11	30
Female	8	9	17
Age in Years			
Mean	15.3	9.2	12.7
Median	17	10	14
Range	6 to 21	2 to 17	2 to 21
Age groups, n			
2 to 11	7	11	18
12 to 16	6	8	14
>16	14	1	15
Race / Ethnicity, n			
White – Not Hispanic	13	7	20
White – Hispanic	4	3	7
Black – Not Hispanic	3	5	8
Hispanic	2	3	5
Asian	1	1	2
American Indian /Alaskan Native	1		1
Missing or Other	1	1	2
Weight in Kg			
Mean	60.1	36.0	50.0
Median	58.5	37.7	53.5
Range	16.6 to 127	12.3 to 67.2	12.3 to 127
Weight ranges, n			
< 40 Kg	6	10	16
40 to 60 Kg	8	8	16
> 60 Kg	13	2	15
BSA (m^2)			
Mean	1.5	1.1	1.4
Median	1.6	1.2	1.5
Range	0.69 to 2.57	0.54 to 1.8	0.54 to 2.6
BSA range, n			
< 1.0 m^2	5	9	14
1.0 to 1.8 m^2	12	10	24
> 1.8 m^2	10	1	9
Karnofsky / Lansky Score			
Mean	89	90	88
Median	90	90	90
Range	60 to 100	70 to 100	60 to 100

Subject Population by Dose Group (copied from sponsor's report)

Table 5: Subject Populations

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)

BID = twice daily; DLT = dose-limiting toxicity; MPN = myeloproliferative neoplasm.

Exposure: (copied from sponsor's report)
A total of 47 subjects received at least 1 dose of ruxolitinib and were included in the Safety Population . Mean and median total doses were 37.8 and 30.0 mg, respectively. The mean duration of dosing for all dose groups combined was 45.3 days, with a median duration of 28 days and interquartile range of 24 to 28 days. Overall, the longest duration of exposure was 502 days (ie, a single subject in the 15-mg/m^2 BID dose group completed 17 cycles). In the 50-mg/m^2 BID dose group, no subject received less than 27 days of ruxolitinib treatment, and the maximum duration of treatment was 98 days.

Efficacy: (derived from sponsor's report)
No objective responses were achieved in subjects with solid tumors. The majority of subjects had progressive disease (66.7%), and the remaining subjects had stable disease (29.6%) or missing data (3.7%). No dose-related trends were noted in the proportion of subjects who had a best response of stable or progressive disease.

For subjects with hematological malignancies, 1 subject (5%) with JAK2-mutant polycythemia vera (PV) in the 15 mg/m^2 dose group achieved a best response of partial remission and had received 17 complete cycles of ruxolitinib before discontinuing the study due to her physician's decision that participating in the study was no longer in the subject's best interest. The remaining subjects with hematological malignancies had stable disease (20%), progressive disease (45%), or missing data (30%).

Pharmacokinetics: (copied from sponsors report "INCYTE-DMB-17.16.1")

- After single oral dose administration, INCB018424 was rapidly absorbed, with median t_{max} ~1 to 2 hours, then declined in a monophasic with a mean terminal-phase disposition $t_{½}$ of approximately 2 to 3 hours, similar to that observed in adult patients.

- Age-related oral clearance was observed with lower clearance in younger patients (12.3 L/hr and 15.8 L/hr, respectively, for age < 12 years and age ≥ 12 years). These differences were independent of BSA-corrected dose level but not clinically significant.
- The exposures ($AUC_{0-\infty}$ and C_{max}) to INCB018424 in pediatric patients after a 50 mg/m^2 single dose were comparable to those in healthy adult patients after the 100 mg dose (or 58.8 mg/m^2 based on mean adult BSA of 1.70 m^2).
- The overall pharmacokinetic profile of ruxolitinib in pediatric patients appeared to be similar to that observed in adults. Similar clearance, volume of distribution, and half-life were observed across the dose groups studied.

Pharmacodynamic: (derived from Loh 2015)
Plasma inhibitory activity assay results showed median peak inhibition of 44.8% for pJAK2 , 58.9% for pSTAT5, and 62.3% for pS6 by phosphoflow cytometric analysis at C1D1H4. Median inhibition at C1D15 steady state was 21.5% for pJAK2, 46.3% for pSTAT5, and 59.2% for pS6, demonstrating some loss of JAK/STAT pathway inhibition at trough (P<0.0001 for both pJAK2 and pSTAT5), but sustained PI3K/mTOR pathway inhibition. A subset of patients demonstrated increased phosphoprotein levels at steady state and loss of signaling inhibition, suggesting signaling upregulation during treatment. With the exception of increased peak pSTAT5 inhibition at dose level 2 (21 mg/m^2) and dose level 5 (50 mg/m^2), further increases in signaling inhibition were not observed with increasing doses of ruxolitinib.

In vivo inhibition of signal transduction was also observed in part B patients' blood specimens analyzed by whole blood phosphoflow cytometry. Three BALL patient specimens studied in these assays demonstrated modest inhibition of pJAK2, pSTAT5, and pS6 at steady-state dosing. However, *ex vivo* exposure of blood specimens to

Safety: (copied from sponsor's report)

Table 14: Overall Summary of Treatment-Emergent Adverse Events (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)

Deaths
Overall, 12 subjects who were enrolled in this study died; this included 9 subjects who had a fatal TEAE, 2 subjects who died during the follow-up period (more than 30 days after the last dose of study drug), and 1 subject who was enrolled but not treated. Of the e9 deaths associated with a TEAE, 2 were categorized as possibly related to study drug.

- Subject 815746 dose level 39 mg/m^2 BID, a 10-year-old black/African-American male with ALL, experienced increased creatinine and acute kidney injury on day 17 of therapy. He was on no other nephrotoxic drugs. Ruxolitinib was discontinued. The creatinine increase and acute kidney injury were DLTs. He patient died on day 20 after cardiac arrest.

  The investigator considered the events of death NOS, cardiac arrest Grade 4, hyperkalemia Grade 3, creatinine increased Grade 3, and hypermagnesemia increased Grade 3 as probably related to leukemia and possibly related to study drug. The Sponsor considered the events of death NOS, cardiac arrest Grade 4, hyperkalemia Grade 3, creatinine increased Grade 3 and hypermagnesemia increased Grade 3 as probably related to progressing leukemia rather than to study drug administration, although these events could not be conclusively considered unrelated to study drug.

- Subject 794670, a 19-year-old female who had a solid tumor in the left thoracic area, received ruxolitinib at a dose of 21 mg/m^2 BID for 5 days (total of 210 mg administered) and permanently discontinued study drug on Day 9 due to refusal of further Protocol therapy. She died on Day 9 due to multiple organ dysfunction syndrome (verbatim: multi-organ failure). The multiple organ failure was considered possibly related to study drug and was reported as a DLT.

  A limited autopsy (including collection of lung, tumor and liver tissue) revealed no evidence of bacterial, viral or fungal infection, pericardial disease, or other conditions that contributed to the subject's death. The postmortem examination did not reveal evidence of toxic injury to the liver, and autopsy pathology was consistent with hypoperfusion injury to the liver. Therefore, it was likely that the multi-organ failure was due to hypoxic/ischemic injury due to extreme dehydration and hypotension, and the investigator's causality assessment was based on the temporal relationship of the event to the initiation of study drug.

Adverse Events

TEAEs Reported in More Than 15% of Patients (copied from sponsor's report)

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)	
Headache	4 (44.4)	0 (0.0)	6 (50.0)	6 (54.5)	1 (16.7)	17 (36.2)
Hyponatremia	4 (44.4)	4 (44.4)	5 (41.7)	1 (9.1)	3 (50.0)	17 (36.2)
Vomiting	5 (55.6)	1 (11.1)	3 (25.0)	6 (54.5)	2 (33.3)	17 (36.2)
Hypoalbuminemia	3 (33.3)	1 (11.1)	5 (41.7)	4 (36.4)	3 (50.0)	16 (34.0)
Abdominal pain	4 (44.4)	1 (11.1)	4 (33.3)	4 (36.4)	2 (33.3)	15 (31.9)
Hypophosphatasemia	3 (33.3)	0 (0.0)	5 (41.7)	4 (36.4)	2 (33.3)	14 (29.8)
Pyrexia	2 (22.2)	2 (22.2)	4 (33.3)	4 (36.4)	2 (33.3)	14 (29.8)
Constipation	4 (44.4)	2 (22.2)	5 (41.7)	2 (18.2)	0 (0.0)	13 (27.7)
Diarrhoea	4 (44.4)	0 (0.0)	5 (41.7)	3 (27.3)	1 (16.7)	13 (27.7)
Sinus tachycardia	2 (22.2)	2 (22.2)	5 (41.7)	3 (27.3)	1 (16.7)	13 (27.7)
Decreased appetite	3 (33.3)	2 (22.2)	3 (25.0)	2 (18.2)	2 (33.3)	12 (25.5)
Blood bilirubin increased	2 (22.2)	1 (11.1)	4 (33.3)	4 (36.4)	0 (0.0)	11 (23.4)
Pain in extremity	4 (44.4)	0 (0.0)	3 (25.0)	2 (18.2)	2 (33.3)	11 (23.4)
Blood creatinine increased	1 (11.1)	1 (11.1)	4 (33.3)	1 (9.1)	2 (33.3)	9 (19.1)
Cough	2 (22.2)	0 (0.0)	3 (25.0)	1 (9.1)	3 (50.0)	9 (19.1)
Dyspnea	1 (11.1)	2 (22.2)	1 (8.3)	3 (27.3)	2 (33.3)	9 (19.1)
Blood alkaline phosphatase increased	1 (11.1)	1 (11.1)	4 (33.3)	2 (18.2)	0 (0.0)	8 (17.0)

Grade 3 or Higher TEAEs Reported in More Than 5% of Patients (copied from sponsor's report)

MedDRA System Organ Class 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 (%)	7 (77.8)	7 (77.8)	12 (100.0)	9 (81.8)	5 (83.3)	40 (85.1)
Blood and lymphatic system disorders						
Anaemia	2 (22.2)	2 (22.2)	7 (58.3)	6 (54.5)	1 (16.7)	18 (38.3)
Febrile neutropenia	2 (22.2)	2 (22.2)	2 (16.7)	0 (0.0)	0 (0.0)	6 (12.8)
Gastrointestinal disorders						
Vomiting	1 (11.1)	1 (11.1)	1 (8.3)	0 (0.0)	0 (0.0)	3 (6.4)
General disorders and administration site conditions						
Death	1 (11.1)	0 (0.0)	1 (8.3)	4 (36.4)	0 (0.0)	6 (12.8)
Investigations						
Alanine aminotransferase increased	2 (22.2)	2 (22.2)	1 (8.3)	0 (0.0)	0 (0.0)	5 (10.6)
Aspartate aminotransferase increased	2 (22.2)	1 (11.1)	1 (8.3)	0 (0.0)	1 (16.7)	5 (10.6)
Lymphocyte count decreased	2 (22.2)	2 (22.2)	6 (50.0)	1 (9.1)	2 (33.3)	13 (27.7)
Neutrophil count decreased	1 (11.1)	0 (0.0)	6 (50.0)	5 (45.5)	2 (33.3)	14 (29.8)
Platelet count decreased	5 (55.6)	2 (22.2)	5 (41.7)	3 (27.3)	1 (16.7)	16 (34.0)
White blood cell count decreased	1 (11.1)	1 (11.1)	4 (33.3)	1 (9.1)	2 (33.3)	9 (19.1)
Metabolism and nutrition disorders						
Decreased appetite	0 (0.0)	1 (11.1)	1 (8.3)	0 (0.0)	1 (16.7)	3 (6.4)
Hypokalemia	2 (22.2)	1 (11.1)	2 (16.7)	1 (9.1)	0 (0.0)	6 (12.8)
Hyponatremia	0 (0.0)	1 (11.1)	1 (8.3)	0 (0.0)	1 (16.7)	3 (6.4)
Hypophosphatasemia	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	1 (16.7)	3 (6.4)
Respiratory, thoracic and mediastinal disorders						
Dyspnea	0 (0.0)	2 (22.2)	0 (0.0)	2 (18.2)	0 (0.0)	4 (8.5)
Hypoxia	0 (0.0)	1 (11.1)	0 (0.0)	3 (27.3)	0 (0.0)	4 (8.5)

Treatment Related TEAEs Reported in More Than 10% of Patients (copied from sponsor's report)

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)	10 (83.3)	10 (90.9)	6 (100.0)	44 (93.6)
Anaemia	1 (11.1)	4 (44.4)	6 (50.0)	7 (63.6)	6 (100.0)	24 (51.1)
Neutrophil count decreased	2 (22.2)	2 (22.2)	5 (41.7)	5 (45.5)	5 (83.3)	19 (40.4)
Platelet count decreased	4 (44.4)	3 (33.3)	5 (41.7)	3 (27.3)	4 (66.7)	19 (40.4)
White blood cell count decreased	2 (22.2)	3 (33.3)	5 (41.7)	3 (27.3)	5 (83.3)	18 (38.3)
Aspartate aminotransferase increased	2 (22.2)	2 (22.2)	4 (33.3)	1 (9.1)	4 (66.7)	13 (27.7)
Lymphocyte count decreased	1 (11.1)	4 (44.4)	2 (16.7)	1 (9.1)	4 (66.7)	12 (25.5)
Nausea	4 (44.4)	3 (33.3)	2 (16.7)	2 (18.2)	1 (16.7)	12 (25.5)
Alanine aminotransferase increased	1 (11.1)	2 (22.2)	3 (25.0)	2 (18.2)	3 (50.0)	11 (23.4)
Fatigue	0 (0.0)	2 (22.2)	3 (25.0)	2 (18.2)	3 (50.0)	10 (21.3)
Hypocalcaemia	3 (33.3)	2 (22.2)	2 (16.7)	2 (18.2)	0 (0.0)	9 (19.1)
Abdominal pain	1 (11.1)	1 (11.1)	2 (16.7)	2 (18.2)	1 (16.7)	7 (14.9)
Blood creatinine increased	0 (0.0)	1 (11.1)	2 (16.7)	1 (9.1)	1 (16.7)	5 (10.6)
Headache	2 (22.2)	0 (0.0)	1 (8.3)	1 (9.1)	1 (16.7)	5 (10.6)
Hyperglycemia	3 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)	1 (16.7)	5 (10.6)
Hypokalemia	2 (22.2)	1 (11.1)	0 (0.0)	0 (0.0)	2 (33.3)	5 (10.6)
Vomiting	2 (22.2)	1 (11.1)	0 (0.0)	2 (18.2)	0 (0.0)	5 (10.6)

Assessment of DLTs (derived from sponsor's report)

For subjects with solid tumors, all subjects who received study drug were also evaluable for DLTs. No subjects experienced a DLT at the starting dose of 15 mg/m^2 BID, and therefore only 3 subjects were treated at this dose level prior to escalation to the 21 mg/m^2 BID dose. Six subjects with solid tumors were treated at each of the other dose levels (ie, (21, 29, and 39 mg/m^2 BID) prior to sequentially enrolling and treating subjects at the next higher (ie, escalated) dose; no more than 2 subjects experienced a DLT at any of these individual dose levels, and therefore, 6 subjects were also treated at the 50 mg/m^2 BID dose level, which was the highest dose level planned for evaluation in this study per Protocol.

Determination of RP2D/ MTD

Table Summarizing DLT's for Cycle 1(copied from Loh 2015)

Stratum	Dose level (mg/m^2)	Number of patients entered	Number of patients evaluable	Number of patients with DLT	Toxicity (grade)
Part A	15	4	3	0	–
	21	6	6	1	ALT (4), dehydration (3), hypotension (3), multi-organ failure (5), nausea (3), vomiting (3)
	29	6	6	1	Neutropenia (4)
	39	6	6	1	Neutropenia (4)
	50	6	6	1	CPK increased (4)
Part B	15	6	4	0	–
	21	3	1	0	–
	29	6	3	0	–
	39	6	2	1	Creatinine (3), acute kidney injury (3)

REVIEWER COMMENT:
The trial was designed to evaluate doses of ruxolitinib up to 50 mg/m^2 BID for a 28 day period. The dose of 50 mg/m^2 BID is higher than the recommended dose of ruxolitinib for the approved adult indications. The dose did not exceed the MTD according to the study design and the investigators determined 50 mg/m^2 BID to be the RP2D. This dose was used to design study 2 of the WR.

There is insufficient information available on an appropriate dose for extended administration of this dose given the limitations of a population appropriate for the initial dose finding study in a pediatric population.

Conclusions:
Doses of ruxilitinib of 50mg/m^2 BID for 28 days did not exceed the MTD. The sponsor has used this information to design study 2 of the WR, "A Phase 2 Study of the JAK1/JAK2 Inhibitor Ruxolitinib With Chemotherapy in Children With De Novo High-Risk CRLF2-Rearranged and/or JAK Pathway–Mutant Acute Lymphoblastic Leukemia." The starting dose of ruxilitinib in combination with chemotherapy will be 40 mg/m^2 BID, if tolerated, 50 mg/m^2 will be evaluated.

Appendix 1 – Labeling Review

Section 8.4 Pediatric Use		
Current Label	Proposed Revision (b) (4)	FDA Final
The safety and effectiveness of Jakafi in pediatric patients have not been established.		The safety and effectiveness of Jakafi in pediatric patients have not been established. Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to < 12 years), and 14 adolescents (age 12 to <17 years). The dose levels tested were 15, 21, 29, 39, or 50 mg/m^2 twice daily in 28-day cycles with up to 6 patients per dose group. Overall, 38 (81%) patients were treated with no more than a single cycle of Jakafi, while 3, 1, 2, 3 patients received 2, 3, 4, and 5 or more cycles, respectively. Although a protocol-defined maximal tolerated dose was not observed, there was insufficient exposure to establish a recommended Phase 2 dose. The safety profile in children was similar to that seen in adults.

Appendix 2 - Exclusivity Review for WR Study 1

Timeframe for submitting reports of the studies: Study 1 – July 1, 1917	Submitted June 15, 2017 NDA 202192; Seq 0139	Assessment
Type of Study – Study 1 Primary Objectives: • To define the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of oral ruxolitinib administered twice daily to children with relapsed or refractory solid tumors and leukemias.	The objectives of Study ADVL1011 were the objectives outlined in the WR.	Assessment • The study determined a RP2D carried forward into study 2 of the WR – met requirement as defined in the protocol that is determination of a tolerable dose for 28 days of exposure. Note: Study 2 will further evaluate the RP2D of extended exposure of rituximab in combination with chemotherapy.
• To define and describe the toxicities of ruxolitinib administered on this schedule in patients with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms (MPNs).		• The study report included a description of toxicities reported in the study population – met requirement
• To characterize the pharmacokinetics of ruxolitinib in children with relapsed or refractory solid tumors, leukemias, or MPNs.		• The PK results of the trial were described in a separate report (INCYTE-DMB-17.16.1). – met requirement
Secondary Objectives: • To assess the antitumor activity of ruxolitinib within the context of a phase 1 study.		• The study report described tumor response in patients with solid tumors (no responses) and in hematologic disease (1 PR in patient with PV) – met requirement
• To assess the biologic activity of ruxolitinib upon JAK-STAT signaling in patients with relapsed or refractory solid tumors, leukemia or MPNs.		• PD evaluation was done and reported in Loh 2015 publication. – met requirement
• To assess the biologic activity of ruxolitinib upon phosphosignaling and mutation burden in patients whose leukemias or MPNs have known CRLF2 and/or JAK mutations.		• No JAK1 or JAK2 point mutations or increased TSLPR staining by flow cytometry were identified in leukemia patients enrolled on study 1. The biologic activity of rituximab will be further evaluated in study 2. - met requirement to the extent possible in the population enrolled

Patients to be Studied: • Age group in which study will be performed: 2 to 21 years. • Number of patients to be studied: Up to 106 subjects to determine the RP2D.	Age of patients entered 2 to 21, mean 12.7, median 14 years. Overall, 47 subjects were analyzed for safety (including 27 with solid tumors and 20 with leukemias or MPNs); 37 subjects were analyzed for DLTs and efficacy (including 27 with solid tumors and 10 with leukemias or MPNs).	Assessment – The age of the patients entered met the criteria of the WR. - met requirement The number of patients enrolled was adequate to determine the RP2D for 28 day exposure as specified in the protocol. – met requirement
Study endpoints: Primary Endpoints • Determination of the RP2D of ruxolitinib in patients with solid tumors. • Safety and tolerability of ruxolitinib • Pharmacokinetic endpoints for the study drug will include maximum observed plasma drug concentration (Cmax), time to maximum concentration (Tmax), and study drug exposure (AUC0-t) measured as the area under the single-dose plasma concentration-time curve	The RP2D was determined to be 50 mg/m^2 BID for a 28 day exposure as specified in the protocol.	The highest evaluated dose as specified in the protocol of 50 mg/m^2 BID. This dose did not exceed the MTD and was determined to be the RP2D of a 28 day course of ruxolitinib for children with relapsed or refractory cancer – met requirement as specified in the protocol.
Statistical information • The analyses will utilize only descriptive statistics.	The results reported were descriptive.	Met requirement

Appendix 3 – References

Loh, ML, Tasian. SK, Rabin, KR, et al., 2015, A Phase 1 dosing study of ruxolitinib in children with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms: A Children's Oncology Group Phase 1 Consortium Study (ADVL1011), Pediatr Blood Cancer, 62:1717-1724.

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/s/

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11/20/2017