NDA MULTIDISCIPLINARY REVIEW AND EVALUATION

Application Number	NDA 202192 S-027
Application Type	SE-8; Response to Written Request
Priority or Standard	Priority
Submit Date	6/24/2022
Received Date	6/24/2022
PDUFA Goal Date	12/24/2022
Office/Division	OOD/DHM1
Review Completion Date	12/19/2022
Applicant	Incyte Corporation
Established Name	Ruxolitinib
Trade Name	Jakafi
Pharmacologic Class	Kinase inhibitor
Formulations	Tablet (5 mg, 10 mg, 15 mg, 20 mg, 25 mg)
Recommendation on Regulatory Action	Approval of revised labeling

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REVIEWERS OF THE MULTIDISCIPLINARY REVIEW AND EVALUATION

Office of Clinical Pharmacology Reviewer(s)	Hongfei Zhang, Ph.D.
Office of Clinical Pharmacology Team Leader(s)	Nan Zheng, Ph.D.
Clinical Reviewer	Emily Jen, MD, PhD
Clinical Team Leader	Donna Przepiorka, MD, PhD
Statistical Reviewer	Haiyan Chen, PhD
Statistical Team Leader	Jonathan Vallejo, PhD
Associate Director for Labeling (OOD)	Elizabeth Everhart, MSN, RN, ACNP
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD
Division Director (OCP)	Brian Booth, PhD
Division Director (OB)	Mark Levenson, PhD
Division Director (DHM1)	Angelo de Claro, MD

Additional Reviewers of Application

Regulatory Project Manger (DHM1)	Sheila Ryan, PharmD, MPH
Associate Director for Safety (OCE)	Shan Pradhan, MD
OPDP	Melissa Khashei, PharmD
OSE/DMEPA	Nicole Iverson, PharmD; Hina Mehta, PharmD

GLOSSARY

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report PD pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy SAE serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 EXECUTIVE SUMMARY

1.1 Product Introduction

Drug Established Name:	Ruxolitinib
Trade Name:	Jakafi
Dosage Forms:	Tablets (5, 10, 15, 20, and 25 mg)
Chemical Class:	Heterocyclic pyrazolyl-substituted pyrrolopyrimidine
Therapeutic Class:	Kinase inhibitor
Mechanism of Action:	Inhibits JAK1 and JAK2, thereby blocking the action of cytokine signaling through the JAK-STAT pathway in hematopoiesis and immune function

Jakafi is approved for treatment of patients with intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF; for treatment of patients with polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea; for treatment of steroid-refractory acute graft-versus-host disease in adult and pediatric patients 12 years and older; and for treatment of chronic graft-versus-host disease after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older. A Written Request for Study 1 and Study 2 was issued on 12/11/2015 and last amended on 7/23/2021. Study 1 was reviewed under Supplement 015. The present supplement was submitted to provide the results of Study 2 in the Written Request and to revise the US Prescribing Information (USPI) to include those results.

1.2 Recommendations on Regulatory Action

The review team recommends approval of the revision to USPI Section 8.4 under 505B(g)(2) of the Food, Drug, and Cosmetic Act. The review team also considers the WR to be fulfilled.

1.3 Basis for the Recommendations

Study INCB 18424-269 (NCT02723994) was a single-arm dose-finding, dose-expansion study of ruxolitinib in combination with the augmented BFM (aBFM) regimen in pediatric patients with de novo high-risk CRLF2-rearranged and/or JAK pathway-mutant (Ph-like) ALL. After completing the Induction phase, eligible participants were assigned to 1 of 4 cohorts (Cohorts A-D) based on CRLF2-R status, presence of JAK mutation, and/or MRD status. The accrued subjects included 2 infants, 42 children, and 62 adolescents.

Part 1 of Study INCB 18424-269 used a rolling 6 design to test ruxolitinib doses of 10-50 mg/m^2 BID 14 days on/14 days off in a 28-day cycle and 40 mg/m^2 BID daily in 28-day cycles. The objective of Part 1 was to determine the recommended Phase 2 dose (RP2D) based on dose-limiting toxicities (DLTs) through Day 29 of Delayed Intensification. Once the RP2D was determined, the treatment dose for all subjects would be escalated to the RP2D for the remainder of the treatment course. The Applicant reported that 50 mg/m^2 BID 14 days on/14 days off was the RP2D. The allowance for intrapatient dose escalation was a major confounding factor for the analyses needed for selection of the RP2D, and the review team determined that the totality of PK, PD, safety, efficacy, and tolerability data as submitted did not support 50 mg/m^2 BID 14 days on/14 days off as the RP2D.

Part 2 of Study INCB 18424-269 was a single-arm trial of ruxolitinib 50 mg/m^2 BID 14 days on/14 days off with the aBFM regimen in 4 subpopulation cohorts. The primary objective of Part 2 was to determine the 3-year EFS for patients in Cohorts A and B. The Applicant reported 3-year EFS of 67.4% (95% CI: 41.5%, 83.7%) in Cohort A, and 65.3% (95% CI: 36.2%, 83.6%) in Cohort B, and the statistical reviewer confirmed these results. However, the review team determined that the single-arm design was not appropriate to test efficacy using a time-to-event endpoint nor did the design allow for isolation of the contribution of ruxolitinib to the combination, (b) (4)

In accordance with 505B(g)(2), the review team recommended stating in USPI Section 8.4 that the safety and effectiveness of ruxolitinib were not established for treatment of Ph-like ALL. Although the results of the Study INCB 18424-269 were not sufficient to determine a safe and effective dose of ruxolitinib in combination with the aBFM regimens and were not adequate to support an indication, the Division concluded that, technically, the terms of the WR were met. The details of the Division's evaluation of the Applicant's response to the WR are provided in a separate review.[1]

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application					
X	The patient experience data that was submitted as part of the application, include:				Section
	□	Clinical outcome assessment (COA) data, such as			
			□	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			

[1] NDA 202192 Pediatric Exclusivity Determination Checklist dated 12/1/2022.

	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Natural history studies	
	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	X	Other: Patient feedback on taste and ease of administration of ruxolitinib minitab capsule	8.3.7
□	Patient experience data that was not submitted in the application, but was considered in this review.		
	□	Input informed from participation in meetings with patient stakeholders	
	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Other: (Please specify):	
□	Patient experience data was not submitted as part of this application.		

2 THERAPEUTIC CONTEXT

2.1 Analysis of Condition

Not applicable

2.2 Analysis of Current Treatment Options

Not applicable

3 REGULATORY BACKGROUND

3.1 U.S. Regulatory Actions and Marketing History

11/16/11	Regular approval granted for treatment of patients with intermediate- or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults
12/4/14	Regular approval granted for treatment of patients with polycythemia vera (PV) who have an inadequate response to or cannot tolerate hydroxyurea
5/24/19	Regular approval granted for treatment of steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older

9/22/21	Regular approval granted for treatment of chronic graft-versus-host-disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older

3.2 Summary of Presubmission/Submission Regulatory Activity

The development of ruxolitinib was initiated under IND 077456, and IND 147055 has been used for trials in GVHD and leukemia specifically. Study ADLV1011 was not conducted by the Applicant; Study INCB18424-269 is being conducted under IND 147055. The following are the key activities related to this supplement:

10/20/2011	Biopharmaceutic review concluded that the waiver request for a BE study comparing the oral solution/suspension vs. the oral tablets is acceptable. This was confirmed by biopharmaceutics review on 12/23/2015.
6/25/2015	Type C meeting to discuss studies of ruxolitinib in children is preparation for a proposed pediatric study request (PPSR). Key advice: • The published report for ADLV1011 does not support 50 mg/m^2 BID as the RP2D in children. • The studies as proposed would not support a new indication. • The addition of (b) (4) to the crushed tablets may require additional justification to support a biowaiver request.
12/11/15	WR issued for Study 1 (ADVL1011) and Study 2 (INCB 18424-269) to provide data on PK, safety, and activity of ruxolitinib in children with cancer using an age-appropriate formulation
7/18/2016	Orphan designation granted for treatment of acute lymphoblastic leukemia.
9/15/16	WR Amendment #1 amended the timeframe for submitting reports from Study 1 from 1/1/17 to 7/1/17
12/6/2017	Supplement 015 approved with revisions to USPI Section 8.4 based on the final report for ADVL1011. The clinical and clinical pharmacology reviewers concluded that an RP2D was not established.
10/26/2018	Supplement 016 approved with revisions to USPI Section 8.4 based on juvenile animal studies.
7/23/21	WR Amendment #2 updated INCB 18424-269 to clarify accrual target and describe sufficient follow-up for appropriate estimation of 3-year EFS
6/24/22	Supplement 027 submitted with study report for INCB 18424-269 to support updates to Section 8.4 of the USPI and with a request for pediatric exclusivity
12/1/2022	Applicant notified of Pediatric Exclusivity.

4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1 Office of Scientific Investigations (OSI)

This supplement does not support an efficacy claim based on new efficacy data; therefore, no clinical site inspections were requested.

4.2. Product Quality

There is no new product quality information in this supplement. Specifically, a pediatric formulation was not proposed for marketing.

4.3 Devices and Companion Diagnostic Issues

There are no proposed companion diagnostics for this supplement.

5 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No new nonclinical data were submitted in this supplement.

6 CLINICAL PHARMACOLOGY

6.1 Executive Summary

A Written Request was issued for Study 1 (ADVL1011) and Study 2 (INCB 18424-269) to provide data on PK, safety, and activity of ruxolitinib in children with cancer using an age-appropriate formulation. The result from Study 1 was submitted in Supplement 015. In the current sNDA, the Applicant submitted the results of Study 2 (INCB 18424-269), "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" in the Written Request and to update Section 8.4 Pediatric Use in the US Prescribing Information to include results from Study INCB 18424-269.

Study 2 included a dose finding phase (Part 1; 10 to 50 mg/m^2 ruxolitinib twice daily [BID] 14

days on/14 days off and 40 mg/m^2 ruxolitinib BID continuous in 28-day cycles) and a dose expansion phase (Part 2) at the selected RP2D of 50 mg/m^2 BID 14 days on/14 days off, added to a standard postinduction augmented Berlin-Frankfurt-Münster (aBFM) multiagent chemotherapy regimen. Ruxolitinib was provided in Study 2 as oral tablets in 5 mg and 25 mg strengths and as oral minitab capsules in 5 mg and 10 mg strengths for patients unable to swallow tablets. For patients unable to swallow tablets, minitab capsules could be opened and contents mixed with a small amount of food or drink or dissolved in water for administration through a nasogastric or gastrostomy tube; tablets could also be crushed and prepared in the same way. No relative bioavailability (BA) or food effect studies have been conducted for crashed tablets and minitab capsules. A request to waive a relative BA study for the crushed tablet is based on fast dissolution and bioavailability of ruxolitinib (BCS Class 1). See more details in previous Quality Review under IND 077456.

The Office of Clinical Pharmacology has reviewed the information provided in this supplement. The Applicant is not seeking new indications based on Study 2. There is insufficient information to support PK comparison between formulations. Similar T_{max}, C_{max} and $AUC_{0\text{-}4hr}$ were observed across the age groups studied (***Table 1***).

Study 2 from the Applicant's Written Request is considered as fulfilled from a clinical pharmacology perspective, because it generated PK data using appropriate formulations (i.e., intact tablet, crushed tablet, or minitab) in pediatric patients.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

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

- intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults. Depending on patient's baseline platelet count, the starting dose is in a range of 5-20 mg BID
- polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea. The starting dose is 10 mg BID.
- steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older. The starting dose is 5 mg BID.
- chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older. The starting dose is 10 mg BID.

Clinical pharmacology properties of ruxolitinib are summarized below:

- C_{max} and AUC increased proportionally over a single dose range of 5 to 200 mg
- Oral absorption is estimated to be ≥ 95%

- T_{max}: within 1-2 hours post-dose
- A high-fat meal has no food effect on the PK
- Elimination half-life
  - Ruxolitinib: approximately 3 hrs
  - Ruxolitinib and metabolites: approximately 6 for (all active metabolites contribute to 18% of the overall pharmacodynamic activity)
- Metabolized by CYP3A4 and to a lesser extent by CYP2C9
- High variability in CL/F (% CV)
  - 17.7 L/h in women and 22.1 L/h in men with MF (39%)
  - 12.7 L/h (42%) in patients with PV
  - 11.8 L/h (63%) in patients with aGVHD
  - 9.7 L/h (51%) in patients with cGVHD
- Dose adjustment is recommended for patients with hepatic impairment, renal impairment, or patients taking concomitant medications with strong CYP3A4 inhibitors.
- No clinically relevant differences in ruxolitinib pharmacokinetics were observed based on age (12-73 years), race (White, Asian), sex, or weight (29-139 kg).

In the current submission, the Applicant submitted results from Study 2 (INCB 18424-269) in pediatric and adolescent young adult participants with high-risk Ph-like B-ALL. The PK sampling schedule in this study is not sufficient to support a comprehensive characterization of the PK profiles in the study population; however, available data do not suggest major differences in the observed PK parameters (e.g., T_{max}, C_{max} and AUC_{0-4hr}) across different age groups.

6.2.2 General Dosing and Therapeutic Individualization

See prior reviews for the original and supplemental NDAs. This submission does not involve changes to the dosing instructions.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

See prior reviews for this original and supplemental NDAs.

6.3.2 Clinical Pharmacology Questions

1. What is the impact of age on PK exposure in the study population?

In study 2, there are limited PK sampling time points to adequately characterize the full PK profile of ruxolitinib in the study population. The half-life and AUC_{0-inf} cannot be derived because the PK sampling schedule did not cover the elimination phase of ruxolitinib, but T_{max},

C_{max}, and AUC_{0-4hr} can be calculated. While the sample size was limited in patients less than 12 years of age, these PK parameters do not suggest apparent differences across age groups for patients at least 2 years of age who received the same dosing regimen (***Table 1***).

Table 1. Summary of the PK parameters (mean ± SD) of ruxolitinib by age group

Treatment	Age group (years)	N	AUC_{0-4h} (nmol·h/L)	Cmax (nmol/L)	Tmax (hr)
50 mg/m^2, BID 14 days on/ 14 days off	2 to < 6	5	6910.2 ± 2497.1	2742.0 ± 1153.7	1 (0.9-2.1)
	6 to < 12	5	8298.1 ± 3795.1	3178 ± 444.2	1 (1-4.4)
	12 to < 17	15	5784.6 ± 1583.8	2362 ± 600.1	1.1 (0.9-3.8)
	17 to < 21	14	6359.9 ± 2881.6	2692.1 ± 1155.4	1 (0.9-3.7)

T_{max}: median (minimum-maximum)
Source: FDA analysis

2. What is the impact of formulation on PK exposure in the study population?

The crushed tablet was allowed in Study 2 based on BCS I classification and in vitro dissolution study results. Dosing records about which patients took the crushed tablets was not collected in Study 2. Additionally, the limited sample size precluded meaningful comparison of PK between minitab capsules and the tablets (***Table 2***). Therefore, clinical PK data from Study 2 do not support an assessment on the relative bioavailability of the crushed tablets or the minitab capsules as compared to the intact tablets. However, the prior review of the request to waive a relative BA study for the crushed tablet and the minimal number of patients on minitabs support the reporting of PK data from a pooled dataset regardless of formulation (***Table 1***).

Table 2. Summary of dose normalized PK parameters (Minitab) of ruxolitinib from Study 2

Visit	Formulation	N	AUC_{0-4h} (nM*h/mg)	AUC_{all} (nM*h/mg)	AUC_{0-t} (nM*h/mg)	C_{max} (nM/mg)	t_{max} (h)
CONSOLIDATION DAY 1	Mini-tab	1	54.5	54.5	54.5	18.9	0.983
	Tab	43	73.5 ± 36.3 (65.7)	73.8 ± 36.2 (66.0)	73.8 ± 36.2 (66.0)	31.5 ± 19.5 (27.6)	1.2 (0.8 - 4.0)
Delayed Intensification DAY 1	Mini-tab	3	229 ± 117 (211)	231 ± 116 (213)	231 ± 116 (213)	93.6 ± 53.0 (84.4)	1.0 (1.0 - 2.0)
	Tab	54	89.8 ± 40.8 (82.0)	93.9 ± 47.8 (84.7)	93.9 ± 47.8 (84.7)	37.0 ± 17.5 (33.4)	1.0 (0.8 - 4.4)

Source: Applicant's response to IR

7 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

7.1 Table of Clinical Studies

Table 3. Clinical Studies Supporting the Safety and Efficacy

Study	Trial Design	Study Population	Treatment	Study Endpoints	Countries and Centers
INCB 18424-269 *NCT02723994* (On-going)	Single-arm open-label dose-escalation dose-expansion trial	1-21 yrs old with Ph-like ALL Part 1: n ≤ 30 Part 2: A and B - n ≤ 42 C and D - n ≤ 25	aBFM Chemotherapy plus Part 1: Ruxolitinib 10-50 mg/m^2 BID for 14-28 days of 28-day cycles Part 2: Ruxolitinib RP2D	Part 1: RP2D Part 2: 3-yr EFS	US: 61 sites

Study INCB 18424-269 was the only trial submitted in this supplement.

7.2 Review Strategy

The key materials used for the review of efficacy and safety included the sNDA dataset, clinical study reports, case report forms, and responses to the review team's Information Requests.

The datasets used in the review of Study INCB 18424-269 are:

- Initial Submission: \\CDSESUB1\evsprod\NDA202192\0280\m5\datasets

Table 4. sNDA Submission and Amendments Reviewed

SN	Received	Category	Subcategory
0280	6/24/22	Original	sNDA – Response to Written Request
0283	8/30/22	Clinical IR	Response to Filing Letter Comments
0285	9/30/22	Clinical IR	Response to Information Request

The clinical review of efficacy and safety was based on an analysis of Study INCB 18424-269. The primary efficacy endpoint and major safety analyses were reproduced or audited. Analyses by the statistical reviewers were performed using SAS 9.4 (b) (4) Safety analyses were performed using MedDRA-Based Adverse Event Diagnostics (MAED) version 3.5 (FDA, Silver Spring, MD).

8 STATISTICAL AND CLINICAL EVALUATION

8.1 Review of Relevant Individual Trials Used to Support Efficacy

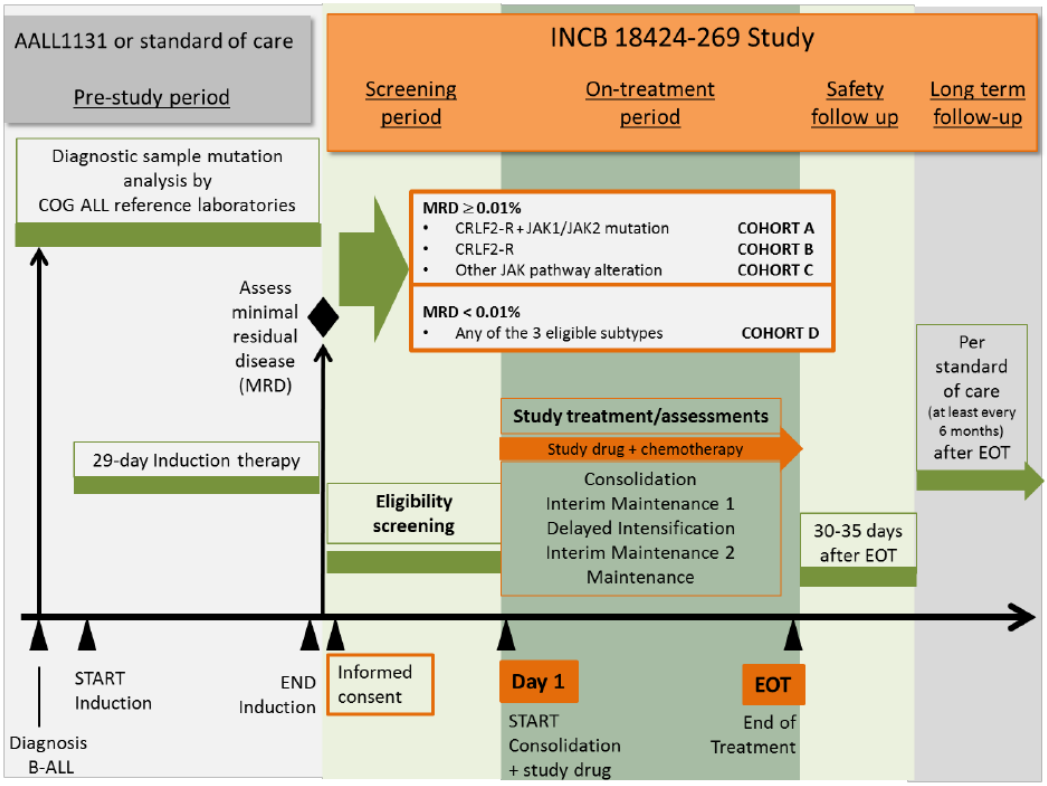
8.1.1. INCB 18424-269

INVESTIGATIONAL PLAN

Trial Design

INCB 18424-269 is a single-arm dose-finding, dose-expansion study of ruxolitinib in combination with multiagent chemotherapy in pediatric patients with de novo high-risk CRLF2-rearranged and/or JAK pathway-mutant (Ph-like) ALL. Patients were treated with the augmented BFM regimen (Induction, Consolidation, Interim Maintenance 1, Delayed Intensification, Interim Maintenance 2, and Maintenance) and ruxolitinib at the assigned dose. After completing Induction therapy (target duration of 29-35 days), eligible participants in both parts of the study were assigned to 1 of 4 cohorts based on CRLF2-R status, presence of JAK mutation, and/or MRD status.

Figure 1. INCB 18424-269 Study Design



Source: INCB 18424-269 Protocol Amendment 4, Figure 2

Part 1 dose-escalation and de-escalation followed a rolling 6 design. Toxicity was assessed during the first 3 courses of chemotherapy (consolidation, IM1, DI) at which point ruxolitinib would have been co-administered with all major cytotoxic agents in the aBFM regimen.

Once the RP2D was selected, subjects were enrolled in the Part 2 dose-expansion. The primary endpoint was 3-year EFS assessed independently in Cohorts A and B.

Key Eligibility Criteria

- Age ≥ 1 year and ≤ 21 years at time of leukemia diagnosis

- Newly-diagnosed de novo HR Ph-like B-ALL meeting ≥ 1 of the following:
    - Age ≥ 10 years at diagnosis
    - WBC ≥ 50 Gi/L
    - CNS3 leukemia at diagnosis
    - Systemic steroid pretreatment without presteroid WBC documentation

- Diagnostic marrow or peripheral blood sample with gene expression profiling and downstream genetic testing submitted under COG biology or treatment studies that demonstrate Ph-like expression profile (i.e., LDA-positive as tested by low density microarray testing at the COG ALL reference laboratory or TriCore laboratory at the University of New Mexico) AND must contain 1 of the following genetic lesions:
    - CRLF2 rearrangement with confirmed JAK1 or JAK2 mutation (JAK+)
    - CRLF2 rearrangement without JAK mutation
    - Other JAK pathway alterations with or without CRFL2-R or CRLF2-R with unknown JAK status

- Completed 4-drug regimen induction therapy (modified aBFM or equivalent) on AALL1131 or successor study, or per institutional standard of care for HR B-ALL

Treatment Plan

Ruxolitinib was given in combination with aBFM backbone chemotherapy following the established treatment phases consolidation, interim maintenance 1 (IM1), delayed intensification (DI), interim maintenance 2 (IM2), and maintenance. Most dose levels tested were on a 14 days on/14 days off schedule. Modifications to this schedule in some phases of treatment to align with administration of chemotherapy are described in the footnote to Table 5. Intrapatient dose escalation was also allowed; once the proposed RP2D was identified, the dose was increased to that for all study participants at lower doses.

Table 5. INCB 18424-269 Ruxolitinib Administration

Treatment Group	Part 1	Part 2
Study Treatment Name	Ruxolitinib	
Dose Formulation	Tablet Minitab capsule	
Unit Dose Strengths	5- and 25-mg oral tablets 5- and 10-mg minitab capsules	
Dose Regimen	Starting dose of 40 mg/m^2 BID 14 days on/14 days off De-escalation doses of 30, 20, and 10 mg/m^2 BID 14 days on/14 days off Escalation doses of 50 mg/m^2 BID 14 days on/14 days off and 40 mg/m^2 BID in 28-day cycles	50 mg/m^2 BID 14 days on/14 days off
Route of Administration	Oral	
Administration Instructions	Tablets were taken with water, without regard to food. For participants unable to swallow tablets: Minitab capsules were opened and contents mixed with a small amount of food or drink or dissolved in water for administration through a nasogastric or gastrostomy tube; tablets could also be crushed and prepared in the same way.	
Packaging and Labeling	Provided in bottles, labeled as required per country requirement	
Current/Former Name or Alias	INCB018424, ruxolitinib	

Note: To align with administration of chemotherapy, discontinuous administration of ruxolitinib was generally 14 days on/14 days off; exceptions included 14 days on/21 days off during Interim Maintenance 1 and 10 days on/10 days off during Interim Maintenance 2.

Source: INCB 18424-269 CSR Table 2

Monitoring Plan

INCB 18424-269 included a comprehensive monitoring plan described in Section 6.2 of the protocol. CBCs were conducted weekly through DI, ~q10 days in IM2, and monthly in maintenance. Blood chemistries and AE assessments were conducted every 1-4 weeks depending on the phase of therapy (assessed more often during more intensive phases). MRD was assessed at the end of consolidation.

Statistical Analysis Plan

The key information of the Statistical Analysis Plan is summarized as follows:

- The primary efficacy endpoint was a secondary objective for only Part 2 of the study only, defined as EFS at 3 years from Day 1 for subjects in Cohorts A and B beginning treatment at the RP2D.

Statistical Reviewer Comment: Of note, although there were no efficacy endpoints prespecified in the SAP for Part 1 by the applicant, the SAP defines the "evaluable population" to be "all subjects who receive at least 1 dose of study drug at the RP2D. This will include subjects in both Part 1 and Part 2." For this reason, in this review, the efficacy evaluable population includes all 118 patients treated at the RP2D, including 8 from Part 1 and 110 from Part 2.

- All statistical analyses are exploratory in nature. Unless otherwise specified, all CIs provided will be at the 95% confidence level.

- Sample size calculation vs actual enrollment in Part 2: With a sample size of 42 subjects each in Cohorts A and B, assuming a 3-year EFS of 65% for MRD+ CRLF2-R/JAK+ or CRLF2-R/JAK(-) subjects treated on Study AALL0232 (Loh et al 2013), and with 10% of subjects lost to follow-up, the study will have at least 80% power to detect an improvement in the primary endpoint (3-year EFS) to 80%, using a one-sided Type I error rate of 0.10. An estimated 129 subjects are planned for in Part 2 (42 subjects in Cohort A, 42 subjects in Cohort B, and the remainder in Cohorts C and D). Thus, the expected total sample size for the study is approximately 153 subjects. Enrollment of an additional 17 subjects will be allowed to cover the estimated 10% inevaluable rate, thus making the total number of enrolled subjects up to 170.

- The Study actually enrolled 150 patients (52 in Cohort A and 35 in Cohort B) among which 118 patients (44 in Cohort A and 31 in Cohort B) made up the evaluable population, i.e., all of whom received ruxolitinib at the RP2D of 50 mg/m2 BID 14 days on/14 days off, either during Part 1 (8 participants) or Part 2 (110 participants).Analysis population: the evaluable population defined above was used for efficacy analyses.

- There were no prespecified criteria for selection of the RP2D.

- Efficacy endpoints:

  -Primary: 3-year EFS from Study Day 1; Events of relapse, progression, or death were defined as follows:

  • Evidence of medullary relapse based upon bone marrow aspirate testing with morphology, immunophenotyping, and genetic analyses
  • Progression of CNS leukemia
  • New or relapsed testicular involvement
  • Occurrence of second malignancy
  • Receipt of second-line therapy
  • Death (any cause)

• For participants having failed Induction, progression of disease: − Confirmed increase in peripheral blasts of > 25% or a doubling of bone marrow blasts

Clinical TL Review Comment: The definition of EFS as prespecified in the protocol is not the definition usually used for regulatory actions. Since this trial is not supporting an efficacy claim, for the purposes of this review, the EFS endpoint data will be used as submitted, and the endpoints will not be independently adjudicated by the reviewers.

-Secondary: Minimum residual disease (MRD, defined as MRD ≥ 0.01% is MRD+; MRD < 0.01% is MRD-, i.e., remission), OS

- Interim analysis: Two interim analyses for futility were prespecified at 2.25 yrs and 4.5 yrs after the first subject enrolling to be conducted in Cohort A and Cohort B, respectively. The probability of stopping the study at either the first or second interim analysis will be approximately 2.5% if the true 3-year EFS is 80% and 45% if the 3-year EFS is 65%.

  The first interim analysis was performed as planned. The results didn't cross the futility boundary for combined Cohorts A and B. The study continued.

- Analysis methods:
  -for Binary variables: point estimate with 95% CIs were calculated.
  -for Time to event variables: Kaplan-Meier Method was used.

Statistical Reviewer Comment: The definition of 3-year EFS was discussed and agreed with FDA. Of note, the primary efficacy endpoint, 3-year EFS in this single arm study is exploratory in nature, from which no confirmatory effectiveness of ruxolitinib in the proposed indication can be claimed. Please refer to Sections Study Results, 8.2 Integrated Review of Effectiveness, and 8.4 Statistical Issues.

In addition, although the results of secondary/exploratory endpoints, such as 3-year EFS estimate for Cohorts C and D, MRD- rate, and OS, etc. were provided by the Applicant, they have not been confirmed by FDA.

Protocol Amendments

Amendment 1 (28 Jan 2016)	Minor changes to schedule of assessment. No changes to study design, dose-escalation plan, eligibility, or study schedule.
Amendment 2 (23 May 2016)	Clarified instructions for restarting study drug following delay for toxicity or permanent discontinuation after repeat toxicity requiring dose reduction

Amendment 3 (3 Oct 2017)	Update doses of ruxolitinib in the dose-escalation based on emerging data showing that exposure at 40 mg/m^2 appears to achieve substantial pharmacological inhibition of the molecular target • Dose level 1b added – 40 mg/m^2 continuous dosing • Dose level 3 removed – 50 mg/m^2 BID 21 days on/7 days off • Dose level 4 removed – 50 mg/m^2 continuous dosing Enrollment estimate adjusted for Part 1 from 24 to 36
Amendment 4 (17 June 2019)	Include instructions for use of mini-tab capsules Add objective to evaluate palatability/usability of mini-tab

Clinical TL Review Comment: The overall design is consistent with the elements listed in the WR for Study 2.

STUDY RESULTS

Compliance with Good Clinical Practices

The Applicant states in the INCB 18424-269 Clinical Study Report that the trial was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Financial Disclosure

INCB 18424-269 was not intended to demonstrate the efficacy of ruxolitinib in support of a new indication. Therefore, this study is not considered a covered clinical study, and financial disclosure statements are not required.

Data Quality and Integrity

In general, the data file quality for INCB 18424-269 appeared to be acceptable for review.

Patient Disposition

The study was initiated on September 30, 2016, and it was ongoing at the time of data cutoff on January 5, 2022. As of the cutoff date, 150 subjects were enrolled on study. All 150 received at least one dose of ruxolitinib and were included in the safety evaluable population. A total of 118 subjects received the proposed RP2D of 50 mg/m^2 BID 14 days on/14 days off, including 8 subjects enrolled in Part 1 and 110 subjects enrolled in Part 2; these patients comprise the efficacy evaluable population. The disposition of these subjects is described in the table below.

Table 6. INCB 18424-269 Subject Disposition

Variable, n (%)	aBFM Regimen + Ruxolitinib		
	50 mg/m² BID 14 Days On/14 Days Off[a] (N = 118)	All Other (N = 32)	Total (N = 150)
Continuing treatment	44 (37.3)	0 (0.0)	44 (29.3)
Completed treatment	15 (12.7)	19 (59.4)	34 (22.7)
Discontinued treatment early	59 (50.0)	13 (40.6)	72 (48.0)
Primary reason for early discontinuation from treatment			
Adverse event	7 (5.9)	3 (9.4)	10 (6.7)
Death	4 (3.4)	1 (3.1)	5 (3.3)
Noncompliance with study treatment	2 (1.7)	0 (0.0)	2 (1.3)
Physician decision	6 (5.1)	1 (3.1)	7 (4.7)
Withdrawal by participant	5 (4.2)	1 (3.1)	6 (4.0)
Relapse or progression	13 (11.0)	4 (12.5)	17 (11.3)
Medullary relapse	4 (3.4)	1 (3.1)	5 (3.3)
Progression of CNS leukemia	9 (7.6)	3 (9.4)	12 (8.0)
Persistent disease	22 (18.6)	3 (9.4)	25 (16.7)
Phase completed			
Consolidation	96 (81.4)	30 (93.8)	126 (84.0)
Interim Maintenance 1	75 (63.6)	29 (90.6)	104 (69.3)
Delayed Intensification	63 (53.4)	26 (81.3)	89 (59.3)
Interim Maintenance 2	59 (50.0)	23 (71.9)	82 (54.7)
Maintenance	15 (12.7)	19 (59.4)	34 (22.7)
Withdrawn from study	16 (13.6)	4 (12.5)	20 (13.3)
Reason for withdrawal from the study			
Death	13 (11.0)	4 (12.5)	17 (11.3)
Lost to follow-up	1 (0.8)	0 (0.0)	1 (0.7)
Withdrawal by participant	2 (1.7)	0 (0.0)	2 (1.3)

Source: INCB 18424-269 CSR Table 4

Protocol Violations/Deviations

Major protocol deviations included those related to informed consent (13%), entry criteria (8%), and concomitant medications (4%).

- Deviations related to consent were generally due to late administration of an updated ICF or assessments performed as SOC prior to initial ICF, results of which were used to satisfy screening requirements in lieu of repeated the tests.
- Deviations related entry criteria included procedures performed as SOC in the days before initial ICF and missing laboratory tests.
- Deviations related to concomitant medications included subjects taking prohibited concomitant medication (CBD oil, n = 1), failure to reduce ruxolitinib dose when CYP3A4 inhibitor was administered (n = 2), errors in timing of 6MP (n = 2), and administration of

cytarabine in Induction (n = 1)

- Deviations NOS were reported for 34% of subjects – most were related to delay/early administration of study treatment or missed study assessments

Table 7. INCB 18424-269 Protocol Deviations

Variable, n (%)	aBFM Regimen + Ruxolitinib		
	50 mg/m^2 BID 14 Days On/14 Days Off[a] (N = 118)	All Other (N = 32)	Total (N = 150)
Participants who had any Protocol deviations	105 (89.0)	31 (96.9)	136 (90.7)
Adverse event	6 (5.1)	2 (6.3)	8 (5.3)
Informed consent	14 (11.9)	5 (15.6)	19 (12.7)
Entry criteria	10 (8.5)	2 (6.3)	12 (8.0)
Concomitant medications	5 (4.2)	1 (3.1)	6 (4.0)
Noncompliance with study treatment	46 (39.0)	20 (62.5)	66 (44.0)
Noncompliance with study procedure – missed assessment	94 (79.7)	30 (93.8)	124 (82.7)
Other	35 (29.7)	16 (50.0)	51 (34.0)

[a] To align with administration of chemotherapy, discontinuous administration of ruxolitinib was generally 14 days on/14 days off; exceptions included 14 days on/21 days off during Interim Maintenance 1 and 10 days on/10 days off during Interim Maintenance 2.

Source: INCB 18424-269 CSR Table 12

Demographic and Disease Characteristics

Table 8 below presents the demographics and disease characteristics of patients in Study INCB 18424-269.

Table 8. INCB 18424-269 Demographics and Disease Characteristics

	Part 1 N = 40	Part 2 N = 110
Median age (years), range	14 (1 – 21)	15 (1 – 21)
Age Group		
• < 2 years	1 (1%)	1 (1%)
• ≥ 2 to < 6 years	5 (3%)	13 (9%)
• ≥ 6 to < 12 years	7 (5%)	17 (11%)
• ≥ 12 to < 17 years	15 (10%)	47 (31%)
• ≥ 17 years	12 (8%)	32 (21%)
Sex		
• Female	13 (33%)	29 (26%)
• Male	27 (67%)	81 (74%)
Race		
• White	33 (83%)	71 (65%)
• Asian	1 (3%)	6 (5%)

Table 8. INCB 18424-269 Demographics and Disease Characteristics

	Part 1 N = 40	Part 2 N = 110
• Black/African American	0 (0%)	3 (3%)
• Other	6 (15%)	30 (25%)
Ethnicity		
• Hispanic or Latino	17 (43%)	66 (60%)
• Not Hispanic or Latino	22 (55%)	36 (33%)
• Other	0 (0%)	3 (3%)
• Not reported or unknown	1 (3%)	5 (5%)
CRLF2-R status		
• Not rearranged	6 (15%)	17 (15%)
• Rearranged	34 (85%)	93 (85%)
JAK Pathway status		
• JAK1 mutation	2 (5%)	10 (9%)
• JAK2 mutation	14 (35%)	44 (40%)
• JAK1 and JAK2 mutation	2 (5%)	2 (2%)
• Other JAK pathway alteration	16 (40%)	44 (40%)
• Unknown	6 (15%)	10 (9%)
MRD status at start of study		
• MRD ≥ 0.01%	24 (60%)	89 (81%)
• MRD < 0.01%	16 (40%)	21 (19%)
Cohort		
• A	10 (7%)	42 (28%)
• B	8 (5%)	27 (18%)
• C	6 (4%)	21 (14%)
• D	16 (11%)	20 (13%)

Source: FDA Review

Statistical Reviewer Comment: FDA agreed the Applicant's report that "Most participants were White/Caucasian (66.9%). The majority of participants were Hispanic or Latino (58.5%), which is consistent with the known high incidence of CRLF2-R Ph-like ALL in this population and is considered adequate representation of children of ethnic and racial minorities, taking into account what is known for this disease population."

Clinical TL Review Comment: The accrued population is consistent with the elements of the patients to be studied as listed in the WR.

Treatment Compliance

Treatment compliance was assessed by tablet count at study visits. The Applicant reported median compliance (total dose taken/total dose prescribed) of 99% (range 92 – 100). See Section 8.3 for a description of relative dose intensity by dose cohort.

Efficacy Results – Primary Endpoint

There were 44 participants in cohort A and 31 participants in cohort B that were in the evaluable population, i.e., participants who were treated at the RP2D of 50 mg/m^2. Below Table 9 presents the results of the primary efficacy endpoint, 3-year EFS, for Cohorts A & B.

Table 9. 3-Year EFS for Cohort A and Cohort B, Efficacy Evaluable Set

Endpoint	Cohort A N=44	Cohort B N=31
3-yr EFS[1] rate, %	67	65
95% CI	(42, 84)	(36, 84)
Median EFS (months)	NR[2]	NR
95% CI	(25.6, NR)	(23.5, NR)
Duration of follow-up (months)		
median	17.3	14.3
range	(0.2, 51.3)	(0.2, 53.7)

[1]Please refer to Section the Statistical Analysis Plan for the definition of EFS and related discussion.
[2]NR = not reached

Source: FDA Analysis

In addition, FDA reviewer summarized the historical EFS outcomes from the two references (**Larsen et al 2016** and **Burke et al 2019**) as follows:

Historical EFS outcomes
Larsen et al 2016: 1) Reported Study AALL0232, which enrolled participants between January 2004 and January 2011. Patients with newly diagnosed B-ALL age 1 to 9 years with initial WBC ≥ 50,000/mL or 10 to 30 years with any WBC were eligible. 2) Key efficacy results: 5-yr EFS rates of 80% (95% CI: 78%, 81%) for high-dose methotrexate and 75% (95% CI: 74%, 77%) for Capizzi methotrexate. 3) Please refer to the original paper "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4981974/" for details.
Burke et al 2019: 1) Reported Study AALL1131, which enrolled participants between February 2012 and February 2017. Patients with newly diagnosed high-risk B-ALL age 1 to 9 years with initial WBC ≥ 50,000/mL or 10 to 30 years with any WBC were eligible. 2) Key efficacy results: 4-yr EFS rates of 72% (95% CI: 66%, 79%) for cyclophosphamide/etoposide and 86% (95% CI: 79%, 92%) for a modified Berlin-Frankfurt-Münster regimen. 3) Please refer to the original paper "https://www.haematologica.org/article/view/8901" for details.

The definition of EFS event in Larsen et al 2016 includes induction failure, induction death, relapse of marrow, CNS, testicular, combined +other, second malignancy, or remission death. The definition of EFS event in Burke et al 2019 includes death in remission, relapse of marrow, CNS, other, combined, or second malignant neoplasm. Below Table 10 provides a comparison of EFS event definition among the three studies. Note that these references do not provide the same level of detail as what is available for Study INCB 18424-269.

Table 10. Comparison of EFS Event Definitions

	Study 269	**Larsen (2016)**	**Burke (2019)**
Induction failure	X*	X	?
Relapse of marrow	X	X	X
Second neoplasm	X	X	X
CNS	X	X	X
Testicular	X	X	X
Second line therapy	X	?	?
Death			
In induction	X	X	?
In remission	X	X	X
Other	X	?	?

Source: FDA Analysis

Statistical Reviewer Comment: We found that Study 2 generated an appropriate estimation of 3-year EFS to fulfill the requirements for the Written Request. Although the results of secondary/exploratory endpoints, such as 3-year EFS estimate for Cohorts C and D, MRD-rate, and OS, etc. were provided by the Applicant, they have not been confirmed by FDA.

Of note, the study pre-specified 2 interim analyses for futility at 2.25 years and 4.5 years after the first participant in Part 2 was enrolled, respectively. Since the time of data cutoff (i.e., 01 January 2022) is prior to the time point for the planned second futility analysis (i.e., 4.5 years after first participant in Part 2 was enrolled) no second futility analysis has occurred. There are sufficient data in the submission to estimate 3-year EFS as required in WR Amendment #2. As a result of the adequacy of the current 3-year EFS estimates, a futility analysis at 4.5 years is not statistically appropriate or clinically interpretable, and therefore the 4.5 year futility analysis is not needed to fulfill the WR and the division and PE board agree that the terms of the WR were fairly met with respect to the requirement provide interim analyses to allow an appropriate estimation of the 3-year EFS.

Efficacy Results – Secondary and Other Relevant Endpoints

None.

Subpopulations

See by-cohort analysis above. The subgroups by demographic factors were too small for a meaningful analysis of efficacy.

Efficacy Results – Exploratory and COA (PRO) Endpoints

There were no PRO data submitted to support an efficacy outcome.

Additional Analyses Conducted on the Individual Trial

Dose-Response

Due to the intrapatient dose escalations, it was not possible to conduct a dose-response analysis that would be interpretable.

Clinical TL Review Comment: Due to the intrapatient dose escalations, the efficacy results do not contribute to the determination of the RP2D.

8.2 Integrated Review of Effectiveness

8.2.1 Assessment of Efficacy Across Trials

Methods: The Applicant proposed no new indications and no new intended population. In this supplement, the Applicant submitted one trial, Study INCB 18424-269, in support of a labeling revision in Section 8.4 of the USPI. INCB 18424-269 is a single-arm trial of ruxolitinib added to intensive multiagent chemotherapy for treatment of pediatric patients with Ph-like ALL with a primary efficacy endpoint of 3-year EFS in Cohorts A and B. A number of issues were identified with the study design:

- OS and EFS are the accepted endpoints for treatment of acute leukemia with curative intent. There are substantial limitations to interpretation of time-to-event endpoints with a single-arm trial, so INCB 18424-269 was not designed appropriately to assess the efficacy for a first-line treatment of an acute leukemia.
- INCB 18424-269 tested ruxolitinib in combination with the intensive aBFM regimen. Absent exceptional findings, the single-arm design limits the ability to isolate the contribution of ruxolitinib to the treatment effect of the combination.

Primary Efficacy Endpoint: The primary endpoint was 3-yr EFS. FDA does not usually use a point-in-time EFS rate to assess efficacy of treatments for ALL. Additionally, the Applicant's definition of EFS (events relapse, any-cause death, occurrence of second malignancy, receipt of

second-line therapy, and doubling of marrow blasts or increase in peripheral blasts by > 25%) is not consistent with the EFS definition used for regulatory actions. Hence, the primary endpoint outcome would not support an indication.

The Applicant reported 3-year EFS of 67.4% (95% CI: 41.5%, 83.7%) in Cohort A, and 65.3% (95% CI: 36.2%, 83.6%) in Cohort B, and the statistical reviewer confirmed these results using the method prespecified in the SAP. The Applicant drew no conclusions regarding the meaningfulness of these outcomes, and the review team agrees that no conclusions about efficacy can be made based on these results but that the results do fulfill the EFS reporting requirement of the WR.

Dose/Dose Response: The Applicant concluded that the RP2D of ruxolitinib was 50 mg/m^2 BID 14 days on/14 days off when added to multiagent chemotherapy in children and adolescent young with Ph-like B-ALL. The dose-escalation portion of the trial should have had patients treated at a sufficient range of doses to allow an assessment of dose-response and exposure-response using EFS as the outcome, but because Part 1 of the protocol allowed the dose of ruxolitinib to be increased from the starting dose to 50 mg/m^2 during the course of therapy, an analysis of EFS by dose or exposure would not reflect a specific dose reliably. Therefore, there is not sufficient efficacy data (b) (4)

Additional Efficacy Considerations: As there are no adequate and well-controlled trials of ruxolitinib in adults with Ph-like ALL, there is also no basis for which efficacy could be extrapolated (b) (4)

8.2.2 Integrated Assessment of Effectiveness

The single-arm design of INCB 18424-269 does not isolate the treatment effect of ruxolitinib when used with chemotherapy and is inadequate to establish efficacy for first line treatment of Ph-like ALL in pediatric patients. In the absence of a randomized trial, the efficacy of ruxolitinib in combination with chemotherapy for treatment of Ph-like ALL cannot be confirmed. Nonetheless, the submission did fulfill the study design, objectives, enrollment, treatment, and statistical requirements of the WR. The efficacy results do not contribute to the determination of the RP2D.

8.3 Review of Safety

8.3.1 Safety Review Approach

Selection of the Safety Population

The safety of ruxolitinib monotherapy in pediatric patients with solid tumors or hematologic

malignancies was evaluated in Supplement 015 and is not considered further here. FDA's review of safety for the present supplement included data from 150 subjects treated with at least one dose of ruxolitinib in study INCB 18424-269 including 118 subjects treated at the 50 mg/m^2 x 14 days on/14 days off dose selected for expansion.

Anticipated Safety Issues

In patients with neoplastic disorders, the common adverse reactions (AR) to treatment with ruxolitinib include anemia, thrombocytopenia, bruising, dizziness, headache, and diarrhea. ARs of greatest concern include infection, cytopenias, lipid elevations, and non-melanoma skin cancer. ARs reported with other JAK inhibitors include major adverse cardiovascular events (MACE), thrombosis, and secondary malignancies. The safety profile of ruxolitinib monotherapy did not appear to differ between pediatric and adult patients.[2]

8.3.2 Review of the Safety Database

Overall Exposure

Table 11. INCB 18424-269 – Subjects Who Received ≥ 80% of the Planned* Ruxolitinib Dose by Dose Level and Treatment Phase

	Treatment Phase											
Dose group	**Consolidation**		**IM1**		**Delayed Intensification**		**IM2**		**M1**		**M2**	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
10 mg/m^2 intermittent	6	5 (83%)	6	4 (67%)	6	3 (50%)	5	2 (40%)	4	3 (75%)	4	4 (100%)
20 mg/m^2 intermittent	6	3 (50%)	6	5 (83%)	6	3 (50%)	5	4 (80%)	5	4 (80%)	5	3 (60%)
30 mg/m^2 intermittent	7	3 (43%)	6	3 (50%)	5	1 (20%)	4	4 (100%)	4	4 (100%)	4	4 (100%)
40 mg/m^2 intermittent	6	1 (17%)	6	3 (50%)	6	3 (50%)	6	3 (50%)	5	5 (100%)	5	5 (100%)
50 mg/m^2 intermittent	118	23 (19%)	95	44 (46%)	74	22 (30%)	62	33 (53%)	58	42 (73%)	56	35 (63%)
40 mg/m^2 continuous	7	1 (14%)	6	1 (17%)	6	1 (17%)	6	1 (17%)	5	2 (40%)	5	1 (20%)

Source: Applicant's Response to IR (SN0285)
* Calculated by the Applicant as Delivered Dose Intensity/Standard Dose Intensity X 100 where SDI = (assigned dose in mg prior to any modifications x planned number of days on-treatment in each phase)/minimum number of planned days in each phase

During Part 1, the median duration of treatment was 811 days (range: 14-1185). In the

[2] Clinical Review of NDA 202192 Supplement 015 by Patricia Dinndorf, MD, dated 11/20/2017.

population treated at the 50 mg/m^2 dose, the median duration of treatment was 285 days (range: 2-1174).

Although 50 mg/m^2 was selected as the RP2D, as shown in Table 11, very few subjects were able to receive at least 80% of the planned ruxolitinib dose.

Clinical Reviewer Comment: Although 50 mg/m^2 was selected as the RP2D for expansion based on lack of DLTs, the Applicant's analysis of ruxolitinib dose intensity indicates that this dose was not tolerable for more than 80% of subjects during the first cycle of combination therapy. In fact, only the 10 mg/m^2 dose level had at least 80% of subjects who received ≥ 80% of the planned dose in consolidation. However, even this lowest dose level had poor tolerability in other phases of treatment. Given the small sample sizes for the lower dose cohorts, it is difficult to draw any conclusions regarding which dose was most tolerable across phases of treatment, but tolerability at the 50 mg/m^2 dose remained poor throughout all phases of therapy.

Characteristics of the Safety Population

Table 12. INCB 18424-269 Demographics and Disease Characteristics of the Safety Population

	N = 150
Median age (years), range	14 (1 – 21)
Age Group	
• < 2 years	2 (1%)
• ≥ 2 to < 6 years	18 (12%)
• ≥ 6 to < 12 years	24 (16%)
• ≥ 12 to < 17 years	62 (41%)
• ≥ 17 years	44 (29%)
Sex	
• Female	42 (28%)
• Male	108 (72%)
Race	
• White	104 (69%)
• Asian	7 (5%)
• Black/African American	3 (2%)
• Other	33 (22%)
Ethnicity	
• Hispanic or Latino	83 (56%)
• Not Hispanic or Latino	58 (39%)
• Other	3 (2%)
• Not reported or unknown	6 (4%)
CRLF2-R status	
• Not rearranged	23 (15%)
• Rearranged	127 (85%)

Table 12. INCB 18424-269 Demographics and Disease Characteristics of the Safety Population

	N = 150
JAK Pathway status	
• JAK1 mutation	12 (8%)
• JAK2 mutation	58 (39%)
• JAK1 and JAK2 mutation	4 (3%)
• Other JAK pathway alteration	60 (40%)
• Unknown	16 (11%)
MRD status at start of study	
• MRD ≥ 0.01%	113 (75%)
• MRD < 0.01%	37 (25%)

Source: FDA Review

Adequacy of the Safety Database

In INCB 18424-269:

- Part 1 included treatment across a range of ruxolitinib doses.
- Most participants were White/Caucasian (66.9%). The majority of participants were Hispanic or Latino (58.5%), which is consistent with the known high incidence of CRLF2-R Ph-like ALL in this population and is considered adequate representation of children of ethnic and racial minorities, taking into account what is known for this disease population.

The size of the safety database and inclusion of subjects in all pediatric age groups is adequate for an evaluation of the safety of ruxolitinib in combination with chemotherapy in pediatric patients given that the safety profile for ruxolitinib has been established in other disease settings.

8.3.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of the data submitted are adequate for review of safety. It should be noted that in Part 1 of the trial, escalation of ruxolitinib from the assigned dose to 50 mg/m^2 was allowed during the treatment period, and adae.xpt did not include the actual dose at the time of the reported adverse event, so the reliability of conclusions regarding dose-toxicity is limited.

Categorization of Adverse Events

AEs were reported by investigator verbatim term and coded by the Applicant using MedDRA version 24.0. Events were graded using CTCAE version 4.03. FDA used the grouped terms below for the analyses of safety.

Grouped Term	Basis
Bacterial infection	HLGT Bacterial infectious disorders
Diarrhoea	HLT Diarrhoea (excl infective)
Dizziness	Vestibular disorders (SMQ)
Dyspnoea	HLT Breathing abnormalities
Fatigue	HLT Asthenic conditions
Fungal infection	HLGT Fungal infectious disorders
Gastrointestinal pain	HLT Gastrointestinal and abdominal pains (excl oral and throat)
Haemorrhage	Haemorrhage terms (excl laboratory terms) (SMQ)
Infections	HLGT Infections - pathogen unspecified
Jaundice	HLT Cholestasis and jaundice
Oedema	HLT Oedema NEC
Rash	HLT Rashes, eruptions and exanthems NEC
Renal injury	HLT Renal failure and impairment
Thrombosis	Embolic and thrombotic events (SMQ)
Viral infection	HLGT Viral infectious disorders

Routine Clinical Tests

The schedule of safety monitoring for INCB 18424-269 is described in section 8.1. The schedule of examinations and testing was adequate to assess the risks of safety events.

8.3.4 Safety Results

Deaths

There were no TEAEs in ADAE.xpt listed as Grade 5, but AEs with fatal outcome were reported in 3% (5/150) of subjects in the safety population.

- All events were reported in subjects receiving the 50 mg/m^2 dose.
- All events occurred during Delayed Intensification (DI) and in the setting of infection.
- Four of the five events were considered at least possibly related to ruxolitinib and chemotherapy.

(b) (6) – 18-year-old male treated with ruxolitinib at 50 mg/m^2 died on Study Day 156 (DI) 1 day after his last dose of ruxolitinib of brain edema. This patient was originally assigned to 10 mg/m^2 dosing, but his dose was increased to 50 mg/m^2 around Day 80. On Day 147 he underwent lumbar puncture for Day 1 of DI (ANC 2.2 Gi/L). He subsequently developed headaches and back pain. Laboratory analysis showed Grade 4 elevation of liver enzymes which were considered by the investigator to be related to ruxolitinib and doxorubicin. MRI showed possible subdural hematoma at the LP site; head CT was unremarkable. Ruxolitinib was interrupted on Day 155. On Day 156 he had altered mental status, fever, SIADH, and respiratory distress. Blood cultures were negative and viral panel was positive for

rhino/enterovirus. His ANC was 1.8 Gi/L. He was electively intubated and deteriorated quickly, progressing to multiple-organ-failure and DIC. ECMO was initiated but his condition continued to deteriorate. Head CT showed diffuse cerebral edema with brain stem ischemia and the family elected to discontinue ECMO. The investigator assessed that there was "not a reasonable possibility" that cerebral edema, respiratory distress, and shock were related to ruxolitinib or study treatment and assessed that there was a reasonable possibility that other medication/ procedure (unspecified) caused the events. Alternative causality listed was sepsis. The applicant indicated that assessment was confounded by underlying leukemia but there are no data to support that the subject had active disease. However, the sequence of events from the LP to development of cerebral edema and death is a reasonable alternative cause. This death is considered unlikely to be related to ruxolitinib.

(b) (6) – 16-year-old male treated with ruxolitinib at 50 mg/m^2 died on Study Day 174 (DI) 6 days after his last dose of ruxolitinib of multiple-organ-failure (MOF) including heart failure in the setting of disseminated varicella zoster and varicella hepatitis. The applicant indicated that assessment was confounded by underlying leukemia but there are no data to support that the subject had active disease. This death is considered at least possibly related to ruxolitinib and chemotherapy.

(b) (6) – 6-year-old female treated with ruxolitinib at 50 mg/m^2 died on Study Day 182 (DI) 7 days after her last dose of ruxolitinib of sepsis. This death is considered at least possibly related to ruxolitinib and chemotherapy.

(b) (6) – 17-year-old female treated with ruxolitinib at 50 mg/m^2 died on Study Day 189 (DI) 32 days after her last dose of ruxolitinib of E. coli enterocolitis and sepsis. During treatment for sepsis, she developed SOS and fluid overload, was intubated, and had an open laparotomy that found extensive bowel necrosis. COD was listed as enterocolitis. The applicant indicated that assessment was confounded by underlying leukemia but there are no data to support that the subject had active disease. This death is considered at least possibly related to ruxolitinib and chemotherapy.

(b) (6) – 20-year-old male treated with ruxolitinib at 50 mg/m^2 died on Study Day 238 (DI) 35 days after his last dose of ruxolitinib of mucormycosis. On Day 204 he was diagnosed with septic shock in the setting of neutropenia. Blood cultures were positive for E. coli, K. pneumoniae, and E. cloacae. He was treated with multiple antibiotics and pressors as well as a stress dose of hydrocortisone. His respiratory status improved but he was started on CVVH for renal failure. On Day 208, IV acyclovir was started "for infection" (organism not specified). On Day 209 his condition worsened and on Day 210 he was started on ECMO. On Day 223 his lower respiratory tract cultures were positive for Rhizopus and records indication Grade 4 pulmonary mucormycosis on Day 205. Management for sepsis and MOF continued until he was made DNR on Day 238. This death is considered at least possibly related to ruxolitinib and chemotherapy.

Serious Adverse Events

On treatment SAEs were reported in 88% of subjects. The most common SAEs (≥ 30%) by SOC were blood and lymphatic system disorders (65%), infections and infestations (47%), gastrointestinal disorders (37%), and general disorders and administration site conditions (36%).

Dropouts and/or Discontinuations Due to Adverse Effects

- ARs that lead to ruxolitinib discontinuation in more than one subject included leukemia and infections (2% each).
- Common ARs leading to treatment interruptions included neutropenia (53%), infections (30%), thrombocytopenia (21%), febrile neutropenia (18%), and gastrointestinal disorders (16%) (subjects may have had treatment interruption for multiple ARs).
- The most common reasons for ruxolitinib dose reduction were infections, hypertriglyceridemia, other laboratory abnormalities, and gastrointestinal disorders.

Table 13. INCB 18424-269 Adverse Reactions Leading to Ruxolitinib Discontinuation, Interruption, or Dose Reduction

	aBFM Regimen + Ruxolitinib		
Number (%) of Participants With	50 mg/m^2 BID 14 Days On/14 Days Off[a] (N = 118)	All Other (N = 32)	Total (N = 150)
Any TEAE	116 (98.3)	32 (100.0)	148 (98.7)
Ruxolitinib treatment-related TEAEs	99 (83.9)	31 (96.9)	130 (86.7)
Serious TEAEs	101 (85.6)	31 (96.9)	132 (88.0)
Grade 3 or higher TEAEs	115 (97.5)	32 (100.0)	147 (98.0)
TEAEs leading to discontinuation of ruxolitinib	9 (7.6)	5 (15.6)	14 (9.3)
TEAEs leading to temporary interruption of ruxolitinib	78 (66.1)	27 (84.4)	105 (70.0)
TEAEs leading to ruxolitinib dose reduction	7 (5.9)	2 (6.3)	9 (6.0)
Fatal TEAEs	4 (3.4)	1 (3.1)	5 (3.3)

[a] To align with administration of chemotherapy, discontinuous administration of ruxolitinib was generally 14 days on/14 days off; exceptions included 14 days on/21 days off during Interim Maintenance 1 and 10 days on/10 days off during Interim Maintenance 2.

Source: INCB 18424-269 CSR Table 22

Significant Adverse Events

Infections

An infection TEAE was reported in 76% of subjects. Fifty-three percent of subjects had a Grade 3-4 infection. No Grade 5 events were reported, but 2 events were listed as fatal. The most common HLTs were upper respiratory tract infections (34%), bacterial infections NEC (23%),

and lower respiratory tract and lung infections (21%). Table 14 shows the range of infectious AEs reported. All listed infections are common with the intensive chemotherapy backbone or are common pediatric illnesses, and it is unclear whether addition of ruxolitinib was associated with an increased risk.

Table 14. INCB 18424-269 Infection TEAEs

Infection Group	Term	N	%
Bacterial Infection	Paronychia	13	9%
	Cellulitis	12	8%
	Clostridium difficile infection/colitis	10	7%
	Staphylococcal infection	6	4%
	Escherichia infection	4	3%
	Folliculitis	4	3%
Fungal Infection	Candida infection	6	4%
	Oral candidiasis	6	4%
Viral Infection	COVID-19/coronavirus infection	21	14%
	Rhinovirus infection	12	8%
	Influenza	10	7%
	Enterovirus infection	8	5%
	Parainfluenzae virus infection	7	5%
	Viral upper respiratory tract infection	7	5%
	Herpes simplex	6	4%
	Molluscum contagiosum	5	3%
	Oral herpes	5	3%
	Respiratory syncytial virus infection	5	3%
Infection – Pathogen Unspecified	Upper respiratory tract infection	41	27%
	Pneumonia	30	20%
	Sepsis/septic shock	21	14%
	Otitis media	14	9%
	Sinusitis	14	9%
	Urinary tract infection	14	9%
	Enterocolitis infectious	9	6%
	Skin infection	9	6%
	Bacteraemia	8	5%
	Conjunctivitis	7	5%
	Device related infection	6	4%
	Gastroenteritis	6	4%
	Rash pustular	5	3%
	Gingivitis	4	3%
	Mucosal infection	4	3%
	Soft tissue infection	4	3%

Source: FDA Analysis

Hypertriglyceridemia

Hypertriglyceridemia is a known AR to ruxolitinib. In INCB 18424-269, triglycerides were assessed on Consolidation Day 1 and then at the start of each treatment phase or more often as clinically indicated.

Hypertriglyceridemia was reported by PT in ADAE.xpt in 42 subjects (28%).

- 8 subjects (5%) had ruxolitinib interrupted due to Grade 3-4 hypertriglyceridemia.
- 2 subjects (1%) had ruxolitinib dose reduced following interruption (1 subject was dose reduced twice)
- 1 subject (1%) had ruxolitinib discontinued due to Grade 4 hypertriglyceridemia

Analysis of laboratory triglyceride values across dose levels identified treatment-emergent hypertriglyceridemia in 58% of subjects.

- Grade 3 hypertriglyceridemia: 15%
- Grade 4 hypertriglyceridemia: 13%
- The majority of cases of Grade 3-4 hypertriglyceridemia were reported in IM1.
- Grade 1-2 hypertriglyceridemia was seen across all dose levels and phases of treatment.
- Grade 3-4 hypertriglyceridemia was observed:
    - 50 mg/m^2 cohort – all phases
    - 40 mg/m^2 cohort – IM1 and IM2
    - 20 and 30 mg/m^2 cohorts and 40 mg/m^2 continuous cohort – IM1

Thrombosis

A thrombosis event was reported in 13% (20/150) of subjects. Nine subjects (6%) experienced a Grade 3-4 event. No events were listed as fatal. Events occurring in more than one subject included the following:

- Venoocclusive liver disease: 5 (3%)
- Embolism: 3 (2%)
- Hemiparesis: 3 (2%)
- Deep vein thrombosis: 2 (1%)
- Pulmonary embolism: 2 (1%)
-

Thrombosis is a known therapy-related complication in subjects with ALL treated with chemotherapy (e.g., asparaginase, steroids). It is unclear whether addition of ruxolitinib was associated with an increased risk.

Cardiac Events

Cardiac failure was reported in one subject (027001) who died of multiple-organ-failure in the setting of sepsis. There were no other reports of cardiac failure and no reports of myocardial infarction or stroke.

Treatment Emergent Adverse Events and Adverse Reactions

Common all grade and Grade ≥ 3 TEAEs across dose levels included cytopenias by preferred term (PT), febrile neutropenia, and GI toxicities.

Common (≥ 30%) TEAEs reported in subjects treated at the 50 mg/m^2 dose are shown below.

Table 15. INCB 18424-269 Common TEAEs in Subjects Treated with Ruxolitinib 50 mg/m^2

PT	All Grade	Grade ≥ 3
Infection*	70%	57%
Febrile neutropenia	55%	54%
Pyrexia	53%	12%
Vomiting	50%	9%
Nausea	48%	9%
Stomatitis	42%	23%
Headache	40%	7%
Fatigue	33%	2%
Abdominal pain	30%	6%

Source: FDA Analysis
*Grouped term

Clinical Reviewer Comment: All observed common TEAEs are also known toxicities with multiagent chemotherapy. Therefore, it is not possible to assess whether addition of ruxolitinib is associated with increased risks based on this single-arm trial.

Laboratory Findings

The Applicant reported that 88% of subjects experienced Grade 4 neutropenia and 72% experienced Grade 4 thrombocytopenia.

AST and ALT values increased from baseline during all treatment phases:

- Elevated ALT at any time on treatment: Grade 3: 61%, Grade 4: 9%
- Elevated AST at any time on treatment: Grade 3: 42%, Grade 4: 0%

Grade 3 creatinine laboratory increases were reported at any time on study in 6 subjects and occurred during interim maintenance or maintenance. All subjects had resolution to within normal levels before the start of the subsequent treatment phase except for one subject with

Grade 2 on Day 1 of the next phase but resolution to normal at following laboratory check. There were no reports of Grade 4 creatinine increases.

These laboratory findings are also consistent with the known toxicities of the aBFM backbone chemotherapy regimen used in prior COG studies. See Section 8.3.4 for discussion of hypertriglyceridemia which is a ruxolitinib-specific AR.

Clinical Reviewer Comment: Duration of neutropenia and thrombocytopenia are difficult to assess given the design of the chemotherapy phases which have recovery periods of unspecified duration built into the plan. Count recovery to ANC ≥ 0.75 Gi/L and platelets ≥ 75 Gi/L is required prior to starting a phase of treatment as well as at one or more timepoints within a phase of treatment. Given the count recovery requirements and because cytopenias were the most common reason for treatment interruption, a potential indirect way to assess time to count recovery is to assess the overall length of the treatment phase. There appears to be a trend for a longer length of consolidation with higher doses of ruxolitinib. This may indicate that patients treated at higher doses required more time to recover. This trend is less clear in subsequent phases of therapy, but once the safety of 40 mg/m^2 and 50 mg/m^2 had been assessed, patients in lower dose cohorts were allowed to increase their doses up to the highest tolerated dose which may explain the smaller variability in phase length in later phases of treatment.

Table 16. INCB 18424-269 Duration of Treatment by Phase

	Median # days (25th – 75th %ile)				
	Consolidation	**IM1**	**DI**	**IM2**	**C Day 1 to DI Day 29***
10 mg/m^2	62 (61.75 – 69.25)	69.5 (64.75 – 79.5)	83 (64.5 – 92)	65.5 (57.5 – 69.75)	172 (161.5 – 192)
20 mg/m^2	68.5 (58 – 78.5)	75 (64.25 – 78)	76 (72 – 83.5)	69 (65.5 – 73)	170 (164.5 – 179.4)
30 mg/m^2	65 (62 – 70.5)	70 (65 – 82)	75.5 (67 – 81)	58.5 (55.75-66.5)	175 (166.5 – 192.5)
40 mg/m^2	77.5 (71.72 – 88.25)	70.5 (62 – 85.5)	75 (70.5 – 77)	59 (58 – 75.5)	189 (179.5 – 199.5)
50 mg/m^2	74 (69 – 81)	72.5 (67.75 – 82.25)	73 (68 – 83)	62 (61 – 69)	182 (172 – 198)
40 mg/m^2 continuous	86 (82.75 – 88.25)	88.5 (72.25 – 95.5)	83 (94.75 – 68.25)	63 (62 – 68.5)	233 (197.25 - 231)
Minimum days per protocol	56	63	56	56	148

Source: FDA Analysis
*Avg 179 days for aBFM per Applicant

Vital Signs

The Applicant reported no significant changes in vital signs from baseline. Prior reviews of ruxolitinib also did not identify expected effects on vital signs, so no additional analyses were performed.

QT/Electrocardiograms (ECGs)

An IRT review (9/6/11) indicated that ruxolitinib has no effect on QT.

In INCB 18424-269 echocardiograms were performed at baseline, DI Day 1, and end of treatment. The Applicant reported that minimal change was observed in ejection fraction and fraction shortening, and that the changes were not considered clinically meaningful.

- Ejection fraction: mean change from baseline to DI Day 1(-1%) or EOT (0.2%)
- Fractional shortening: mean change from baseline to DI Day 1 (-1.3%) or EOT (0.9%)

Immunogenicity

Immunogenicity was not assessed in this submission.

8.3.5 Analysis of Submission-Specific Safety Issues

There were no other submission-specific safety issues.

8.3.6 Safety Analyses by Subgroups

Drug-Demographic Interactions

Age
The sample size across age groups in the Part 1 dose levels is too small to draw any conclusions regarding safety by dose and age group. Patients treated at 50 mg/m^2 included subjects in all age groups (≤ 6 years: 15, 6 to ≤ 12 years: 17, ≥ 12 years: 86). For this dose level, ARs with a ≥ 20% higher risk difference in comparison to the ≥ 12 years group included various individual infectious PTs as well as associated symptoms (pyrexia, irritability, cough, rhinorrhea, etc.).

Age < 6 years vs Age ≥ 12 years:

- Numerically higher incidence of all grade infections (80% vs 71%) and Grade ≥ 3 bacterial infections (40% vs 15%)
- Most were low-grade common pediatric infections (e.g., otitis, croup, conjunctivitis, HFM)
- Grade 3-4: cellulitis, paronychia, pertussis

Age 6 to <12 years vs Age ≥ 12 years: no notable differences in safety

Gender
There were no TEAEs with a risk difference ≥ 20% between sexes.

Race
There were no TEAEs with a risk difference ≥ 20% between white and non-white subjects.

8.3.7 Clinical Outcomes Assessments Informing Tolerability/Safety

No patient-reported outcomes that addressed adverse events were included in this submission.

Data were provided for 6 subjects who completed a questionnaire on the taste and ease of administration of ruxolitinib minitab capsules. Because this formulation is not being marketed, no analyses of these data were performed.

8.3.8 Specific Safety Studies/Clinical Trials (including dose-related safety)

Dose Dependency for Adverse Events

The types of TEAEs reported were similar across dose levels. There was no clear difference in the incidence of TEAEs between dose levels but the high background rate of toxicity with the aBFM chemotherapy regimen and the small sample sizes of the dose cohorts preclude drawing any firm conclusions since a difference of 1 subject would have a large effect on the observed incidence. In Part 1, no DLTs were reported at any dose level. However, there was a trend of increased TEAEs leading to ruxolitinib interruption with increasing ruxolitinib dose level.

Table 17. INCB 18424-269 Ruxolitinib Dose Discontinuation, Interruption, and Reduction due to AR by Dose Level

	aBFM Regimen + Ruxolitinib						
	14 Days On/14 Days Off[a]					Continuous	
Number (%) of Participants With	10 mg/m² BID (N = 6)	20 mg/m² BID (N = 6)	30 mg/m² BID (N = 7)	40 mg/m² BID (N = 6)	50 mg/m² BID (N = 8)	40 mg/m² BID (N = 7)	Total (N = 40)
Any TEAE	6 (100.0)	6 (100.0)	7 (100.0)	6 (100.0)	8 (100.0)	7 (100.0)	40 (100.0)
Ruxolitinib treatment-related TEAEs	6 (100.0)	4 (66.7)	6 (85.7)	6 (100.0)	6 (75.0)	7 (100.0)	35 (87.5)
Serious TEAEs	6 (100.0)	6 (100.0)	7 (100.0)	4 (66.7)	6 (75.0)	6 (85.7)	35 (87.5)
Grade 3 or higher TEAEs	6 (100.0)	6 (100.0)	7 (100.0)	5 (83.3)	7 (87.5)	7 (100.0)	38 (95.0)
TEAEs leading to discontinuation of ruxolitinib	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)
TEAEs leading to temporary interruption of ruxolitinib	2 (33.3)	3 (50.0)	3 (42.9)	4 (66.7)	6 (75.0)	7 (100.0)	25 (62.5)
TEAEs leading to ruxolitinib dose reduction	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)
Fatal TEAEs	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)

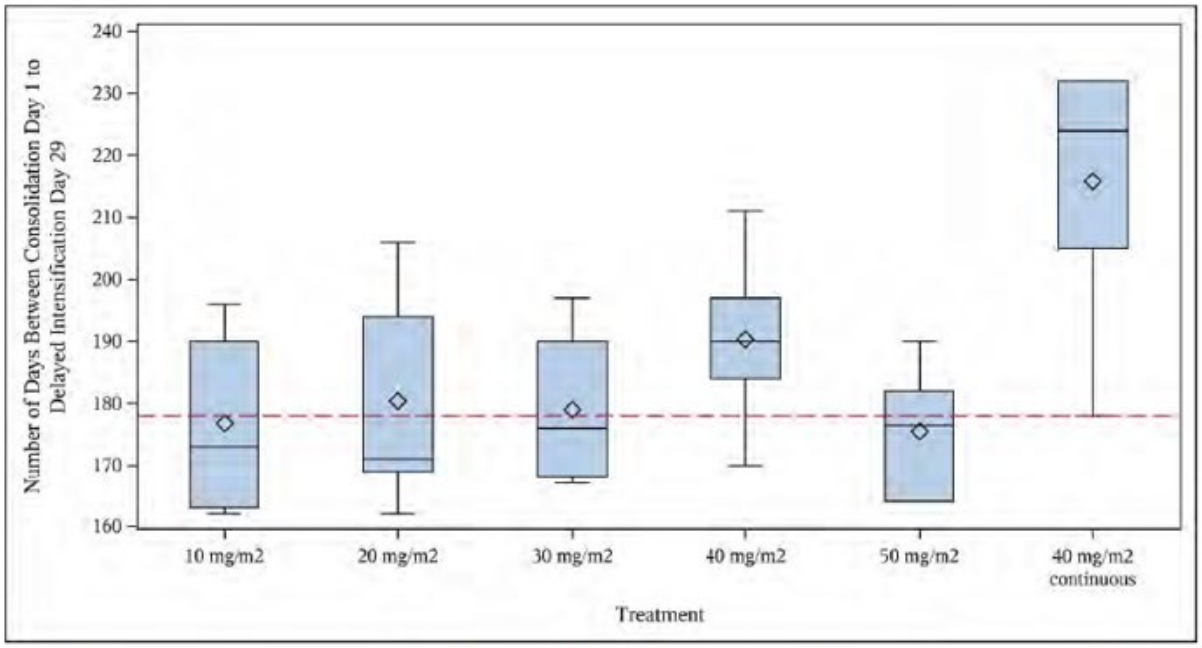
[a] To align with administration of chemotherapy, discontinuous administration of ruxolitinib was generally 14 days on/14 days off; exceptions included 14 days on/21 days off during Interim Maintenance 1 and 10 days on/10 days off during Interim Maintenance 2.

Source: INCB 18424-269 CSR Table 21

The Applicant provided an analysis of timing of treatment compared to historical control (Figure 2). They note that the minimum number of days between Consolidation Day 1 and Delayed

Intensification Day 29 is 147 days while the red dotted line represents the average number of days for this interval reported by COG in comparable studies using the backbone chemotherapy. Based on this, they suggest there was no ruxolitinib dose-related trend and that, with the exception of the 40 mg/m^2 continuous treatment cohort, subjects were able to stay on track with treatment without longer than expected delays.

Figure 2. INCB 18424-269 Time from Consolidation Day 1 to Delayed Intensification Day 29



Note: Expected minimum number of days from Consolidation Day 1 to Delayed Intensification Day 29 = 147 days.
Note: Red reference broken line indicates the average number of days for the interval as reported by COG in comparable studies using aBFM therapy.
Source: INCB 18424-269 CSR Figure 6

Clinical Reviewer Comment: The Applicant concluded that the addition of ruxolitinib did not cause longer treatment delays compared to aBFM alone. However, the analysis of relative dose intensity by treatment phase (Section 8.3.2) indicates that a significant majority of patients did not receive the planned ruxolitinib dose in any given phase of therapy. Therefore, the observed lack of "longer than expected delays" does not represent the use of the planned ruxolitinib 50 mg/m^2 dose in combination with chemotherapy.

Although no new safety findings for ruxolitinib were identified in this study, there were more interruptions of ruxolitinib due to AEs in subjects treated at higher dose levels than at lower dose levels and these were most commonly related to cytopenias or febrile neutropenia. This observation in combination with the dose intensity analysis indicates that 50 mg/m^2 is not the optimal tolerable dose of ruxolitinib for use in combination with chemotherapy.

Time Dependency for Adverse Events

TEAEs leading to interruption of ruxolitinib occurred in all phases of therapy but were most frequent during Consolidation and DI. AEs leading to dose reduction were also reported during Consolidation and DI. The chemotherapy regimen is more intensive during these two cycles.

Table 18. INCB 18424-269 TEAEs by Chemotherapy Phase in Subjects Treated at 50 mg/m^2

Number (%) of Participants With	aBFM Regimen + Ruxolitinib 50 mg/m^2 BID 14 Days On/14 Days Off[a]				
	Consolidation (N = 118)	Interim Maintenance 1 (N = 95)	Delayed Intensification (N = 74)	Interim Maintenance 2 (N = 62)	Maintenance 1 (N = 58)
Any TEAE	112 (94.9)	81 (85.3)	71 (95.9)	54 (87.1)	47 (81.0)
Ruxolitinib treatment-related TEAEs	91 (77.1)	53 (55.8)	61 (82.4)	41 (66.1)	32 (55.2)
Serious TEAEs	80 (67.8)	28 (29.5)	51 (68.9)	22 (35.5)	21 (36.2)
Grade 3 or higher TEAEs	110 (93.2)	70 (73.7)	67 (90.5)	45 (72.6)	36 (62.1)
TEAEs leading to discontinuation of ruxolitinib	5 (4.2)	1 (1.1)	2 (2.7)	0 (0.0)	1 (1.7)
TEAEs leading to temporary interruption of ruxolitinib	60 (50.8)	33 (34.7)	40 (54.1)	28 (45.2)	21 (36.2)
TEAEs leading to ruxolitinib dose reduction	4 (3.4)	0 (0.0)	3 (4.1)	0 (0.0)	0 (0.0)
Fatal TEAEs	0 (0.0)	0 (0.0)	4 (5.4)	0 (0.0)	0 (0.0)

[a] To align with administration of chemotherapy, discontinuous administration of ruxolitinib was generally 14 days on/14 days off; exceptions included 14 days on/21 days off during Interim Maintenance 1 and 10 days on/10 days off during Interim Maintenance 2.

Source: INCB 18424-269 CSR Table 23

Formulation Dependency for Adverse Events

Although INCB 18424-269 allowed for treatment of patients with ruxolitinib as whole tablets, a crushed tablet suspension, or an investigational minitab, the Applicant did not record which subjects received whole tablets or crushed tablet suspension and only a limited number of subjects (n = 6) received the minitab formulation. Therefore, a comparison of safety by formulation cannot be conducted.

8.3.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Non-melanoma skin cancer and secondary malignancies including lymphomas have been reported in subjects receiving ruxolitinib or other JAK inhibitors. In INCB 18424-269 under the SOC Neoplasms:

- Five subjects were reported to have skin papilloma with a verbatim term related to warts.
- One subject with CNS2 disease at diagnosis (< 5 WBC/µL and cytospin positive for blasts)

had a report of cutaneous chloroma (left temple and chest) on study day 110. The patient had discontinued ruxolitinib on Day 83 due to persistent disease. Although most commonly associated with AML and other myeloproliferative disorders, chloromas have rarely been described in patients with ALL in the setting of CNS disease and/or relapse.

- All other reports under this SOC were related to relapse of ALL.

Human Reproduction and Pregnancy

There are no studies of the use of ruxolitinib in pregnant women. Section 8.1 of USPI describes the available animal data.

Pediatrics and Assessment of Effects on Growth

The safety of ruxolitinib in the pediatric population was reviewed in Supplement 015 (see Section 8.4 of the USPI), Supplement 017 (see review), and in this supplement. No differences in safety profile were noted between pediatric patients and adults. The effects of ruxolitinib on growth were not evaluated.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Section 5.3 of the USPI describes the known risk of symptom exacerbation in patients with myeloproliferative neoplasms after abrupt discontinuation of ruxolitinib. In INCB 18424-269 ruxolitinib is given on an intermittent schedule. No cases of exacerbation were reported in this study.

8.3.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

An Empirica Signal Analysis of FAERS through 2022 did not identify new safety signals for ruxolitinib.

Expectations on Safety in the Postmarket Setting

No changes to the approved indications or ruxolitinib dosing in the USPI are recommended based on the data in this supplement. Therefore, the safety risks are not anticipated to change.

8.3.11 Integrated Assessment of Safety

Study INCB 18424-269 assessed the safety of ruxolitinib in combination with multiagent chemotherapy in pediatric patients with Ph-like ALL. Interpretation of the contribution of ruxolitinib to the safety findings in this single-arm trial is difficult given the overlapping

toxicities with the high-intensity chemotherapy backbone.

- There was a trend towards increased incidence of TEAEs leading to ruxolitinib dose interruptions at higher ruxolitinib dose levels compared to lower dose levels. These were due mostly to cytopenias or febrile neutropenia.

- TEAEs leading to interruption of ruxolitinib occurred in all phases of therapy but were more frequent during Consolidation and DI when chemotherapy was most intense.

- The Applicant's analysis of dose intensity indicated low tolerability of all ruxolitinib dose levels tested during most treatment phases. There were no clear data to support any single tested dose level as tolerable across treatment phases.

- No new safety findings were identified for ruxolitinib.

- There were no notable differences in safety by age group in subjects treated with ruxolitinib 50 mg/m^2 in combination with chemotherapy.

Taken together, the safety data provide some information on the use of ruxolitinib in the population studied, (b) (4) (b) (4)

SUMMARY AND CONCLUSIONS

8.4 Statistical Issues

The review team confirmed the 3-year EFS estimates for the primary endpoint cohorts A and B, i.e., the 3-year EFS of 67% (95% CI: 42%, 84%) and 65% (95% CI: 36%, 84%) for Cohort A and Cohort B. The submitted Study 2 generated an appropriate estimation of 3-year EFS to fulfill the requirements for the Written Request. However, the 3-year EFS estimates from a single arm trial is exploratory in nature and is subject to a number of limitations. These limitations include lack of ability to isolate the treatment effect of the ruxolitinib to the combination, differences in definitions of EFS across trials, and the inherent difficulties in interpreting time-to-event endpoints in single-arm trials.

Of note, the study prespecified second interim analysis for futility at 4.5 years after the first participant in Part 2 was enrolled was not needed, since the time of data cutoff (i.e., 01 January 2022) is prior to the time point for the planned second futility analysis and there are sufficient data in the submission to estimate 3-year EFS as required in WR Amendment #2.

8.5 Conclusions and Recommendations

The efficacy and safety of ruxolitinib in combination with chemotherapy for treatment of pediatric patients with Ph-like ALL were assessed but not established based on the data in Study INCB 18424-269. (b) (4) (b) (4) We recommend approval of the supplement with revisions to Section 8.4 of the USPI to provide information regarding this study.

9 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

There was no advisory committee meeting or external consultation for this BLA supplement.

10 PEDIATRICS

Ruxolitinib has Orphan Designation for all approved indications and is therefore exempt from the requirement for pediatric studies under the Pediatric Research Equity Act (PREA).

FDA issued a Written Request (WR) to obtain information on the pharmacokinetics (PK), safety and activity of ruxolitinib using an age-appropriate formulation in children with cancer. The WR included 2 studies:

- Study 1: Protocol ADVL1001 "A Phase 1 Study of JAK Inhibition (INCB018424) In Children with Relapsed or Refractory Solid Tumors, Leukemias, And Myeloproliferative Neoplasms"
  - Submitted and reviewed in Supplement 015 (2017).
  - Safety and activity of ruxolitinib assessed but not established
  - Proposed (b) (4)

- Study 2: Protocol INCB 18424-269 "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 (Ph-like) Acute Lymphoblastic Leukemia"
  - Submitted for review in this supplement.
  - Safety and efficacy of ruxolitinib in combination with chemotherapy assessed but not established
  - Proposed (b) (4) not confirmed

A question arose as to whether the terms of the WR were met if the Applicant was not pursuing marketing of a pediatric formulation. The Division concluded that because the WR required an application for marketing the pediatric formulation if the drug was found to be safe and effective in the studied pediatric population but the results of the studies in the WR did not establish safety and effectiveness in the studied populations, the Applicant's decision to not market the pediatric formulation was not inconsistent with the WR requirement. The details of the Division's evaluation of the Applicant's response to the WR is provided in a separate review.[3] The Division concluded that the terms of the WR were met.

The Pediatric Exclusivity Board voted to grant pediatric exclusivity based on Prong 2. This submission was discussed at OCE-PeRC on 10/19/2022 and at PeRC on 11/15/2022.

11 LABELING RECOMMENDATIONS

11.1 Prescribing Information

The table below provides a high-level summary of the changes made to the USPI for Jakafi (ruxolitinib) NDA 202192/s027. See the USPI attached to the approval letter for final labeling.

Summary of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling
8.4 Pediatric Use	Included detailed information about 2 clinical trials done under a written request.	FDA modified this section to align with recommendations in guidance and to streamline the information so as not to imply (b) (4)

11.2 Patient Labeling

No changes to the patient labeling were proposed by the applicant or added by FDA.

12 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

No new safety issues have been identified that would warrant consideration of a REMS.

[3] NDA 202192 Pediatric Exclusivity Determination Checklist dated 12/1/2022.

13 POSTMARKETING REQUIREMENTS AND COMMITMENTS

The review team did not identify issues that would necessitate a new postmarketing requirement or commitment.

14 APPENDICES

14.1 References

None

14.2 Financial Disclosure

Not applicable

14.3 Nonclinical Pharmacology/Toxicology

None

14.4 OCP Appendices

14.4.1 Individual Studies - Study 2 (INCB 18424-269)

Study 2 was an open-label, nonrandomized study of ruxolitinib added to an aBFM regimen in pediatric and adolescent young adult participants with high-risk Ph-like B-ALL. This study included 2 parts. Part 1, dose finding phase, was to determine the safety of ruxolitinib added to an aBFM regimen. It evaluated 10, 20, 30, 40, 50 mg/m^2 ruxolitinib twice daily (BID) 14 days on/14 days off and 40 mg/m^2 ruxolitinib BID continuous in 28-day cycles for dose escalation. Part 2, dose expansion phase, was to evaluate the efficacy of ruxolitinib at the selected RP2D of 50 mg/m^2 BID 14 days on/14 days off added to an aBFM regimen in children and adolescent young adults. PK sampling time points in the study are listed below:

- Consolidation Day 1 or delayed intensification Day 1: predose, 1, 2, 4 hrs postdose
- Consolidation Day 8: random (at least 1 hr after the morning dose)
- Consolidation Day 15 and 43: Trough (last ruxolitinib dose occurs on the prior day)

A total of 831 plasma PK samples from 136 participants who received treatment were assayed

for ruxolitinib concentrations. A total of 383 ruxolitinib plasma concentrations from 134 participants were excluded from the Sponsor's PK analysis because the profiles had fewer than 3 postdose quantifiable concentrations. The Sponsor conducted PK analysis based on 448 ruxolitinib plasma concentrations from 101 participants across different dosing regimen.

The reviewer conducted independent analysis on the complete PK dataset and applied additional exclusion criteria defined by the Applicant (e.g., samples that are labeled as Dose=0 PK samples, problematic reference dose time, unscheduled PK exclusion, patients with less than 3 postdose PK samples relative to last dose). Neither the reviewer's analysis nor the Sponsor's analysis suggested apparent differences in the observed PK parameters (e.g., C_{max}, $AUC_{0\text{-}4hr}$, T_{max}) across different age groups.

14.5 Additional Clinical Outcomes Assessment Analyses

None

15 DIVISION DIRECTOR (DHM1)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Director, Division of Hematological Malignancies 1 (DHM1)

NDA Multidisciplinary Review and Evaluation
NDA 202192 S-027
Jakafi (ruxolitinib)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Hongfei Zhang, PhD	OCP/DCPI	Sections: 6 and 14.4	X Authored Approved
	Signature: Hongfei Zhang -S Digitally signed by Hongfei Zhang -S Date: 2022.12.01 14:08:34 -05'00'			
Clinical Pharmacology Team Leader	Nan Zheng, PhD	OCP/DCPI	Sections: 6 and 14.4	Authored X Approved
	Signature: Nan Zheng -S Digitally signed by Nan Zheng -S Date: 2022.12.01 15:01:05 -05'00'			
Division Director Clinical Pharmacology	Brian Booth, PhD	OCP/DCPI	Sections: 6 and 14.4	Authored X Approved
	Signature: Brian P. Booth -S Digitally signed by Brian P. Booth -S Date: 2022.12.12 14:32:34 -05'00'			
Statistical Reviewer	Haiyan Chen, PhD	OOD/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	X Authored Approved
	Signature: Haiyan Chen -S Digitally signed by Haiyan Chen -S Date: 2022.12.01 14:33:42 -05'00'			
Statistical Team Leader	Jonathan Vallejo, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	Authored X Approved
	Signature: Jonathon J. Vallejo -S Digitally signed by Jonathon J. Vallejo -S Date: 2022.12.01 14:22:37 -05'00'			
Division Director Statistics	Mark Levenson, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	Authored X Approved
	Signature: Mark S. Levenson -S Digitally signed by Mark S. Levenson -S Date: 2022.12.12 19:19:58 -05'00'			
Clinical Reviewer	Emily Jen, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10	X Authored Approved
	Signature: Emily Y. Jen -S Digitally signed by Emily Y. Jen -S Date: 2022.12.01 13:15:30 -05'00'			
Clinical Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10	Authored X Approved
	Signature: Digitally signed by Donna Przepiorka -S Date: 2022.12.01 13:03:31 -05'00'			

NDA Multidisciplinary Review and Evaluation
NDA 202192 S-027
Jakafi (ruxolitinib)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	X Authored Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S Date: 2022.12.01 14:14:52 -05'00'			
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 1, 4, 5, 12, 13	X Authored Approved
	Signature: *{See appended electronic signature page}*			
Division Director Clinical	R. Angelo de Claro, MD	OOD/DHMI	Sections: All	Authored X Approved
	Signature: *{See appended electronic signature page}*			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DONNA PRZEPIORKA
12/19/2022 06:36:47 AM

ROMEO A DE CLARO
12/19/2022 09:52:04 AM