DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202192

WRITTEN REQUEST – AMENDMENT 1

Incyte Corporation
Attention: Ronald C. Falcone, PhD
Vice President, Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Dr. Falcone:

Please refer to your correspondence dated August 23, 2016, requesting changes to FDA's December 11, 2015 Written Request for pediatric studies for ruxolitinib.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on December 11, 2015, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Timeframe for submitting reports of the studies: Reports of study 1 must be submitted to the Agency by ~~January 1~~ July 1, 2017, and reports of study 2 must be submitted to the Agency on or before July 1, 2022. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated December 11, 2015, as amended by this letter must be submitted to the Agency on or before July 1, 2017 (study 1) and July 1, 2022 (study 2), in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC**

STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Associate Director for Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

BACKGROUND:

The Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway transmits signals from receptors for a number of cytokines and growth factors. Constitutive activation of the JAK-STAT pathway has been demonstrated in a number of cancers that occur in adults and in children, including Philadelphia chromosome-like (Ph-like) B cell acute lymphoblastic leukemia (ALL), lymphoma, neuroblastoma, sarcoma, and several types of brain cancer. In some cases, mutations in JAK1 or JAK2 are the cause of the activation, but mutations or translocations in other components of the JAK-STAT pathway (including cytokine receptor-like factor 2 (CRLF2), erythropoietin receptor (EPOR), Interleukin-7 receptor alpha (IL7RA) or SH2 adaptor protein 3 (SH2B3)) can also drive the neoplastic process. The proportion of each tumor type with a specific genetic abnormality affecting the JAK-STAT pathway is highly variable, but such abnormalities may have implications for prognosis. For example, Ph-like ALL comprises approximately 15% of pediatric high-risk ALL, but this subset is associated with particularly high relapse rates.

Ruxolitinib is an inhibitor of JAK1 and JAK2 approved for the treatment of intermediate and high risk myelofibrosis and for the treatment of polycythemia vera in patients who have had an inadequate response to or are intolerant of hydroxyurea. The antitumor activity of ruxolitinib has been demonstrated in cell lines and xenograft models for a number of cancer types, including Ph-like ALL. There are several on-going trials of ruxolitinib for treatment of cancer with activating mutations in the JAK-STAT pathway in adults.

The current approach to therapy of ALL in children involves consecutive phases of treatment over several years, including induction, consolidation, interim maintenance, delayed intesification and maintenance. Each phase consists of different combinations of chemotherapeutic agents of varying intensity, and effects of adding a new agent, such as ruxolitinib, to each combination may result in different degrees of safety risks. Experimental approaches to improve outcome in children with ALL can involve intensifying or modifying 1 or more of these individual treatment phases.

Most current pediatric oncology studies enroll subjects up to 21 years of age since most children's hospitals in the US admit patients up to age 21. Additionally, due to better outcomes on pediatric ALL regimens, patients in the adolescent/young adult subgroups (17-21) are preferentially referred to pediatric oncologists or treated on therapy regimens originally developed for childhood ALL. However, due to the presence of refractory or resistant disease, this age group also has the worst outcome of any pediatric age group with ALL. Enrolling patients age 18-21 provides required information that is relevant to drug development for pediatric ALL patients. As patients with the specific, molecularly defined subtype of ALL are generally older and since infants with ALL have a biologically unique subtype distinct from Ph-like Bcell precursor ALL, infants < 1year of age and neonates will not be included in this study. To obtain needed information on the pharmacokinetics (PK), safety and activity of ruxolitinib in children with cancer, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study:*

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical 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" 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.

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" is an open-label, single-arm, Phase 1-2 trial of ruxolitinib added on to a well-characterized and commonly used Berlin-Frankfurt-Muenster (BFM) post-induction therapy for pediatric patients with Ph-like ALL. The first portion of the study is a dose-escalation phase to determine the recommended ruxolitinib dose for the combination across phases of therapy through Delayed Intensification. The second portion is a dose-expansion phase in 4 cohorts based on mutation and the minimal residual disease (MRD) status an end of induction:
Cohort A: end-Induction MRD ≥0.01%, CRLF2R and JAK1/JAK2 mutations
Cohort B: end-Induction MRD ≥0.01%, CRLF2R, no JAK mutations
Cohort C: end-Induction MRD ≥0.01%, other JAK pathway alterations (e.g., JAK2 fusions, EPOR fusions, SH2B3 deletions, IL7RA mutations)
Cohort D: end-Induction MRD <0.01% and any CRLF2 or JAK pathway alterations

The primary objective of the second phase is to determine if the 3-yr event-free survival (EFS) in either the CRLF2R/ JAKMutant subgroup or the CRLF2R/JAKwt subgroup is improved in comparison to similarly treated historical controls. A total of 170 subjects will be accrued, including 42 in each of the subgroups analyzed comparatively in the second phase of the study. Follow-up will be for at least 3 yrs.

- *Objective of each 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.

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 2: Primary Objectives:

Part 1: To evaluate initial safety and tolerability and to define the recommended dose of ruxolitinib for Part 2 of the study in combination with multi-agent chemotherapy in patients with newly diagnosed de novo high risk or very high risk (HR/VHR) Philadelphia chromosome-like (Ph-like) CRLF2-rearranged and/or JAK pathway-mutant B-cell (B-ALL).

Part 2: To determine the efficacy of ruxolitinib in combination with chemotherapy for patients with de novo HR/VHR Ph-like CRLF2-R and/or JAK pathway mutant ALL.

Secondary Objectives:

To characterize the safety and potential toxicity of ruxolitinib combined with chemotherapy throughout the course of treatment in patients with de novo HR/VHR Ph-like CRLF2-rearranged and/or JAK pathway mutant ALL.

- To assess the PK of ruxolitinib in combination with chemotherapy in patients.
- To assess rates of MRD at end-Consolidation in end-Induction MRD+ subjects who are treated with ruxolitinib and chemotherapy.
- To measure JAK2 signaling inhibition as a pharmacodynamics (PD) biomarker of ruxolitinib activity and to correlate PD with ruxolitinib PK.
- To evaluate the overall survival (OS) of all subjects receiving ruxolitinib in combination with chemotherapy.

- *Patients to be Studied:*

Study 1:

- *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.

Study 2:

- *Age group in which study will be performed:* 1 to 21 years.

- *Number of patients to be studied:*
  Part 1: Up to 30 subjects
  Part 2: Up to 42 subjects each in Cohorts A and B for evaluation of the efficacy of combination chemotherapy and ruxolitinib. Up to 25 subjects in Cohorts C and D.

  Representation of ethnic and racial minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  Study 1: 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

  Study 2: Primary Endpoints

  Part 1
  - Determination of the RP2D of ruxolitinib in combination treatment.
  - Safety and tolerability of the combination regimen, including laboratory parameters, evaluated by dose level, and dose intensity achieved.

  Part 2
  - EFS at 3 years from Study Day 1 for Cohorts A and B.

  Secondary Endpoints
  - Safety and tolerability of the combination treatment for subjects beginning treatment at the RP2D of ruxolitinib, including dose intensity achieved.
  - Remission rate at end-Consolidation for subjects in Cohorts A, B, and C.
  - MRD value at end-Consolidation as compared with end-Induction for subjects in Cohorts A, B, and C.
  - 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 from administration to the last quantifiable measurable plasma concentration.
  - Pharmacodynamic measurements of leukemia-specific signal transduction will include basal measurements of JAK/STAT-signaling activation in diagnostic bone marrow

specimens and plasma activity inhibitory assays before and during treatment with ruxolitinib and chemotherapy
- Safety profile by phase of treatment through maintenance cycle 1
- Comparison of dose-intensity of concomitant chemotherapy to that for comparably-treated historical controls through maintenance cycle 1
- EFSat 3 years from Day 1 for subjects in Cohorts C and D.
- OS for all subjects from Day 1 until death from any cause.

- *Known Drug Safety concerns and monitoring:*

  Ruxolitinib is known to cause myelosuppression, namely thrombocytopenia, anemia, and neutropenia in some individuals. These cytopenias may increase the risk of infection; serious bacterial, mycobacterial, fungal and viral infections have occurred. Risks associated with ruxolitinib vary according to the study population. In a monotherapy study of ruxolitinib in pediatric patients with leukemia or solid tumors, no major dose limiting side effects were identified. However, long-term use of ruxolitinib has not been fully studied in children, adolescents, or young adults. The risks of combining ruxolitinib with other agents, some of which also cause myelosuppression, are not yet known. Ruxolitinib has been shown to be efficacious in the treatment of myelofibrosis and polycythemia vera in adults, however efficacy has not yet been conclusively demonstrated in other indications. Thus the safety and effectiveness of ruxolitinib in combination with backbone chemotherapy in pediatric leukemia patients have not been established.

  Known potentially fatal or life-threatening risks include thrombocytopenia, anemia, neutropenia, infections (including tuberculosis, Herpes zoster and progressive multifocal leukoencephalopathy), nonmelanoma skin cancer and symptom exacerbation following interruption or discontinuation of Jakafi in patients with myelofibrosis. The most common adverse reactions reported (>10%) were bruising, dizziness, headache, headache, abdominal pain, diarrhea, fatigue, pruritus, dyspnea, and muscle spasms. Common laboratory abnormalities (>20%) included anemia, thrombocytopenia, hypercholesterolemia, elevated ALT, and elevated AST. Study subjects will be monitored for these potential adverse reactions throughout the study.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - *Dosage form:* Ruxolitinib 5 mg and 25 mg tablets
  - *Route of administration:* oral
  - *Regimen:* to be determined and agreed upon in the protocol

Extemporaneous formulations/compounding for children unable to swallow tablets should be preceded by appropriate food effect studies to assure bioavailability.

The studies described above should use an age-appropriate formulation of ruxolitinib. If an age appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of studies and statistical assessments:*

Study 1: The analyses will utilize only descriptive statistics.

Study 2:
In Part 1, the total number of subjects will depend on the number of dose levels tested before the RP2D and DLT of ruxolitinib in combination with backbone chemotherapy treatment is established. Safety data accrued will be summarized using descriptive statistics.

In Part 2, the sample size calculation is based on the survival analysis for the primary endpoint. With a sample size of 42 subjects each in Cohort A and Cohort B, assuming a 3-year EFS 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 expected to be enrolled with 42 subjects each in Cohorts A and Cohort B, and 20 and 25 subjects expected in Cohorts C and D, respectively. Subjects enrolled in Cohorts A and B in Part 1 who are treated at RP2D will be included in the primary analysis.

Toxicity in Part 2 will be monitored continuously in the 4 combined cohorts using Pocock stopping boundaries. Interim analyses for lack of efficacy will be conducted at 2.25 years and 4.5 years after the first subject is enrolled. Both the interim and final analyses will be conducted separately in Cohorts A and B. Tests for futility will be conducted using the one-sample log-rank test.

A clinical study report describing all available data will be written at the time 1 year of follow-up is available for all patients enrolled in the study to fulfill the requirements for the Written Request.

- *Labeling that may result from the studies:* You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that ruxolitinib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety

Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the studies*: Reports of study 1 must be submitted to the Agency by July 1, 2017, and reports of study 2 must be submitted to the Agency on or before July 1, 2022. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GREGORY H REAMAN
09/15/2016