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RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMR Description: 1838-1 Provide safety findings related to the interval of drug discontinuation in at least 75 patients previously entered on INCB-351 to determine if specific cautions are appropriate to describe discontinuation strategies.

PMR Schedule Milestones:	Final Protocol Submission:	INCB-351	
	Study/Trial Completion:	07/2009	
	Final Report Submission:	08/2012	
	Other:	10/2013	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and study INCB18424-352 are designed to follow patients and collect data including adverse event data for approximately 30 days after the last dose of study drug was taken after a patient was discontinued from the study. Data on patients discontinuing from ruxolitinib either from randomized treatment or after crossover to ruxolitinib from either placebo (Study -351) or best available therapy (BAT; Study -352) will be provided. Based on estimated discontinuation rates, we expect to have data for at least 70 patients who discontinued ruxolitinib by the completion date of the trials as noted above. The information regarding safety findings related to the interval of drug discontinuation will be provided in a separate report that combines this data from these studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the post marketing study is to characterize in 150 patients from the ruxolitinib arms of the two randomized phase III studies (INCB-351 and INCB-352) the severity of symptoms of MF or splenomegaly or other adverse events accompany if the discontinuation of ruxolitinib in patients who have previously responded to the drug.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The post marketing commitment pertains to observations to be made with longer follow-up on 150 patients already entered and treated on the two randomized phase III trials INCB-351 and INCB-352, who were randomized to ruxolitinib, who responded as defined in the primary and secondary endpoints of these two trials, and then for some reason discontinued therapy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
See answer to Question 4 above

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- X Other
See answer to Question 4 above
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMR Description: 1838-2 Provide safety findings related to the interval of drug discontinuation in at least 75 patients previously entered on INCB-352 to determine if specific cautions are appropriate to describe discontinuation strategies.

PMR Schedule Milestones:	Final Protocol Submission:	INCB-352 05/2010
	Study/Trial Completion:	08/2012
	Final Report Submission:	10/2013
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and study INCB18424-352 are designed to follow patients and collect data including adverse event data for approximately 30 days after the last dose of study drug was taken after a patient was discontinued from the study. Data on patients discontinuing from ruxolitinib either from randomized treatment or after crossover to ruxolitinib from either placebo (Study -351) or best available therapy (BAT; Study -352) will be provided. Based on estimated discontinuation rates, we expect to have data for at least 150 patients who discontinued ruxolitinib by the completion date of both of the trials. The information regarding safety findings related to the interval of drug discontinuation will be provided in a separate report that combines this data from these studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the post marketing study is to characterize in 150 patients from the ruxolitinib arms of the two randomized phase III studies (INCB-351 and INCB-352) the severity of symptoms of MF or splenomegaly or other adverse events accompany if the discontinuation of ruxolitinib in patients who have previously responded to the drug.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The post marketing commitment pertains to observations to be made with longer follow-up on 150 patients already entered and treated on the two randomized phase III trials INCB-351 and INCB-352, who were randomized to ruxolitinib, who responded as defined in the primary and secondary endpoints of these two trials, and then for some reason discontinued therapy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
See answer to Question 4 above

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - X Other
See answer to Question 4 above
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMR Description:

1838-3 Collect and analyze safety information on myelosuppression for up to 144 weeks of therapy following randomization in the patients entered on INCB-351 who are continuing on therapy past 24 weeks.

PMR Schedule Milestones:

INCB-351
Final Protocol Submission: 07/2009
Study/Trial Completion: 03/2013
Final Report Submission: 12/2013
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and Study INCB18424-352 are currently designed to continue until the last patient remaining on study has completed the 144-week visit and the follow-up visit which occurs approximately 28 days later. We will continue to collect safety information on myelosuppression including laboratory evaluations of RBC, Hgb, platelets, WBC, and ANC as specified in the respective protocols through the completion of the studies. The projected study completion dates for Studies INCB18424-351 and INCB 18424-352 are 3/2013 and 12/2012, respectively. The final reports for both trials will be submitted by 8/2013. The final report submission providing additional safety information on myelosuppression from both trials will be by 08/2013.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the proposed PMR is to provide long term (up to 144 weeks following randomization) follow-up evaluation of patients with MF who were entered into the phase III randomized trials (INCB-351 and INCB-352), randomized to the ruxolitinib arm and to either the placebo or BAT arms, and have been chronically exposed to ruxolitinib therapy, in order to ascertain if long term administration has any consequences for production of red cells, white cells or platelets by the bone marrow.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMR will provide long term (up to 144 weeks following randomization) follow-up evaluation of patients with MF who were entered into the phase III randomized trials (INCB-351 and INCB-352), randomized to the ruxolitinib arm and to either the placebo or BAT arms, and have been chronically exposed to ruxolitinib therapy, in order to ascertain if long term administration has any consequences for production of red cells, white cells or platelets by the bone marrow.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
See answer to question 4 above

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Yes Other
See answer to question 4 above
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMR Description: 1838-4 Collect and analyze safety information on myelosuppression for up to 144 weeks of therapy following randomization in the patients entered on INCB-352 who are continuing on therapy past 48 weeks.

PMR Schedule Milestones:		INCB-352
	Final Protocol Submission:	05/2010
	Study/Trial Completion:	03/2013
	Final Report Submission:	12/2013
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and Study INCB18424-352 are currently designed to continue until the last patient remaining on study has completed the 144-week visit and the follow-up visit which occurs approximately 28 days later. We will continue to collect safety information on myelosuppression including laboratory evaluations of RBC, Hgb, platelets, WBC, and ANC as specified in the respective protocols through the completion of the studies. The projected study completion dates for Studies INCB18424-351 and INCB 18424-352 are 3/2013 and 12/2012, respectively. The final reports for both trials will be submitted by 8/2013. The final report submission providing additional safety information on myelosuppression from both trials will be by 08/2013.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the proposed PMR is to provide long term (up to 144 weeks following randomization) follow-up evaluation of patients with MF who were entered into the phase III randomized trials (INCB-351 and INCB-352), randomized to the ruxolitinib arm and to either the placebo or BAT arms, and have been chronically exposed to ruxolitinib therapy, in order to ascertain if long term administration has any consequences for production of red cells, white cells or platelets by the bone marrow.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMR will provide long term (up to 144 weeks following randomization) follow-up evaluation of patients with MF who were entered into the phase III randomized trials (INCB-351 and INCB-352), randomized to the ruxolitinib arm and to either the placebo or BAT arms, and have been chronically exposed to ruxolitinib therapy, in order to ascertain if long term administration has any consequences for production of red cells, white cells or platelets by the bone marrow.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
See answer to question 4 above

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Yes Other
See answer to question 4 above
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMC Description: 1838-5 Provide longer-term efficacy and safety outcomes of current clinical trial INCB-351 to provide at least 3 year follow-up data.

PMC Schedule Milestones:	Final Protocol Submission:	INCB-351 07/2009
	Study/Trial Completion:	08/2013
	Final Report Submission:	08/2014
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and Study INCB18424-352 are currently designed to continue until the last patient remaining on study has completed the 144-week visit and the follow-up visit which occurs approximately 28 days later (approximately 3 years). We will continue to collect both safety and efficacy data as specified in the respective protocols through completion of the studies. The projected study completion dates for Studies INCB18424-351 and INCB 18424-352 are 3/2013 and 12/2012, respectively. The final report submission with longer-term efficacy and safety outcomes data from both studies is planned for 08/2013.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the PMC proposed is to follow each patient already entered onto the ruxolitinib or the comparator (placebo or BAT) arms of randomized phase III trials INCB-351 and INCB-352 for up to 3 years after randomization in order to collect both safety and efficacy data as specified in the protocols and to then make a final report of the findings by 08/2013.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study proposed in the PMC is to follow each patient already entered onto the ruxolitinib or the comparator (placebo or BAT) arms of randomized phase III trials INCB-351 and INCB-352 for up to 3 years after randomization in order to collect both safety and efficacy data as specified in the protocols and to then make a final report of the findings by 08/2013.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Trial is in progress
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Yes Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMC Description: 1838-6 Provide longer-term efficacy and safety outcomes of current clinical trial INCB-352 to provide at least 3 year follow-up data.

PMC Schedule Milestones:	Final Protocol Submission:	INCB-352 05/2010
	Study/Trial Completion:	08/2013
	Final Report Submission:	08/2014
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and Study INCB18424-352 are currently designed to continue until the last patient remaining on study has completed the 144-week visit and the follow-up visit which occurs approximately 28 days later (approximately 3 years). We will continue to collect both safety and efficacy data as specified in the respective protocols through completion of the studies. The projected study completion dates for Studies INCB18424-351 and INCB 18424-352 are 3/2013 and 12/2012, respectively. The final report submission with longer-term efficacy and safety outcomes data from both studies is planned for 08/2013.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the PMC proposed is to follow each patient already entered onto the ruxolitinib or the comparator (placebo or BAT) arms of randomized phase III trials INCB-351 and INCB-352 for up to 3 years after randomization in order to collect both safety and efficacy data as specified in the protocols and to then make a final report of the findings by 08/2013.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study proposed in the PMC is to follow each patient already entered onto the ruxolitinib or the comparator (placebo or BAT) arms of randomized phase III trials INCB-351 and INCB-352 for up to 3 years after randomization in order to collect both safety and efficacy data as specified in the protocols and to then make a final report of the findings by 08/2013.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Yes Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Yes Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

AMY C BAIRD
11/15/2011

ROBERT C KANE
11/15/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 202192

Name of Drug: Jakafi (ruxolitinib) Tablets

Applicant: Incyte Corporation

Labeling Reviewed

Submission Date: 6/3/2011

Receipt Date: 6/3/2011

Background and Summary Description

NDA 202192 provides for the treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Conclusions/Recommendations

No deficiencies were identified in the review of this labeling.

Regulatory Project Manager

Date

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

/s/

AMY C BAIRD
11/09/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 202192 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Jakafi Established/Proper Name: ruxolitinib Dosage Form: Tablets Strengths: 5, 10, 15, 20, and 25 mg		
Applicant: Incyte Corporation Agent for Applicant (if applicable):		
Date of Application: June 3, 2011 Date of Receipt: June 3, 2011 Date clock started after UN:		
PDUFA Goal Date: December 3, 2011	Action Goal Date (if different):	
Filing Date: 8/2/2011	Date of Filing Meeting: 7/5/2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of patients with myelofibrosis, including thrombocythemia myelofibrosis.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 077456				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>		X		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th data-bbox="203 1446 495 1486">Application No.</th> <th data-bbox="495 1446 771 1486">Drug Name</th> <th data-bbox="771 1446 1060 1486">Exclusivity Code</th> <th data-bbox="1060 1446 1349 1486">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td data-bbox="203 1486 495 1526"></td> <td data-bbox="495 1486 771 1526"></td> <td data-bbox="771 1486 1060 1526"></td> <td data-bbox="1060 1486 1349 1526"></td> </tr> <tr> <td data-bbox="203 1526 495 1566"></td> <td data-bbox="495 1526 771 1566"></td> <td data-bbox="771 1526 1060 1566"></td> <td data-bbox="1060 1526 1349 1566"></td> </tr> <tr> <td data-bbox="203 1566 495 1587"></td> <td data-bbox="495 1566 771 1587"></td> <td data-bbox="771 1566 1060 1587"></td> <td data-bbox="1060 1566 1349 1587"></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p> <p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>	<p>YES</p>	<p>NO</p> <p>X</p>	<p>NA</p>	<p>Comment</p>																

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			QT/IRT
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 11/3/2010 for Clinical and CMC <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): 9/2/2010 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 5, 2011

BLA/NDA/Supp #: 202192

PROPRIETARY NAME: Jakafi

ESTABLISHED/PROPER NAME: ruxolitinib

DOSAGE FORM/STRENGTH: tablets

APPLICANT: Incyte Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Amy Baird	Y
	CPMS/TL:	Janet Jamison	N
Cross-Discipline Team Leader (CDTL)	Edvardas Kaminskas, MD		
Clinical	Reviewer:	Albert Deisseroth, MD	Y
	TL:	Edvardas Kaminskas, MD	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Joseph Grillo, PhD Christine Garnett, PhD Jian Wang, PhD	Y
	TL:	Julie Bullock, PhD	Y
Biostatistics	Reviewer:	Hong Lu, PhD	Y
	TL:	Mark Rothmann, PhD	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wei Chen, PhD	Y
	TL:	Haleh Saber, PhD	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Sue Ching Lin, PhD Joyce Crich, PhD Anne Marie Russell, PhD	N
	TL:	Janice Brown, PhD	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Anthony Orenca, MD	N
	TL:	Tejashri Purohit-Sheth, MD Lauren Iacono-Connors	N
OSE/DMEPA (proprietary name)	Reviewer:	Sue Kang, PhD	N
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

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APPEARS THIS WAY ON ORIGINAL

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority:	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	<ul style="list-style-type: none"> • notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

AMY C BAIRD
11/09/2011

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301 796 8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center:

Division:

Mail Code: HF

Consulting Reviewer Name: Robert Becker, MD

Building/Room #: WO66, Room 5674

Phone #: 301 796 5450

Fax #:

Email Address: robertl.becker@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: Division of Hematology Products

Mail Code: HFD 160

Requesting Reviewer Name: Albert Deisseroth, MD

Building/Room #: WO22, Room 6187

Phone #: 301 796 4864

Fax #: 301 796 9845

Email Address: albert.deisseroth@fda.hhs.gov

RPM/CSO Name and Mail Code: Amy Baird, WO22, Room 1223, HFD-160

Requesting Reviewer's Concurring

Supervisor's Name: Edvardas Kaminskas, MD

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 10-25-11

Requested Completion Date: 10-31-11

Submission/Application Number: 202192
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: 6-3-11

Official Submission Due Date: 12-3-11

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Documents to be returned to Requesting Reviewer? Yes No

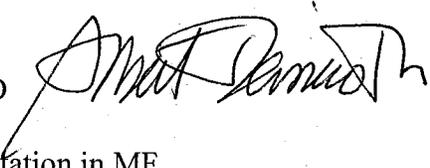
Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF HEMATOLOGY PRODUCTS

DATE: October 25, 2011

FROM: Albert Deisseroth MD, PhD 

SUBJECT: Assay for V617F JAK2 mutation in MF

TO: Dr. Robert Becker, CDRH

THROUGH: Edvardas Kaminskas, M.D., Deputy Division Director (Acting)

Introduction:

The Division of Hematology Products of the Office of Oncology and Hematological Products of OND CDER is in the final stages of reviewing NDA 202192 which proposes an ATP mimetic, ruxolitinib, which at nanomolar concentrations partially inhibits JAK2 by competitively inhibiting the binding of ATP to the catalytic site of JAK2. An activating mutation of JAK2 has been found in 50% of patients with MF.

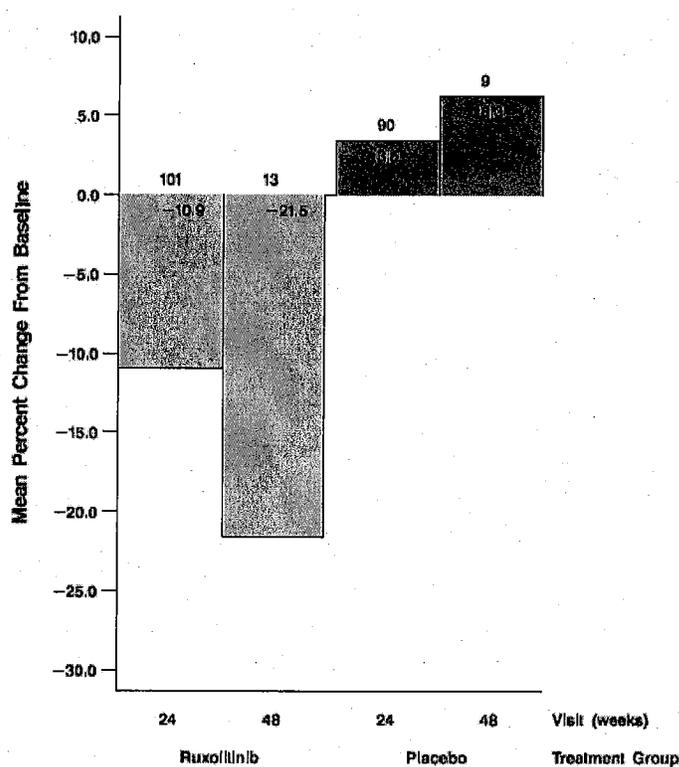
Background on the JAK2 V617F Mutation in MF (page 136 CSR INCB-351)

Recent studies have shown that an activating mutation resulting in a valine to phenylalanine substitution at residue 617 (V617F) in the pseudokinase domain of JAK2 enzyme is present in a high proportion of patients with MPNs.³³ Over expression of JAK2 V617F confers interleukin-3 (IL-3) independence to Ba/F3 cells that co-express a homodimeric type I cytokine receptor, such as the erythropoietin receptor. Transplantation of JAK2 V617F-over expressing hematopoietic cells into mice is sufficient to recapitulate some aspects of MPN disease phenotype, including increased hematocrit, splenomegaly, and decreased survival. In MPN patients, JAK2V617F mutated genotype as well as V617F allele burden (as determined by quantitative PCR) are variably associated with unique hematologic and clinical characteristics of MPNs.³⁴ In addition, following therapy with pegylated interferon in PV patients, no correlation between molecular responses as evidenced by decreased V617F allele burden and hematological responses were noted,³⁵ suggesting that V617F allele burden changes have limited utility to predict clinical response in MPNs.

Analysis of the Percentage of Peripheral Blood White Cells Positive for the V617F JAK2 Mutation at Baseline, and at 24, and 48 Weeks of Ruxolitinib Therapy (page 136 of the CSR for INCB-351):

Nonetheless, given the importance of the JAK2 V617F mutation in MPNs, the percentage of JAK2 V617F mutant allele relative to total JAK2 (wild type JAK2 plus JAK2 V617F, referred to as JAK2V617F allele burden) was assessed in this study to determine what effect, if any, JAK 1/2 inhibition had on JAK2 V617F allele burden. JAK2 V617F allele burden was measured in whole blood at Baseline and Weeks 24 and 48. As shown in Figure 22 (See below), subjects in the ruxolitinib group have a mean percent decrease at Weeks 24 and 48, whereas subjects in the placebo group have mean percent increases at both time points. For subjects in the ruxolitinib group, there was a mean percent change from V617F Baseline values of -10.9% at Week 24 (n = 101, p < 0.0001 from the rank test) and -21.5% at Week 48 (n=13, p = 0.0002 from the rank test). This is in contrast to a mean percent change from V617F Baseline values of 3.5% in the placebo group at Week 24 (n = 90, p=0.0179 from the rank test) and a non-statistically significant change in mean percent change from V617F Baseline of 6.3% at Week 48 in the placebo group (n = 9).

Figure 22 (page 137 CSR INCB 18424-351): Mean Percent Change From Baseline in Percent V617F at Weeks 24 and 48 (Observed Cases)



References on Assay for Percentage of V317F in Patients with MF

33. Guglielmelli, P et al. Identification of patients with poorer survival in primary myelofibrosis based on the burden of JAK2V617F mutated allele. *Blood*. 2009;114(8):1477-83.

34 Vannucchi AM et al. Clinical correlates of JAK2V617F presence or allele burden in myeloproliferative neoplasms: a critical reappraisal. *Leukemia*. 2008;22(7):1299–1307.

35 Kiladjian JJ et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood*. 2008;112(8):3065-72.

Statement of Problem for Dr. Robert Becker's Comment:

About 78% of the patients entered into the two randomized controlled trials of the effects of ruxolitinib treatment on patients with MF on which the marketing application for ruxolitinib for MF is based were V617F positive (therefore 22% negative). Text books usually say that the percentage of patients with MF who are positive for the V617F JAK2 mutation is 50%, and homozygosity for this mutation is found in 13% of patients with MF. A mutation of the transmembrane domain of the thrombopoietin receptor (MPLW5515) has been found in 9% of patients for MF who are negative for V617F. 30% of the patients with MF positive for the MPLW515 mutation are also positive for the JAK2 V617F mutation. Patients with MF who are negative for the JAK2 V617F and MPLW515 mutations still exhibit clonal hematopoiesis suggesting the presence of other yet undiscovered mutations that play a role in the development of MF. Many authorities feel that the clinical presentation and natural histories of patients with MF who are positive or negative for the V617F mutation are similar. It is known also that the hematopoiesis is clonal in both the V617F positive and negative patients. The phosphorylated STAT3 levels are elevated in both the V617F positive and negative patients.

The company's exploratory subgroup analysis (using quantitative PCR-see the attached Blood paper of Guglielmelli-reference 33 above) of the response to ruxolitinib in the patients positive for V617F vs those negative for V617F showed that the point estimates (based upon binomial exact method) of the percent of patients showing $\geq 35\%$ reduction in spleen volume by MRI or CAT scans was 48% in the V617F positive group and 25% in the V617F negative group (95% confidence intervals of the two groups overlapped-see page 139, Figure 23, CSR INCB-351). The company's position is that the clinical presentations, natural history of disease, and response to therapy for the V617F positive and negative

patients are indistinguishable. The company is seeking an indication for ruxolitinib in the treatment of MF irrespective of the presence or absence of the V617F mutation.

Question for Dr. Robert Becker: Given the high likelihood that there are other JAK2 mutations and mutations in other proteins which are upstream of STAT3 which are being missed or not detected by the Guglielmelli quantitative PCR assay, that could produce the symptoms of MF, Dr. Richard Pazdur wanted Dr. Becker's opinion of what requirements or commitments the FDA should be asking of the Sponsoring company (INCYTE) to work with CDRH on validating the assay they are using for the detection of V617F and for attempting to identify the other mutations upstream of STAT3 that may be playing a role in the development of MF.

blood

2009 114: 1477-1483
Prepublished online June 23, 2009;
doi:10.1182/blood-2009-04-216044

Identification of patients with poorer survival in primary myelofibrosis based on the burden of *JAK2V617F* mutated allele

Paola Guglielmelli, Giovanni Barosi, Giorgina Specchia, Alessandro Rambaldi, Francesco Lo Coco, Elisabetta Antonioli, Lisa Pieri, Alessandro Pancrazzi, Vanessa Ponziani, Federica Delaini, Giovanni Longo, Emanuele Ammatuna, Vincenzo Liso, Alberto Bosi, Tiziano Barbui and Alessandro M. Vannucchi

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/s/

AMY C BAIRD
10/25/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Review

Date: October 28, 2011

Reviewer(s): Lissa C. Owens, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Drug Name & Strength(s): Jakafi (Ruxolitinib) Tablets
5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

Application Type/Number: NDA 202192

Applicant/sponsor: Incyte Corporation

OSE RCM #: 2011-2319

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review responds to a request from the Division of Hematology Products for a review of the revised Jakafi (Ruxolitinib) Tablets 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg labels submitted on October 20, 2011 in response to the Division of Medication Error Prevention and Analysis's (DMEPA) previous comments to the Applicant. DMEPA reviewed the initial proposed label and labeling under OSE RCM #2011-2319 dated October 11, 2011.

2 MATERIALS REVIEWED

The revised label and labeling submitted on October 20, 2011 and the OSE review #2011-2319 were evaluated to assess whether the revisions adequately addresses our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised label and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time.

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

4 REFERENCES

OSE Review #2011-2319, Label and Labeling Review for Jakafi (Ruxolitinib) Tablets 5 mg, 10 mg, 15 mg, 20 mg, 25 mg. Owens, Lissa. October 11, 2011.

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/s/

LISSA C OWENS
10/28/2011

CARLOS M MENA-GRILLASCA
10/28/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: October 27, 2011

To: Ann T. Farrell, MD, Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Medical Policy Programs

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): Jakafi (ruxolitinib)

Dosage Form and Route: Tablets, for oral administration

Application Type/Number: NDA 202192

Applicant: Incyte Corporation

OSE RCM #: 2011-3200

1 INTRODUCTION

This review is written in response to a request by the Division of Hematology Products (DHP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert for Jakafi (ruxolitinib) tablets.

On June 3, 2011, Incyte Corporation submitted original New Drug Application (NDA) 202192 for Jakafi (ruxolitinib) tablets. The proposed indication is for the treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. (b) (4)

2 MATERIAL REVIEWED

- Draft Jakafi (ruxolitinib) tablets, for oral administration Patient Package Insert (PPI) received on June 3, 2011 and revised by the review division throughout the current review cycle and received by DMPP on October 20, 2011.
- Draft Jakafi (ruxolitinib) tablets, for oral administration Prescribing Information (PI) received June 3, 2011, revised by the review division throughout the current review cycle and received by DMPP on October 20, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.

- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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immediately following this page

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/s/

LATONIA M FORD
10/27/2011

LASHAWN M GRIFFITHS
10/27/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Direct-to-Consumer Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 27, 2011
To: Amy Baird, Regulatory Health Project Manager, DHP
From: Adora Ndu, Regulatory Review Officer, DDTCP
Subject: NDA 202192
DDTCP comments for JAKAFI™ (Ruxolitinib)
Patient Package Insert

On June 20 2011, DDTCP received a consult request from DHP to review the proposed Patient Package Insert for JAKAFI™ (Ruxolitinib).

DDTCP has reviewed the proposed label using the version of the draft PPI entitled "Ruxolitinib FDA Proposed labeling v9" and offers the following comments.

If you have any questions on the patient labeling, please contact Adora Ndu at 301-796-5114 or adora.ndu@fda.hhs.gov.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ADORA E NDU
10/27/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: 10/19/2011

To: Amy Baird, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Division of Professional Promotion

Subject: Comments on draft labeling (Package Insert) for NDA 202192,
Ruxolitinib

In response to your labeling consult request on June 20, 2011, we have reviewed the draft Package Insert for Ruxolitinib and offer the following comments. Note that these comments are based upon the October 18, 2011 version of the label.

Section	Statement	Comment
14. Clinical Studies	<div style="background-color: #cccccc; width: 100%; height: 100%; display: flex; align-items: center; justify-content: center;"> (b) (4) </div>	<p>We do not consider this secondary endpoint substantial evidence to support promotional claims. This information could be this could be misleading in a promotional context. In addition, there were multiple other secondary endpoints not presented in the PI, thus for consistency, we recommend removing the analysis of this endpoint from the PI.</p> <p>However, if this section is determined essential and is retained, it is recommended to revise the title and description of Table 5. The table only presents the number (%) of patients with ≥ 50% improvement in total symptom score. The title and</p>

		description imply that change from baseline and mean changes are presented, when this information was deleted from a previous version of the labeling.
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/s/

JAMES S DVORSKY
10/19/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: October 11, 2011

Reviewer(s): Lissa C. Owens, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name & Strength(s): Jakafi (Ruxolitinib) Tablets
5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

Application Type/Number: NDA 202192

Applicant/sponsor: Incyte Corporation

OSE RCM #: 2011-2319

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container labels for Jakafi (NDA 202192) for areas of vulnerability that can lead to medication errors.

1.1 PRODUCT INFORMATION

Jakafi is an inhibitor of the Janus kinase family of protein tyrosine kinases (JAK's) that is used in the treatment of myelofibrosis. The recommended starting dose is dependent on platelet count starting at either 15 mg twice daily or 20 mg twice daily with dose adjustments in 5 mg twice daily increments. The maximum daily dose recommended is 50 mg (25 mg twice daily). In patients taking concomitant potent CYP3A4 inhibitors Jakafi is dosed once a day. In patients with hepatic impairment a 25% to 50% dose reduction is recommended. Jakafi will be available in the following strengths:

- 5 mg round white tablets with "INCY" on one side and "5" on the other
- 10 mg round white tablets with "INCY" on one side and "10" on the other
- 15 mg oval white tablets "INCY" on one side and "15" on the other
- 20 mg capsule-shaped white tablets with "INCY" on one side and "20" on the other
- 25 mg oval white tablets with "INCY" on one side and "25" on the other

Jakafi will be supplied in 60-count bottles to be stored at (b) (4) excursions permitted to 15° to 30°C (59° to 86°F).

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 29, 2011 – Images included in Appendix A
- Prescribing Information submitted June 3, 2011 – No image

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

The following section describes the deficiencies identified in our assessment of the labels and labeling.

3.1 CONTAINER LABELS

- a. The established name does not appear to be ½ the size of the proprietary name.
- b. The manner in which the established name and strength are expressed is inconsistent. While the strength of the ruxolitinib phosphate component is expressed as the base, the established name is expressed as a salt.
- c. The Rx Only statement competes in prominence with more relevant information, such as the established name.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels are vulnerable to confusion that could lead to medication errors. We advise the following recommendations be implemented prior to approval.

Container Label

1. Ensure the size of the established name is at least half as large as the letters comprising the proprietary name and has a prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2).
2. Revise the presentation of the established name to read “(Ruxolitinib) Tablets”. As currently presented as the salt form is inconsistent with the presentation of the strength statement in the base form.
3. Decrease the prominence of the ‘TM’ next to the proprietary name by using a smaller font.
4. Decrease the prominence of the color block that appears below the strength to allow for implementation of comment 1.
5. Decrease the prominence of the “Rx only” statement by un-bolding and using a smaller font.
6. Revise the storage conditions statement to read “20° to 25°C (68° to 77°F)”.
7. Revise the statement (b) (4) to read “Usual Dosage: See Prescribing Information”

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

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/s/

LISSA C OWENS
10/11/2011

CARLOS M MENA-GRILLASCA
10/11/2011

CAROL A HOLQUIST
10/11/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 15, 2011

TO: Amy Baird, Regulatory Project Manager
Albert Deisseroth, MD, Medical Officer
Division of Hematology Products

FROM: Anthony Orenca, MD, FACP
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations (*formerly* Division of Scientific Investigations)

THROUGH: Lauren Iacono-Connors, PhD
Acting Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Jean Mulinde, MD
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202192

APPLICANT: Incyte Corporation

DRUG: ruxolitinib

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority (accelerated four-month review)

INDICATIONS: For treatment of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) and post-essential thrombocythemia-myelofibrosis (PET-MF) (b) (4)

CONSULTATION REQUEST DATE: June 20, 2011

DIVISION ACTION GOAL DATE: October 4, 2011

PDUFA DATE: December 3, 2011

I. BACKGROUND:

Myelofibrosis (MF) may present as a *de novo* disorder (primary myelofibrosis [PMF]), or evolve from other myeloproliferative neoplasms, and can be termed either secondary MF, post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF). No drugs are approved in the United States for the treatment of MF. Hydroxyurea, androgens, prednisone, erythropoiesis-stimulating agents, and danazol have been variably used frequently with measurable effect in a few subjects. Busulfan, melphalan, and 2-chlorodeoxyadenosine, have been used in hydroxyurea-refractory subjects. Splenectomy and splenic irradiation are also performed to control spleen size; however, these measures lead to perioperative complications (up to 30%) and fatal outcomes (up to 10%). In addition, allogeneic stem cell transplantation provides a curative option although transplant-related mortality is reported in 22-27% of patients, and not a viable option for subjects greater than 60 years old.

Janus kinases (JAK) play an important role in hematopoietic cytokine receptor signaling by activating a number of signal transducers and activators of transcription (STATs) which regulate genes implicated in the proliferation and survival of malignant cells. While multiple JAK pathway abnormalities have been identified, JAK2 somatic mutations are present in approximately 55-65% of PMF and PET-MF patients, and approximately 96% of PPV-MF patients. JAK inhibitors, such as ruxolitinib, represent potential therapeutic agents.

The Applicant submitted results from Study INCB 18424-351 to support the approval of ruxolitinib for the treatment of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF) (b) (4).

Protocol INCB 18424-351 (a.k.a. Study 351):

Study 351 was a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ruxolitinib to placebo in subjects with PMF, PPV-MF, or PET-MF. Subjects were randomized to receive ruxolitinib or matching placebo tablets. The starting dose was determined based on baseline platelet count. Subjects with baseline platelet count greater than 200,000 per microliter began a dose regimen of 20 mg twice daily. The primary endpoint was the proportion of subjects achieving at least 35% reduction from baseline in spleen volume at Week 24 as measured by MRI (or CT scan in applicable subjects).

This product is a new molecular entity. Verification of data submitted in support of the requested new indication is considered essential by the review division. Two domestic clinical investigator sites and the sponsor were inspected in support of this application.

II. RESULTS (by protocol/site):

Name of CI/ Inspected Entity	City, State	Protocol/ Study Site	Insp. Date	EIR Received Date	Final Classification
Jason Gotlib, M.D.	Stanford, CA	Protocol INCB 18424-351 Site #23	8/15-8/25, 2011	Pending	Pending (Preliminary: NAI)
Carole B. Miller, M.D.	Baltimore, MD	Protocol INCB 18424-351 Site #46	7/25- 7/29, 2011	Pending	Pending (Preliminary: NAI)
Incyte Corporation	Wilmington, DE	SPONSOR	8/15- 8/19, 2011	Pending	Pending (Preliminary: NAI)

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR INSPECTIONS**1. Jason Gotlib, M.D./Site #23**

Stanford Cancer Center

875 Blake Wilbur Drive, Clinic C

Stanford, CA 95405

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from August 15-25, 2011.

A total of 19 subjects were screened, 15 were randomized and completed the study. There was no under-reporting of serious adverse events noted. An audit of records for 17 randomized study subjects was conducted.

During the inspection the following documents were evaluated: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings.

No discrepancies were noted. In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Assessment of data integrity:

The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

2. Carole B. Miller, M.D./Site #46

St. Agnes Health Care, Inc.
900 Caton Avenue
Baltimore, MD 21229

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from July 25-29, 2011.

A total of 8 subjects were screened, randomized, and completed the study. There was no under-reporting of serious adverse events noted. An audit of all enrolled study subjects was conducted.

During the inspection the following documents were evaluated: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

The inspection revealed that the study was conducted adequately. Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices.

d. Assessment of data integrity:

The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

SPONSOR INSPECTION**3. Incyte Corporation**

Rt. 141 & Henry Clay Road
Wilmington, Delaware 19880

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.810, from August 15-19, 2011.

Documents related to site #23 (Jason Gotlib, M.D.) and site #46 (Carole Miller, M.D.), were focused on during the inspection. During the inspection the following items were evaluated: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed FDA forms 1572, monitoring reports, drug accountability records, and training of clinical site staff and site monitors.

b. Limitations of inspection

None.

c. General observations/commentary

The Sponsor maintained adequate oversight of the clinical trial. There were no noncompliant sites and monitoring of the investigator sites was considered adequate.

No salient issues were identified. There was no evidence of under-reporting of adverse events.

d. Assessment of data integrity:

The study appears to have been conducted adequately, and the data submitted by this sponsor appear acceptable in support of the respective indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As part of the PDUFA-related inspections two U.S. clinical investigator sites and the Sponsor were inspected in support of this application, for Protocol INCB 18424-351. The inspections documented general adherence to Good Clinical Practices and applicable regulations governing the conduct of clinical investigations. Preliminary classifications for all three inspections conducted are No Action Indicated (NAI). The data submitted for Study INCB 18424-351 are considered reliable in support of the application.

Note: Observations noted above, for the two clinical sites and Sponsor are based on the preliminary communications from the field investigators; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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Jean Mulinde, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
09/16/2011

LAUREN C IACONO-CONNORS
09/16/2011

JEAN M MULINDE
09/16/2011

Executive CAC

Date of Meeting: September 13, 2011

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
William Taylor, Ph.D., DTOP, Alternate Member
Haleh Saber, Ph.D., DHOT, Team Leader
Wei Chen, Ph.D., DHOT, Presenting Reviewer

Author of Draft: Wei Chen

NDA 202-192

Drug Name: ruxolitinib phosphate

Sponsor: Incyte Corporation

Background: Ruxolitinib phosphate, a new molecular entity, is a small molecule inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs). A topical cream formulation of ruxolitinib phosphate is under investigation for the treatment of psoriasis (IND 77,101). Ruxolitinib phosphate capsules have been developed for the treatment of rheumatoid arthritis (IND 77,455) and myeloproliferative disorders (IND 77,456). ^{(b) (4)}
^{(b) (4)} With this NDA, the sponsor is submitting the results of a 6-month Tg.rasH2 mouse carcinogenicity study. A two-year oral rat carcinogenicity study with ruxolitinib is ongoing.

Tg.rasH2 Mouse Carcinogenicity Study

Carcinogenic assessment in Tg.rasH2 mice was conducted with daily oral (gavage) doses of 0 (0.5% methylcellulose), and 15, 45, 125 mg/kg/day ruxolitinib, in accordance with the Committee's dosing recommendation. Urethane at 1000 mg/kg was used as the positive control. An MTD was reached based on the decreased body weight and decreased weight gain at the high-dose. There were no treatment-related neoplastic lesions at doses tested.

Executive CAC Recommendations and Conclusions:

- The Committee determined that the study was adequate, noting prior FDA protocol concurrence.
- The Committee determined that the study results showed no drug related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\ /Division File, DHOT
/Haleh Saber, Ph.D., Supervisory Pharmacologist, DHOT
/Wei Chen, Ph.D., DHOT
/Amy Baird, DHOT
/ASeifried, OND-IO

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/s/

ADELE S SEIFRIED
09/14/2011

DAVID JACOBSON KRAM
09/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Drug Substance CMC Reviewer: Sue Ching Lin, CMC Reviewer
Drug Product CMC Reviewer: Joyce Crich, CMC Review
Janice Brown, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: SueChing.Lin@fda.hhs.gov and Joyce.Crich@fda.hhs.gov
Phone: (301)-Sue Ching: 301-796-1403 Joyce: 301-796-3882

Fax.: (301)-CMC Reviewer's FAX number

Through: Sarah Pope Miksinski, Chief Branch 2
Phone: (301)-796-1436

and

Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 202192

Name of Product: Ruxolitinib Phosphate Tablets

Applicant: Incyte Corporation

Applicant's Contact Person: Ronald C. Falcone, Ph.D.

Address: Route 141 & Henry Clay Road, Building 336, Wilmington, DE 19880

Telephone: 301-498-6700 Fax: 301-425-2734

Date NDA Received by CDER: **6/3/2011**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP:

Special Handling Required: Yes

DATE of Request: **September 8, 2011**

DEA Class: N/A

Requested Completion Date: **10/21/2011**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **12/3/2011**

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the

laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # (b) (4)
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P. (1 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg tablets)
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1, pg. 1
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1.
Supporting Data for Accuracy, Specificity, etc.				3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
IC/018424/011	Identification: HPLC Retention Time	3.2.P.5.3	0	Drug Product Identity test
IC/018424/011	Assay	3.2.P.5.3	0	Drug Product Potency
IC/018424/004	Assay	3.2.S.4.1	0	Drug Substance Potency
IC/018424/001	Chiral Purity	3.2.S.4.1	0	Drug Substance Chiral Purity and Related Substance test
IC/018424/029 and IC/018424/004.02	Related Substance	3.2.S.4.1	0	ID and Assay of Related Substance (b) (4) and INCB018424

Additional Comments: Ruxolitinib is supplied as 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg tablets. The recommended starting dose of ruxolitinib is 15 mg given orally twice daily for patients with a platelet count between 100,000 and 200,000/ μ L and 20 mg twice daily for patients with an initial platelet count of > 200,000/ μ L. The highest human therapeutic dose is 25 mg bid orally..

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)

6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

JANICE T BROWN
09/08/2011

SARAH P MIKSINSKI
09/08/2011

JEANNIE C DAVID
09/08/2011
ONDQA Methods Validation Project Manager

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	202,192
Brand Name	Ruxolitinib
Generic Name	INCB018424
Sponsor	Incyte Corporation
Indication	Myelofibrosis
Dosage Form	Tablets
Drug Class	JAK inhibitor
Therapeutic Dosing Regimen	10-25 mg b.i.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	25 mg b.i.d. or 100 mg q.d. for multiple dosing 200 mg as single dose (highest single dose tested) was well tolerated.
Submission Number and Date	29 June 2011
Review Division	DDOP / HFD 150

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of INCB018424 (25-mg single dose and 200-mg single dose) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between INCB018424 (25-mg single dose and 200-mg single dose) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, partially blinded, four-period crossover study, 50 healthy subjects received INCB018424 25-mg single dose, INCB018424 200-mg single dose, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for INCB018424 (25 mg and 200 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
INCB018424 25 mg	24	2.2	(-0.5, 4.9)
INCB018424 200 mg	12	2.2	(0.0, 4.4)
Moxifloxacin 400 mg*	1.5	10.4	(7.4, 13.5)

* Multiple endpoint adjustment of 3 time points was applied.

The suprathreshold dose (200-mg single dose) produces mean C_{\max} values 7.6-fold the mean C_{\max} for the therapeutic dose (25-mg single dose). Given the low accumulation ratio observed with b.i.d. dosing (9%), rapid terminal half-life (3.2 h), and reported steady-state C_{\max} for 50 mg b.i.d. (2710 nM which is 1.8-fold the 25-mg single-dose C_{\max} from the current study), the C_{\max} observed following a single dose INCB018424 25 mg is an acceptable representation of steady-state C_{\max} with 25-mg b.i.d. dosing. The concentrations for the suprathreshold dose are above those for the predicted worst case scenario (drug interaction with a potent CYP3A4 inhibitor such as ketoconazole). For such patients a 30% increase in INCB018424 C_{\max} was observed in addition to a 48% reduction in clearance. Predicted steady-state C_{\max} for INCB018424 25 mg b.i.d. in these patients is 1.7-fold the steady-state C_{\max} in patients not administered a potent CYP3A4 inhibitor for the same INCB018424. This exposure is within the concentration range studied in the TQT study and showed no detectable prolongations of the QT-interval.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

The sponsor proposed the following language in the package insert.

12.4 Thorough QT Study

(b) (4)

2.2 QT-IRT PROPOSED LABEL

QT-IRT recommends the following label language. Our recommendations are suggestions only. We defer final decisions regarding labeling to the review division.

Section 12.2 Pharmacodynamics

The effect of single dose ruxolitinib 25 mg and 200 mg on QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 47 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the

largest placebo adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 200 mg is adequate to represent the high exposure clinical scenario.

3 BACKGROUND

3.1 PRODUCT INFORMATION

INCB018424 phosphate is an inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases that is in development for the treatment of primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (PPV-MF) and post essential thrombocythemia myelofibrosis (PET-MF).

INCB018424 Phosphate tablets are also under development for the treatment of patients with rheumatoid arthritis under IND 77,455.

3.2 MARKET APPROVAL STATUS

Ruxolitinib is not approved for marketing in any country .

3.3 PRECLINICAL INFORMATION

From eCTD, Pharmacology Written Summary

“The in vitro effects of ruxolitinib on ionic currents in voltage-clamped human embryonic kidney cells (HEK293) that stably express the human ether-à-go-go-related gene (hERG) were determined. Ruxolitinib was evaluated in a GLP study at 10, 100 and 300 µM [INCYTE-DMB- 06.187.1]. All experiments were performed at physiological temperature (35 ± 2°C). Ruxolitinib inhibited hERG current by (mean ± SEM): 3.8 ± 0.2% at 10 µM (n = 3), 40.3 ± 1.6% at 100 µM (n = 3) and by 74.1 ± 0.2% at 300 µM (n = 3) versus 0.6 ± 0.5% (n = 3) for the vehicle control. hERG inhibition at 100 µM and 300 µM of ruxolitinib was significant (P < 0.05), when compared to vehicle control values. The IC50 for the inhibitory effect of ruxolitinib on the hERG potassium current was 131.6 µM. The Cmax at the highest proposed therapeutic dose in humans (25 mg bid) is 1.48 µM (0.049 µM unbound). Therefore, the risk of meaningful inhibition of hERG in humans given ruxolitinib appears to be nonexistent. Additionally, in a study to assess the effects of ruxolitinib on heart rate corrected QT intervals in healthy subjects compared with moxifloxacin [INCB 18424-138], ruxolitinib at a dose of 200 mg did not cause prolongation of ventricular repolarization.

“In order to evaluate the cardiovascular system effects of ruxolitinib, the compound was administered as a single oral dose (gavage) at dosage levels of 0, 3, 10 or 30 mg/kg to four male beagle dogs in a GLP study [T06-10-01]. Only male animals were selected because toxicokinetic parameters were similar in male and female dogs [T06-09-07]. Dosing was conducted according to a Latin square design such that each radiotelemetry-implanted dog received each treatment once, with a 3-4 day washout period between doses. Each treatment group was represented on each day of testing. Heart rate (derived from arterial waveforms), arterial blood pressure (systolic, diastolic, calculated mean, and pulse pressure), body temperature, and ECG were collected for a 30-second period every 10 minutes for at least 24 hrs following dosing.

“All animals survived to study termination. Clinical observations were conducted at 5 and 24 hrs post-dose. After administration of 30 mg/kg ruxolitinib, injected sclera of one or both eyes was noted in 3 out of 4 animals at the 5 hrs post-dose observation timepoint. Emesis was noted after administration of 30 mg/kg ruxolitinib at 5 hrs post-dose in 2 out of 4 animals. These clinical observations (injected sclera and emesis) were considered to be test-article related but not adverse.

“Administration of ruxolitinib at a dose of 30 mg/kg (the highest dose tested) resulted in significantly lower pulse pressure, as well as lower systolic, diastolic, and calculated mean arterial pressure (up to 53%, 41%, 31%, and 33%, respectively) when compared to the control group. These changes peaked at approximately 2-3 hrs post-dose after which mean arterial blood pressure values began to recover. Although arterial blood pressure continued to recover, lower values were noted for up to 24 hrs in the 30 mg/kg dose group compared to the control group. Mean arterial pressure is presented in Figure 3. Systolic, diastolic, and pulse pressures demonstrated similar profiles. Hemodynamic changes after administration of ruxolitinib at a dose of 30 mg/kg were considered adverse.”

3.4 PREVIOUS CLINICAL EXPERIENCE

From ISS

“The proportion of subjects treated with ruxolitinib with normal ECG evaluations at Baseline who subsequently developed abnormal ECG findings was low in the Phase 3 studies. In both Phase 3 studies, a higher proportion of subjects in the ruxolitinib group had a sitting systolic blood pressure ≥ 160 mmHg or an increase from Baseline $\geq 25\%$ compared with the comparator group, the majority of which were single episodes. In Study INCB 18424-351, a higher proportion of subjects in the ruxolitinib group had a sitting diastolic blood pressure ≥ 95 mmHg compared with the placebo group, all of which were single episodes. A similar pattern was seen in Study CINC424A2352 (see Section 6.1). Mean systolic and diastolic blood pressure in the ruxolitinib groups remained similar to Baseline levels throughout the study.

“Overall, there do not seem to be clinically significant changes in ECGs or blood pressure in subjects treated with ruxolitinib. A small decrease in median heart rate (approximately 8 bpm) was noted in subjects treated with ruxolitinib in Study INCB 18424-351 and this may be associated with lower levels of circulating inflammatory cytokines in these subjects. This is discussed in further detail in the Study INCB 18424-351 CSR.”

“For the identification and evaluation of common AEs that are potentially related to ruxolitinib, INCB 18424-351 is considered the most informative study, as it is randomized, double-blinded, and placebo-controlled. The most frequently reported AE by MedDRA preferred term in the Phase 3 Population was thrombocytopenia, which was reported by 39.2% of ruxolitinib-treated subjects, 9.3% of subjects in the placebo group, and 9.6% of subjects in the BAT group. Anemia was the second most frequently reported AE and occurred in 35.5% of ruxolitinib-treated subjects as compared with 13.9% in placebo-treated subjects and 12.3% in subjects in the BAT group.

Table 2: Common Adverse Events (≥1% Incidence in the Total Ruxolitinib Group) with Greater Frequency in the Ruxolitinib Group as Compared with Placebo and/or BAT in the Phase 3 Population

Preferred Term	Study INCB 18424-351			Study CINC424A2352			Total
	Ruxolitinib (N=155)	Placebo (N=151)	Difference	Ruxolitinib (N=146)	BAT (N=73)	Difference	Ruxolitinib (N=301)
Thrombocytopenia	53 (34.2)	14 (9.3)	24.9	65 (44.5)	7 (9.6)	34.9	118 (39.2)
Anemia	48 (31.0)	21 (13.9)	17.1	59 (40.4)	9 (12.3)	28.1	107 (35.5)
Hemoglobin decreased	22 (14.2)	6 (4.0)	10.2	4 (2.7)	2 (2.7)	0	26 (8.6)
Headache	23 (14.8)	8 (5.3)	9.5	15 (10.3)	3 (4.1)	6.2	38 (12.6)
Contusion	22 (14.2)	8 (5.3)	8.9	3 (2.1)	1 (1.4)	0.7	25 (8.3)
Dizziness	23 (14.8)	10 (6.6)	8.2	10 (6.8)	4 (5.5)	1.4	33 (11.0)
Platelet count decreased	15 (9.7)	4 (2.6)	7	10 (6.8)	2 (2.7)	4.1	25 (8.3)
Weight increased	10 (6.5)	2 (1.3)	5.1	14 (9.6)	0	9.6	24 (8.0)
Flatulence	8 (5.2)	1 (0.7)	4.5	2 (1.4)	0	1.4	10 (3.3)
Cardiac murmur	11 (7.1)	5 (3.3)	3.8	6 (4.1)	2 (2.7)	1.4	17 (5.6)
Pyrexia	17 (11.0)	11 (7.3)	3.7	20 (13.7)	7 (9.6)	4.1	37 (12.3)
Chills	8 (5.2)	3 (2.0)	3.2	3 (2.1)	0	2.1	11 (3.7)
Procedural pain	5 (3.2)	0	3.2	2 (1.4)	1 (1.4)	0	7 (2.3)
Hematocrit decreased	7 (4.5)	2 (1.3)	3.2	0	1 (1.4)	-1.4	7 (2.3)
Hematoma	4 (2.6)	0	2.6	12 (8.2)	3 (4.1)	4.1	16 (5.3)
Hematuria	4 (2.6)	0	2.6	2 (1.4)	1 (1.4)	0	6 (2.0)
Wheezing	5 (3.2)	1 (0.7)	2.6	0	0	0	5 (1.7)
Red blood cell count decreased	4 (2.6)	0	2.6	0	0	0	4 (1.3)
Urinary tract infection	11 (7.1)	7 (4.6)	2.5	10 (6.8)	2 (2.7)	4.1	21 (7.0)
Arthralgia	17 (11.0)	13 (8.6)	2.4	18 (12.3)	5 (6.8)	5.5	35 (11.6)
Pneumonia	13 (8.4)	9 (6.0)	2.4	3 (2.1)	5 (6.8)	-4.8	16 (5.3)
Pain in extremity	19 (12.3)	15 (9.9)	2.3	17 (11.6)	3 (4.1)	7.5	36 (12.0)
Vomiting	19 (12.3)	15 (9.9)	2.3	13 (8.9)	1 (1.4)	7.5	32 (10.6)
Diarrhea	36 (23.2)	32 (21.2)	2	34 (23.3)	8 (11.0)	12.3	70 (23.3)
Palpitations	4 (2.6)	1 (0.7)	1.9	7 (4.8)	1 (1.4)	3.4	11 (3.7)
Neutropenia	4 (2.6)	1 (0.7)	1.9	5 (3.4)	1 (1.4)	2.1	9 (3.0)

Preferred Term	Study INCB 18424-351			Study CINC424A2352			Total
	Ruxolitinib (N=155)	Placebo (N=151)	Difference	Ruxolitinib (N=146)	BAT (N=73)	Difference	Ruxolitinib (N=301)
Chest pain	7 (4.5)	4 (2.6)	1.9	1 (0.7)	4 (5.5)	-4.8	8 (2.7)
Influenza like illness	3 (1.9)	0	1.9	2 (1.4)	0	1.4	5 (1.7)
Meniscus lesion	4 (2.6)	1 (0.7)	1.9	1 (0.7)	0	0.7	5 (1.7)
Tooth abscess	3 (1.9)	0	1.9	1 (0.7)	0	0.7	4 (1.3)
Balance disorder	4 (2.6)	1 (0.7)	1.9	0	0	0	4 (1.3)
Cardiomegaly	4 (2.6)	1 (0.7)	1.9	0	0	0	4 (1.3)
Dry eye	4 (2.6)	1 (0.7)	1.9	0	0	0	4 (1.3)
Fluid overload	4 (2.6)	1 (0.7)	1.9	0	0	0	4 (1.3)
Blast cells present	3 (1.9)	0	1.9	0	0	0	3 (1.0)
Excoriation	3 (1.9)	0	1.9	0	0	0	3 (1.0)
Myocardial infarction	3 (1.9)	0	1.9	0	0	0	3 (1.0)
Insomnia	18 (11.6)	15 (9.9)	1.7	9 (6.2)	5 (6.8)	-0.7	27 (9.0)
Cystitis	2 (1.3)	0	1.3	8 (5.5)	3 (4.1)	1.4	10 (3.3)
Herpes zoster	3 (1.9)	1 (0.7)	1.3	7 (4.8)	0	4.8	10 (3.3)
Bradycardia	3 (1.9)	1 (0.7)	1.3	4 (2.7)	0	2.7	7 (2.3)
Fluid retention	3 (1.9)	1 (0.7)	1.3	4 (2.7)	0	2.7	7 (2.3)
Blood urea increased	2 (1.3)	0	1.3	4 (2.7)	0	2.7	6 (2.0)
Post procedural hemorrhage	3 (1.9)	1 (0.7)	1.3	3 (2.1)	1 (1.4)	0.7	6 (2.0)
Neutrophil count increased	3 (1.9)	1 (0.7)	1.3	2 (1.4)	0	1.4	5 (1.7)
Productive cough	3 (1.9)	1 (0.7)	1.3	2 (1.4)	0	1.4	5 (1.7)
Skin infection	3 (1.9)	1 (0.7)	1.3	2 (1.4)	0	1.4	5 (1.7)
Muscular weakness	4 (2.6)	2 (1.3)	1.3	1 (0.7)	0	0.7	5 (1.7)
Atioventricular block first degree	2 (1.3)	0	1.3	2 (1.4)	0	1.4	4 (1.3)
Toothache	2 (1.3)	0	1.3	2 (1.4)	1 (1.4)	0	4 (1.3)
Hypoesthesia	3 (1.9)	1 (0.7)	1.3	1 (0.7)	0	0.7	4 (1.3)
Tinnitus	3 (1.9)	1 (0.7)	1.3	1 (0.7)	0	0.7	4 (1.3)

Source: ISS, Table 25.

“There were 28 on-study deaths in the Phase 3 population: 20 deaths in Study INCB 18424-351 (9 in the ruxolitinib group and 11 in the placebo group) and 8 deaths in Study INC424A2352 (4 in the ruxolitinib group and 4 in the BAT group).

Table 3: Electrocardiogram Abnormalities in the Phase 3 Population

	INCB 18424-351		INCB 18424-352		Total
	Ruxolitinib (N=155)	Placebo (N=151)	Ruxolitinib (N=146)	BAT (N=73)	Ruxolitinib (N=301)
Patient-years of exposure	106.63	88.31	132.07	52.77	238.70
QTcF (msec)					
New > 450	10 (6.8)	7 (4.9)	6 (4.4)	1 (1.7)	16 (5.6)
New > 480	0	5 (3.4)	1 (0.7)	2 (3.2)	1 (0.3)
New > 500	3 (1.9)	1 (0.7)	0	0	3 (1.0)
Increase from Baseline > 30	18 (11.6)	21 (14.1)	19 (13.4)	8 (12.5)	37 (12.5)
Increase from Baseline > 60	1 (0.6)	6 (4.0)	0	0	1 (0.3)
QTcB (msec)					
New > 450	19 (13.8)	18 (14.4)	15 (11.1)	4 (7.0)	34 (12.5)
New > 480	0	7 (4.8)	2 (1.4)	3 (4.8)	2 (0.7)
New > 500	2 (1.3)	4 (2.7)	0	2 (3.2)	2 (0.7)
Increase from Baseline > 30	13 (8.4)	23 (15.4)	20 (14.1)	6 (9.4)	33 (11.1)
Increase from Baseline > 60	3 (1.9)	6 (4.0)	2 (1.4)	0	5 (1.7)
HR (bpm)					
Increase from Baseline > 25% and > 100 bpm	2 (1.3)	4 (2.7)	5 (3.5)	2 (3.1)	7 (2.3)
Decrease from Baseline > 25% and < 50 bpm	3 (1.9)	1 (0.7)	3 (2.1)	0	6 (2.0)
PR (bpm)					
Increase from Baseline > 25% and > 200 msec	5 (3.3)	1 (0.7)	8 (5.7)	1 (1.6)	13 (4.5)
QRS (msec)					
Increase from Baseline > 25% and > 110 msec	0	7 (4.7)	2 (1.4)	0	2 (0.7)

Source: ISS, Table 54”

Reviewer’s comment: No syncope, seizures or ventricular arrhythmias were reported. From the 28 deaths reported in phase 3 studies, two had cardiac arrest as main cause of death. Both cases were confounded, one by the normal disease progression and the other by pneumonitis.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of INCB018424’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 77,456.

The sponsor submitted the study report INCB 18424-138 for INCB018424, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

An Assessment of Heart Rate Corrected QT Intervals in Healthy Subjects Dosed with

Single Doses of INCB018424 Compared with Moxifloxacin

4.2.2 Protocol Number

INCB 18424-138

4.2.3 Study Dates

Date first patient enrolled: 05 October 2009

Date last patient completed: 25 November 2009

4.2.4 Objectives

4.2.4.1 Primary

- To confirm a lack of effect of INCB018424 on the heart rate corrected QT interval

4.2.4.2 Secondary

- To determine the safety and tolerability of INCB018424 in healthy adult subjects when administered orally and to determine the pharmacokinetics of INCB018424 in the blood plasma of adult healthy subjects

4.2.5 Study Description

4.2.5.1 Design

This will be a randomized, 4-way crossover study evaluating the effects of placebo, 25 mg INCB018424, 200 mg INCB018424, and 400 mg moxifloxacin on the heart-rate corrected QT interval in healthy subjects. The study was double-blind with regard to INCB018424 and placebo and open-label for moxifloxacin. The total duration of subject participation in the study from screening through discharge was approximately 64 days. Fifty subjects were planned to be enrolled.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The study was double-blind with regard to INCB018424 and placebo and open-label for moxifloxacin (positive control).

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Treatment A: INCB018424 25 mg (1 active and 7 placebo tablets)

Treatment B: INCB018424 200 mg (8 active tablets)

Treatment C: Placebo (8 tablets)

Treatment D: Moxifloxacin 400 mg (1 tablet)

Single doses of INCB018424, placebo, and moxifloxacin were administered to each subject according to the randomization scheme in 1 of 8 treatment sequences (Group 1: ABCD, BDAC, CADB, and DCBA; Group 2: BCAD, CDBA, ABDC, and DACB). Two groups of subjects were randomized using different William squares. Subjects were divided equally between the 2 groups.

Table 4: William Square for Group 1 (top) and Group 2 (bottom)

	Period 1	Period 2	Period 3	Period 4
Sequence 1	A	B	C	D
Sequence 2	B	D	A	C
Sequence 3	C	A	D	B
Sequence 4	D	C	B	A

	Period 1	Period 2	Period 3	Period 4
Sequence 1	B	C	A	D
Sequence 2	C	D	B	A
Sequence 3	A	B	D	C
Sequence 4	D	A	C	B

4.2.6.2 Sponsor’s Justification for Doses

“For myelofibrosis, the highest dose being evaluated in Phase 3 studies is 25 mg b.i.d. Therefore, this study evaluated the highest likely clinical dose to be evaluated in Phase 3 (25 mg) and a suprathapeutic dose of 200 mg, which should produce plasma concentrations well above those for the highest potential clinical dose, even in the presence of a potent CYP3A4 inhibitor.”

(Source: INCB018424 study report, Section 9.4.4, Pg 29)

Reviewer’s Comment: INCB018424 was administered 25 mg b.i.d. clinically but was evaluated as a single dose in this TQT study. However, given the low accumulation ratio with b.i.d. dosing (9%), rapid terminal half-life (3.2 h), and reported steady-state C_{max} from other studies using 50 mg b.i.d. (2710 nM which is 1.8-fold the 25-mg single-dose C_{max} from the current study), the C_{max} observed following a single dose INCB018424 25 mg for this TQT study is an acceptable representation of steady-state C_{max} with 25 mg b.i.d.

Drug-drug interaction studies indicated a 30% increase in C_{max} when coadministered with ketoconazole, in addition to a 48% reduction in clearance. Predicted steady-state

C_{max} for INCB018424 25 mg b.i.d. in these patients is 1.7-fold the steady-state C_{max} with the 25-mg single dose. This exposure is within the concentration range from the 200-mg supratherapeutic dose studied in the TQT study.

The hepatic impairment study indicated a decrease a 8%, 22% and 15% decrease in C_{max} for patients with mild, moderate, and severe hepatic impairment, respectively, compared to normal patients. Concurrently, clearance decreased by 47%, 22%, and 39% for patients with mild, moderate, and severe hepatic impairment, respectively, compared to normal patients. Each of these scenarios would result in a lower increase in C_{max} compared to the drug-drug interaction results from ketoconazole. As such, the ketoconazole exposures are an appropriate high exposure scenario for assessing QT prolongation.

4.2.6.3 Instructions with Regard to Meals

Study drug was administered orally followed by 240 mL water and was taken following an overnight fast of at least 10 hours. Subjects then abstained from water for 1 hour post-dose. Subjects remained fasting and sitting or semi-recumbent for 3 hours post-dose, at which point a meal was served.

(Source: INCB018424 study report, Section 9.4.4, Pg 29)

Reviewer's Comment: Administration with a high fat meal decreased INCB018424 by 24%. As such, doses were administered orally after at least a 10 h fast from food to ensure maximum INCB018424 exposure.

4.2.6.4 ECG and PK Assessments

On Day 1 of Period 1, triplicate ECG readings were obtained from 12-lead Holter monitors at 90, 60, and 30 minutes before administration. On Days 8, 15 and 22, 12-lead Holter monitoring began approximately 30 to 60 minutes before administration. On Days 1, 8, 15, and 22, triplicate 12-lead ECG readings were obtained from 12-lead Holter monitors at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours after each dose.

Venous blood samples were collected to measure plasma concentrations of INCB018424 and moxifloxacin at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours post-dose for each period.

Reviewer's Comment: The PK and ECG assessments are adequate to capture QT at peak concentration of INCB018424 ($T_{max} \sim 1.5$ h) and potential delayed effects up to 24 h postdose.

4.2.6.5 Baseline

The average of triplicate ECG readings obtained from 12-lead Holter monitors at 90, 60, and 30 minutes before administration at each period was used as baseline.

4.2.7 ECG Collection

A (b) (4) provided standardized digital Holter recorders, protocol specific training manuals and all other accessories that are required to perform continuous

12-lead ECG data recording. A representative from the (b) (4) was responsible for training the Investigator and his/her research staff to insure a comprehensive understanding of the ‘step-by-step’ procedures that must be performed to obtain and transmit the ECG data.

A ‘true’ 12-lead Holter recorder was used to capture ECG data. A flashcard was used to collect the ECG data. All ECG data collected during the monitoring period was transmitted to the (b) (4) where it will be extracted and analyzed in digital format.

4.2.8 Sponsor’s Results

4.2.8.1 Study Subjects

Fifty subjects were enrolled in the study. Forty-seven (94%) subjects completed all 4 treatment periods. One subject discontinued because of an AE (headache and vomiting), which was judged not related to study drug. Two subjects withdrew consent.

Table 5: Summary of Demographics and Baseline Characteristics

Variable	Total (N=50)
Age (yrs)	
Mean (± SD)	33 (± 11.95)
Min, Max	18, 55
Gender - n (%)	
Male	25 (50.0)
Female	25 (50.0)
Ethnicity - n (%)	
Hispanic or Latino	2 (4.0)
Not Hispanic or Latino	48 (96.0)
Race - n (%)	
White	40 (80.0)
Black	1 (2.0)
Asian	5 (10.0)
American Indian or Alaska Native	4 (8.0)
Native Hawaiian	0
Height (cm)	
Mean (± SD)	170.28 (± 9.536)
Min, Max	146.3, 190.2
Weight (kg)	
Mean (± SD)	69.35 (± 10.418)
Min, Max	50.3, 89.6
BMI (kg/m ²)	
Mean (± SD)	23.84 (± 2.404)
Min, Max	19.5, 28

Source: CSR, Table 6

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

“The primary analysis was performed using a repeated-measure, mixed-effects, linear model that included fixed effects of treatment sequence, study treatment, study period, ECG time point, and treatment-by-ECG time point interaction. The within-subject correlation was modeled over time using an AR(1) covariance structure.

“The response variable for the above model, QTcF, was the change from the Day 1 predose baseline.

“All 4 treatments were included in the analysis, although only the 2 INCB018424 doses and placebo were used for testing the primary hypothesis. All inferences were based on the least square means estimated from this model.

“For each time point, the mean difference between each INCB018424 dose and placebo is presented, along with a 1-sided 95% upper confidence bound on the difference. The upper bound was calculated with reference to the Student’s t distribution. Primary attention was placed on the largest time-matched upper confidence bound of the QTcF difference between each INCB018424 dose and placebo for each of the comparisons made using the model stated above.”

The largest observed mean difference from placebo in baseline-corrected QTcF for the 25 mg dose was 1.69 ms at 2 hours after administration, and the largest upper bound of the confidence interval was 5.15 ms at this same time. The largest observed mean difference from placebo for the 200 mg dose is 3.28 ms at 12 hours after administration, and the largest upper bound of the confidence interval is 6.62 ms at this same time. Therefore, the primary hypothesis was rejected and the study is deemed negative for QT interval prolongation.

Reviewer’s Comments: Please see the reviewer’s analysis in section 5.2.1.

4.2.8.2.2 Assay Sensitivity

The assay sensitivity of the study was assessed by placing a 1-sided lower 99% confidence bound on the mean differences between moxifloxacin and placebo at 1, 2, 3, 4, and 6 hours postdose. The lower bound was above 5 ms at 3 of these times (1, 2, and 3 hours after administration), and the overall trend of the moxifloxacin response was as expected (with a rapid rise and gradual return to near baseline by the end of 24 hours), demonstrating that the study had assay sensitivity.

Reviewer’s Comments: The reviewer used 95% C.I. while adjusted for three time points; the analysis is in section 5.2.1.

4.2.8.2.3 Categorical Analysis

The numbers of subjects with QTcF intervals >450 ms, >480 ms, and >500 ms are summarized in Table 23 to 25 of the ECG Report. Three subjects on INCB018424 200 mg (Subjects 2, 18, 27) and 2 each on placebo (Subjects 2 and 18) and INCB018424 25 mg (Subjects 2 and 33) had 1 or more QTcF intervals > 450 ms. None of the subjects on either INCB018424 dose or on placebo had a QTcF interval > 480 ms at any time point evaluated. Thus, the outlier analysis confirmed the findings for the central tendency.

The number of subjects with increases from the Day 1 pre-dose baseline in QTcF intervals > 30 ms and > 60 ms are summarized in Table 26 and 27 of the ECG Report. One subject on placebo (Subject 18) had a single increase in QTcF > 30 ms, and none of the subjects on either INCB018424 dose had such an increase at any time point evaluated. None of the subjects had an increase from the Day 1 pre-dose baseline in QTcF > 60 ms at any time point evaluated.

4.2.8.2.4 Additional Analyses

Heart rate:

“Results for changes in heart rate are shown in the ECG Report along with 2-sided 95% confidence intervals on the mean differences from placebo. All changes in heart rate were minimal and without clinical relevance. The data indicate that only small increases over placebo were seen, maximally 3.71 (CI 1.38 to 6.04) bpm in the INCB018424 200-mg treatment arm compared to placebo at 1.5 hours. This was actually a -0.20 bpm change compared with the baseline value for the 200-mg dose group, but as the placebo group decreased by -3.90 bpm at that time point, this was an increase in heart rate compared with placebo.”

PR and QRS:

“The number of subjects with a QRS interval > 110 ms that was also a 25% increase over the Day 1 predose baseline and the number with a PR interval >200 ms that was also a 25% increase over the Day 1 predose baseline are summarized in Table 28 and 29 of the ECG Report.

None of the subjects met either criterion at any time point evaluated. Small decreases (not placebo-corrected) were seen in QRS intervals at all time points with the exception of a mean QRS increase of 0.2 ms at 4 hours for the INCB018424 200-mg treatment. Small increases (not placebo-corrected) were seen in PR intervals with a maximum increase of 6.3 ms at 1 hour for the INCB018424 200-mg treatment. Similar changes were seen following placebo dosing. Neither finding is considered clinically relevant.”

4.2.8.3 Safety Analysis

No subjects had a TEAE of syncope, seizure, ventricular tachycardia, or ventricular fibrillation. No subject died during the study. No SAEs occurred during the study.

One subject discontinued because of TEAEs of headache and vomiting. These events occurred on Day -1 of Period 2 following administration of placebo in Period 1 and were judged as unrelated to study drug.

The most frequently reported treatment-related TEAE was headache, which occurred in 8 (16%) subjects overall (see Table 14.3.1.8). It was also the most frequently reported TEAE within any treatment group. Treatment-related headache was reported by 3 (6.4%) subjects in the INCB018424 25 mg group, 2 (4.2%) subjects in the INCB018424 200 mg group, 1 (2.0%) subjects in the placebo group, and 2 (4.2%) subjects in the moxifloxacin 400 mg group. Other treatment-related TEAEs reported were dizziness (2 subjects, 4%), diarrhea (1 subject, 2%), abdominal discomfort (1 subject, 2%), dysgeusia (1 subject, 2%), flatulence (1 subject, 2%), nausea (1 subject, 2%), and vertigo (1 subject, 2%).

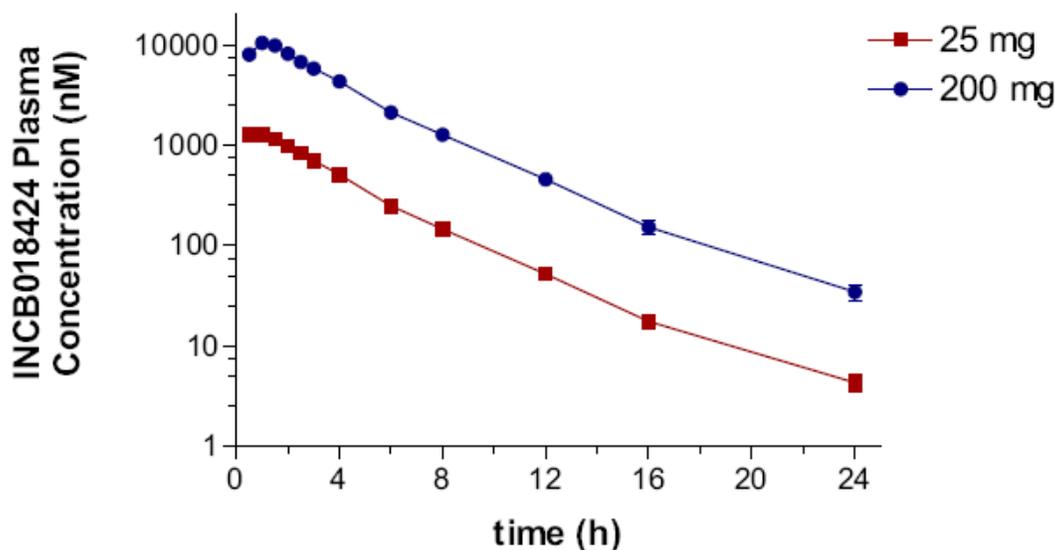
4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Figure 1 presents the mean INCB018424 plasma concentrations for individual subjects receiving 25 mg and 200 mg of INCB018424. INCB018424 pharmacokinetic parameters (C_{max} and AUC_{0-24}) for individual subjects receiving 25 mg and 200 mg of INCB018424

are summarized in Table 6. C_{max} and AUC values in the thorough QT study were 7.6- and 8.1-fold those following administration of single dose 200-mg INCB018424 compared with single dose 25-mg INCB018424.

Figure 1: INCB018424 Plasma Concentration (Mean) in Healthy Subjects Receiving a Single Dose of 25 or 200 mg INCB018424



(Source: INCB018424 study report, Section 11.2, Figure 1, Pg 44)

Table 6: Summary of INCB018424 Pharmacokinetic Parameters

Dose (mg)	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	AUC _{0-t} (nM·h)	AUC _{0-∞} (nM·h)	CL/F (L/h)	V_z/F (L)
25	47	1510 ± 400	0.96 ± 0.5	2.6 ± 0.9	5290 ± 1640	5320 ± 1680	16.8 ± 5.01	59.1 ± 11.4
		1460	0.86	2.5	5060	5080	16.1	58.0
200	48	11500 ± 3120	1.1 ± 0.4	2.7 ± 0.55	42800 ± 14300	43000 ± 14500	16.9 ± 5.45	62.6 ± 15.0
		11100	1.1	2.6	40600	40700	16.0	60.9

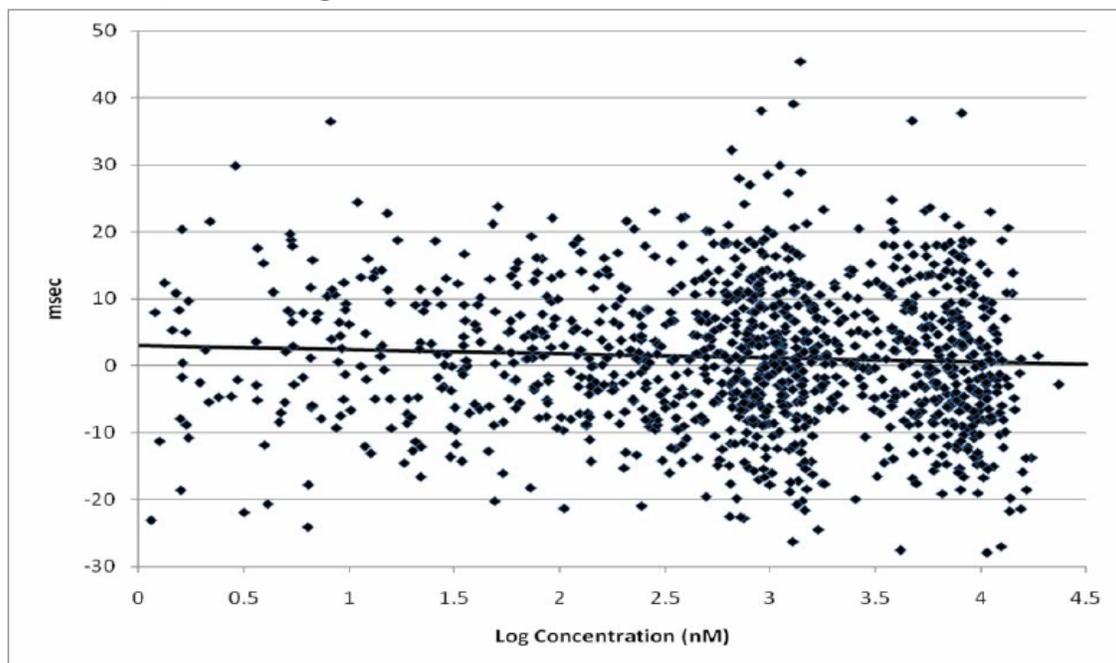
Parameter values are mean ± SD and geometric mean.

(Source: INCB018424 study report, Section 11.2, Table 8, Pg 44)

4.2.8.4.2 Exposure-Response Analysis

The relationship between the placebo-subtracted differences in changes from the Day 1 pre-dose baseline in QTcF intervals and \log_{10} INCB018424 plasma concentration was assessed. A scatter plot of $\Delta\Delta\text{QTcF}$ versus \log_{10} INCB018424 plasma concentration is shown in Figure 2, along with the fitted regression line. The linear regression had an intercept of 3.0 and a slope of -0.6 (p-value = 0.372). The non-statistically significant slope indicates that there was no relationship between changes in QTcF and \log_{10} INCB018424 plasma concentration.

Figure 2: Time-Matched Differences From Placebo in Changes From Day 1 Predose Baseline in QTcF vs. Log INCB018424 Concentration



(Source: INCB018424 study report, Section 11.4, Table 8, Pg 51)

Reviewer's Analysis: A plot of $\Delta\Delta QTcF$ vs .INCB018424 concentrations is presented in Figure 5.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor only provided two fixed corrections, QTcF and QTcB, so we evaluated the appropriateness of the correction methods. Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

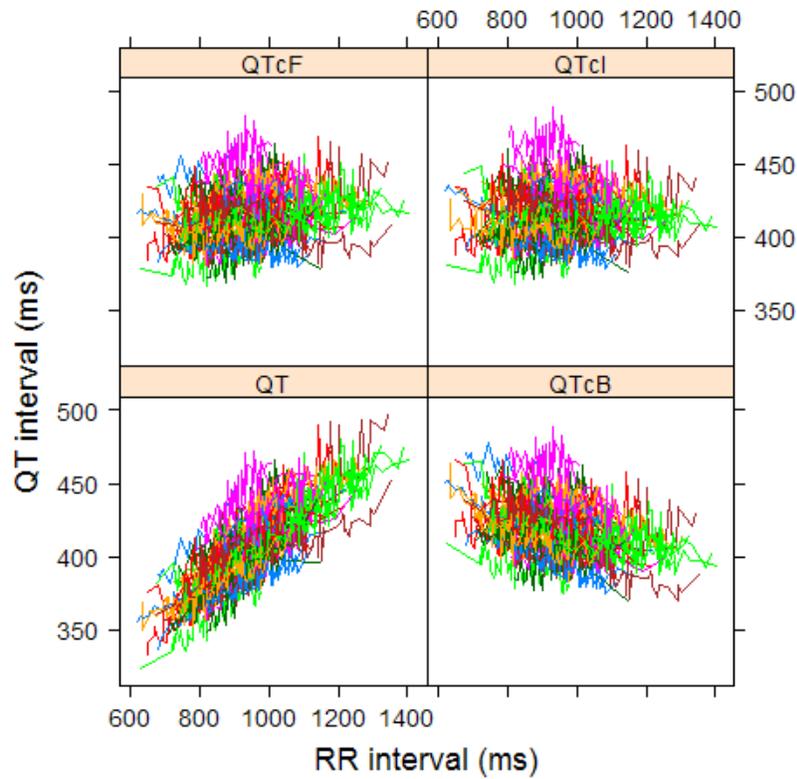
QTcB usually overcorrect, we confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 7, it also appears that QTcF is the better correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	Treatment									
	INCB018424 200 mg		INCB018424 25 mg		Moxifloxacin 400 mg		Placebo		All	
Method	N	MSSS	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	48	0.0050	47	0.0029	48	0.0037	49	0.0037	50	0.0030
QTcF	48	0.0033	47	0.0020	48	0.0052	49	0.0021	50	0.0020

The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for INCB018424

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes time point, sequence, and period as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 8: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = INCB018424 25 mg

	INCB018424 25 mg Δ QTcF	Placebo Δ QTcF	$\Delta\Delta$ QTcF	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-0.9	-0.1	-0.8	(-3.4, 1.8)
1	-1.4	-0.5	-0.9	(-3.4, 1.5)
1.5	-0.3	-0.3	0.0	(-2.3, 2.3)
2	-0.2	-1.5	1.3	(-1.0, 3.6)
2.5	1.6	1.2	0.4	(-1.9, 2.6)
3	1.1	0.6	0.5	(-2.3, 3.3)
4	-5.8	-5.6	-0.2	(-2.5, 2.1)
6	-9.8	-9.7	-0.1	(-2.3, 2.1)
8	-5.9	-5.9	0.0	(-2.1, 2.2)
12	-6.7	-7.3	0.6	(-1.7, 2.8)
16	1.0	0.5	0.5	(-1.7, 2.7)
24	-2.6	-4.8	2.2	(-0.5, 4.9)

Table 9: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = INCB018424 200 mg

	INCB018424 200 mg Δ QTcF	Placebo Δ QTcF	$\Delta\Delta$ QTcF	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-3.2	-0.1	-3.1	(-5.7, -0.6)
1	-4.4	-0.5	-3.9	(-6.3, -1.5)
1.5	-2.3	-0.3	-1.9	(-4.2, 0.4)
2	-3.1	-1.5	-1.6	(-3.9, 0.7)
2.5	-0.7	1.2	-1.9	(-4.1, 0.4)
3	1.2	0.6	0.6	(-2.2, 3.4)
4	-5.7	-5.6	-0.0	(-2.4, 2.3)
6	-9.5	-9.7	0.2	(-2.0, 2.4)
8	-4.9	-5.9	1.0	(-1.1, 3.2)
12	-5.1	-7.3	2.2	(-0.0, 4.4)
16	2.1	0.5	1.6	(-0.6, 3.8)
24	-4.6	-4.8	0.2	(-2.5, 2.9)

The largest upper bounds of the 2-sided 90% CI for the mean difference between INCB018424 25 mg and placebo, and between INCB018424 25 mg and placebo were 4.9 ms and 4.4 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in following table. The largest unadjusted 90% lower confidence interval is 8.1 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.4 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 10: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = Moxifloxacin 400 mg

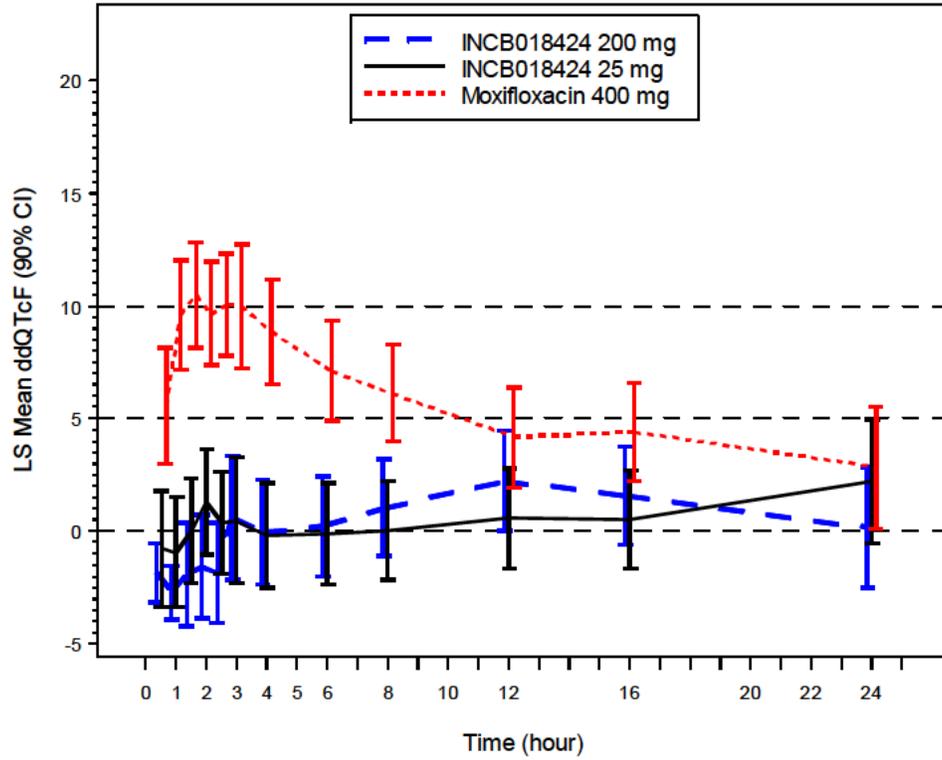
	Moxifloxacin 400 mg Δ QTcF	Placebo Δ QTcF	$\Delta\Delta$ QTcF	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	5.5	-0.1	5.6	(2.2, 8.9)
1	9.1	-0.5	9.6	(6.5, 12.7)
1.5	10.1	-0.3	10.4	(7.4, 13.5)
2	8.2	-1.5	9.6	(6.6, 12.6)
2.5	11.3	1.2	10.1	(7.1, 13.0)
3	10.6	0.6	10.0	(6.4, 13.6)
4	3.2	-5.6	8.8	(5.8, 11.8)
6	-2.6	-9.7	7.1	(4.2, 10.0)
8	0.2	-5.9	6.1	(3.3, 8.9)
12	-3.1	-7.3	4.2	(1.3, 7.0)
16	4.9	0.5	4.4	(1.6, 7.2)
24	-1.9	-4.8	2.8	(-0.7, 6.3)

* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 4: Mean and 90% CI $\Delta\Delta Q_{TcF}$ Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms and above 480 ms. No subject's QTcF was above 500 ms.

Table 11: Categorical Analysis for QTcF

Treatment Group	Total N		Value \leq 450 ms		450 ms<Value \leq 480 ms		480 ms<Value \leq 500 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	50	2272	48 (96.0%)	2200 (96.8%)	2 (4.0%)	72 (3.2%)	0 (0.0%)	0 (0.0%)
INCB018424 200 mg	48	575	45 (93.8%)	561 (97.6%)	3 (6.3%)	14 (2.4%)	0 (0.0%)	0 (0.0%)
INCB018424 25 mg	47	562	45 (95.7%)	556 (98.9%)	2 (4.3%)	6 (1.1%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	48	571	39 (81.3%)	529 (92.6%)	8 (16.7%)	41 (7.2%)	1 (2.1%)	1 (0.2%)
Placebo	49	586	46 (93.9%)	575 (98.1%)	3 (6.1%)	11 (1.9%)	0 (0.0%)	0 (0.0%)

Table 12 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 12: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Value \leq 30 ms		30 ms<Value \leq 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
INCB018424 200 mg	48	575	47 (97.9%)	572 (99.5%)	1 (2.1%)	3 (0.5%)
INCB018424 25 mg	47	562	47 (100%)	562 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	48	571	47 (97.9%)	570 (99.8%)	1 (2.1%)	1 (0.2%)
Placebo	47	564	46 (97.9%)	563 (99.8%)	1 (2.1%)	1 (0.2%)

5.2.2 HR Analysis

The same statistical analysis was performed based on heart rate. The point estimates and the 90% confidence intervals are presented in Table 13 and Table 14. The largest upper limits of 90% CI for the HR mean differences between INCB018424 25 mg and placebo and INCB018424 200 mg and placebo are 2.3 bpm and 4.9 bpm, respectively.

Table 13: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group = INCB018424 25 mg

Time/(hr)	INCB018424 25 mg Δ HR	Placebo Δ HR	$\Delta\Delta$ HR	
	Mean (bpm)	Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0.5	-1.6	-2.5	0.9	(-0.2, 2.1)
1	-1.1	-1.9	0.8	(-0.4, 1.9)
1.5	-2.3	-3.2	0.9	(-0.2, 2.0)
2	-0.7	-1.7	1.0	(-0.2, 2.1)
2.5	-2.2	-2.7	0.6	(-0.5, 1.6)
3	-0.9	-1.2	0.3	(-0.9, 1.5)
4	6.9	7.8	-0.9	(-2.2, 0.5)
6	7.4	8.2	-0.8	(-2.3, 0.8)
8	2.1	2.7	-0.6	(-2.0, 0.7)
12	8.5	8.0	0.5	(-1.0, 2.0)
16	-1.0	-1.8	0.8	(-0.7, 2.3)
24	3.3	2.6	0.7	(-0.7, 2.2)

Table 14: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group = INCB018424 200 mg

Time/(hr)	INCB018424 200 mg Δ HR	Placebo Δ HR	$\Delta\Delta$ HR	
	Mean (bpm)	Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0.5	-0.2	-2.5	2.3	(1.2, 3.5)
1	1.4	-1.9	3.2	(2.1, 4.3)
1.5	0.6	-3.2	3.8	(2.7, 4.9)
2	1.9	-1.7	3.6	(2.4, 4.7)
2.5	-0.2	-2.7	2.5	(1.5, 3.6)
3	1.2	-1.2	2.4	(1.3, 3.6)
4	7.6	7.8	-0.2	(-1.5, 1.1)
6	7.4	8.2	-0.7	(-2.3, 0.8)
8	2.5	2.7	-0.2	(-1.6, 1.1)
12	8.5	8.0	0.5	(-1.0, 2.0)
16	-1.4	-1.8	0.4	(-1.1, 1.9)
24	2.7	2.6	0.1	(-1.3, 1.6)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 15 and Table 16. The largest upper limits of 90% CI for the PR mean differences between INCB018424 25 mg and placebo and INCB018424 200 mg and placebo are 4.6 ms and 6.1 ms, respectively.

The categorical analysis results for PR are presented in Table 17.

**Table 15: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = INCB018424
25 mg**

	INCB018424 25 mg ΔPR	Placebo Δ PR	$\Delta\Delta$ PR	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	1.8	1.0	0.8	(-1.1, 2.7)
1	2.7	0.0	2.7	(0.9, 4.4)
1.5	2.0	-0.4	2.4	(0.3, 4.6)
2	1.4	-0.3	1.7	(-0.4, 3.8)
2.5	1.2	-1.2	2.4	(0.4, 4.4)
3	1.5	-1.2	2.6	(0.6, 4.6)
4	-0.9	-0.8	-0.1	(-2.0, 1.8)
6	-4.1	-4.7	0.5	(-1.2, 2.3)
8	-3.2	-4.4	1.2	(-0.8, 3.2)
12	-1.0	-1.8	0.8	(-1.0, 2.7)
16	2.8	1.4	1.4	(-0.7, 3.6)
24	0.0	-1.5	1.5	(-0.7, 3.8)

**Table 16: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = INCB018424
200 mg**

	INCB018424 200 mg Δ PR	Placebo Δ PR	$\Delta\Delta$ PR	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	3.6	1.0	2.6	(0.7, 4.5)
1	4.3	0.0	4.2	(2.5, 6.0)
1.5	3.6	-0.4	4.0	(1.9, 6.1)
2	2.8	-0.3	3.1	(1.0, 5.2)
2.5	2.1	-1.2	3.3	(1.3, 5.3)
3	2.3	-1.2	3.5	(1.5, 5.5)
4	-2.1	-0.8	-1.3	(-3.2, 0.6)
6	-5.3	-4.7	-0.7	(-2.4, 1.1)
8	-4.1	-4.4	0.3	(-1.7, 2.3)
12	-2.5	-1.8	-0.7	(-2.5, 1.2)
16	2.7	1.4	1.3	(-0.8, 3.5)
24	0.9	-1.5	2.4	(0.2, 4.6)

Table 17: Categorical Analysis for PR

Treatment Group	Total		Value≤200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	50	2272	48 (96.0%)	2200 (96.8%)	2 (4.0%)	72 (3.2%)
INCB018424 200 mg	48	575	47 (97.9%)	567 (98.6%)	1 (2.1%)	8 (1.4%)
INCB018424 25 mg	47	562	45 (95.7%)	547 (97.3%)	2 (4.3%)	15 (2.7%)
Moxifloxacin 400 mg	48	571	45 (93.8%)	558 (97.7%)	3 (6.3%)	13 (2.3%)
Placebo	49	586	47 (95.9%)	574 (98.0%)	2 (4.1%)	12 (2.0%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 18 and Table 19. The largest upper limits of 90% CI for the PR mean differences between INCB018424 25 mg and placebo and INCB018424 200 mg and placebo are 2.6 ms and 3.2 ms, respectively. There are no subjects who experienced QRS interval greater than 110 ms in both treatment groups.

Table 18: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = INCB018424 25 mg

	INCB018424 25 mg Δ QRS	Placebo Δ QRS	$\Delta\Delta$ QRS	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	0.1	-0.3	0.4	(-0.4, 1.1)
1	-0.4	-0.7	0.3	(-0.6, 1.2)
1.5	0.0	-0.6	0.6	(-0.3, 1.5)
2	0.3	-0.8	1.1	(0.2, 1.9)
2.5	-0.4	-0.8	0.4	(-0.5, 1.4)
3	-0.6	-0.8	0.2	(-0.7, 1.1)
4	1.1	0.9	0.1	(-0.7, 0.9)
6	-0.6	-1.7	1.0	(0.1, 2.0)
8	-0.4	-0.9	0.4	(-0.6, 1.4)
12	0.3	-1.4	1.6	(0.7, 2.6)
16	1.4	0.4	1.0	(-0.2, 2.1)
24	-0.7	-0.8	0.1	(-0.8, 1.1)

Table 19: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = INCB018424 200 mg

	INCB018424 200 mg Δ QRS	Placebo Δ QRS	$\Delta\Delta$ QRS	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-0.1	-0.3	0.2	(-0.5, 1.0)
1	-0.3	-0.7	0.4	(-0.5, 1.3)
1.5	-0.7	-0.6	-0.1	(-1.0, 0.7)
2	-0.8	-0.8	-0.0	(-0.9, 0.8)
2.5	-0.1	-0.8	0.8	(-0.2, 1.8)
3	-0.0	-0.8	0.7	(-0.2, 1.6)
4	1.6	0.9	0.7	(-0.1, 1.5)
6	-0.2	-1.7	1.4	(0.5, 2.4)
8	-0.0	-0.9	0.8	(-0.2, 1.8)
12	0.9	-1.4	2.2	(1.3, 3.2)
16	1.3	0.4	0.9	(-0.2, 2.0)
24	-0.1	-0.8	0.7	(-0.2, 1.7)

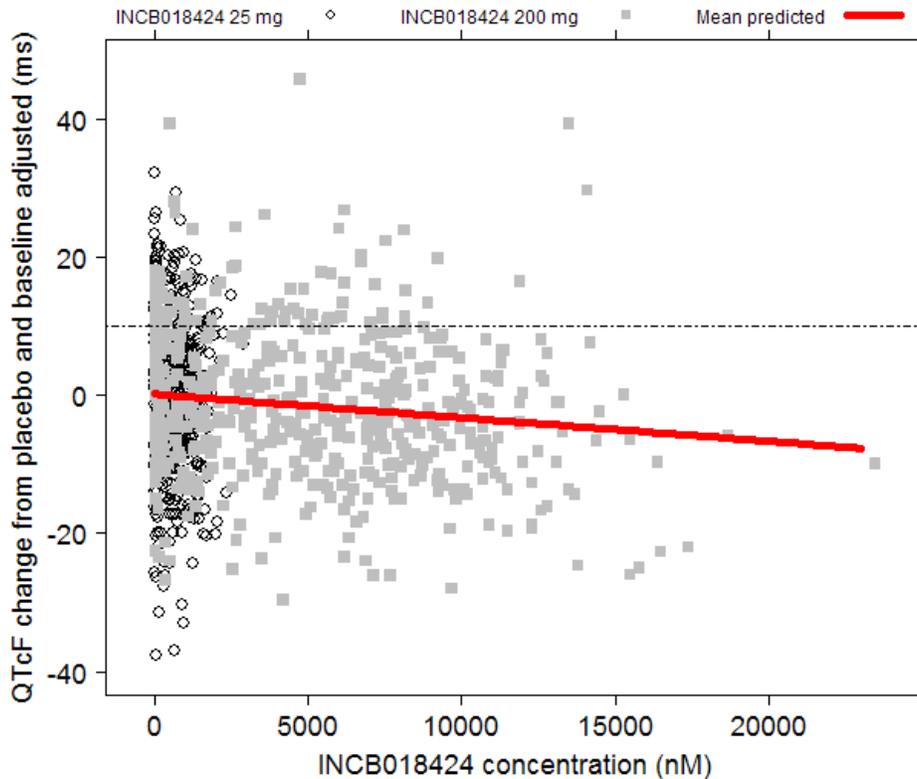
Table 20: Categorical Analysis for QRS

Treatment Group	Total		Value≤100 ms		100 ms<Value≤110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	50	2272	45 (90.0%)	2164 (95.2%)	5 (10.0%)	108 (4.8%)
INCB018424 200 mg	48	575	42 (87.5%)	540 (93.9%)	6 (12.5%)	35 (6.1%)
INCB018424 25 mg	47	562	43 (91.5%)	534 (95.0%)	4 (8.5%)	28 (5.0%)
Moxifloxacin 400 mg	48	571	45 (93.8%)	546 (95.6%)	3 (6.3%)	25 (4.4%)
Placebo	49	586	45 (91.8%)	570 (97.3%)	4 (8.2%)	16 (2.7%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The exposure-response relationship between $\Delta\Delta\text{QTcF}$ and INCB018424 concentrations is visualized in Figure 5 with no evident increase in $\Delta\Delta\text{QTcF}$ with increasing exposure of INCB018424.

Figure 5: $\Delta\Delta$ QTcF vs. INCB018424 Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. According to ECG warehouse statistics less than 1.5% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Two subjects had a PR slightly >200 ms at baseline.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology

Therapeutic dose	10 - 25 mg BID	
Maximum tolerated dose	25 mg BID or 100 mg QD for multiple dosing 200 mg as single dose (highest single dose tested) was well tolerated.	
Principal adverse events	Reversible thrombocytopenia Reversible leukopenia	
Maximum dose tested	Single Dose	200 mg
	Multiple Dose	50 mg BID or 100 mg QD in healthy volunteers 50 mg BID or 200 mg QD in myelofibrosis patients
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean C_{max} = 7.10 μ M (CV% = 19%) Mean $AUC_{0-\infty}$ = 30.7 μ M*h (CV% = 8.6%)
	Multiple Dose	Mean C_{max} : 4.89 μ M (CV% = 22%) for 100 mg QD 2.71 μ M (CV% = 36%) for 50 mg BID Mean AUC_{0-24h} : 17.1 μ M*h (CV% = 27%) for 100 mg QD 17.0 μ M*h (CV% = 31%) for 50 mg BID
Range of linear PK	5 - 200 mg, oral	
Accumulation at steady state	BID doses, Mean $AUC_{0-\tau}$ accumulation = 9.0% (CV% = 6.4%) QD dose, no $AUC_{0-\tau}$ accumulation observed	
Metabolites	<p>Parent compound is the predominant entity in circulation. The mean plasma C_{max} and AUC values for total radioactivity (INCB018424 + metabolites) were ~ 2-fold higher than for INCB018424, suggesting metabolites represent ~ 50% of the circulating drug-related material. Two hydroxylated metabolites in plasma (INCB027598 and INCB025264) were identified as the major metabolites (30% and 14% of parent based on AUC_{0-24}). Other INCB018424-related peaks were < 10% of INCB018424 levels and consisted of mono- and di-hydroxylated and ketone metabolites. Further work to investigate minor metabolites in human plasma is ongoing.</p> <p>The table below shows the activity (IC_{50} values) for the major circulating metabolites in JAK1, 2 and 3 enzyme assays, as well as cell-based assays measuring IL-6 induced proliferation in INA-6 cells (INA6) and IL6 induced</p>	

Metabolites (Cont'd)	STAT3 phosphorylation in human whole blood (hWBA Stat3p). To quantify the pharmacodynamic contribution of parent AND all the active metabolites in circulation, a whole blood pStat3 assay has been established and was used to characterize the single and multiple dose pharmacodynamics of INCB018424.						
		% parent (based on AUC)	JAK1 (nM)	JAK2 (nM)	JAK3 (nM)	INA6 (μ M)	hWBA Stat3p (μ M)
	INCB018424	100	1.9	0.4	6.3	0.2	0.28
	INCB025264 (M16)	14	12	2.5	31	1.1	0.23
INCB027598 (M18)	30	15	2.8	29	1.0	1.5	
Absorption	Absolute/Relative Bioavailability	INCB018424 has characteristics of BCS Class I compound (high solubility and high permeability) with an estimated 95% of orally administered dose absorbed. A formal relative bioavailability study has not been conducted. The mean pharmacokinetic parameters following single oral dose of 25 mg INCB018424 solution in sterile water (study INCB 18424-134, a mass balance and metabolite profile study) were generally similar to that observed with 25 mg tablets (Study INCB 18424-131, a single dose study in healthy volunteers). Results from these two separate clinical studies indicate INCB018424 tablets exhibit near-complete relative oral bioavailability.					
	T _{max}	<ul style="list-style-type: none"> • Parent - Median T_{max} 1.5 h (range 0.5 - 6.0 h) • Metabolites – Median T_{max} 2.0 h (range 1.0 - 6.0 h) 					
Distribution	Vd/F or Vd	Mean Vd/F = 90 L (CV% = 29%)					
	% bound	Mean % bound 96.7% (CV% = 18%)					
Elimination	Route	<ul style="list-style-type: none"> • Primary route is metabolic biotransformation (\geq 95% of dose). 73.61 \pm 10.18% and 21.92 \pm 5.95% of drug-related material excreted in urine and feces, respectively • Excretion of parent drug in urine and feces combined contribute to < 1% of dose 					
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean t_{1/2} 3.2 h (CV% = 28%) • After a single oral dose of ¹⁴C-INCB018424, the terminal half-life of total drug-related material in plasma (INCB018424 + metabolites) was 5.8 h (CV = 13%). No plasma metabolites observed after 12 h post-dose. 					
	CL/F or CL	Mean Cl/F = 20.5 L/h (CV% = 31%)					

Intrinsic Factors	Clinical pharmacology studies to specifically evaluate the role of these intrinsic factors have not been conducted. However, covariate analysis was performed using data from Phase 1 studies and the results are summarized below.	
	Age	Age had no significant effect on INCB018424 PK in the range of 18 to 54 years old.
	Sex	No significant difference in PK parameters was observed between male and female subjects after the PK parameters were normalized to body weight.
	Race	No significant difference in PK observed between African-Americans and Caucasians. The ratios (90% CI) of dose normalized exposures between African-Americans and Caucasians were 1.13 (1.00, 1.27) for $AUC_{0-\infty}$ and 0.91 (0.79, 1.05) for C_{max} .
Extrinsic Factors	Hepatic & Renal Impairment	<p>A PK study in hepatic function impaired subjects (Study INCB 18424-137) is underway and will be completed by the end of 2009.</p> <p>A study was conducted in patients with varying degrees of renal impairment (Study INCB 18424-142) and the preliminary data indicates that INCB018424 C_{max} and AUC were essentially unchanged ranging from 79-116% and 93-122%, respectively, as compared to the corresponding values observed in normal healthy subjects.</p>
	Drug interactions	<ol style="list-style-type: none"> 1. Study INCB 18424-133, DDI with potent and moderate CYP3A4 inhibitors: mean increase in INCB018424 C_{max} and AUC was 32% and 91%, respectively, with the coadministration of ketoconazole, and mean increase in INCB018424 C_{max} and AUC was 8.0% and 27%, respectively, with the coadministration of erythromycin. 2. Study INCB 18424-135, DDI with potent CYP3A4 inducer: mean reduction in INCB018424 C_{max} and AUC was 52% and 71%, respectively, following the pretreatment of rifampin. There was no clinically relevant effect on pharmacodynamic activity (IL-6 induced STAT3 phosphorylation) likely secondary to a concomitant increase in active metabolites. 3. Study INCB 18424-136, DDI with methotrexate: mean increase in both INCB018424 C_{max} and AUC was 8% ($p>0.05$), with the coadministration of methotrexate, not felt to be

Extrinsic Factors (Cont'd)	Drug interactions (Cont'd)	clinically significant. No significant change in the pharmacokinetics of methotrexate and 7-hydroxy methotrexate following administration of INCB018424.
	Food Effects	Administration with high-fat meal moderately decreased INCB018424 mean C_{max} by 24% and slightly increased INCB018424 mean AUC by 4%.
Expected High Clinical Exposure Scenario	The worst case scenario is in the setting of concomitant use of potent CYP3A4 inhibitors. Co-administration of INCB018424 with ketoconazole, a potent CYP3A4 inhibitor, caused a 1.3-fold increase in maximum plasma INCB018424 concentrations and 1.9-fold increase in INCB018424 exposure (ie, AUC). Thus the C_{max} for a 25 mg BID dose in the presence of a potent CYP3A4 inhibitor would be 1.56 μ M, compared with 7.10 μ M for the 200 mg single dose proposed in the TQT Study INCB 18424-138. The AUC for a 25 mg BID dose in the presence of a potent CYP3A4 inhibitor would be 17.2 μ M*h, compared with 30.7 μ M*h for the 200 mg single dose proposed in Study INCB 18424-138. Therefore, with concomitant dosing of potent CYP inhibitors such as ketoconazole, a dose reduction of ~ 50% for INCB018424 is warranted.	

6.2 SCHEDULE OF TREATMENT ASSESSMENTS

Assessment	Screening Phase	Treatment Phase (Periods 1, 2, 3, and 4)			End-of-Treatment/ CRU Discharge	Follow-up or Early Termination
	Visit Day (Range): Day -28 to -2	Check-in Days -1, 7, 14, and 21	Days 1, 8, 15, and 22	Days 2, 9, 16, and 23	Days 2, 9, 16, and 23	Day 36 ± 3
Informed consent	X					
Inclusion/exclusion criteria	X	X ^a				
Medical history	X					
Prior/concomitant medications	X	X	X	X	X	X
Height and body weight	X					
Comprehensive physical examination	X				X	X
Targeted physical assessment		X	X			
Vital signs ^b	X	X	X	X		X
Clinical safety laboratories ^c	X	X		X		X
Urinalysis ^c	X					X
Hepatitis and HIV screen ^c	X					
FSH (postmenopausal females only) ^c	X					
Pregnancy test (female subjects only) ^c	X	X				X
Drug screen ^d	X	X				
12-lead electrocardiograms ^e	X	X				X
Holter monitoring ^e			X	X		
Confined to CRU ^f		X	X	X		
Discharge from CRU					X	
Randomization ^g			X ^a			
Study medication dosing ^h			X			
Plasma pharmacokinetic sampling ⁱ			X	X		
Adverse event assessment ^j	X	X	X	X	X	X

^a Only for Period 1.

^b Vital signs (oral temperature; heart rate; respiratory rate; and automated, seated blood pressure and pulse) were obtained at screening; check-in; and on Day 1 prior to dosing and at approximately 1, 2, 3, 6, and 24 hours post-dose for each dosing period.

^c See [Appendix 2 of the Protocol](#) for a list of laboratory analytes. A serum pregnancy test was obtained at screening and follow-up/ET. A urine pregnancy test was obtained at check-in for each dosing period.

^d See [Appendix 2 of the Protocol](#) for a list of drugs-of-abuse. Alcohol screen was not included at screening. Alcohol screen was included at check-in for each dosing period.

^e Standard ECGs were performed at screening, check-in for each dosing period, and follow-up. Triplicate 12-lead ECG readings were obtained from 12-lead Holter monitors predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours post-dose for each dosing period. On Day 1 only, triplicate 12-lead ECG readings were obtained from 12-lead Holter monitors at 90, 60, and 30 minutes prior to dosing.

^f Subjects were admitted to the CRU on the day prior to dosing for Periods 1, 2, 3, and 4, then discharged the day after dosing.

^g Study drug randomization occurred on Day 1 or Day -1 consistent with site procedures for Period 1 only.

^h Study drug was administered according to the randomization schedule.

ⁱ Blood samples for PK analysis were collected predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours post-dose (after ECG readings from Holter monitors were completed).

^j Adverse events were assessed at least when vital signs were taken.

Abbreviations: CRU=clinical research unit; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus.

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/s/

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DSI CONSULT: Request for Clinical Inspections

Date: June 14, 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Lauren Iacono-Connors, Acting Team Leader
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Albert Deisseroth, MD, Clinical Reviewer, Division of Hematology Products
Ann Farrell, MD, Acting Director, Division of Hematology Products

From: Amy Baird, Regulatory Product Manager, Division of Hematology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 202192

Applicant/ Applicant contact information (to include phone/email): Incyte Corporation
Ronald Falcone, PhD
VP, Regulatory Affairs
Rt 141 & Henry Clay Road
E336
Wilmington, DE 19880-0336
Tele: 302-498-6846
Email: rfalcone@incyte.com

Drug Proprietary Name: Ruxolitinib Phosphate Tablets

NME or Original BLA (Yes/No): NME

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

PDUFA: 12/3/11

Action Goal Date: 10/4/11

Inspection Summary Goal Date: 8/22/11

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
<p>Stanford Cancer Center 875 Blake Wilbur Drive, Clinic C Stanford, CA 95405</p> <p>PI: Jason Gotlib, MD, MS TEL: 650-736-1253 FAX: (650)724-5203 EMAIL:jason.gotlib@stanford.edu</p>	<p>INCB 18424-351</p>	<p>15</p>	<p>Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis</p>
<p>St. Agnes Health Care, Inc. 900 Caton Avenue Baltimore, MD 21229</p> <p>PI: Carole B. Miller, MD TEL: 410-369-2090 FAX: (410) 368-3517 EMAIL: cmiller@stagnes.org</p>	<p>INCB 18424-351</p>	<p>8</p>	<p>Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis</p>

III. Site Selection/Rationale

Proposal for DSI Inspections for NDA 202192

There are two randomized phase III trials:

- a. INCB 18424-351 (Conducted in the USA, Canada and Australia)
- b. CINC424A2352 (Conducted in Europe)

In the US trial, INCB 18424-351, 309 patients were entered and randomized in 89 sites:

- USA entered 237 patients in 68 sites
- Canada entered 24 patients in 6 sites
- Australia entered 48 patients in 48 sites

I am proposing a site visit at Site #23, because it was the top of all the clinical sites for accrual at an academic center, and a site visit at Site #46, because it was the third highest accruing center and appears to be a proprietary health care facility.

Site#	Name of PI	Institution	Number of Patients
023	Jason Gotlib	Stanford U Stanford, CA	15
046	Carole Miller	St. Agnes Health Care, Inc. Baltimore, MD	8

Rationale for DSI Audits

For the US phase III trial, I am proposing a site visit at Site #23, because it was the top of all the clinical sites for accrual at an academic center, and a site visit at Site #46, because it was the third highest accruing center and appears to be a proprietary health care facility.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

Page 4-Request for Clinical Inspections

Should you require any additional information, please contact Amy Baird, Regulatory Project Manager, at 301-796-4969 or Albert Deisseroth, MD, Clinical Reviewer, at 301-796-4864.

Concurrence: (as needed)

_____ Medical Reviewer
_____ Division Director

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/s/

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06/16/2011

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06/20/2011

ALBERT B DEISSEROTH
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