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APPLICATION NUMBER:

208712Orig1s000

INTEGRATED REVIEW

NDA 208712
Vonjo (pacritinib)

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	208712
Priority or standard	Priority
Submit date(s)	3/30/2021
Received date(s)	3/30/2021
PDUFA goal date	11/30/2021
Division/office	Division of Nonmalignant Hematology (DNH)
Review completion date	Click or tap to enter a date.
Established/proper name	pacritinib
(Proposed) proprietary name	Vonjo
Pharmacologic class	Kinase Inhibitor
Code name	N/A
Applicant	CTI BioPharma Corp
Dosage form(s)/formulation(s)	Capsules
Dosing regimen	Oral twice daily (BID)
Applicant proposed indication(s)/ population(s)	Treatment of adult patients with intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)
Proposed SNOMED indication	Treatment of adult patients with intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)
Regulatory action	Accelerated approval
Approved dosage (if applicable)	200 mg administered orally (b) (4)
Approved indication(s)/ population(s) (if applicable)	Treatment of adults with intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with thrombocytopenia with a baseline platelet count of $<50\times10^9$/L
Approved SNOMED term for indication (if applicable)	Myelofibrosis

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NDA 208712
Vonjo (pacritinib)

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Glossary

AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BAT	best available therapy
BCRP	breast cancer resistance protein
BID	twice daily
BSEP	bile salt export pump
CI	confidence interval
C_{max}	maximum concentration
CT	computerized tomography
CV	coefficient of variation
DDI	drug-drug interaction
DIPSS	Dynamic International Prognostic Scoring System
EC_{50}	half maximal effective concentration
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
FMI	final market image
GFP	green fluorescent protein
GI	gastrointestinal
HD	high dose
HED	human equivalent dose
HPLC	high-performance liquid chromatography
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration
IND	investigational new drug
ITT	intent-to-treat
JAK	Janus-associated kinase
LD	low dose
MACE	major adverse cardiac events
MAXD	maximum decrease
MD	mid dose
MF	myelofibrosis
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
MRI	magnetic resonance imaging
mTSS	modified total symptom score
NDA	new drug application
NOAEL	no observed adverse effect level
OFV	objective function value
OS	overall survival

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PBPK	physiological based pharmacokinetic
PD	pharmacodynamic
PET	post-essential thrombocythemia
PI	prediction intervals
PK	pharmacokinetic
PKPD	pharmacokinetic-pharmacodynamic
PMF	primary myelofibrosis
PMR	postmarketing requirement
po	per oral
PPI	proton pump inhibitor
PPV	post-polycythemia vera
P3CT	Phase 3 clinical trial
QD	once daily
RBC	red blood cell
STAT	signal transducers and activators of transcription
SPV	spleen volume
SPVr	spleen volume responder
SVR	spleen volume reduction
TDI	time dependent inhibition
T_{max}	time to maximum concentration
TSS	total symptom score
ULN	upper limit of normal
VPC	visual predictive check

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I. Executive Summary

1. Summary of Regulatory Action

The Applicant, CTI BioPharma Corp, submitted this New Drug Application (NDA) for pacritinib (proposed tradename Vonjo), an inhibitor of Janus-associated kinase 2 (JAK2) and Fms-like receptor tyrosine kinase 3 (FLT3), for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) who have platelet counts below 50,000/µL. The proposed dose is 200 mg orally twice daily.

MF is a myeloproliferative neoplasm characterized by abnormal bone marrow function that can result in bone marrow fibrosis, extramedullary production of blood cells in the spleen and associated splenomegaly, and constitutional symptoms and signs such as weight loss, early satiety, pruritis, night sweats, bone pain, and cachexia. Patients with MF have an increased risk of progression to acute myelogenous leukemia.

There is substantial evidence of effectiveness of pacritinib 200 mg BID on spleen volume reduction (SVR) compared to best available therapy (off-label treatments or no treatment) in patients with intermediate or high-risk MF and baseline platelet counts below 50,000/µL. This finding is based on evidence from PERSIST-2, an adequate and well-controlled trial as well as confirmatory evidence from a Phase 2 dose-finding study (PAC203) and PERSIST-1, a study that evaluated the same total daily dose of pacritinib on SVR but as 400 mg QD, as well as an expectation that the extent of spleen volume reduction seen in the trial would not occur spontaneously over 6 months in patients with intermediate and high-risk MF.

Currently, there are no drugs approved for patients with intermediate or high-risk MF who have platelet counts below 50,000/µL. The two approved drugs for MF, ruxolitinib and fedratinib, were both studied in patients with higher baseline platelet counts and can further lower the level of platelets. The approved labeling for both drugs only provide dosing recommendations for initiating therapy in patients with baseline platelet counts of at least 50,000/µL. In addition, ruxolitinib's labeling states to interrupt dosing for platelet counts less than 50,000/µL, and fedratinib's labeling states to interrupt dosing for grade 4 thrombocytopenia (platelet count <25,000/µL) or grade 3 thrombocytopenia (platelet count 25,000 to 50,000/µL) with active bleeding. Therefore, there is a significant unmet medical need for an effective therapy for patients with MF and platelet counts below 50×10^9/L.

Pacritinib has shown a compelling effect on SVR but has not shown a compelling effect on a clinical outcome that directly assesses how a patient feels, functions, or survives. However, the findings on SVR are reasonably likely to predict an improvement in the signs and symptoms of MF assessed using the modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (mTSS), a clinical outcome assessment used together with SVR for traditional approval of MF therapies. Therefore, given the lack of drugs that are FDA-approved for intermediate and high-risk MF in patients with platelet counts below 50,000/µL, a serious and life-threatening disease with unmet need, and the compelling findings of pacritinib in this population on SVR, we conclude that pacritinib should receive accelerated approval for this use.

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These benefits outweigh the risks (which include diarrhea, thrombocytopenia and bleeding that may require dose modifications or interruptions, prolonged QTc interval, and potential risks associated with other members in the JAK inhibitor class), when pacritinib is used according to the labeling. The ongoing PACIFICA trial will be required to verify and describe the clinical benefit of pacritinib on mTSS.

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2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Myelofibrosis (MF) is a rare disorder of the hematopoietic cells that can lead to anemia, thrombocytopenia, and splenomegaly. • Thrombocytopenia in patients with MF appears to be associated with poorer patient survival. • Patients experience pain, fatigue, bleeding, and other symptoms (pruritis, night sweats, early satiety, bone pain), which can be significant and debilitating. • As the disease progresses it can become more debilitating and can be fatal at late stages.	Myelofibrosis is a rare disorder of abnormal maturation of the blood cells with serious clinical complications (anemia, thrombocytopenia, splenomegaly) and significant-debilitating symptoms. The disease can be fatal at later stages.

Current treatment options	• There are two drugs approved for MF, ruxolitinib and fedratinib, both Janus-associated kinase (JAK) 2 inhibitors.
	  – Both drugs are indicated for intermediate and high-risk disease.
	  – Both drugs can lower platelet counts, further increasing the risk for thrombocytopenia and bleeding in this patient population predisposed to thrombocytopenia. The approved labeling for both drugs only provides dosing recommendations for initiating therapy in patients with baseline platelet counts of at least 50,000/µL. Ruxolitinib's labeling states to interrupt dosing for platelet counts less than 50,000/µL, and fedratinib's labeling states to interrupt dosing for grade 4 thrombocytopenia or grade 3 thrombocytopenia (platelet count 25,000-50,000/µL) with active bleeding.
		Effective treatments are available for MF, but approved therapies can further lower platelet counts, are not labeled for initiation in patients with platelet counts below 50,000/µL and require dosing interruption and modification for patients who develop platelet counts below 50,000/µL while on treatment.
		There is a significant unmet medical need for MF patients with platelet counts below 50,000/µL.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– Fedratinib also has a risk for Wernicke encephalopathy, which can be severe and fatal, but this risk may be reduced through close monitoring and thiamine repletion. • Other treatment options include (1) bone marrow transplantation, which can be curative but not all patients are eligible, and the procedure has significant morbidity and mortality, (2) splenectomy, and (3) off-label therapies such as hydroxyurea, glucocorticoids, and erythropoietic agents.	
Benefit	• In the PERSIST-2 trial, after 24 weeks of therapy, spleen volume reduction (SVR) of ≥35%, as assessed on MRI or CT scan, was achieved in 21.6% of pacritinib 200 mg BID-treated patients compared to 2.8% of best available therapy (BAT)-treated patients (p<0.001). Similarly, in the subgroup of patients with baseline platelet counts below 50,000/µL, 29.0% of pacritinib 200 mg BID-treated patients and 3.1% of BAT-treated patients achieved SVR ≥35% (p<0.01). • After 24 weeks of therapy, pacritinib did not provide compelling evidence of effectiveness on the Total Symptom Score (TSS), a clinical outcome assessment of signs and symptoms of MF, when compared with BAT (p=0.08). This may be related to an underpowered trial that was discontinued prematurely when the pacritinib program was placed on a clinical hold (the safety issues have since been resolved – see Risk and Risk Management). • SVR ≥35% is reasonably likely to predict clinical benefit on the signs and symptoms of MF assessed using the modified TSS (that excludes fatigue), which together with SVR ≥35% has been used for traditional approval for MF therapies.	Pacritinib 200 mg BID has a compelling effect on SVR, a surrogate endpoint that is reasonably likely to predict clinical benefit on the signs and symptoms of MF. Pacritinib has not yet shown a compelling effect on a clinical outcome (a direct measure of how patients feel, function, or survive). The effect of pacritinib on SVR was demonstrated in patients with intermediate or high-risk MF who had baseline platelet counts below 50,000/µL compared to BAT (which includes off-label treatments or a "watch and wait" approach). Therefore, the effect of pacritinib on SVR was shown in a population with a serious and life-threatening disease who do not currently have FDA-approved treatment options. A confirmatory trial (PACIFICA) is underway with coprimary endpoints of SVR and mTSS and will be required to verify and describe the clinical benefit of pacritinib.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	- The most common serious adverse reactions with pacritinib 200 mg BID were anemia (8% versus 3% with BAT), thrombocytopenia (6% versus 2% with BAT), cardiac failure (4% versus 3% with BAT), pyrexia (4% versus 2% with BAT), and squamous cell carcinoma of the skin (3% versus 0% with BAT). - The most common reasons for drug interruption in ≥2% of patients in the pacritinib 200 mg BID group (and at an incidence higher than with BAT) were anemia (5%), thrombocytopenia (4%), diarrhea (3%), nausea (3%), cardiac failure (3%), and neutropenia (2%). - Adverse reactions requiring study drug dosing reduction in ≥2% of patients in the pacritinib 200 mg BID group included thrombocytopenia (2%), neutropenia (2%), conjunctival hemorrhage (2%), and epistaxis (2%), all of which occurred at a slightly higher incidence than with BAT. - The most common adverse reactions with pacritinib 200 mg BID were diarrhea (reported in about 50% of patients), thrombocytopenia, nausea, anemia, and peripheral edema, all of which occurred at a higher incidence with pacritinib 200 mg BID than BAT. - Like the other approved JAK inhibitors for MF, pacritinib has the potential for the same increased risk of lymphoma and other malignancies (excluding non-melanoma skin cancer), thrombosis and MACE associated with tofacitinib, another JAK inhibitor approved for rheumatoid arthritis. These risks were not established in the pacritinib program, but the trials for this rare disease cannot definitively exclude these risks. - Safety analysis of the PERSIST-1 trial that compared pacritinib 400 mg QD to BAT (and an unscheduled interim analysis of the PERSIST-2 trial) identified in the fall and winter of 2015-2016	Key risks associated with pacritinib 200 mg BID include thrombocytopenia, bleeding events, and diarrhea. These risks may be mitigated by close monitoring and dose adjustments. The potential for QTc interval prolongation will be included as a Warning, with recommendations to avoid drugs that can cause QTc prolongation, manage electrolyte abnormalities, and interrupt pacritinib, if needed. Like with the other approved JAK inhibitors for MF, pacritinib will have the same class Warning about the risks of lymphoma and other malignancies, thrombosis and MACE seen with tofacitinib. These risks have not been established with pacritinib 200 mg BID but the trials for this rare disease cannot definitively exclude these serious risks. Because the MACE results appear more favorable for pacritinib 200 mg BID than pacritinib 400 mg QD, the Applicant is seeking approval of the 200 mg BID dosing regimen. Drug-drug interactions can be adequately mitigated with labeling. For the drug-drug interactions and pharmacokinetic effects of hepatic impairment that have not been adequately assessed, labeling will state to avoid such use while awaiting results of required postmarketing trials/studies. The required PACIFICA postmarketing trial for verifying and describing clinical benefit will also further assess the risks of pacritinib 200 mg BID compared to physicians' choice of therapy in patients with MF and platelet counts <50,000/µL.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	a numerical excess of deaths on the pacritinib 400 mg QD arm as compared to BAT. This resulted in a clinical hold for both trials. • An updated analysis of deaths based on all available data and accounting for differences between treatment arms in patient-year exposures show a numerically lower rate of MACE with pacritinib 200 mg BID compared to BAT in PERSIST-2, and a slightly higher rate of MACE with pacritinib 400 mg QD compared to BAT in both PERSIST-1 and PERSIST-2. Pacritinib 400 mg QD has modestly higher systemic exposures and maximal concentrations compared to pacritinib 200 mg BID, but there is significant overlap in exposures between these dosing regimens, such that one would not expect these two regimens to differ substantially with regard to MACE risk. Based on these analyses there is no signal for MACE with pacritinib 200 mg BID. Overall conclusions are limited by the low event rates, particularly for the BAT arms, and because the studies were not designed nor powered to definitively evaluate MACE, and no formal statistical analyses were prospectively planned. • Among the patients with platelet counts <50×10^9/L at baseline in PERSIST-2, overall bleeding events were numerically higher with BAT than pacritinib, with comparable rates of serious hemorrhagic events per 100 patient-years for pacritinib 200 mg BID (28.0) and BAT (26.8), but some patients required dose interruption or discontinuation due to bleeding. • Pacritinib can prolong the QTc interval. For example, 200 mg BID resulted in a maximum mean (90% confidence interval) change in QTcF from baseline of 11 (90% CI 5-17) msec, and there were small imbalances in the percentage of	

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients with QTc prolongation >500 msec or QTc increase from baseline of ≥60 msec. There were no cases of arrhythmia attributed to QTc interval prolongation. • There are known drug-drug interactions (e.g., CYP3A4 inhibitors and inducers can significantly alter pacritinib exposures), but also some potential drug-drug interactions that have not been adequately assessed (e.g., CYP1A2, CYP3A4, CYP2C19, BCRP, OCT1, and P-gp transporters). • The impact of hepatic impairment on pacritinib 200 mg exposures has not been studied.	

2.2. Conclusions Regarding Benefit-Risk

MF is a rare, serious, life-threatening disease. Patients with intermediate or high-risk MF with platelet counts below 50,000/µL lack FDA-approved treatments. The two approved JAK inhibitors for MF, ruxolitinib and fedrotinib, were not tested in patients with baseline platelet counts below 50,000/µL and their approved labeling only provides dosing recommendations for initiating therapy in patients with baseline platelet counts of at least 50,000/µL. Ruxolitinib's labeling states to interrupt dosing for platelet counts less than 50×10^9/L, and the fedratinib labeling states to interrupt dosing for grade 4 thrombocytopenia or for grade 3 thrombocytopenia (platelet count 25,000 to 50,000/µL) with active bleeding. Therefore, there is an unmet medical need for patients with intermediate or high-risk MF with platelet counts below 50,000/µL.

Pacritinib 200 mg BID has a compelling effect on SVR, a surrogate endpoint that is reasonably likely to predict clinical benefit on the signs and symptoms of MF. In the PERSIST-2 trial, after 24 weeks of therapy, spleen volume reduction (SVR) of ≥35%, as assessed on MRI or CT scan, was achieved in 21.6% of pacritinib 200 mg BID-treated patients compared to 2.8% of patients treated with BAT (p<0.001). Similarly, in the subgroup of patients with baseline platelet counts below 50,000/µL, 29.0% of pacritinib 200 mg BID-treated patients and 3.1% of BAT-treated patients achieved SVR ≥35% (p<0.01). However, pacritinib has not yet shown a compelling effect on a direct measure of clinical benefit (i.e., how a patient feels, functions or survives). This may be related to an underpowered trial that was discontinued prematurely when the pacritinib program was placed on a clinical hold due to excess deaths (this safety concern has since been resolved). The Applicant has an ongoing trial (PACIFICA) that is comparing pacritinib 200 mg BID to physician's choice of therapy in patients with MF and platelet counts below 50,000/µL and is using the same clinical outcome assessment used for traditional approval of the other JAK inhibitors for MF.

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Using the definitions in Table 3, Figure 1 shows a relative benefit-risk plot for the pacritinib 200 mg BID and 400 mg QD dosing regimens compared to BAT among patients whose platelet count at baseline was below 50×10^9/L (50,000/μL) in the PERSIST-2 study. The figures show the benefit of pacritinib on SVR and point estimates that favor pacritinib on both the Total Symptom Score (TSS) clinical outcome assessment as well as the exploratory modified TSS used for the other JAK inhibitors approved for MF. The figure also shows that important safety concerns—such as death, cardiovascular AEs, bleeding AEs, thrombotic AEs, anemia, and infection—are not different among the treatment groups, although some of the point estimates favor BAT and these analyses are limited by the small numbers of events. Many of the identified risks with pacritinib are risks with the other JAK inhibitors (e.g., diarrhea with fedratinib, thrombocytopenia and bleeding with both ruxolitinib and fedratinib, class risks based on the findings with tofacitinib for rheumatoid arthritis) and can similarly be adequately mitigated with labeling as was done for those drugs. Labeling would also adequately mitigate pacritinib's other identified risks (e.g., drug-drug interactions, QTc interval prolongation).

One option is to await the results of the ongoing PACIFICA trial and decide whether to grant traditional approval then based on its results. This will delay access to this promising therapy for patients with more advanced MF who lack other FDA-approved treatment options. Use of the accelerated approval pathway is appropriate and intended for situations such as this. Pacritinib is more likely than not expected to show an effect on the signs and symptoms of MF in an adequately designed and powered trial. The statistical miss in PERSIST-2 (p=0.08) on the clinical outcome assessment is likely related to an underpowered trial (based on an optimistic assumed effect size) that was further underpowered when the trial was stopped prematurely due to the clinical hold, yielding evaluable data for three-fourths of the intended sample size. Exploratory analyses using the same clinical outcome assessment as that used for the two other JAK inhibitors show nominal statistical significance for pacritinib 200 mg BID. While these data are not compelling due to the lack of type 1 error control, they are suggestive that pacritinib will likely have an effect on clinical symptoms of MF.

Based on these considerations, we conclude that the effects of pacritinib 200 mg BID on SVR is reasonably likely to predict clinical benefit and outweighs the risks for this intermediate and advanced patient population with a serious and life-threatening disease and no other FDA-approved treatments.

Table 3. Benefit-Risk Value Tree

Outcome	Definition
Benefits	
SVR	Proportion with ≥35% SVR from baseline to Week 24 based on MRI or CT
Symptom improvement	TSS: Proportion with ≥50% reduction in TSS from baseline to Week 24 based on Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF TSS 2.0)
	mTSS: Proportion with ≥50% reduction in TSS from baseline to Week 24 based on modified MPN-SAF TSS 2.0 (fatigue excluded)
Risks	
Death	Proportion of patients who died by Week 24
Cardiovascular	Proportion of patients with congestive heart failure, cardiac failure, ejection fraction decreased, or left ventricular failure by Week 24
Thrombosis	Proportion of patients with deep vein thrombosis, pulmonary embolism, or arterial thrombosis by Week 24
Bleeding	Major: Proportion of patients with ICH plus bleeding into a critical area or organ by Week 24
	Grade ≥3: Proportion of patients with Grade ≥3 bleeding CTCAE v 4.03 by Week 24
	Any SAE: Proportion of patients with bleeding classified as serious per protocol by Week 24
Thrombocytopenia	Proportion of patients with platelet count <50,000/µL by Week 24
Anemia	Proportions of patients with anemia (hemoglobin <10 g/dL) by Week 24
Infections	Proportion of patients with infections Grade ≥3 and 4 (CTCAE v. 4.03) by Week 24
Diarrhea	Proportion of patients with diarrhea leading to discontinuation by Week 24

Source: Reviewer's definitions.
Abbreviations: CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ICH, intracerebral hemorrhage; MPN-SAF TSS 2.0, Myeloproliferative Neoplasm Symptom Assessment Form; MRI, magnetic resonance imaging; mTSS, modified total symptom score; SAE, serious adverse event; SVR, spleen volume reduction; TSS, total symptom score

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Figure 1. Benefit-Risk Forest Plot for Pacritinib: Baseline Platelet Count <50×10^9/L
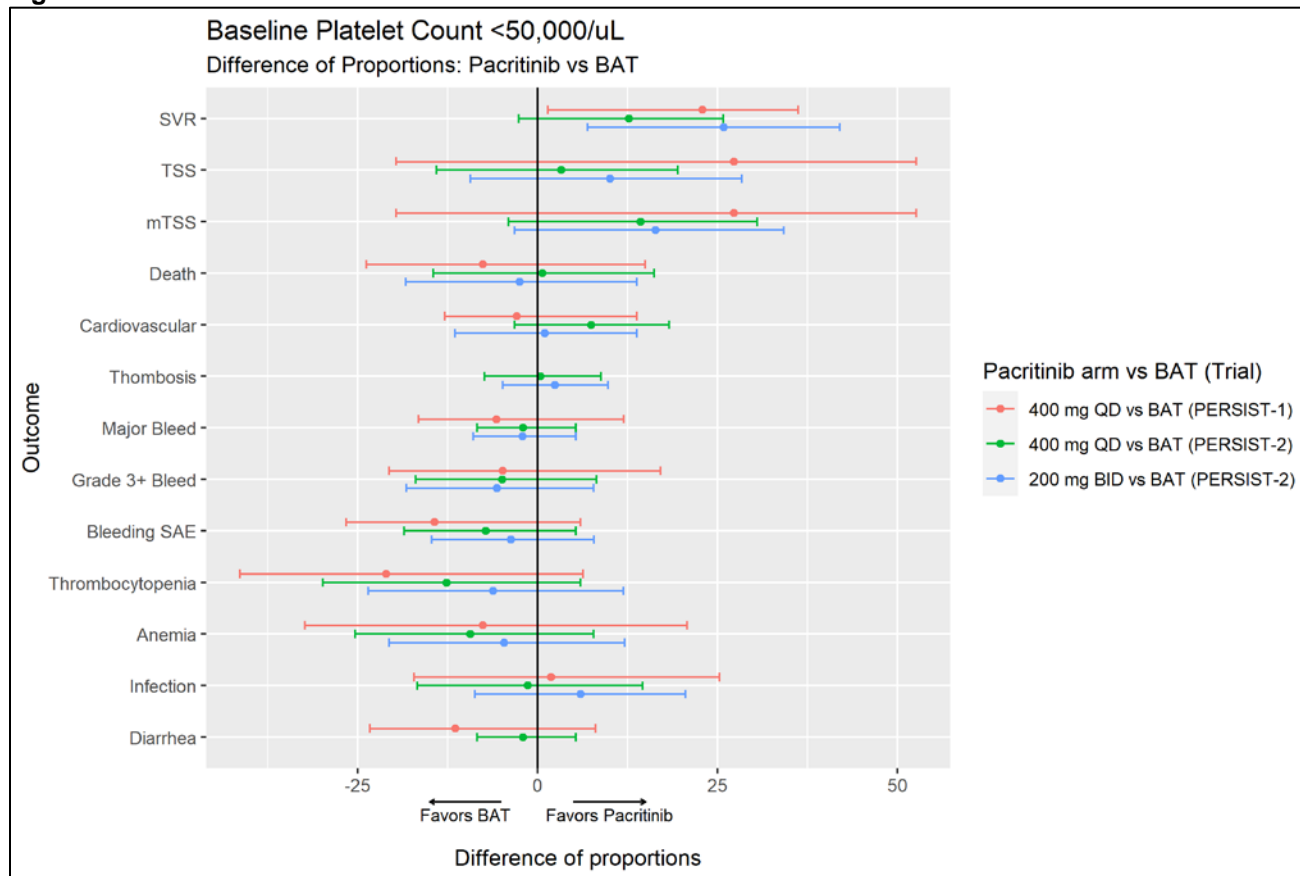
Source: Reviewer's analysis.
Abbreviations: BAT, best available therapy; BID, twice daily; mTSS, modified total symptom score; QD, once daily; SAE, serious adverse event; SVR, spleen volume reduction; TSS, total symptom score

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II. Interdisciplinary Assessment

3. Introduction

Myelofibrosis (MF) is a Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) that includes primary myelofibrosis (PMF), post-polycythemia vera (PPV)-MF and post-essential thrombocythemia (PET)-MF, with an incidence of 1.46 per 100,000 cases annually ([Tefferi 2005](#)). The clinical picture of MF is variable, but typically includes signs of ineffective and extramedullary hematopoiesis, such as anemia, leucoerythroblastosis, symptomatic organomegaly (spleen, liver) causing abdominal pain and early satiety, night sweats, pruritis, bone pain. and fatigue. MF is associated with point mutations in JAK2V617F, MPLW515L, as well as abnormalities in the calreticulin gene ([Masarova et al. 2018](#)).

Pacritinib is an orally administered Janus-associated kinase (JAK)-2 inhibitor for adults with intermediate- or high-risk PPV-MF or PET-MF with a baseline platelet count of $<50\times10^9$/L. Pacritinib also inhibits the FLT3 tyrosine kinase inhibitor (see Section 5 in this review for details). The recommended dose for pacritinib is 200 mg orally twice daily. Data supporting the indication for pacritinib was obtained from the Phase 3 PERSIST-2 study. Additional supportive data were obtained from the dose-ranging Phase 2 PAC203 study. This review focuses on the safety and efficacy data from the PERSIST-2 study.

The goal of treatment for most patients with MF is to provide relief from signs and symptoms of the disease. Conventional treatment, which has limited impact on patient survival, includes a wait-and-see approach for asymptomatic patients, erythropoiesis-stimulating agents, androgens, or immunomodulatory drugs for anemia, cytoreductive drugs such as hydroxyurea for the splenomegaly and constitutional symptoms, and splenectomy or radiotherapy in selected patients ([Cervantes 2014](#)). The discovery of the JAK-2 mutation triggered the development of molecular targeted therapy of MF. The two approved JAK inhibitors for MF (ruxolitinib and fedratinib), are effective in both JAK2-positive and JAK2-negative MF. However, although these approved JAK inhibitor drugs have changed the therapeutic landscape of MF, there is no clear indication of a disease-modifying effect. Allogeneic stem cell transplantation remains the only curative therapy of MF, but due to its associated morbidity and mortality, it is usually restricted to eligible high- and intermediate-2–risk MF patients ([Cervantes 2014](#)). To improve current therapeutic results, the combination of JAK inhibitors with other agents is currently being tested, and newer drugs are being investigated but are not the focus of this review.

Clinical features, such as older age, lower hemoglobin and absolute neutrophil count, higher blasts and higher fibrosis, higher Dynamic International Prognostic Scoring System (DIPSS) risk score, more cytogenetic abnormalities, as well as progression rate to acute myeloid leukemia (AML) can impact survival in patients with MF. Thrombocytopenia also increases the risk for bleeding. Thrombocytopenia, i.e., platelet counts $<100\times10^9$/L, may be seen in patients with MF, with an overall incidence around 26% ([Mesa et al. 1999](#)). Severe thrombocytopenia, i.e., platelets counts $<50\times10^9$/L, occurs overall in about 11 to 16% of patients with MF, and only in 2 to 6% of those with PET-MF and PPV-MF ([Mesa et al. 1999](#); [Masarova et al. 2018](#)). Thrombocytopenia has a negative prognostic impact and this diagnostic criterion has been incorporated in the DIPSS ([Alhuraiji et al. 2016](#)). Thrombocytopenia may also be observed as an

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adverse reaction to ruxolitinib and fedratinib. For example, the ruxolitinib product label (approved September 27, 2021 under new drug application [NDA] 202192) states that in patients with MF undergoing ruxolitinib therapy, the most common hematologic adverse reactions (incidence >20%) are thrombocytopenia and anemia and that dosing of ruxolitinib should be interrupted for platelet counts less than 50×10^9/L. The fedratinib product label (approved August 16, 2019 under NDA 212327) states that for patients with MF undergoing fedratinib therapy the dosing of fedratinib should be interrupted for Grade 4 thrombocytopenia (platelet counts below 25×10^9/L) or Grade 3 thrombocytopenia (platelet counts below 50×10^9/L) with active bleeding until the thrombocytopenia has resolved to Grade 2 (below 75×10^9/L) or lower grade or has returned to baseline. In addition, the pivotal efficacy and safety trials for both ruxolitinib and fedratinib excluded patients with platelet counts below 50×10^9/L. Therefore, there is an unmet medical need for a safe and effective therapy for the treatment of patients with Intermediate and High-risk MF whose platelet counts are below 50×10^9/L.

The approvals of ruxolitinib and fedratinib were based on success of the two following coprimary endpoints: the proportion of patients with ≥35% spleen volume reduction (SVR) assessed with CT or magnetic resonance imaging (MRI), and ≥50% improvement in a modified version of the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAFmTSS) with the fatigue measure removed. Both were assessed as change from baseline to Week 24. The 35% SVR threshold as measured by CT or MRI is thought to correspond to a long-established clinical measure of response based on palpation of the spleen. A ≥50% reduction in the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) is considered to be an important component of the clinical assessment of response to therapy in patients with MF and is incorporated into the International Working Group-Myeloproliferative Neoplasms Research and Treatment and European LeukemiaNet consensus revised response criteria for MF (Tefferi et al. 2013).

The benefit risk assessment focuses on the proposed 200 mg BID regimen of pacritinib in the identified patient population with an unmet medical need, i.e., patients with intermediate or high-risk MF with baseline platelet counts below 50×10^9/L. This review also considers the findings from [REDACTED] (b) (4) pacritinib 400 mg once daily (QD) dose, which has the same total daily dose as the 200 mg BID regimen, and which was not previously considered to have a favorable benefit-risk assessment based on an imbalance in mortality compared to best available therapy in the PERSIST-1 study (see Clinical Review of NDA 208712 by Dr. Vishal Bhatnagar in the Division of Hematology Products, now Division of Nonmalignant Hematology (final signature date February 24, 2018).

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3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Premature Stopping of PERSIST-2

The Applicant proposes the PERSIST-2 study as the main support for efficacy of pacritinib 200 mg BID. Dosing in PERSIST-2 was stopped prematurely when the trial was placed on clinical hold for safety issues that emerged in PERSIST-1. As a result, only about three-fourths of the planned enrollment had evaluable efficacy data. We considered whether the data from the prematurely stopped trial could support the efficacy of pacritinib.

3.1.1.2. PERSIST-2 Failed on One Coprimary Efficacy Endpoint

PERSIST-2 had two coprimary efficacy endpoints at Week 24: The proportion of patients with SVR ≥35% and the proportion of patients with ≥50% reduction in the TSS. The trial was successful on the SVR endpoint but not on the TSS endpoint.

3.1.1.3. Pacritinib 400 mg QD Appears Less Effective on SVR than Pacritinib 200 mg BID in PERSIST-2

In PERSIST-2, the efficacy of pacritinib 400 mg QD on SVR appears smaller than that of 200 mg BID despite 400 mg QD having modestly higher systemic exposure and C_{max} compared to 200 mg BID. One would expect that a dosing regimen with higher pharmacokinetic exposures would lead to better, or at least comparable effects compared to a dosing regimen with lower pharmacokinetic exposures.

3.1.1.4. Scientific Basis for Establishing Substantial Evidence of Effectiveness

A conclusion of substantial evidence of effectiveness requires evidence from at least two adequate and well-controlled trials, one adequate and well-controlled trial that is the functional equivalent of two adequate and well-controlled trials, or one adequate and well-controlled trial plus confirmatory evidence. The approach used for pacritinib should be clearly articulated.

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Major Adverse Cardiac Events

An excess of major adverse cardiac events due to deaths was reported in PERSIST-1 with pacritinib 400 mg QD compared to BAT. An assessment of MACE and deaths using the updated safety database, including PERSIST-2, is needed.

3.1.2.2. Bleeding

Pacritinib is proposed for a patient population at increased risk of bleeding. It is important to assess whether pacritinib further increases the risk of bleeding in this population.

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3.2. Approach to the Review

This review resulted from the integrated efforts of several multidisciplinary review teams. The Office of Pharmaceutical Quality Application Technical Lead was Dhanalakshmi Kasi. The nonclinical pharmacology/toxicology team included Jeffrey Quinn, Pedro DelValle and Todd Bourcier. The clinical pharmacology team included Li Wang and Sudharshan Hariharan. The efficacy analysis was carried out by Sarabdeep Singh, Yeh-Fong Chen and Tom Gwise of Biostatistics. The safety analysis was carried out by Andrew Dmytrijuk. Leila Lackey provided support for the discussion of the benefit risk assessment. Virginia Kwitkowski lead the labeling. The Project Manager was Caden Brennan. The Cross-Discipline Team Leader was Albert Deisseroth, the clinical division Deputy Director. The clinical trials on which the program was based are listed in Table 4.

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Table 4. Clinical Trial Submitted in Support of Efficacy and/or Safety Determinations[1] for Pacritinib

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
NCT02055781	Adult patients with Int-, Int-2 or High-risk PMF, PPV MF or PET MF. Thrombocytopenia with platelet count equal to or below 100x10⁹/L; Splenomegaly equal to or greater than 5 cm below left costal margin; TSS equal to or greater than 13 based on the MPN-SAF-TSS 2.0	Control type: Best available therapy (BAT) Randomization: 1:1:1 Blinding: Single Blind for radiology assessment of SVR Biomarkers: SVR and TSS	Drug: Pacritinib BID Dosage: 200 mg Number treated: 106 patients Duration (quantity and units): 106 patients evaluable with at least 24 weeks of therapy Also, pacritinib 400 mg QD treatment arm and best available therapy (BAT) treatment arm	Primary: Coprimary efficacy endpoints were the proportion of subjects achieving a ≥35% reduction in SVR from baseline to Week 24, by MRI or CT; and the proportion of patients with a ≥50% reduction in TSS from baseline to Week 24, as measured by the MPN-SAF TSS 2.0)	311	96 study centers worldwide

Source: Reviewer.
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with Actual Enrolled.
Abbreviations: BID, twice daily; DB, double-blind; MC, multicenter; MF, myelofibrosis; N, number of subjects; QD, once daily; R, randomized; SVR, spleen volume reduction; TSS, total symptom score

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4. Patient Experience Data

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	The second coprimary endpoint of the study was the proportion of subjects with a ≥50% reduction from baseline to Week 24, as measured by the MPN-SAF TSS 2.0. This endpoint is discussed in Section 6 Assessment of Effectiveness.
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		No other patient experience data submitted.
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	Not applicable.
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

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5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class	Kinase inhibitor.
Mechanism of action	Pacritinib is a kinase inhibitor with activity against Janus-associated kinase 2 (JAK2) and Fms-like receptor tyrosine kinase 3 (FLT3). Pacritinib inhibits both wild-type JAK2 and the JAK2V617F mutant form that is common in patients with myeloproliferative neoplasms. Pacritinib also exhibits inhibitory activity against additional cellular kinases (such as colony-stimulating factor 1 and interleukin 1 receptor-associated kinase 1), the clinical relevance of which is unknown.
Active moieties	Pacritinib
QT interval prolongation	The risk of QT prolongation associated with oral administration of pacritinib is not adequately characterized in the thorough QT (TQT) study (Study PAC107). The study evaluated QT effects of pacritinib using a 400 mg single dose. The peak concentration (C_{max} ~3774 ng/mL) observed with the studied dose is not expected to cover the therapeutic exposures (C_{max} ~9400 ng/mL) associated with the proposed dose at steady state (i.e., 200 mg twice daily). Because the TQT study cannot be used to assess proarrhythmic risk following clinically relevant exposures, QTc effects were evaluated in Study PAC203 in patients with primary or secondary myelofibrosis. In this study, 12-lead ECGs were collected from all patients in triplicate, at 1-hour predose and 4-hours postdose on Day 1 of Week 1 and the end of Weeks 4, 12, and 24. In 54 patients receiving 200 mg pacritinib BID, the maximum mean increase in QTcF from baseline was 11 (90% CI 5.3-16.7) ms. Because of the potential for QT prolongation with pacritinib treatment, appropriate warnings and precautions including risk mitigation strategies are recommended in labeling.
General Information	
Bioanalysis	Validated LC-MS/MS methods were used to determine the concentrations of pacritinib and its metabolites in human plasma and urine (as applicable to individual studies).
Healthy subjects versus patients	The population pharmacokinetics analysis suggests that myelofibrosis patients show similar AUC and slightly lower C_{min} relative to healthy subjects at steady state. However, the magnitude of the difference in exposure is not considered to be of clinical relevance.

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Characteristic	Drug Information
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	**Table 7. Pharmacokinetic Parameters of Pacritinib From the Population PK Model in Patients With Myelofibrosis** | Parameter	Geometric Mean (CV%)	Dose | |---|---|---| | AUC (μg·h/mL) | 95.6 (33%) | 200 mg BID | | C_{max} (μg/mL) | 8.42 (32%) | 200 mg BID | Source: Reviewer's analysis. Abbreviations: AUC, area under the plasma concentration-time curve; BID, twice daily; C_{max}, maximum concentration; CV, coefficient of variation
Range of effective dosage(s) or exposure	A dose-response relationship was established in the Phase 2 PAC203 study. The pacritinib 200 mg BID dose group had a greater proportion of patients achieving 35% reduction in spleen volume reduction (SVR) at Week 24 compared to 100 mg QD and 100 mg BID dose groups.
Maximally tolerated dosage or exposure	In two studies (PAC203 and PERSIST-2), administration of pacritinib 200 mg BID was generally well tolerated. In the PERSIST-1 study, increased mortality, higher rates of serious bleeding events and heart failure were observed in the pacritinib 400 mg QD arm compared to best available therapy (which includes (i) any physician-selected treatment for primary myelofibrosis, post-polycythemia vera-myelofibrosis, or post-essential thrombocythemia-myelofibrosis, with the exclusion of JAK2 inhibitors, and (ii) no treatment).
Dosage proportionality	Pacritinib pharmacokinetics increase in a less than dose-proportional manner over a range of 100 and 400 mg (Study SB1518-2010-004). The ratios of AUC and C_{max} between 400 mg and 100 mg were 2.47 and 1.87, respectively.
Accumulation	Accumulation ratio for AUC in myelofibrosis patients at 200 mg BID: 2.69
Time to achieve steady-state	Steady-state PK was achieved within 1 week.
Bridge between to-be-marketed and clinical trial formulations	No major changes to the composition of the pacritinib capsule formulation were introduced during clinical development, except that a manufacturing site change for pacritinib active pharmaceutical ingredient was reported. A Phase I study (PAC108) was conducted for bridging the Phase 3 Clinical Trial (P3CT) formulation (Reference) and Final Market Image (FMI) formulation (Test) in healthy subjects. The bioequivalence of the two formulations was demonstrated.
Absorption	
Bioavailability	Pacritinib pharmacokinetics increase in a less than dose-proportional manner over a range of 100 and 400 mg (Study SB1518-2010-004). The ratios of AUC and C_{max} between 400 mg and 100 mg are 2.47 and 1.87, respectively.
T_{max}	The median T_{max} was 5 hours (range 2-8 hours) when administered as two single 100 mg pacritinib capsules.
Food effect (fed/fasted) Geometric least-squares mean and 90% CI	Two 100 mg capsules of pacritinib taken with a high-fat, high calorie breakfast: (Study SB1518-2010-006) Ratio of $AUC_{0-\infty}$ (%): 1.17 (1.10 to 1.23) Ratio of C_{max} (%): 1.11 (1.05 to 1.18) T_{max} (median): 5.5 hours (fasted) or 6 hours (fed) Study was completed with the Phase II/III capsule which is similar to the to-be-marketed product Based on these results, pacritinib can be taken regardless of food.

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Characteristic	Drug Information
Distribution	
Volume of distribution	Vss: 229 L (range: 156 to 591 L) in patients with myelofibrosis following 200 mg BID
Plasma protein binding	Pacritinib is mainly bound to albumin in human plasma and α1-acidic glycoprotein. The mean protein binding of pacritinib in human plasma was 98.8% at 10 µg/mL (clinically relevant concentration). Pacritinib showed a decreasing trend for plasma protein binding at higher concentrations; i.e., 97.7% (fu=2.3%) and 97.1% (fu=2.9%) at 25 and 50 µg/mL, respectively.
Drug as substrate of transporters	In vitro drug transporter assessment showed that pacritinib was not a substrate for bile salt export pump (BSEP), P-glycoprotein (P-gp), organic-anion-transporting polypeptides1B1, OATP1B3, organic cation transporter 1 (OCT1), or breast cancer resistance protein (BCRP). More detailed information on the substrate activity of pacritinib is presented in Section III.14.1.
Elimination	
Mass balance results	Following administration of 400 mg pacritinib (4×100 mg capsules)/100 µCi [^{14}C]pacritinib (suspension), 6% of the dose was recovered in urine and 87% was recovered in feces. A negligible amount of unchanged drug was excreted in feces and urine. Two major metabolites, M1 (oxidation product) and M2 (O-dealkylation product), in human whole plasma represented 9.6% and 10.5% of parent drug exposure, respectively. Based on an in vitro JAK2 inhibition assay, M1 and M2 exhibited approximately 37% and 9% of the pharmacological activity of pacritinib, respectively. Considering the relative exposure of the metabolites to pacritinib and their pharmacological activities, the two metabolites are unlikely to play a significant role in the pharmacological activity of pacritinib.
Clearance	The mean (CV%) apparent plasma clearance for pacritinib following 200 mg is 1.08 L/h (44%).
Half-life	The mean terminal half-life ($t_{1/2}$) is approximately 33.5 hours (range 22.3 to 44.6 hours).
Metabolic pathway(s)	In vitro studies demonstrated that pacritinib is predominantly metabolized by CYP3A4.
Primary excretion pathways (% dosage)	Pacritinib undergoes virtually complete hepatic metabolism and the contribution of renal elimination is negligible.
Intrinsic Factors and Specific Populations	
Body weight	Body weight is not a statistically significant covariate on pacritinib's volume of distribution and clearance.
Age	Age is not a statistically significant covariate on pacritinib's volume of distribution and clearance.
Renal impairment	Dose adjustment is not warranted in patients with any degree of renal impairment. Pacritinib C_{max} and AUC were similar in subjects with mild (eGFR 60-89 mL/min as estimated by MDRD study equation) and moderate (eGFR 30-59 mL/min) renal impairment compared to subjects with normal renal function (eGFR ≥90 mL/min). Compared to subjects with normal renal function, pacritinib C_{max} increased by 24% in severe (eGFR 15-29 mL/min) renal impairment group and 33% in subjects with ESRD. AUC_{0-72h} values increased by 31% and 25% in severe renal impairment and subjects with ESRD, respectively. Because the magnitude of pacritinib exposure increase in severe renal impairment and ESRD subjects is similar to the increase in exposure observed with 400 mg QD, a regimen having unfavorable benefit-risk, the review team recommends avoiding use of pacritinib in patients with eGFR <30 mL/min/1.73m^2.

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Characteristic	Drug Information
Hepatic impairment	Compared to subjects with normal hepatic function, pacritinib geometric mean AUC decreased by 8.5%, 36% and 45% in subjects with mild (Child-Pugh A), moderate (Child-Pugh B), or severe hepatic impairment (Child-Pugh C), respectively. Pacritinib geometric mean C_{max} decreased by 22%, 47% and 57% in subjects with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function. The reason for the decrease in pacritinib exposure in hepatic impairment is not well understood. Moreover, it should be noted that the study was conducted with 400 mg and as such the results may not be extrapolated to the clinically relevant dose of 200 mg. Therefore, the review team recommends a postmarketing requirement to study the pharmacokinetics of the 200 mg dose in hepatic impairment and, in the meantime, avoiding use of pacritinib in patients with moderate and severe hepatic impairment.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	In vitro assessment demonstrated that pacritinib is a time-dependent inhibitor of cytochrome P450 (CYP)1A2 and CYP3A4, a reversible inhibitor of CYP1A2, CYP3A4 and CYP2C19, and an inducer of CYP1A2 and CYP3A4.
Inhibition/induction of transporter systems	In vitro assessment demonstrated that pacritinib is an inhibitor of P-gp, BCRP, and OCT1.

Source: Reviewer-generated table.

Abbreviations: AUC, area under the plasma concentration-time curve; BID, twice daily; CI, confidence interval; C_{max}, maximum concentration; C_{min}, minimum concentration; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; FMS, feline McDonough sarcoma; JAK, Janus-associated kinase; LC-MS/MS, liquid chromatography with tandem mass spectrometry; MF, myelofibrosis; PK, pharmacokinetics; QD, once daily; QTcF, Fridericia's corrected QT interval; STAT, signal transducer and activator or transcription; T_{max}, time to maximum concentration; V_{ss}, volume at steady state

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5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. Primary Pharmacology

Pacritinib inhibits Janus-associated kinase 2, $JAK2^{V617F}$, and FMS-like tyrosine kinase 3 (FLT3), with half inhibitory concentration (IC_{50}) values of 1nM, 3nM, and 3.9nM, respectively. Pacritinib inhibited the proliferation of human leukemia and lymphoma cell lines selected for their dependence on either of the target kinases (IC_{50} 30 to 240nM). Consistent with the antiproliferative activities, exposure to pacritinib resulted in reductions of phospho-JAK2, phospho-signal transducers and activators of transcription (STAT)3, or phospho-STAT5 proteins with subsequent induction of apoptosis in the relevant cell lines. Pacritinib exhibits inhibitory activity against multiple cellular kinases; however, the clinical relevance of the combined inhibition of these kinases with regard to therapeutic effectiveness in the myelofibrosis patient population is unknown. The primary metabolites of pacritinib (M1 and M2) are pharmacologically active at the proposed therapeutic dose. The in vitro kinase inhibition profiles of pacritinib and the M1/M2 metabolites can be found in Section III.13.1.1.

5.1.2. Animal Model Data Showing Proof of Concept

Two proof-of-concept studies were conducted in murine models of myelofibrosis whose pathology is driven by excessive JAK2 activity, recapitulating the dysregulated JAK/STAT pathway described in human myelofibrosis. These models allow for measurement of endpoints considered relevant to human myelofibrosis, including liver and spleen size, leukocytosis, thrombocytopenia and anemia (Table 8). These studies used nude mice bearing Ba/F3-JAK2^{WT} cells, a murine interleukin-3-dependent pro-B cell line ectopically overexpressing wild-type JAK2. In the first study, the disease state was allowed to develop in mice for 12 days to model late stage or spent phase myeloproliferative disease (myelofibrosis) prior to pacritinib treatment. Untreated mice bearing Ba/F3 JAK2^{WT} cells developed the hallmark symptoms of late-stage myeloproliferative disease, including hyperplasia of the liver, splenomegaly, severe leukocytosis, thrombocytopenia, and anemia. Pacritinib treatment (100 mg/kg/day, 6 days) alleviated clinical symptoms including leukocytosis, thrombocytopenia, and anemia. However, hyperplasia of the liver, and splenomegaly were not reduced in mice presenting with the symptoms of late-stage myeloproliferative disease when pacritinib was administered at 100 mg/kg/day for 6 days.

In the second study, the disease state was allowed to develop in mice for 3 days to model the early stages of myeloproliferative disease, when not all the symptoms of the spent phase have manifested (i.e., anemia), prior to initiating pacritinib treatment. Untreated mice bearing Ba/F3 JAK2^{WT} cells developed leukocytosis, hyperplasia of the liver, splenomegaly, and mild thrombocytopenia but not anemia. In addition, untreated mice bearing Ba/F3 JAK2^{WT} cells demonstrated a significant increase in green fluorescent protein (GFP)-positive cells in the bone marrow and in the peripheral blood mononuclear cell populations, reflecting appropriate homing of the GFP-labeled Ba/F3 JAK2^{WT} cells to relevant biological compartments. Pacritinib treatment (150 mg/kg BID, for 14 days) alleviated clinical symptoms—including leukocytosis, hyperplasia of the liver, and splenomegaly—and significantly reduced the number of GFP-positive cells in the peripheral blood mononuclear cell population. The number of GFP-positive

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cells in the bone marrow was not affected by the administration of pacritinib at 150 mg/kg BID for 14 days.

A third proof-of-concept study was conducted in nude mice bearing Ba/F3-JAK2^{V617F} cells, a JAK2-dependent leukemia. In that study, the disease state was allowed to develop in mice for 4 days to model the early stages of myeloproliferative disease, prior to initiating pacritinib treatment. Untreated mice bearing Ba/F3-JAK2^{V617F} cells presented with a significant increase in GFP-positive cells in the blood and developed leukocytosis, hyperplasia of the liver, and splenomegaly, but not thrombocytopenia or anemia which are typically associated with late-stage myeloproliferative disease. Pacritinib treatment (150 mg/kg, BID, for 14 days) alleviated clinical symptoms including leukocytosis, hyperplasia of the liver, and splenomegaly, and significantly reduced the number of GFP-positive cells in the blood.

The most frequent genetic alteration observed in patients with myelofibrosis is the JAK2^{V617F} mutation, and while two of the proof-of-concept studies employed Ba/F3 cells bearing wild-type JAK2, it should be recognized that these results are consistent with the concept that JAK2 inhibitors, like pacritinib, function irrespective of the type of JAK2 mutation or kinase activity as these compounds are intended to inhibit both wild-type and mutated JAKs.

The final proof-of-concept study was conducted in nude mice bearing MV4-11 cells, a human FLT3-dependent acute myeloid leukemia cell line with a FLT3 internal tandem duplication mutation. In this study, tumors were allowed to develop in mice for 9 days, prior to initiating pacritinib treatment. Treatment of mice bearing MV4-11 tumors with pacritinib for 21 days resulted in a significant and dose-dependent reduction in tumor growth, with complete tumor regression in mice dosed at 25 mg/kg/day (20%), 50 mg/kg/day (60%), and 100 mg/kg/day (88%), respectively. Acute myeloid leukemia develops in some patients with MF.

Table 8. Pacritinib Effects on Clinically Relevant Endpoints in Animal Models of Myeloproliferative Disease

Parameter	Mouse Model			
	JAK2^{WT}	JAK2^{WT}	JAK2^{V617F}	MV4-11
MPD stage modeled	Late	Early	Early	Late
Pacritinib dose (mg/kg/day)	100	150	150	100
Treatment duration (days)	6	14	14	21
Clinically relevant endpoints				
Hepatomegaly	✓ (N)	✓ (A)	✓ (A)	NA
Splenomegaly	✓ (N)	✓ (A)	✓ (A)	NA
Leukocytosis	✓ (A)	✓ (A)	✓ (A)	NA
Thrombocytopenia	✓ (A)	✓ (A)	NA	NA
Anemia	✓ (A)	NA	NA	NA
Increased PBMCs	NA	✓ (A)	✓ (A)	NA
Bone marrow monocytosis	NA	✓ (N)	NA	NA
AML tumors	NA	NA	NA	✓ (A)
Bone marrow fibrosis	NA	NA	NA	NA

Source: Reviewer constructed summary table of mouse model studies submitted to the new drug application.
✓ indicates the clinically relevant endpoint was present in the mouse model.
(A) indicates the clinically relevant endpoint was alleviated by pacritin b.
(N) indicates the clinically relevant endpoint was not alleviated by pacritinib.
Abbreviations: AML, acute myeloid leukemia; JAK2, Janus-associated kinase 2; MPD, myeloproliferative disorder; MV-411, biphenotypic B-myelomonocytic leukemia with a 4;11 translocation and FLT3 ITD (internal tandem duplication) mutation; NA, not applicable; PBMC, peripheral blood mononuclear cell; V617F, kinase activating point mutation; WT, wild-type

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6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

Applicant's Proposed Dosing Regimen

The proposed dosage of pacritinib for patients with platelet counts of less than 50×10^9/L is 200 mg orally twice daily. Pacritinib may be taken with or without food. Dose modifications for diarrhea, thrombocytopenia, and hemorrhage are described in Table 9, Table 10, and Table 11, respectively (based on the criteria used in PERSIST-2 ▓▓▓▓▓▓ (b) (4)
▓▓▓). Dose levels for pacritinib ▓▓▓▓▓▓ (b) (4) reduction are as follows: 200 mg twice daily (initial starting dose), 100 mg twice daily, 100 mg daily. Discontinue pacritinib in patients unable to tolerate a dose of 100 mg daily.

Table 9. Dosage Modification for Pacritinib-Related Diarrhea

CTCAE Grade	Management/Action
Grade 3 or 4	Hold pacritinib until the diarrhea resolves to Grade 1* or lower or baseline. Restart pacritinib at the last given dose.
	If diarrhea recurs, hold pacritinib until it resolves to Grade <1 or baseline. Restart pacritinib at 50% of the last given dose.
	Concomitant antidiarrheal treatment is required for patients restarting pacritinib.

▓▓▓▓▓▓ (b) (4)
* Increase of <4 stools per day over baseline.
Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events

Table 10. Dose Modification for Pacritinib-Related Thrombocytopenia

CTCAE Grade	Action
For clinically significant worsening of thrombocytopenia that lasts more than 7 days or is associated with bleeding:	Hold pacritinib. Restart pacritinib at the same dose or dose that is 50% of the last given dose once the toxicity has resolved.

▓▓▓▓▓▓ (b) (4)
Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events

Table 11. Dose Modification for Hemorrhage

CTCAE Grade	Action
Grade 2	Hold pacritinib until hemorrhage resolves. Restart pacritinib at the last given dose.
	If hemorrhage recurs, hold pacritinib until resolution then restart at 50% of the last given dose.
Grade 3	Hold pacritinib until hemorrhage resolves.
	Restart pacritinib at 50% of the last given dose.
	If bleeding reoccurs, discontinue pacritinib
Grade 4	Discontinue pacritinib

▓▓▓▓▓▓ (b) (4)
Current CTCAE (v. 5.03) grading of bleeding is dependent on the site of bleeding in the body. The current CTCAE bleeding criteria are generally consistent with bleeding defined according to CTCAE v. 2.0 criteria and which have been widely used by clinical practitioners. The hemorrhage bleeding CTCAE v. 2.0 bleeding criteria are as follows for reference: Grade 1=mild without need for blood product transfusion; Grade 2=moderate/intermittent bleeding not requiring blood product transfusion; Grade 3=bleeding requiring blood product transfusion; Grade 4=catastrophic bleeding requiring nonelective surgical intervention.
Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events

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Selection of Dosing Regimen for the Phase 3 Trial

A dose-finding Phase 2 study (PAC203) was conducted to identify the recommended dosage of pacritinib for pivotal trials. Three dose levels of pacritinib, 100 mg QD, 100 mg BID, and 200 mg BID, were selected to allow adequate characterization of dose-response relationships for the efficacy and safety of pacritinib. A dose-response relationship was established for spleen response, with higher Week 24 spleen volume reduction rates (SVR) observed in the pacritinib 200 mg BID group (9.3%) compared to lower doses (100 mg BID, 1.8%; 100 mg QD, 0%). Furthermore, the safety profile of the pacritinib 200 mg BID dose was acceptable, with no excess high-grade cardiac or bleeding events compared to lower doses.

Evaluation of the Proposed Dosing Regimen

The Applicant proposed the recommended dose of 200 mg BID based upon both efficacy and safety findings. As noted above, in Study PAC203, patients in the pacritinib 200 mg BID arm showed better therapeutic effects (increased Week 24 SVR) compared to lower-dose groups (100 mg BID and 100 mg QD). In addition, the safety profile of the pacritinib 200 mg BID dose was acceptable. Pacritinib 400 mg QD was tested in the PERSIST-1 and PERSIST-2 trials. In PERSIST-2, the pacritinib 200 mg BID group, as compared to the pacritinib 400 mg QD group, showed higher rates of Week 24 SVR (29% versus 18%) and TSS response (23% versus 16%).

In PERSIST-2, the percentage of patients reporting diarrhea was 69% with pacritinib 400 mg QD, 53% with pacritinib 200 mg BID and 39% with BAT in PERSIST-2. The percentages for Grade 3 diarrhea were: 5% with pacritinib 400 mg QD, 4% with pacritinib 200 mg BID, and 2% with BAT. The percentage of patients reporting thrombocytopenia was 34% with pacritinib 400 mg QD, 37% with pacritinib 200 mg BID, and 33% with BAT. The corresponding percentages for Grade 3 thrombocytopenia were 32%, 35%, and 32%, respectively. Additionally, safety results in PERSIST-1 showed greater mortality in the pacritinib 400 mg QD group compared to the BAT arm (26% versus 6%) as well as higher rates of serious bleeding events (7% versus 1%) and heart failure (7% versus 2%) in the pacritinib 400 mg QD group compared to the BAT arm. These safety findings are further assessed in the Safety section of this review. Collectively, the proposed dosing regimen is reasonable from an efficacy and safety perspective.

Further support for the proposed dosing regimen of pacritinib is provided by exposure-response/ safety analyses of data from the three clinical studies (PAC203, PERSIST-1, and PERSIST-2), which are briefly described below.

The pacritinib concentration versus spleen volume reduction (SVR) modeling (pharmacokinetic-pharmacodynamic [PKPD] model) demonstrated that the magnitude of SVR decrease from baseline was dependent on pacritinib plasma exposure. Predictions of treatment response (>35% SVR) using the model indicated that response rate reached a plateau (about 25%) at pacritinib area under the concentration-time curve (AUC) ≥181.2 h·µg/mL (geometric mean AUC following 200 mg BID). Exposure versus safety analyses also demonstrated that several adverse events—including thrombocytopenia, bleeding and hemorrhage—were exposure dependent.

The PKPD and exposure-safety models were used to assess the effects of dose reductions on the effectiveness and safety of pacritinib in patients who respond to 200 mg BID treatment but experience intolerable side effects. Simulation results suggested that for subjects who are responders at 200 mg BID but experience toxicity, 38% (95% CI 34% to 41%) remain responders at 100 mg BID and 24% (95% CI 21% to 27%) would continue to experience adverse

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events. At 100 mg QD, only 15% (95% CI 13% to 17%) would remain responders whereas 25% (95% CI 21% to 27%) would have adverse events. It should be noted, however, that the rates of adverse events at 100 mg QD and 100 mg BID are comparable to the model estimated rate of composite adverse events (i.e., bleeding, hemorrhage, anemia, or thrombosis) at zero pacritinib concentration (i.e. without pacritinib treatment). Therefore, the proposed dose-reductions appear reasonable.

Further details of the safety analyses comparing the pacritinib 400 mg QD, 200 mg BID and BAT treatment groups and exposure-response analysis are provided in Sections 7 and III.14.3, respectively.

6.2. Clinical Trial Intended to Demonstrate Efficacy

6.2.1. Study PERSIST-2

The Applicant had submitted a Special Protocol Assessment request for this trial, and we had issued an Agreement letter. We also agreed with several revisions to the trial design. However, we subsequently issued a rescind agreement letter after a substantial new scientific issue arose regarding the safety of the 400 mg QD dose (see Section III.12).

Overview and Objectives

To support the proposed indication, the Applicant conducted a randomized, Phase 3 Study, PERSIST-2, titled "A Multicenter, Randomized, Controlled, Phase 3 Study Comparing the Efficacy and Safety of 2 Dose Regimens 400 mg QD and 200 mg BID of Pacritinib With Best Available Therapy (BAT)."

Primary Objectives

The coprimary objectives of this study were to:

- Compare the efficacy of pacritinib pooled QD and BID groups with BAT and compare the efficacy of pacritinib BID and pacritinib QD with BAT individually, as evaluated by two coprimary efficacy endpoints:
  - Proportion of patients with a ≥35% SVR from baseline to Week 24, as measured by MRI or computerized tomography (CT).
  - Proportion of patients achieving a ≥50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

Secondary Objectives

- Compare the efficacy of 400 mg QD pacritinib with BAT by evaluating the proportion of subjects achieving a ≥35% reduction in spleen volume and the proportion of subjects achieving a ≥50% reduction in TSS.
- Compare the efficacy of 200 mg BID pacritinib with BAT by evaluating the proportion of subjects achieving a ≥35% reduction in spleen volume and the proportion of subjects achieving a ≥50% reduction in TSS.

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Study Design

The PERSIST-2 study was a multicenter, randomized, controlled, Phase 3 trial. It compared the efficacy and safety of two dose schedules of pacritinib in pooled and individual arm analyses versus BAT in subjects with thrombocytopenia and primary myelofibrosis (PMF), post-polycythemia vera MF or post-essential thrombocythemia MF.

A total of 311 eligible subjects was randomized in a 1:1:1 allocation to one of three treatment arms:

- Pacritinib 400 mg taken orally, QD.
- Pacritinib 200 mg taken orally, BID.
- BAT.

BAT included any physician-selected treatment for PMF, PPV MF, or PET MF, such as approved JAK2 inhibitors (administered according to the package insert for subjects with thrombocytopenia) and included any treatment received before study entry. For example, BAT may have included ruxolitinib, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents. BAT also included no treatment ("watch and wait") or symptom-directed treatment without MF-specific treatment. BAT agents could be used alone, in combination, sequentially, and intermittently, as clinically indicated by standards of care.

During the study, subjects taking pacritinib were not to receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV MF, or PET MF. Subjects were not to receive splenic irradiation or a splenectomy while receiving study treatment.

Spleen volume was measured by MRI or CT at baseline and every 12 weeks thereafter through 48 weeks postrandomization or until progression of disease or withdrawal from study treatment. MRI without contrast was the preferred modality. Imaging was performed without contrast agents. The analysis of the primary outcome included all randomized subjects who completed the Week 24 MRI or CT evaluation, exhibited disease progression, or discontinued study treatment, whichever occurred first (patients who had disease progression or discontinued study treatment were classified as nonresponders). An independent radiology facility, blinded to the treatment assignments, was used to measure spleen volumes. For each patient, the same imaging modality was generally used throughout the study. Two independent radiologists, blinded to all patient and site identifiers and treatment assignments, measured the spleen volume. In the case of significant disagreement between the first two radiologists, a third independent radiologist, also blinded to all patient and site identifiers and treatment assignments, adjudicated the spleen volume measurement. Spleen size was assessed as the distance below the left costal margin at the midclavicular line on physical examination.

Symptoms were recorded daily (using MPN-SAF TSS 2.0) to 48 weeks post-treatment initiation or until the end of study treatment, whichever occurred first.

Subjects were followed for safety, overall survival (OS), progression-free survival, leukemia-free survival, frequency of red blood cell (RBC) and platelet transfusions, and other exploratory endpoints. OS analysis was planned after long term follow up, i.e., 3 years after the last patient's Week 24 visit or their end date of treatment with the initially assigned study drug, whichever was first. Bone marrow biopsies were obtained at or prior to baseline as required for study eligibility and at Week 24 and were evaluated by local pathology laboratories.

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An Independent Data Monitoring Committee monitored the safety of pacritinib. No interim efficacy analysis was performed.

For subjects who were no longer taking pacritinib or those in the BAT arm who were no longer receiving study treatment, follow-up for survival and leukemic progression continued until 3 years past Week 24 or past termination of all study treatment, whichever occurred first.

On February 8, 2016, the Food and Drug Administration (FDA) placed a full clinical hold on pacritinib due to the safety concerns seen in the PERSIST-1 study. As a result of the clinical hold, study treatment was discontinued in all patients, but follow-up for OS and leukemia-free survival continued. The cutoff date for the survival analysis was August 19, 2016. At the time of the clinical hold, not all patients had a chance to reach the Week 24 study visit. As a result, the primary efficacy analyses in PERSIST-2 were performed on a subset of the intent-to-treat (ITT) population (all randomized patients), which is referred to as the ITT-Efficacy Population and is defined as all patients randomized 22 weeks prior to the day of the clinical hold (with consideration for the 2-week window allowed for study visits). Time to event analyses (e.g., OS) were performed based on the ITT All Randomized population, and the primary analyses were censored at the date of the clinical hold (February 8, 2016), with secondary analyses censored at the cutoff date of August 19, 2016.

Study Population

A total of 311 patients was randomized 1:1:1 to receive oral pacritinib 400 mg QD (104 [33.4%] patients), pacritinib 200 mg BID (107 [34.4%] patients), or investigator-determined BAT (100 [32.2%] patients). At the time of the clinical hold, 75 patients in the pacritinib 400 mg QD, 74 patients in the pacritinib 200 mg BID, and 72 patients in the BAT group were randomized at least 22 weeks prior to the clinical hold with consideration for the 2-week window allowed for study visits and comprised the ITT Efficacy population, which is considered the study population.

Key Inclusion and Exclusion Criteria

Inclusion Criteria

Each subject had to meet the following criteria to be eligible for the study:

- Intermediate 1 or 2 or High-risk PMF (primary myelofibrosis), PPV MF (post-polycythemia vera myelofibrosis), or PET MF (post-essential thrombocythemia myelofibrosis).
- Thrombocytopenia (platelet count ≤100,000/µL) at any time after signing informed consent.
- Informed consent could be signed up to 35 days prior to randomization.
- Palpable splenomegaly ≥5 cm below the left costal margin in the midclavicular line by physical examination.
- TSS ≥13 on the MPN-SAF-TSS 2.0, not including the inactivity question.
- Age ≥18 years.
- Eastern Cooperative Oncology Group performance status 0 to 3.
- Peripheral blast count <10%.
- Absolute neutrophil count >500/µL.

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- Subjects who were platelet– or RBC transfusion–dependent were allowed to participate.
- Adequate liver and renal function, defined by liver transaminases (aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase and alanine aminotransferase (ALT)/ serum glutamic-pyruvic transaminase) ≤3×upper limit of normal (ULN) (AST/ALT ≤5×ULN if transaminase elevation was related to MF), direct bilirubin ≤4× ULN, and serum creatinine ≤2.5 mg/dL.
- At least 6 months from prior splenic irradiation.
- At least 12 months from prior ^{32}P therapy.
- At least 1 week since prior treatment (most recent dose) with a potent cytochrome P450 3A4 (CYP3A4) inhibitor.
- At least 2 weeks since receiving any treatment for PMF, PPV MF, or PET MF.
- If fertile, males and females had to agree to use effective birth control methods during the study.
- Willing to undergo and able to tolerate frequent MRI or CT assessments during the study.
- Able to understand and willing to complete symptom assessments using a patient-reported outcomes instrument.
- Able to understand and willing to sign the informed consent form.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

- Any gastrointestinal or metabolic condition that could interfere with absorption of oral medication.
- Life expectancy of less than 6 months.
- Prior treatment with more than two JAK2 inhibitors or pacritinib.
- There was no maximum cumulative prior JAK2 inhibitor treatment (approved or investigational).
- Completed allogeneic stem cell transplantation or were eligible for and willing to complete allogeneic stem cell transplantation.
- History of splenectomy or planning to undergo splenectomy.
- Uncontrolled intercurrent illness, including but not limited to ongoing active infection, psychiatric illness, or social situation that, in the judgment of the treating physician, would limit compliance with study requirements.
- Active bleeding requiring hospitalization during the screening period.
- Other malignancy within the last 3 years, other than curatively treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, organ-confined or treated nonmetastatic prostate cancer with negative prostate-specific antigen, in situ breast carcinoma after complete surgical resection, or superficial transitional cell bladder carcinoma.
- Inflammatory or chronic functional bowel disorder, such as Crohn's disease, inflammatory bowel disease, chronic diarrhea, or constipation.
- Clinically symptomatic and uncontrolled cardiovascular disease.
- History of any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure.
- New York Heart Association Class III or IV congestive heart failure.

- Subjects with National Cancer Institute Common Terminology Criteria for Adverse Events grade 2 cardiac arrhythmias may have been considered for inclusion with the approval of the medical monitor if the arrhythmias were stable, asymptomatic, and unlikely to affect patient safety. Subjects were excluded if they had ongoing cardiac dysrhythmias of Common Terminology Criteria for Adverse Events grade ≥3, corrected QT interval prolongation >450 ms, or other factors that increase the risk for QT interval prolongation (e.g., heart failure, hypokalemia [defined as serum potassium <3.0 = mEq/L that is persistent and refractory to correction], or family history of long QT interval syndrome).
- Erythropoietic agent within 28 days prior to randomization.
- Thrombopoietic agent within 14 days prior to randomization.
- Known seropositivity for human immunodeficiency virus.
- Known active hepatitis A, B, or C virus infection.
- Women who were pregnant or lactating.

Study Efficacy Endpoints

Coprimary Endpoint

- The first coprimary efficacy endpoint of the study was the proportion of subjects achieving a ≥35% reduction in spleen volume from baseline to Week 24, as measured by MRI or CT, based on independent radiology facility reads. In diagnostic radiology, as a standard, a 50% reduction in the palpable size of the spleen (as measured by the centimeters by which the spleen tip was palpable beneath the left costal margin), which is considered to be a clinically meaningful reduction in volume in MF, corresponds to a 35% reduction in volume as measured by CT or MRI. This same efficacy endpoint was used in the pivotal trials for the approval of the two existing treatments for MF.

- The second coprimary endpoint of the study was the proportion of subjects with a ≥50% reduction from baseline to Week 24, on the MPN-SAF TSS 2.0. The TSS is a patient-reported outcome that assesses a variety of symptoms related to MF. It is completed daily. This same coprimary efficacy endpoint was used in the pivotal trials for the approval of the two existing treatments for MF except that the tiredness item was not used in those trials. The TSS endpoint algorithm was as follows:

  — The daily TSS was the sum of the scores for the following symptoms: tiredness, early satiety, abdominal discomfort, night sweats, pruritus, bone pain, and pain under ribs on the left side. Zero is the minimum score and ten the most severe for an individual item.
  — The baseline TSS was the mean of the daily TSS over the 7 consecutive days prior to the start of treatment.
  — The Week 24 TSS was the mean of the daily TSS obtained during the 28 consecutive days prior to the Week 24 spleen volume scan date (or Week 24 visit date if scan date was missing).

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Exploratory Endpoints

The exploratory endpoints of the study were:

- Overall survival.
- Progression-free survival.
- Leukemia-free survival.
- Time to achievement of ≥35% reduction in spleen volume from baseline by MRI or CT.
- Duration of maintenance of ≥35% reduction in spleen volume from baseline.
- Best response in spleen volume by MRI or CT.
- Duration of treatment.
- Achievement of RBC transfusion independence.
- Achievement of reduced RBC transfusion dependence.
- Clinical improvement in hemoglobin level.
- Frequency of RBC transfusions.
- Achievement of platelet transfusion independence.
- Clinical improvement in platelet count.
- Frequency of platelet transfusions.
- Change in JAK2^{V617F} allele burden.
- Quality of life, as measured by the EQ-5D-5L and European Organisation for Research and Treatment of Cancer QLQ-C30 version 3.0.

Statistical Analysis Plan

Sample Size Determination

For sample size calculations, the proportions of subjects achieving a ≥35% reduction in spleen volume at Week 24 were assumed to be 5% in the BAT arm, 25% in the pacritinib QD arm, and 25% in the pacritinib BID arm. These assumptions were made based on response rates seen in the ruxolitinib COMFORT-II randomized controlled trials and pacritinib's SB1518-2007-001 and SB1518-2008-003 Phase 2 trials. It was also assumed that the proportion of subjects achieving a ≥50% reduction in TSS at Week 24 is 5% in the BAT arm, 45% in the pacritinib QD arm, and 45% in the pacritinib BID arm. These assumptions were made based on response rates seen in the ruxolitinib COMFORT-II randomized controlled trial.

With these assumptions, the original sample size of 300 subjects (100 in the QD pacritinib arm, 100 in the pacritinib BID arm, and 100 in the BAT arm) was planned for the study. For the primary hypothesis (pooled pacritinib QD/BID versus BAT), this sample size provided >99% power to detect a treatment difference in SVR and a treatment difference in TSS reduction at an α-level (two-sided) of 0.05.

This sample size also provided 96% power to detect a treatment difference in SVR and >99% power to detect a treatment difference in TSS reduction at an α-level (two-sided) of 0.025 for testing the secondary hypotheses independently, i.e., when comparing the endpoints in the pacritinib QD arm with the BAT arm and comparing the endpoints in the pacritinib BID arm with the BAT arm.

Assuming a 10% dropout rate, there was ≥93% power to detect the treatment differences specified above. A Fisher's exact test was used for the purpose of sample size calculation.

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The subjects randomized at least 22 weeks prior to the FDA full clinical hold were used to evaluate the study objectives. It is estimated that a total of 220 subjects met this definition. With the same assumptions mentioned above, this sample size provides 97% and >99% power to test the primary hypothesis (pooled pacritinib QD/BID versus BAT) of a treatment difference in SVR and a treatment difference in TSS reduction, respectively, at an α-level (two-sided) of 0.05. This sample size also provides 86% power to detect a treatment difference in SVR and >99% power to detect a treatment difference in TSS reduction at an α-level (two-sided) of 0.025 for testing the secondary hypotheses independently, i.e., when comparing the endpoints in the pacritinib QD arm with the BAT arm and comparing the endpoints in the pacritinib BID arm with the BAT arm.

Randomization

Eligible patients were centrally randomized in a 1:1:1 allocation to receive either pacritinib 400 mg QD, pacritinib 200 mg BID, or BAT. Randomization was stratified by geographic region (United States versus Canada versus Europe versus rest of the world), risk category (Intermediate 1 versus Intermediate 2 versus High risk) and by baseline rebound platelet count (≤100,000/μL versus >100,000/μL). To be included in the >100,000/μL group, patients must have met both of the following criteria: 1) baseline platelet count >100,000/μL and 2) >50% increase above their first qualifying platelet value after consent. The first qualifying platelet value after informed consent and the most recent platelet count obtained prior to randomization was the basis for determining platelet rebound stratification.

For patients who received any platelet transfusions during this period, a pretransfusion platelet count was obtained within 8 hours prior to transfusion, and this platelet count was used for stratification.

Interim Analysis

No interim analysis was planned.

Missing Data

Patients with missing Week 24 spleen volume, including those who met the criteria for disease progression or dropped out of the study before Week 24, were considered to have not achieved the ≥35% reduction.

Patients with a missing Week 24 TSS, including those who met the criteria for disease progression or dropped out of the study before Week 24, were considered to have not achieved the ≥50% reduction.

On August 27, 2021, the Agency issued an Information Request to the Applicant to examine the impact of missing data and dropouts with several sensitivity analyses, especially due to the clinical hold. The Agency also requested the Applicant provide the average SVR and TSS over time figures to better understand the drug's effect throughout the study.

Primary Efficacy Analysis

The primary analysis of the improvement in SVR and TSS was to compare the proportion of patients achieving a ≥35% reduction in spleen volume and a ≥50% reduction in TSS from baseline to Week 24. The numbers and percentages of patients achieving reduction in SVR and

TSS from baseline to Week 24 was summarized by the three arms (400 mg QD, 200 mg BID, and BAT). The treatment differences in the proportions comparing the pooled pacritinib arms (400 mg QD+200 mg BID) to the BAT arm, the 400 mg QD arm to the BAT arm, and the 200 mg BID arm to the BAT arm were determined using Fisher's exact test. The 95% (97.5% for individual pacritinib arm comparisons) confidence intervals for these three comparisons were produced based on the Agresti-Caffo method.

Multiple Comparison

A closed, step-down procedure was used to test the hypotheses to ensure an overall Type I error rate of 5% (Figure 2). The primary hypothesis was first tested at a two-sided alpha of 0.05 for comparing the pooled doses with BAT for each coprimary endpoint individually, with a successful study claimed if both reached statistical significance. If the study achieved its primary objective, then the secondary hypotheses would be tested concurrently for comparing individual doses with BAT, each with a two-sided alpha of 0.025. Each secondary hypothesis would be accepted if each endpoint reached statistical significance.

Figure 2. Testing Procedure for Primary and Secondary Hypotheses
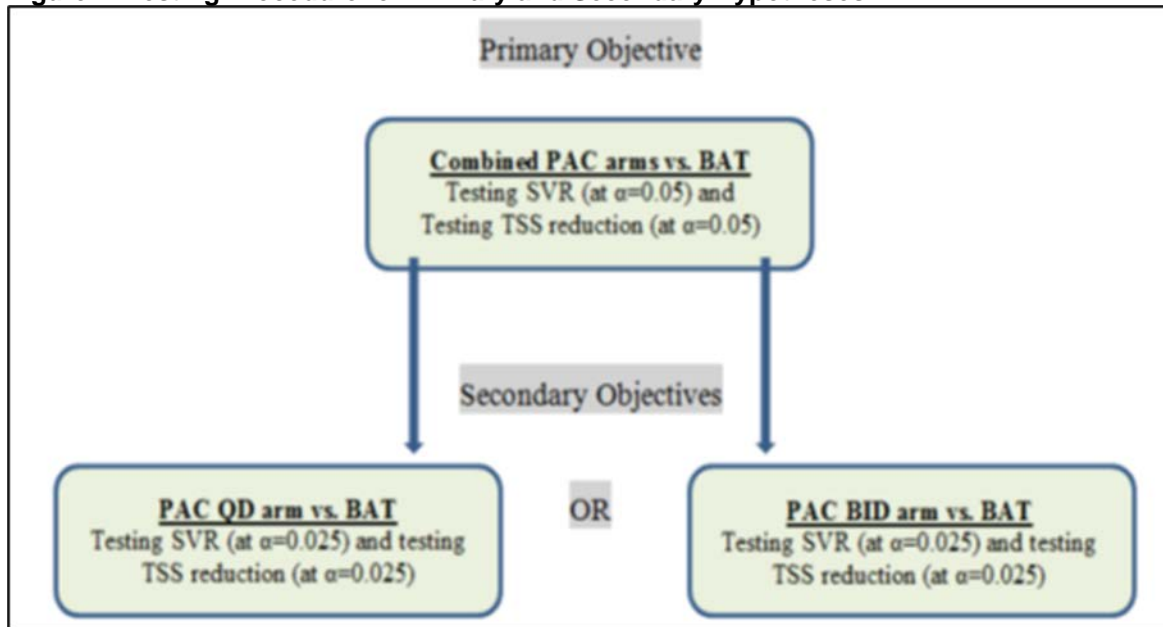
Source: Page 58 of the study report.
Abbreviations: BAT, best available therapy; BID, twice daily; PAC, pacritinib; QD, once daily; SVR, spleen volume reduction; TSS, total symptom score

Subgroup Analysis

Subgroup analyses were planned to evaluate any potential impact of demographics or baseline disease characteristics on the primary and secondary endpoints. Subgroups based on stratification factors include region (North America versus Europe versus rest of the world), Dynamic International Prognostic Scoring System risk category (Intermediate 1 versus Intermediate 2 versus High risk) and baseline platelet count ($\leq$100,000/μL versus >100,000/μL). Depending on the sample size, other subgroups proposed for the analyses were gender, age group (<65 years versus $\geq$65 years), race (Caucasian versus non-Caucasian), prior treatment with JAK2 inhibitors (yes versus no), and, importantly, baseline platelet count (<50,000/μL versus $\geq$50,000/μL)—a

focus of this review given the unmet need in this population. Additionally, BAT patients treated with ruxolitinib were analyzed separately.

Secondary Efficacy Analyses

The treatment differences in the proportions comparing the pooled pacritinib arms to BAT, 400 mg QD alone to BAT, and 200 mg BID alone to BAT were tested within strata defined by region (United States versus Canada versus Europe versus rest of the world), risk category (Intermediate 1 versus Intermediate 2 versus High), and baseline platelet count ($\leq$100,000/μL versus >100,000/μL; <50,000/μL versus $\geq$50,000/μL), in the strata with sufficient patients for valid statistical testing. The exact Cochran–Mantel–Haenszel test was used to test if treatment differences were preserved across strata.

The Cochran–Mantel–Haenszel analysis was repeated with the proportion of patients achieving a $\geq$50% reduction in TSS from baseline to other postbaseline time points. In addition, for the ITT efficacy population, descriptive statistics of the percentage change in TSS from baseline to post-baseline visits was presented by treatment arm.

Exploratory Analyses

Overall Survival

OS was defined as the time from the date of randomization to the date of death due to any cause. OS analysis was planned after long-term follow up, i.e., 3 years after the last patient's Week 24 visit or their end date of treatment with the initially assigned study drug, whichever was first. If a patient was alive or the survival status was unknown by the time of this analysis, survival was censored at the date the patient was last known to be alive, regardless of whether patients crossed over to a pacritinib regimen from BAT.

Leukemia-Free Survival

Leukemia-free survival was defined as the time from the start of treatment to the date of leukemic transformation or death due to any cause. Leukemic transformation was defined as the first date of an increase in peripheral blood blast percentage to $\geq$20% sustained for $\geq$8 weeks and/or a bone marrow blast count $\geq$20%. Patients were censored at the date of last assessment for leukemic transformation if they were alive with no documented transformation before analysis. Patients who crossed over during the study were censored at the last assessment date prior to crossing over.

RBC Transfusion Independence

A patient was defined as RBC transfusion independent at any time point if that patient had no RBC transfusion in at least 3 months (90 days) preceding that time point. The patient was RBC transfusion dependent if, in the preceding 3 months (90 days), they were transfused with $\geq$2 RBC units per month on average. RBC transfusion independence/dependence is indeterminate if they were transfused with between 0 and 2 RBC units per month on average in that surveillance period. The frequency of RBC transfusion was defined by the number of units of RBC transfused per month over a specific period of time.

Post Hoc Analysis of MPN-SAF TSS Data

The pivotal studies leading to approval of both ruxolitinib and fedratinib used a modified analysis of the MPN-SAF TSS that excluded the individual symptom score of "tiredness." Tiredness was excluded from the TSS for those applications because "tiredness" is the result of so many confounding factors that it is of limited utility in measuring the effect of therapy. In hindsight, CTI stated that they should not have used MPN-SAF TSS 2.0 and rather should have used the same TSS analysis used in the ruxolitinib and fedratinib applications for the PERSIST-2 study. Therefore, the Applicant conducted a post hoc analysis of the TSS results on the pooled pacritinib 400 mg QD and pacritinib 200 mg BID groups in PERSIST-2 that excluded tiredness.

6.2.2. Results of Analyses, PERSIST-2

This section presents the efficacy results for the overall trial with a focus on the prespecified subgroup of patients with platelet counts $<50\times10^9$/L, which is a population with unmet need.

Patient Disposition

A total of 311 patients was randomized (1:1:1) to treatment with pacritinib 400 mg QD (104 patients), pacritinib 200 mg BID (107 patients), or BAT (100 patients). Of them, 75 patients in the pacritinib 400 mg QD group, 74 patients in the pacritinib 200 mg BID group, and 72 patients in the BAT group reached Week 24 and comprised the intent-to-treat (ITT) Efficacy population (Table 12).

Patients discontinued the initial study drug mostly because of physician's decision (4.1% in the pacritinib 200 mg BID group, 6.7% in the pacritinib 400 mg QD group, and 57.7% in the BAT group). The rate of study drug discontinuation due to an adverse event (AE) was highest in the pacritinib 400 mg QD group (14.7%) as compared to 11% in the 200 mg BID pacritinib group and 5.6% in the BAT group (Table 12). The rate of study drug discontinuation due to progressive disease was highest in the BAT group (9.9%) as compared to 8.2% for pacritinib 200 mg BID and 5.3% for pacritinib 400 mg QD (Table 12). Patients who discontinued their initial treatment due to the clinical hold were captured in the category *Other*.

The majority (66.7%) of patients randomized to BAT crossed over to pacritinib (Table 12). At the time of the clinical hold, 35.7% of patients had discontinued the study: 44.0% in the pacritinib 400 mg QD group, 24.3% in the pacritinib 200 mg BID group, and 38.9% in the BAT group. The most common reason for study discontinuation was death.

Table 12. Patient Disposition in PERSIST-2 (ITT Efficacy Population)

Disposition	Pacritinib 400 mg QD N=75 n (%)	Pacritinib 200 mg BID N=74 n (%)	BAT N=72 n (%)
Patients who were randomized	75 (100)	74 (100)	72 (100)
Patients who received any dose of study drug	75 (100)	73 (98.6)	71 (98.6)
Patients who discontinued study drug[1]	75 (100)	73 (100)	71 (100)
Adverse events	11 (14.7)	8 (11.0)	4 (5.6)
Death	5 (6.7)	2 (2.7)	4 (5.6)
Progressive disease	4 (5.3)	6 (8.2)	7 (9.9)
Withdrawal by patient	6 (8.0)	4 (5.5)	1 (1.4)
Physician decision	5 (6.7)	3 (4.1)	41 (57.7)
Noncompliance with study drug	1 (1.3)	0	0
Other	43 (57.3)	50 (68.5)	14 (19.7)
Patients who discontinued the study[2, 3]	33 (44.0)	18 (24.3)	28 (38.9)
Death	17 (51.5)	15 (83.3)	16 (57.1)
Withdrawal by patient	7 (21.2)	1 (5.6)	4 (14.3)
Physician decision	5 (15.2)	1 (5.6)	2 (7.1)
Other	4 (12.1)	1 (5.6)	6 (21.4)
Patients who crossed over from BAT to pacritinib	NA	NA	48 (66.7)

Source: Page 31 of the Clinical Summary.
[1] Percentages are based on the number of patients who discontinued study drug.
[2] Percentages are based on the number of patients who discontinued the study.
[3] End of study represents information available at the time of database lock.
Note: The ITT Efficacy Population in PERSIST-2 is based on the ITT Population truncated on the day of the clinical hold (i.e., patients randomized prior to September 7, 2015).
Abbreviations: BAT, best available treatment; BID, twice daily; ITT, intent-to-treat; NA, not applicable; QD, once daily

Of the patients with baseline platelet counts of less than $50{\times}10^9$/L, the majority of those in the BAT group discontinued study drug due to physician's decision (Table 13). Like with the overall trial, the majority of the patients randomized to BAT in this subgroup crossed over to either 400 mg QD or 200 mg BID pacritinib (65.6%). Patients who discontinued their initial treatment due to the clinical hold were captured in the category *Other*.

Rates of study discontinuation were generally higher in this subgroup than for the overall study, and the majority of study discontinuations was due to death.

Table 13. Patient Disposition in PERSIST-2 Patients With Baseline Platelet Counts Less Than $50{\times}10^9$/L (ITT Efficacy Population)

Disposition	Pacritinib 400 mg QD N=38 n (%)	Pacritinib 200 mg BID N=31 n (%)	BAT N=32 n (%)
Patients who were randomized	38 (100)	31 (100)	32 (100)
Patients who received any dose of study drug	38 (100)	30 (96.8)	31 (96.9)
Patients who discontinued study drug[1]	38 (100)	30 (100)	31 (100)
Adverse event	5 (13.2)	5 (16.7)	3 (9.7)
Death	3 (7.9)	2 (6.7)	3 (9.7)
Progressive disease	2 (5.3)	3 (10.0)	3 (9.7)
Withdrawal by patient	4 (10.5)	2 (6.7)	0
Physician decision	4 (10.5)	1 (3.3)	19 (61.3)
Noncompliance with study drug	0	0	0
Other	20 (52.6)	17 (56.7)	3 (9.7)

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Patients who discontinued the study[2, 3]	22 (57.9)	11 (35.5)	16 (50.0)
Death	12 (54.5)	10 (90.9)	11 (68.8)
Withdrawal by patient	4 (18.2)	0	2 (12.5)
Physician decision	4 (18.2)	1 (9.1)	1 (6.3)
Other	2 (9.1)	0	2 (12.5)
Patients who crossed over from BAT to pacritinib	NA	NA	21 (65.6)

Source: Page 32 of the Clinical Summary.
[1] Percentages are based on the number of patients who discontinued study drug.
[2] Percentages are based on the number of patients who discontinued the study.
[3] End of study represents information available at the time of database lock.
Note: The ITT Efficacy Population in PERSIST-2 is based on the ITT Population truncated on the day of the clinical hold (i.e., patients randomized prior to September 7, 2015).
Abbreviations: BAT, best available treatment; BID, twice daily; ITT, intent-to-treat; NA, not applicable; QD, once daily

Demographic Characteristics and Baseline Characteristics

Across all treatment arms, most patients were white and ≥65 years of age (Table 14). The pacritinib 200 mg BID arm had fewer women and slightly younger patients than the other arms. The other demographic characteristics of the ITT Efficacy population were generally balanced among the three treatment arms: pacritinib 400 mg QD, pacritinib 200 mg BID, and BAT.

Table 14. Summary of Demographic Characteristics in PERSIST-2 (ITT Efficacy Population)

Characteristic	Pacritinib 400 mg QD N=75	Pacritinib 200 mg BID N=74	BAT N=72
Age (years)			
N	75	74	72
Mean (SD)	68.8 (8.6)	66.1 (8.0)	67.3 (9.8)
SEM	0.99	0.93	1.16
Median	69.0	67.0	68.5
IQR	64.0, 75.0	61.0, 72.0	63.0, 73.5
Minimum, maximum	39, 85	39, 85	32, 83
Age subgroup, n (%)			
<65 years	22 (29.3)	28 (37.8)	21 (29.2)
≥65 years	53 (70.7)	46 (62.2)	51 (70.8)
Gender, n (%)			
Female	37 (49.3)	26 (35.1)	33 (45.8)
Male	38 (50.7)	48 (64.9)	39 (54.2)
Race, n (%)			
White	65 (86.7)	67 (90.5)	64 (88.9)
Unknown[1]	6 (8.0)	4 (5.4)	5 (6.9)
Asian	2 (2.7)	1 (1.4)	2 (2.8)
Native Hawaiian or Other Pacific Islander	1 (1.3)	2 (2.7)	1 (1.4)
Black or African American	1 (1.3)	0	0
Other	0	0	0
Race subgroup, n (%)			
Caucasian	65 (86.7)	67 (90.5)	64 (88.9)
Non-Caucasian	10 (13.3)	7 (9.5)	8 (11.1)
Ethnicity, n (%)			
Non-Hispanic or Latino	67 (89.3)	66 (89.2)	65 (90.3)
Hispanic or Latino	1 (1.3)	2 (2.7)	3 (4.2)
Not reported[2]	5 (6.7)	6 (8.1)	3 (4.2)
Unknown[2]	1 (1.3)	0	1 (1.4)
Missing	1 (1.3)	0	0

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Characteristic	Pacritinib 400 mg QD N=75	Pacritinib 200 mg BID N=74	BAT N=72
BMI (kg/m²)[3]			
N	73	71	72
Mean (SD)	25.2 (5.4)	25.1 (3.5)	24.7 (3.8)
Median	24.1	24.8	24.2
IQR	21.7, 27.9	22.4, 27.8	22.5, 27.0
Minimum, maximum	15.5, 46.0	17.4, 34.8	16.9, 38.0
Geographic region, n (%)			
North America	32 (42.7)	29 (39.2)	31 (43.1)
Oceania	6 (8.0)	6 (8.1)	4 (5.6)
East Europe	10 (13.3)	10 (13.5)	9 (12.5)
West Europe	19 (25.3)	19 (25.7)	19 (26.4)
Russia	8 (10.7)	10 (13.5)	9 (12.5)

Source: Page 34 of the Clinical Summary.
[1] Race was not collected for patients who were not allowed to be asked per local regulations.
[2] Ethnicity was not collected for patients who were not allowed to be asked per local regulations.
[3] BMI (kg/m²) = weight (kg) ÷ [height (cm) ÷ 100]², rounded to two decimal places.
Note: The ITT Efficacy Population in PERSIST-2 is based on the ITT Population truncated on the day of the clinical hold (i.e., patients randomized prior to September 7, 2015).
Abbreviations: BAT, best available therapy; BID, twice daily; BMI, body mass index; IQR, interquartile range; ITT, intent-to- treat; QD, once daily; SD, standard deviation; SEM, standard error of the mean

The demographics of the subgroup of patients with baseline platelet counts less than $50 \times 10^9/L$ were similar to that of the overall trial population (Table 15).

Table 15. Demographic Characteristics of PERSIST-2 Patients With Baseline Platelet Counts Less Than $50 \times 10^9/L$ (ITT Efficacy Population)

Characteristic	Pacritinib 400 mg QD N=38	Pacritinib 200 mg BID N=31	BAT N=32
Age (years)			
N	38	31	32
Mean (SD)	68.7 (7.4)	67.1 (7.9)	70.4 (7.8)
Median	68.0	67.0	71.0
IQR	64.0, 75.0	62.0, 72.0	66.0, 75.5
Minimum, maximum	52, 84	50, 84	50, 83
<65 years, n (%)	11 (28.9)	12 (38.7)	7 (21.9)
≥65 years, n (%)	27 (71.1)	19 (61.3)	25 (78.1)
Gender, n (%)			
Female	16 (42.1)	12 (38.7)	16 (50.0)
Male	22 (57.9)	19 (61.3)	16 (50.0)
Race, n (%)			
White	31 (81.6)	30 (96.8)	30 (93.8)
Unknown[1]	5 (13.2)	0	1 (3.1)
Asian	1 (2.6)	0	1 (3.1)
Native Hawaiian or other Pacific Islander	0	1 (3.2)	0
Black or African American	1 (2.6)	0	0
Other	0	0	0
Race subgroup, n (%)			
Caucasian	31 (81.6)	30 (96.8)	30 (93.8)
Non-Caucasian	7 (18.4)	1 (3.2)	2 (6.3)

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Characteristic	Pacritinib 400 mg QD N=38	Pacritinib 200 mg BID N=31	BAT N=32
Ethnicity, n (%)			
Non-Hispanic or Latino	33 (86.8)	30 (96.8)	30 (93.8)
Not reported[2]	3 (7.9)	1 (3.2)	1 (3.1)
Hispanic or Latino	0	0	1 (3.1)
Unknown[2]	1 (2.6)	0	0
Missing	1 (2.6)	0	0
BMI (kg/m^2)[3]			
N	36	29	32
Mean (SD)	26.5 (5.7)	25.3 (3.8)	23.7 (3.8)
Median	25.3	25.7	23.0
IQR	23.0, 29.0	22.6, 27.8	21.0, 25.7
Minimum, maximum	17.7, 46.0	17.4, 34.8	16.9, 33.3
Geographic region, n (%)			
North America	19 (50.0)	12 (38.7)	12 (37.5)
Oceania	0	3 (9.7)	1 (3.1)
East Europe	4 (10.5)	3 (9.7)	2 (6.3)
West Europe	11 (28.9)	10 (32.3)	13 (40.6)
Russia	4 (10.5)	3 (9.7)	4 (12.5)

Source: Page 35 of the Clinical Summary.
[1] Race was not collected for patients who were not allowed to be asked per local regulations.
[2] Ethnicity was not collected for patients who were not allowed to be asked per local regulations.
[3] BMI (kg/m^2) = weight (kg) ÷ [height (cm) ÷ 100]^2, rounded to two decimal places.
Note: The ITT Efficacy Population in PERSIST-2 is based on the ITT Population truncated on the day of the clinical hold (i.e., patients randomized prior to September 7, 2015).
Abbreviations: BAT, best available treatment; BID, twice daily; BMI, body mass index. ITT, intent-to-treat; QD, once daily; SD, standard deviation

Disease Demographics—Overall Trial Population

In the ITT Efficacy population, the percentage of patients with Intermediate 1, Intermediate 2, and High risk DIPSS was 16.0%, 53.3%, and 30.7% in the pacritinib 400 mg QD group, respectively; 18.9%, 51.4%, and 29.7% in the pacritinib 200 mg BID group, respectively; and 18.1%, 51.4%, and 30.6% in the BAT group, respectively.

A larger percentage of patients in the pacritinib 200 mg BID group had primary MF (74.3%) than in the pacritinib 400 mg QD group (61.3%), and the BAT group (59.7%).

A smaller percentage of patients had PET MF in the pacritinib 200 mg BID group (6.8%) than in the pacritinib 400 mg QD group (17.3%) and the BAT group (18.1%).

The percentage of patients who had received prior JAK2 therapy was balanced across the three treatment groups: 44.0% of patients in the pacritinib 400 mg QD group, 44.6% in the pacritinib 200 mg BID group, and 47.2% of patients in the BAT group.

Disease Demographics—Platelet Count <50×10^9/L Subgroup

The percentage of patients with a platelet count less than 50×10^9/L was 50.7% in the pacritinib 400 mg QD group, 41.9% in the pacritinib 200 mg BID group, and 44.4% in the BAT group.

The percentage of patients with baseline platelet counts less than 50×10^9/L in the Intermediate 1, Intermediate 2, and High risk in the DIPSS prognostic groups were 13.2%, 57.9%, and 28.9% in the pacritinib 400 mg QD group, respectively; 9.7%, 51.6%, and 38.7% in the pacritinib 200 mg BID group, respectively; and 6.3%, 46.9%, and 46.9% in the BAT group, respectively.

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A larger percentage of patients in the pacritinib 200 mg BID group (77.4%) had primary MF than in the pacritinib 400 mg QD group (60.5%) and the BAT group (68.8%). A smaller percentage of patients had PET MF in the pacritinib 200 mg BID group (6.5%) than in the pacritinib 400 mg QD group (21.1%) and the BAT group (21.9%).

The percentage of patients who had received prior JAK2 inhibitor therapy was similar among the treatment groups: 42.1% in the pacritinib 400 mg QD group, 38.7% in the pacritinib 200 mg BID group, and 40.6% in the BAT group.

The most common agents used by patients with baseline platelet counts less than 50×10^9/L in the BAT group were ruxolitinib (38.7% [12 of 31]), watch and wait (32.3% [10 of 31]), and hydroxyurea (25.8% [8 of 31]).

Efficacy Results—Primary Endpoint

Because of the clinical hold placed by the FDA on pacritinib, the study treatment was discontinued in all patients. At the time of the clinical hold, only patients in the ITT Efficacy population were able to complete 24 weeks of follow-up. To investigate the robustness of the treatment effect, the statistical reviewer conducted analyses for the efficacy coprimary endpoints by including all patients who did not complete 24 weeks of follow-up in the ITT All Randomized population as nonresponders. The review team also investigated the need for adjusting the study significance level in the final analyses due to the early termination of the trial. An Information Request was sent to the Applicant for this issue and the Applicant stated that this is the only analysis they had performed.

The review team agrees that the efficacy analyses provided in this NDA, which do not take the clinical hold into account when determining the study significance level, were valid.

Spleen Volume

In PERSIST-2 for the ITT Efficacy population, the primary endpoint was met for SVR. There was a statistically significant difference between treatment groups in the proportion of patients achieving ≥35% SVR from baseline to Week 24, with a larger proportion of patients in the pacritinib 400 mg QD + 200 mg BID pooled group (26 of 149 [17.4%] patients) achieving ≥35% SVR than the BAT group (2 of 72 [2.8%] patients; p=0.0019) (Table 16). These findings were consistent for the All Randomized population Table 17.

Table 16. Proportion of Subjects Achieving a ≥35% Spleen Volume Reduction From Baseline to Week 24, ITT Efficacy Population

Statistic	Pacritinib 400 mg QD +200 mg BID (N=149)	Pacritinib 400 mg QD (N=75)	Pacritinib 200 mg BID (N=74)	BAT (N=72)
Number (%)	26 (17.4)	10 (13.3)	16 (21.6)	2 (2.8)
95% CI	11.7, 24.5	6.6, 23.2	12.9, 32.7	0.3, 9.7
Difference[1] (95% CI)	14.7 (6.4, 22.8)	10.6 (-0.1, 20.5)	18.8 (6.4, 30.2)	
P-value compared to BAT	0.0019	0.03	0.0007	

Source: FDA reviewer.
[1] Difference is PAC−BAT.
Abbreviations: BAT, best available treatment; BID, twice daily; CI, confidence interval; PAC, pacritin b; QD, once daily

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Table 17. Proportion of Subjects Achieving a ≥35% Spleen Volume Reduction From Baseline to Week 24, All Randomized Patients

	Treatment			
Statistic	Pacritinib 400 mg QD +200 mg BID (N=211)	Pacritinib 400 mg QD (N=104)	Pacritinib 200 mg BID (N=107)	BAT (N=100)
Number (%)	26 (12.3)	10 (9.6)	16 (14.5)	2 (2)
95% CI	8.2, 17.5	4.7, 17.0	8.8, 23.1	0.2, 7.0
Difference[1] (95% CI)	10.3 (5.10, 15.5)	7.6 (1.3, 13.9)	14 (5.7, 20.2)	
p-Value compared to BAT	0.002	0.03	0.0009	

Source: FDA reviewer.
[1] Difference is PAC−BAT.
Abbreviations: BAT, best available treatment; BID, twice daily; CI, confidence interval; PAC, pacritin b; QD, once daily

Following a test of the pooled treatment groups versus BAT, an analysis of pacritinib 200 mg BID versus BAT demonstrated that a larger proportion of patients treated with pacritinib 200 mg BID (21.6%) achieved ≥35% SVR from baseline at Week 24 compared to patients treated with BAT (2.8%) (p=0.0007; Table 18). The results for the subgroup of patients with baseline platelet counts less than 50×10^9/L were: pacritinib 200 mg BID, 29.0%; BAT, 3.1% (p=0.006).

As shown in the tables above, the treatment effect on SVR with pacritinib 400 mg QD was smaller than with 200 mg BID. This finding is at odds with the modestly higher systemic exposure for 400 mg QD compared to 200 mg BID, but the confidence intervals for the treatment effects overlap considerably. Of note, in PERSIST-1, the SVR endpoint was achieved in 19.1% of patients (42/220) treated with pacritinib 400 mg QD compared to 4.7% of patients (5/107) on BAT (p<0.001), which is more consistent with the result for 200 mg BID in PERSIST-2.

Table 18. Proportion of Patients With ≥35% Reduction in Spleen Volume From Baseline to Week 24—PERSIST-2 (ITT Efficacy Population and Patients With Platelet Counts Less Than 50×10^9/L)

	ITT Efficacy Population		Patients With Platelet Counts Less Than 50×10^9/L	
Statistic	Pacritinib 200 mg BID (N=74)	BAT (N=72)	Pacritinib 200 mg BID (N=31)	BAT (N=32)
Number (%)	16 (21.6)	2 (2.8)	9 (29.0)	1 (3.1)
95% CI[1]	12.9, 32.7	0.3, 9.7	14.2, 48.0	0.1, 16.2
Difference, PAC-BAT	18.8		25.9	
CI[2]	6.4, 30.2		4.3, 44.5	
p-Value[3]	0.0007		0.006	

Source: Page 22 of the Clinical Summary.
[1] 95% CIs are based on the Clopper-Pearson method.
[2] CIs are based on the Agresti-Caffo method. 97.5% CIs are presented.
[3] p-value from Fisher's exact test.
Note: For PERSIST-2, the ITT Efficacy Population is based on the ITT Population truncated on the day of the clinical hold (i.e., patients randomized prior to September 7, 2015).
Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; ITT, intent-to-treat; PAC, pacritin b

A waterfall plot of the percentage of change in spleen volume from baseline to Week 24 is presented in Figure 3 for the PERSIST-2 patients with platelet counts less than 50×10^9/L. In general, patients treated with pacritinib 200 mg BID showed a greater decrease in spleen volume compared to patients treated with BAT.

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Figure 3. Percentage Change From Baseline in Spleen Volume at Week 24 in PERSIST-2 Patients With Less Than 50×10^9/L Platelet Counts (ITT Efficacy Population)
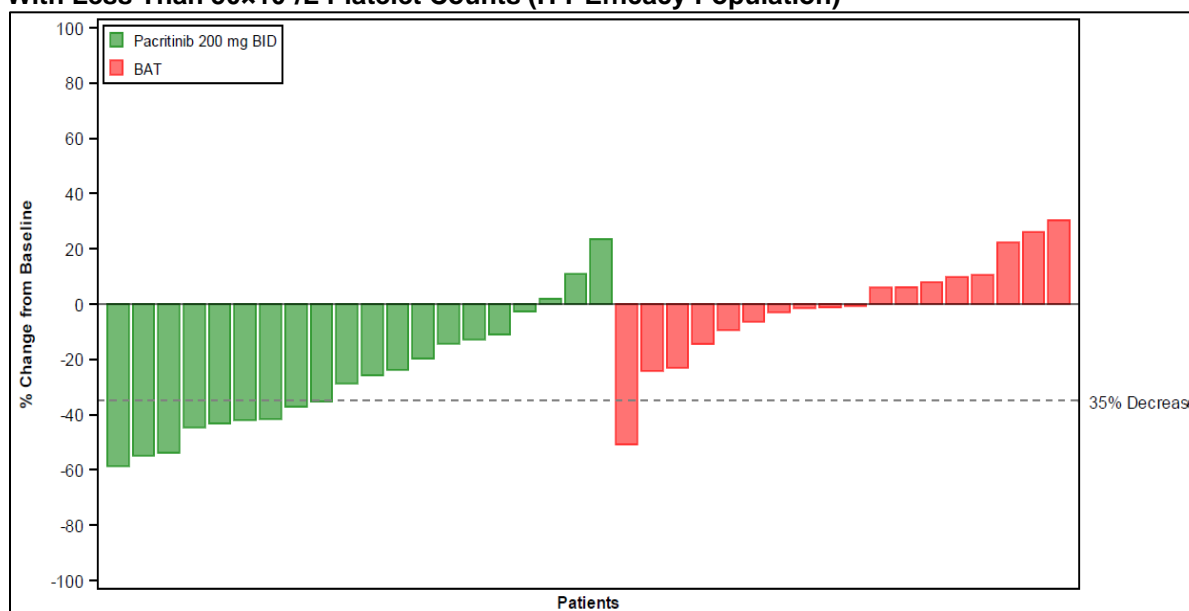
Source: Page 23 of the Clinical Summary.
Note: The ITT Efficacy Population is based on the ITT Population truncated on the day of the clinical hold, i.e., patients randomized prior to September 7, 2015.
Abbreviations: BAT, best available therapy; BID, twice daily; ITT, intent-to-treat

Original TSS

In PERSIST-2, the difference between the pacritinib and BAT arms in the proportion of patients who achieved a ≥50% reduction in the original TSS (which included tiredness) from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 was a coprimary endpoint and was not statistically significant: 37 of 149 (24.8%) patients in the pacritinib 400 mg QD+200 mg BID pooled group showed a reduction of the TSS by at least 50%, compared to 10 of 72 (13.9%) patients in BAT group. The p-value for the difference between the two arms was p=0.08 (Table 19). The statistical miss on this coprimary endpoint could be related to the lower TSS response rate for pacritinib 400 mg QD (discussed below) and the reduced power of the trial, which was stopped early due to the clinical hold, generating data on about three-fourths of the intended sample size.

The proportion of patients who achieved a ≥50% reduction in the original TSS was larger for patients in the pacritinib 200 mg BID treatment group (24 of 74 [32.4%] as compared to the BAT treatment group (10 of 72 [13.9%]; nominal p=0.01) (Table 19). However, there was no preserved type 1 error control for this comparison because the TSS failed on the combined pacritinib group comparison to BAT.

In the subgroup of patients in PERSIST-2 with baseline platelet counts less than 50×10^9/L, the TSS responder rate was 22.6% in the pacritinib 200 mg BID arm (7 of 31 patients) and 12.5% in the BAT arm (4 of 32 patients); p=0.34.

Similar to the observation with SVR, the treatment effect on TSS with pacritinib 400 mg QD was smaller than with 200 mg BID, perhaps associated with the higher rate of drug interruptions in the 400 mg QD versus 200 mg BID arms. As shown in Table 12, the dropout rate in PERSIST-2 was higher in the pacritinib 400 mg QD arm than in the pacritinib 200 mg BID arm (44% versus

43

24%). The statistical review team was concerned whether the insignificant findings on TSS observed from the pooled arms or the 400 mg QD arm compared with BAT was due to the higher dropout rate in the pacritinib 400 mg QD arm than in the pacritinib 200 mg BID arm. We asked the Applicant to perform sensitivity analyses to further examine the impact of dropouts. The results from these sensitivity analyses showed that the insignificant findings observed in the pooled groups and in the 400 mg QD group as compared to BAT was not due to a higher dropout rate in the 400 mg QD group.

In PERSIST-1, TSS was a secondary endpoint analyzed in about 45% of patients who were administered the MPN-SAF TSS 2.0, which was introduced as a protocol amendment while the trial was underway. The TSS endpoint was achieved in 19.0% of these patients (19/100) treated with pacritinib 400 mg QD compared to 10.4% of patients (5/48) on BAT (p=0.24). However, nine of the 100 pacritinib-treated patients had missing baseline TSS 2.0 values and 16 had missing Week 24 TSS 2.0 values compared with three of the 48 BAT-treated patients missing baseline TSS 2.0 values and three missing Week 24 TSS 2.0 values. An analysis of the patients who had both valid baseline and Week 24 TSS 2.0 scores showed a TSS response rate of 36% with pacritinib 400 mg QD and 14% with BAT (nominal p=0.03).

Although the above analyses are not conclusive for substantial evidence of effectiveness on TSS, they support the potential for pacritinib to improve TSS in an adequately designed and powered trial.

Table 19. Proportion of Patients With at Least 50% Reduction in Original Total Symptom Score (Including Tiredness) in PERSIST-2 (ITT Efficacy Population and Patients With Platelet Counts Less Than 50×10⁹/L)

Statistic	ITT Efficacy Population				Patients With Baseline Platelet Counts Less Than 50×10^9/L		
	Pacritinib QD+BID (N=149)	Pacritinib 400 mg QD (N=75)	Pacritinib 200 mg BID (N=74)	BAT (N=72)	Pacritinib 400 mg QD (N=38)	Pacritinib 200 mg BID (N=31)	BAT (N=32)
Number (%)	37 (24.8)	13 (17.3)	24 (32.4)	10 (13.9)	6 (15.8)	7 (22.6)	4 (12.5)
95% CI[1]	18.1, 32.6	9.6, 27.8	22.0, 44.3	6.9, 24.1	6.0, 31.3	9.6, 41.1	3.5, 29.0
Difference[2]	10.9	3.4	18.5	-	3.3	10.1	-
CI[3]	-0.4, 21.0	-10.2, 16.8	2.8, 33.3	-	-16.4, 21.9	-12.0, 31.1	-
p-Value vs. BAT[4]	0.08	0.65	0.01	-	0.75	0.34	-

Source: Page 57 of the Integrated Summary of Efficacy.
[1] 95% CIs are based on the Clopper-Pearson method.
[2] Difference is PAC−BAT.
[3] CIs are based on the Agresti-Caffo method. A 95% CI is presented for the pooled pacritinib group and 97.5% CIs are presented otherwise.
[4] p-Value by Fisher's exact test.
Note: For PERSIST-2, the ITT Efficacy Population is based on the ITT Population truncated on the day of the clinical hold (i.e., patients randomized prior to September 7, 2015).
Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; ITT, intent-to-treat; PAC, pacritinib; QD, once daily

Table 20 shows the TSS results for the ITT All Randomized population. The results were similar to those observed in the ITT Efficacy population.

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Table 20. Proportion of Patients With at Least 50% Reduction in Original Total Symptom Score (Including Tiredness) in PERSIST-2 (ITT All Randomized Patients)

Statistic	Pacritinib 400 mg QD +200 mg BID (N=211)	Pacritinib 400 mg QD (N=104)	Pacritinib 200 mg BID (N=107)	BAT (N=100)
Number (%)	37 (17.5)	13 (12.5)	24 (22.4)	10 (10)
95% CI[1]	12.6, 23.3	6.8, 20.4	14.9, 31.5	4.9, 17.6
Difference[2]	7.5	2.5	12.4	-
CI[3]	-0.86, 14.9	-6.3, 11.2	2.2, 22	-
p-Value compared to BAT[4]	0.09	0.66	0.02	-

Source: FDA reviewer.
[1] 95% CIs are based on the Clopper-Pearson method.
[2] Difference is PAC−BAT
[3] CIs are based on the Agresti-Caffo method. A 95% CI is presented for the pooled pacritinib group and 97.5% CIs are presented otherwise.
[4] p-value from Fisher's exact test.
Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; ITT, intent-to-treat; PAC, pacritinib; QD, once daily

Modified TSS

As noted previously, because the two JAK inhibitors approved for MF (ruxolitinib and fedratinib) used a modified TSS (excluding tiredness) in their trials, the Applicant also conducted post hoc analyses for the modified TSS. The Applicant's analyses showed that the proportion of patients in the pacritinib 400 mg QD+200 mg BID pooled group who achieved ≥50% reduction in the modified TSS was 30.9% (46 of 149 patients), which was greater than[that observed with BAT (13.9% [10 of 72 patients]; nominal p=0.008) (Table 21).

Pacritinib 200 mg BID suggested improvement (≥50% reduction of the modified TSS) in the modified TSS compared to BAT (35.1% and 13.9%, respectively; nominal p=0.004). In the subgroup of patients with baseline platelet counts less than 50×10^9/L, the percentage of patients that showed a ≥50% reduction of the mTSS was 25.8% with pacritinib (8 of 31 patients) and 9.4% with BAT (3 of 32 patients; p=0.11).

Table 21. Proportion of Patients With at Least 50% Reduction in the Modified Total Symptom Score (Excluding Tiredness) at Week 24 in PERSIST-2 (ITT Efficacy Population and Patients With Platelet Counts Less Than 50×10⁹/L)

Statistic	ITT Efficacy Population Pacritinib QD+BID (N=149)	Pacritinib 400 mg QD (N=75)	Pacritinib 200 mg BID (N=74)	BAT (N=72)	Patients With Baseline Platelet Counts Less Than 50×10⁹/L Pacritinib 400 mg QD (N=38)	Pacritinib 200 mg BID (N=31)	BAT (N=32)
Number (%)	46 (30.9)	20 (26.7)	26 (35.1)	10 (13.9)	9 (23.7)	8 (25.8)	3 (9.4)
95% CI[1]	23.6, 39.0	17.1, 38.1	24.4, 47.1	6.9, 24.1	11.4, 40.2	11.9, 44.6	2.0, 25.0
Difference[2]	17.0	12.8	21.2	-	14.3	16.4	-
CI[3]	5.3, 27.2	-2.3, 27.1	5.3, 36.1	-	-6.5, 33.0	-5.8, 36.8	-
p-Value vs. BAT[3]	0.008	0.06	0.004	-	0.20	0.11	-

Source: Page 58 of the Integrated Summary of Efficacy.
[1] 95% CIs are based on the Clopper-Pearson method.
[2] Difference is PAC−BAT.
[3] CIs are based on the Agresti-Caffo method. A 95% CI is presented for the pooled pacritinib group and 97.5% CIs are presented otherwise.
[4] p-Value by Fisher's exact test.
Note: For PERSIST-2, the ITT Efficacy Population is based on the ITT Population truncated on the day of the clinical hold (i.e., patients randomized prior to September 7, 2015).
Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; ITT, intent-to-treat; PAC, pacritinib; QD, once daily

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Table 22 lists the mTSS results for the ITT All Randomized population. The results were similar to those observed in the ITT Efficacy population.

Table 22. Proportion of Patients With at Least 50% Reduction in the Modified Total Symptom Score (Excluding Tiredness) at Week 24 in PERSIST-2 (ITT All Randomized Population)

Statistic	Pacritinib 400 mg QD +200 mg BID (N=211)	Pacritinib 400 mg QD (N=104)	Pacritinib 200 mg BID (N=107)	BAT (N=100)
Number (%)	46 (21.8)	20 (19.2)	26 (24.2)	10 (10)
95% CI[1]	16.4, 28.0	12.1, 28.1	16.5, 33.5	4.9, 17.6
Difference[2]	11.8	9.2	14.2	-
CI[3]	3.08, 19.4	-0.65, 18.7	3.8, 24.0	-
p-value compared to BAT[4]	0.01	0.07	0.009	-

Source: FDA reviewer.
[1] 95% CIs are based on the Clopper-Pearson method.
[2] Difference is PAC−BAT.
[3] CIs are based on the Agresti-Caffo method. A 95% CI is presented for the pooled pacritinib group and 97.5% CIs are presented otherwise.
[4] p-Value by Fisher's exact test.
Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; ITT, intent-to-treat; PAC, pacritinib; QD, once daily

On September 23, 2021, the Agency requested the Applicant submit SVR, TSS, and mTSS results for patients with baseline platelet counts greater than 50×10^9/L. The results are provided in Table 23. Similar to the results discussed above, the proportion of patients who responded on SVR was higher in the 200 mg BID (14.3%) group as compared to the 400 mg QD (8.6%) group. The same trend was observed for both the TSS and mTSS endpoints.

Table 23. Proportion of Patients With ≥35% Reduction in SPV, With at Least 50% Reduction in the Total and Modified Symptom Score at Week 24 in PERSIST-2 (ITT Efficacy Population and Patients With Platelet Counts Greater Than 50×10^9/L)

Statistic	Pacritinib 400 mg QD (N=35)	Pacritinib 200 mg BID (N=42)	BAT (N=39)
SVR			
Number (%)	3 (8.6)	6 (14.3)	1 (2.6)
95% CI[1]	1.8, 23.1	5.4, 28.5	0.06, 13.5
Difference, PAC-BAT	6	11.7	-
CI[2]	-6.0, 17.9	-1.6, 23.7	
TSS			
Number (%)	7 (20)	16 (38.1)	6 (15.4)
95% CI[1]	8.4, 36.9	23.6, 54.4	5.9, 30.5
Difference, PAC-BAT	4.6	22.7	-
CI[2]	-13.0, 22.1	3.1, 40.0	
mTSS			
Number (%)	10 (28.6)	17 (40.5)	6 (15.4)
95% CI[1]	14.6, 46.3	25.6, 56.7	5.9, 30.5
Difference, PAC-BAT	13.2	25.1	-
CI[2]	-6.0, 31.4	5.3, 42.4	

Source: Risk-Benefit Information Request table, page 16.
[1] 95% CIs are based on the Clopper-Pearson method.
[2] CIs are based on the Agresti-Caffo method. A 95% CI is presented for the pooled pacritinib group and 97.5% CIs are presented otherwise.
Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; ITT, intent-to-treat; mTSS, modified total symptom score; PAC, pacritinib; QD, once daily; SPV, spleen volume; SVR, spleen volume reduction; TSS, total symptom score

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Efficacy Results—Other Subgroups

Sex

The proportion of patients who achieved ≥35% reduction in spleen volume was similar in males and females in PERSIST-2 (Table 24). Response rates by sex were similar in patients with baseline platelet counts less than $50×10^9$/L. However, due to the small number of patients, trends in the subgroup with severe thrombocytopenia should be interpreted with caution.

Table 24. Proportion of Patients With at Least 35% Reduction in Spleen Volume From Baseline to Week 24 by Sex in PERSIST-2 Efficacy Results Secondary Endpoint (ITT Population and Patients With Platelet Counts Less Than $50×10^9$/L)

| | ITT Population | | Patients With Baseline Platelet Counts Less Than $50×10^9$/L | |
| | PERSIST-2[1] | | PERSIST-2 | |
Statistic	Pacritinib 200 mg BID	BAT	Pacritinib 200 mg BID	BAT
Males	N=48	N=48	N=19	N=16
With ≥35% reduction, n (%)	11 (22.9)	1 (2.6)	6 (31.6)	1 (6.3)
95% CI[2]	12.0, 37.3	0.1, 13.5	12.6, 56.6)	0.2, 30.2
Difference (97.5% CI)[3]	20.4 (3.6, 34.6)		25.3 (-6.2, 50.6)	
Females	N=26	N=33	N=12	N=16
With ≥35% reduction, n (%)	5 (19.2)	1 (3.0)	3 (25.0)	0
95% CI[2]	6.6, 39.4	0.1, 15.8	5.5, 57.2	0.0, 20.6
Difference (97.5% CI)[3]	16.2 (-3.8, 35.2)		25.0 (-6.6, 52.7)	

Source: Page 84 of the Clinical Summary.
[1] For PERSIST-2, the ITT Population refers to the ITT Efficacy Population, which is based on the ITT Population truncated on the day of the clinical hold (i.e., patients randomized prior to September 7, 2015).
[2] 95% CIs are based on the Clopper-Pearson method.
[3] 97.5% CIs are based on the Agresti-Caffo method.
Note: Percentages in each subgroup are based on the number of patients in that subgroup.
Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; ITT, intent-to-treat

The proportion of patients who achieved ≥50% reduction in the modified TSS (i.e., excluding tiredness) was similar in males and females in the PERSIST-2 ITT Efficacy population (Table 25). Among patients with baseline platelet counts <$50×10^9$/L, the difference in response rate between pacritinib 200 mg BID and BAT was smaller for females than for males in PERSIST-2. These trends were also observed in the original TSS (i.e., including tiredness) scores. However, due to the small number of patients, differences should be interpreted with caution.

Table 25. Proportion of Patients With at Least 50% Reduction in the Modified TSS (Excluding Tiredness) From Baseline to Week 24 by Sex in PERSIST-2 (ITT Population and Patients With Platelet Counts Less Than $50×10^9$/L)

| | ITT Population | | Patients With Baseline Platelet Counts Less Than $50×10^9$/L | |
| | PERSIST-2[1] | | PERSIST-2 | |
Statistic	Pacritinib 200 mg BID	BAT	Pacritinib 200 mg BID	BAT
Males	N=48	N=39	N=19	N=16
With ≥50% reduction, n (%)	17 (35.4)	4 (10.3)	6 (31.6)	1 (6.3)
95% CI[2]	22.2, 50.5	2.9, 24.2	12.6, 56.6	0.2, 30.2
Difference (97.5% CI)[3]	25.2 (4.8, 42.8)		25.3 (-6.2, 50.6)	

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	ITT Population		Patients With Baseline Platelet Counts Less Than 50×10⁹/L	
	PERSIST-2[1]		PERSIST-2	
	Pacritinib		Pacritinib	
Statistic	200 mg BID	BAT	200 mg BID	BAT
Females	N=26	N=33	N=12	N=16
With ≥50% reduction, n (%)	9 (34.6)	6 (18.2)	2 (16.7)	2 (12.5)
95% CI[2]	17.2, 55.7	7.0, 35.5	2.1, 48.4	1.6, 38.3
Difference (97.5% CI)[3]	16.4 (-9.6, 41.0)		4.2 (-26.7, 36.3)	

Source: Page 85 of the Clinical Summary.
[1] For PERSIST-2, the ITT Population refers to the ITT Efficacy Population, which is based on the ITT Population truncated on the day of the clinical hold (i.e., patients randomized prior to September 7, 2015).
[2] 95% CIs are based on the Clopper-Pearson method.
[3] 97.5% CIs are based on the Agresti-Caffo method.
Note: The values for N are based on patients in the ITT Population using the MPN-SAF TSS 2.0.
Note: Percentages in each subgroup are based on the number of patients in each subgroup.
Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; ITT, intent-to-treat; MPN-SAF, Myeloproliferative Neoplasm-Symptom Assessment Form; TSS, total symptom score

Age

The proportion of patients who achieved a ≥35% reduction in spleen volume was higher in patients ≥65 years of age compared to those <65 years of age in PERSIST-2, including among patients with baseline platelet counts less than 50×10⁹/L (Table 26). Response rates were higher for patients treated with pacritinib 200 mg BID compared to BAT in PERSIST-2 in patients ≥65 years of age and those <65 years of age. However, due to the small number of patients, any differences should be interpreted with caution.

Table 26. Proportion of Patients With at Least 35% Reduction in Spleen Volume From Baseline to Week 24 by Age in PERSIST-2 (ITT Population and Patients With Platelet Counts Less Than 50×10⁹/L)

	ITT Population		Patients With Baseline Platelet Counts Less Than 50×10⁹/L	
	PERSIST-2[1]		PERSIST-2	
	Pacritinib		Pacritinib	
Statistic	200 mg BID	BAT	200 mg BID	BAT
<65 years	N=28	N=21	N=12	N=7
With ≥35% reduction, n (%)	4 (14.3)	0	2 (16.7)	0
95% CI[2]	4.0, 32.7	0.0, 16.1	2.1, 48.4	0.0, 41.0
Difference (97.5% CI)[3]	14.3 (-5.7, 30.3)		16.7 (-23.7, 44.3)	
≥65 years	N=46	N=51	N=19	N=25
With ≥35% reduction, n (%)	12 (26.1)	2 (3.9)	7 (36.8)	1 (4.0)
95% CI[2]	14.3, 41.1	0.5, 13.5	16.3, 61.6	0.1, 20.4
Difference (97.5% CI)[3]	22.2 (5.4, 37.5)		32.8 (4.4, 57.0)	

Source: Page 87 of the Clinical Summary.
[1] For PERSIST-2, the ITT Population refers to the ITT Efficacy Population, which is based on the ITT Population truncated on the day of the clinical hold (i.e., patients randomized prior to September 7, 2015).
[2] 95% CIs are based on the Clopper-Pearson method.
[3] 97.5% CIs are based on the Agresti-Caffo method.
Note: Percentages in each subgroup are based on the number of patients therein.
Abbreviations: BAT, best available therapy; BID, twice daily; CI, confidence interval; ITT, intent-to-treat

Given the lack of consistency in observed trends across these age subgroups and the small sizes of many subgroups, these findings should be interpreted with caution.

The proportion of patients who achieved ≥50% reduction in the modified TSS (i.e., excluding tiredness) was similar in patients ≥65 years of age (26%) and those <65 years of age (25%), and

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response rates were numerically higher among patients treated with pacritinib 200 mg BID compared to BAT. However, given the small samples sizes, these findings should be interpreted with caution.

Race

The proportion of patients in PERSIST-2 treated with pacritinib 200 mg BID who achieved ≥35% reduction in spleen volume was higher in non-Caucasian patients. However, due to the small numbers of non-Caucasian patients enrolled, results in this subgroup should be interpreted with caution. Among Caucasian patients, response rates to pacritinib 200 mg BID were lower among patients with baseline platelet counts less than 50×10^9/L; no conclusions could be drawn for response rates among non-Caucasian patients with severe thrombocytopenia due to the small sample size.

The proportion of patients treated with pacritinib 200 mg BID who achieved ≥50% reduction in TSS was similar in Caucasian patients compared with non-Caucasian patients in PERSIST-2, and differences in response rate between pacritinib 200 mg BID and BAT were also similar between Caucasians and non-Caucasians.

The proportion of patients who achieved ≥50% reduction in the modified TSS (i.e., excluding tiredness) was higher in Caucasian patients compared to non-Caucasian patients in PERSIST-2, regardless of baseline platelet count or treatment assignment, though due to the small number of non-Caucasian patients, any differences should be interpreted with caution.

Prior Treatment with JAK2 Inhibitors

The proportion of patients who achieved ≥35% reduction in spleen volume was higher in patients with no prior treatment with JAK2 inhibitors (24%) compared with patients with prior treatment history with JAK2 inhibitors (18%) in PERSIST-2. A similar finding was observed in the subgroup of patients with baseline platelet counts less than 50×10^9/L. However, due to the small number of patients, any differences should be interpreted with caution.

The proportion of patients who achieved ≥50% reduction in TSS was similar in patients with no prior treatment with JAK2 inhibitors compared with patients with prior treatment history with JAK2 inhibitors in PERSIST-2. In patients on pacritinib 200 mg BID with baseline platelet counts less than 50×10^9/L, response rates were higher among JAK inhibitor-naïve patients (26%) compared to those who had received prior JAK inhibitor therapy (17%) on PERSIST-2.

The proportion of patients who achieved ≥50% reduction with the modified TSS (i.e., excluding tiredness) was higher in patients with no prior treatment with JAK2 inhibitors (39%) compared with patients with prior treatment history (30%). However, due to the small number of patients, any differences should be interpreted with caution.

Efficacy Results—Exploratory Endpoints

Overall Survival

An ITT analysis of deaths in PERSIST-2 censored on February 8, 2016, the date of the clinical hold, demonstrated that the death rate was not different between the BAT and pacritinib 400 mg QD groups and was numerically lower in the pacritinib 200 mg BID group and the pacritinib 400 mg QD+200 mg BID pooled group. The death rates were 15 of 104 (14.4%) patients for

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400 mg QD pacritinib, 10 of 107 (9.3%) patients for pacritinib 200 mg BID, 25 of 211 (11.8%) patients for pacritinib 400 mg QD+200 mg BID pooled group, and 14 of 100 (14.0%) patients for the BAT group.

Survival probability was similar for all treatment groups through Week 24: 91% for both pacritinib groups and the pacritinib 400 mg QD+200 mg BID pooled group, and 90% for BAT.

The ITT analysis of overall survival censored at the time of the clinical hold (February 8, 2016) showed a hazard ratio (HR) of 0.90 (95% confidence interval [CI] 0.47, 1.73) for the pacritinib 400 mg QD+200 mg BID pooled group versus BAT, 0.68 (95% CI 0.30, 1.53) for pacritinib 200 mg BID versus BAT, and 1.18 (95% CI 0.57, 2.44) for pacritinib 400 mg QD versus BAT (Figure 4 and Figure 5). In the longer-term analysis censored at the study cutoff date of August 19, 2016, the HRs were similar: 1.03 for pacritinib 400 mg QD+200 mg BID pooled group versus BAT, 0.89 for pacritinib 200 mg BID versus BAT, and 1.19 for pacritinib 400 mg QD versus BAT.

Figure 4. Overall Survival in PERSIST-2 Censored on February 8, 2016, Pooled Pacritinib Group Versus BAT (ITT All Randomized Population)
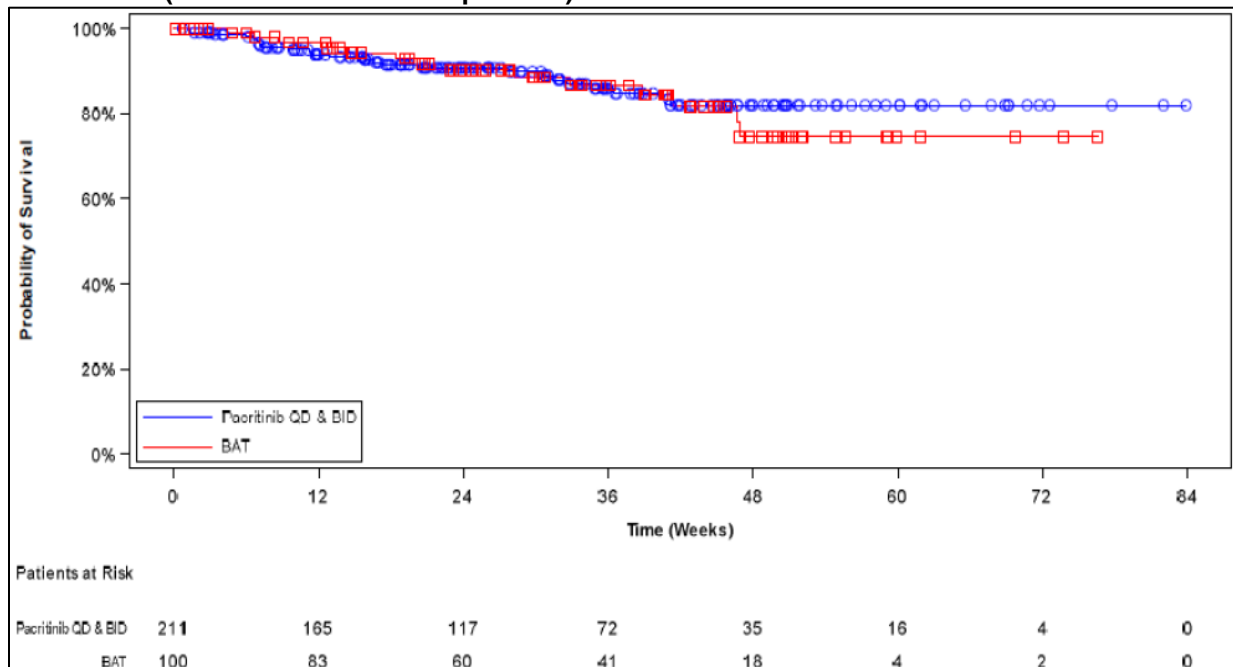
Source: Page 77 of the Clinical Summary.
Abbreviations: BAT, best available therapy; BID, twice daily; ITT, intent-to-treat; QD, once daily

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Figure 5. Overall Survival in PERSIST-2 Censored on February 8, 2016 (ITT All Randomized Population)
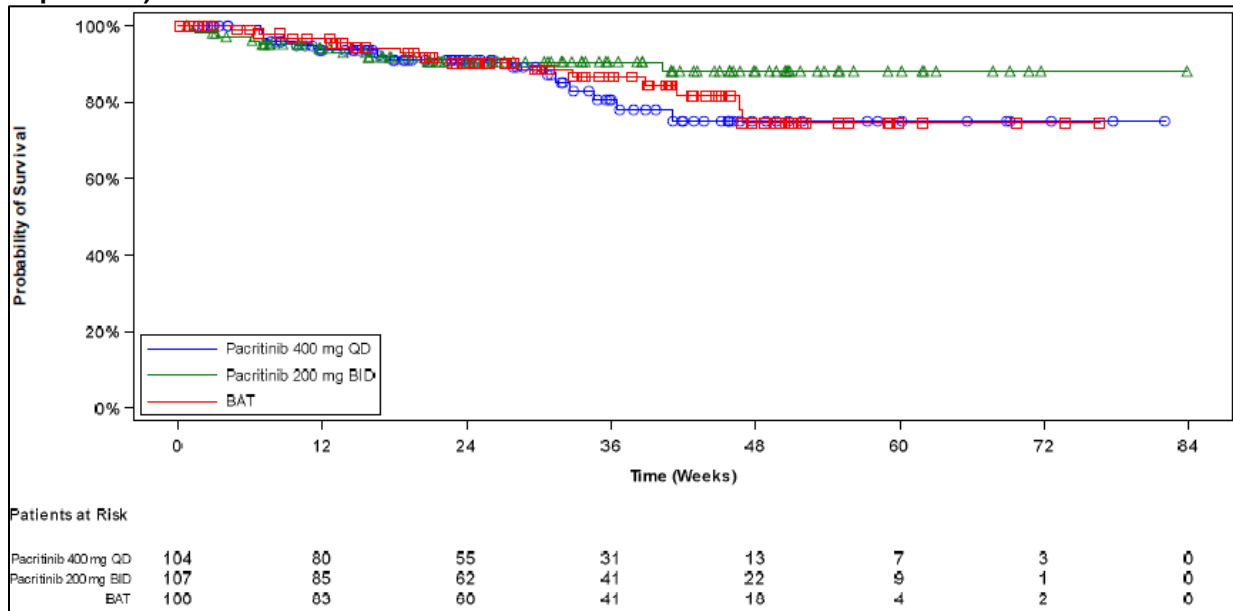
Source: Page 78 of the Clinical Summary.
Abbreviations: BAT, best available therapy; BID, twice daily; ITT, intent-to-treat; QD, once daily

In the subgroup of patients with baseline platelet counts less than 50×10^9/L, the death rates were 10 of 52 (19.2%) patients for pacritinib 400 mg QD, 9 of 46 (19.6%) patients for pacritinib 200 mg BID, and 10 of 43 (23.3%) patients for the BAT group. Survival probability at Week 24 was 84% for both the pacritinib 400 mg QD and BAT groups and 80% for the pacritinib 200 mg BID group. The survival probabilities for pacritinib 400 mg QD and pacritinib 200 mg BID were not statistically different from the BAT group (p=0.99 and p=0.87, respectively). The ITT analysis of overall survival of this subgroup censored at the time of clinical hold (February 8, 2016) showed a HR of 0.93 (95% CI 0.38, 2.29) for pacritinib 200 mg BID versus BAT and 1.01 (95% CI 0.42, 2.44) for pacritinib 400 mg QD versus BAT (Figure 6).

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Figure 6. Overall Survival Censored on February 8, 2016, in PERSIST-2 Patients With Baseline Platelet Counts Less Than 50×10^9/L (ITT All Randomized Population)
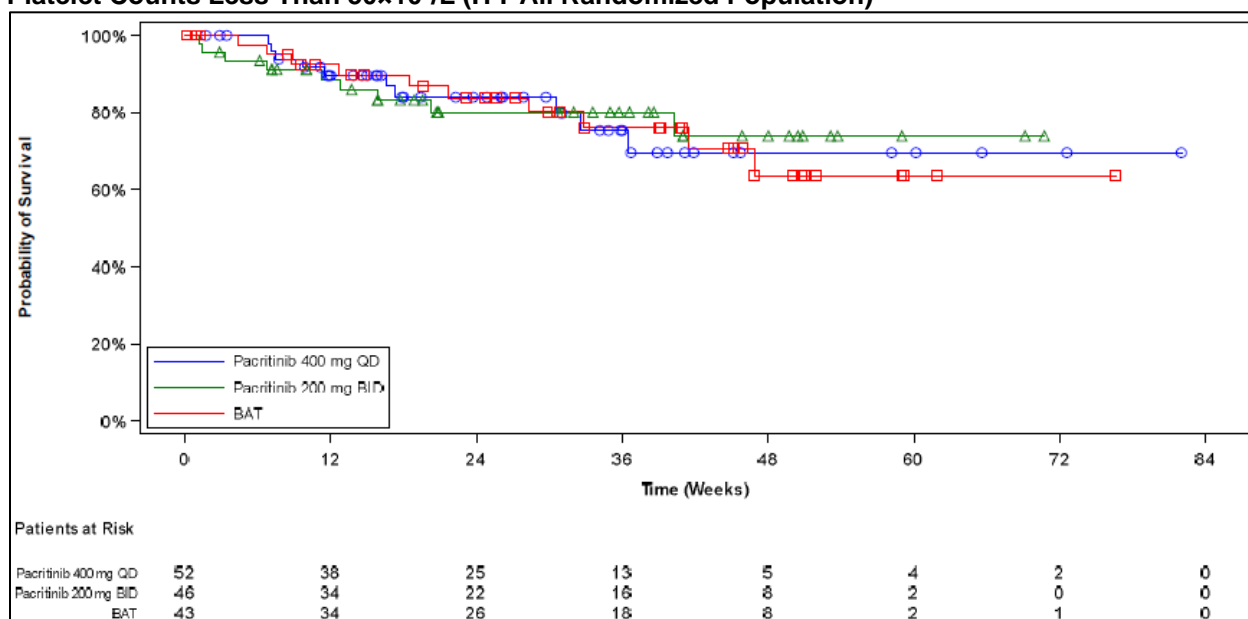
Source: Page 79 of the Clinical Summary.
Abbreviations: BAT, best available therapy; BID, twice daily; ITT, intent-to-treat; QD, once daily

Data Quality and Integrity

The quality of the original data submission was adequate. In general, the reviewers were able to perform independent review and confirm the Applicant's analysis results using the submitted datasets.

Materials reviewed include the protocols and study report for this study. Data provided in Study Data Tabulation Model and Analysis Dataset Model formats are acceptable.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Premature Stopping of PERSIST-2

Issue

Dosing in PERSIST-2 was stopped prematurely when the trial was placed on clinical hold for safety issues that emerged in PERSIST-1. As a result, only about three-fourths of the planned enrollment had evaluable efficacy data. We considered whether the data from the prematurely stopped trial could support the efficacy of pacritinib.

Assessment

The primary efficacy analyses were performed at Week 24 and focused on the ITT-Efficacy Population, defined as all patients randomized 22 weeks prior to the day of the clinical hold (with consideration for the 2-week window allowed for study visits). To assess the robustness of these results, we also conducted sensitivity analyses on all randomized patients instead of only

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patients who had evaluable efficacy data by classifying those patients with missing data as non-responders. The efficacy findings were consistent in both analyses. In addition, the study was stopped because of our imposition of a clinical hold, and not for other reasons or at the Applicant's discretion. There were no interim analyses conducted prior to the final analysis and, therefore, no need for an alpha penalty.

Despite the premature stopping of the trial, PERSIST-2 shows compelling evidence of an effect of pacritinib on SVR (p=0.002 on the primary analysis), including in the subgroup of patients with platelet counts below 50×10^9/L (p=0.006 for pacritinib 200 mg BID).

Conclusion

The premature stopping of the trial may have contributed to underpowering for the TSS endpoint, but it is still possible to conclude that there is a compelling effect of pacritinib on SVR, including in the subgroup of patients with platelet counts below 50×10^9/L.

6.3.2. PERSIST-2 Failed on One Coprimary Efficacy Endpoint

Issue

PERSIST-2 had two coprimary efficacy endpoints at Week 24: The proportion of patients with SVR ≥35% and the proportion of patients with ≥50% reduction in the TSS. The trial was successful on the SVR endpoint but not on the TSS endpoint.

Background

Typically, a trial with coprimary efficacy endpoints is considered positive only when all the coprimary efficacy endpoints succeed. PERSIST-2 was estimated to have at least 93% power with 100 patients per treatment group based on an assumed TSS response rate of 45% with pacritinib and 5% with BAT using response rates seen with another JAK inhibitor, and assuming 10% dropout. Dosing in the trial was stopped prematurely when it was placed on clinical hold for safety issues that emerged in PERSIST-1. As a result, only about three-fourths of the planned enrollment had evaluable efficacy data. The coprimary efficacy results for TSS comparing the pooled pacritinib doses to BAT showed a TSS responder rate of 24.8% for the pooled pacritinib doses and 13.9% for BAT, with a treatment difference of 10.9% (95% CI -0.4, 21.0), p=0.08. Because this p-value exceeded 0.05, there was no remaining alpha for statistically testing the individual pacritinib doses versus BAT.

Assessment

The factors that may have contributed to the statistical miss on the TSS include an overly optimistic assumed treatment effect on the power calculations, premature stopping of dosing in the trial due to the clinical hold (which resulted in further underpowering of the trial), and an unexpected small treatment effect with pacritinib 400 mg QD. The treatment effect for pacritinib 400 mg QD versus BAT was 3.4% compared to a treatment effect for pacritinib 200 mg BID versus BAT of 18.5%.

Therefore, there is not compelling evidence of an effect of pacritinib on TSS. However, several lines of evidence suggest the potential for pacritinib to improve TSS in an adequately designed

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and powered trial. First, the TSS effect of 32.4% with pacritinib 200 mg BID compared to 13.9% with BAT was nominally statistically significant. Second, in PERSIST-1, the 400 mg QD dose had a numerically larger effect on TSS than it did in PERSIST-2, as discussed in Section 6.2.2. Third, an exploratory analysis using the modified TSS (which excludes tiredness and was used as an endpoint for the two JAK inhibitors approved for MF) was nominally statistically significant for the combined pacritinib treatment groups versus BAT and for pacritinib 200 mg BID versus BAT and showed a larger treatment effect for 400 mg QD than the nonmodified TSS.

Conclusion

While the above analyses are not compelling for an effect of pacritinib on TSS, they support the potential for pacritinib to improve TSS in an adequately designed and powered trial. There is, however, compelling evidence of an effect on SVR with pacritinib 200 mg BID, including in patients with platelet counts below 50×10^9/L.

6.3.3. Pacritinib 400 mg QD Appears Less Effective on SVR Than Pacritinib 200 mg BID in PERSIST-2

Issue

In PERSIST-2, the efficacy of pacritinib 400 mg QD on SVR appears smaller than that of 200 mg BID despite 400 mg QD having modestly higher systemic exposure and C_{max} compared to 200 mg BID. One would expect that a dosing regimen with higher pharmacokinetic exposures would lead to better, or at least comparable effects compared to a dosing regimen with lower pharmacokinetic exposures.

Assessment

As discussed in Section 6.2.2, although the treatment effect on SVR with pacritinib 400 mg QD is smaller than with 200 mg BID, the confidence intervals for the treatment effects overlap considerably. Furthermore, in PERSIST-1, the SVR endpoint was achieved in 19.1% of patients treated with pacritinib 400 mg QD compared to 4.7% of patients on BAT (p<0.001), which is more consistent with the SVR response rates of 21.6% for pacritinib 200 mg BID and 2.8% for BAT in PERSIST-2.

Conclusion

It is unclear why the efficacy on SVR in PERSIST-2 with pacritinib 400 mg QD arm is less than that with 200 mg BID. As discussed above, it is not possible to conclude definitively that 400 mg QD is, in fact, less efficacious than 200 mg BID. The confidence intervals for the treatment effects on SVR overlap considerably and the effect of pacritinib 400 mg QD on SVR in PERSIST-1 appears comparable to that seen with 200 mg BID on SVR in PERSIST-2.

6.3.4. Scientific Basis for Establishing Substantial Evidence of Effectiveness

Issue

A conclusion of substantial evidence of effectiveness requires evidence from at least two adequate and well-controlled trials, one adequate and well-controlled trial that is the functional equivalent of two adequate and well-controlled trials, or one adequate and well-controlled trial plus confirmatory evidence. The approach used for pacritinib should be clearly articulated.

Background

In PERSIST-2, there was a compelling effect of pacritinib 200 mg BID on SVR in the overall trial population and in the subgroup of patients with platelet counts below 50×10^9/L. Other data with pacritinib 200 mg BID comes from Study PAC203, a Phase 2, randomized, open-label dose-finding trial. We considered whether Study PAC203 should be considered a second adequate and well-controlled trial or confirmatory evidence for the effect of pacritinib 200 mg BID on SVR. We also assessed whether there were other sources of evidence supporting a compelling effect of pacritinib on SVR.

Assessment

Study PAC203 was an open-label, randomized, Phase 2 trial that compared pacritinib 100 mg QD, 100 mg BID, and 200 mg BID in patients with primary or secondary MF (DIPSS risk score of Intermediate-1 to High Risk), who were previously treated with ruxolitinib. There were approximately 50 patients in each treatment group. The percentage reduction in spleen volume was the primary efficacy endpoint and was assessed blindly based on MRI or CT scan imaging at baseline, Week 12, and Week 24. A supportive measure included the percentage of patients with SVR≥35%. The primary objective of this trial was to explore the dose-response relationship for further clinical trials. There was no formal statistical hypothesis. Efficacy analyses were based on the full analysis set defined as randomized patients who received at least one dose of study medication. At Week 24, the median percent reduction in spleen volume was 10% for the 200 mg BID regimen, 0% for the 100 mg BID regimen and 7% for 100 mg QD. Five of fifty-four patients (9.3%; 95% CI 3.1, 20.3) on pacritinib 200 mg BID had SVR ≥35% at Week 24 compared to none of the 52 patients on pacritinib 100 mg QD and one (1.8%) of 55 patients on pacritinib 100 mg BID. Among the patients with baseline platelets <50,000/µL, there were four patients with SVR ≥35%, all of whom received pacritinib 200 mg BID. The Applicant's approach to missing data was not clearly described in the protocol or statistical analysis plan, and as noted previously, there was no formal statistical hypothesis testing. Therefore, we agree with the Applicant that this trial is not sufficient to serve as a second adequate and well-controlled trial. There is some support for a dose-response relationship, and we agree that this trial can serve as part of the confirmatory evidence of effectiveness.

Additional confirmatory evidence of effectiveness includes the effect of pacritinib 400 mg QD on SVR compared to BAT in PERSIST-1. As noted previously, that trial showed a response rate on SVR of 19.1% of patients treated with pacritinib 400 mg QD compared to 4.7% of patients on BAT (p<0.001). These data with the same total daily dose as 200 mg BID (and only modestly higher C_{max} and AUC) provide additional confirmatory evidence for the efficacy of pacritinib on SVR.

Conclusion

The Applicant has established substantial evidence of effectiveness of pacritinib 200 mg BID on SVR based on evidence from one adequate and well-controlled trial (PERSIST-2) plus confirmatory evidence from PAC203 and PERSIST-1. These data, together with an expectation that patients with intermediate and high-risk MF would not have spontaneous SVR ≥35% over 6 months, provide compelling evidence of a treatment effect with pacritinib on spleen size.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Toxicological characterization of pacritinib was assessed in mice (1, 4, and 26 weeks), rats (1, 4, and 13 weeks), dogs (1, 4, and 39 weeks) and rabbits (embryo-fetal development) during repeat-dose toxicology studies. Mice and dogs were considered the most relevant nonclinical species for toxicological evaluations based on the similarity of their pacritinib metabolic profile to humans and the sufficient bioavailability observed in these nonclinical species. The in vivo metabolites identified in rats and rabbits were, in general, similar to those observed in humans, indicating that these species were also toxicologically relevant for assessment of pacritinib metabolites. No unique human metabolites of pacritinib were observed in healthy human subjects (PAC102). No definitive risks were identified during in vitro and in vivo safety pharmacology assessments. Pacritinib inhibited human ether-à-go-go-related gene (hERG) potassium channel with a mean IC_{50} of 3μM, substantially higher than free plasma concentrations at clinical exposure (human maximum concentration [C_{max}] at 200 mg twice daily [BID], free fraction 240nM). These studies are discussed in more detail in Section III.13.1.1.2.

The results of the nonclinical toxicology studies were consistent with the expected mechanism of action of JAK2 and/or FLT3 inhibition whereby the production of hematopoietic cell lines are reduced. Notable findings included an increase in mortality and/or morbidity, decreased food consumption and decreased body weight gain and/or body weight loss in mice, rats, rabbits, and dogs. Lymphoid tissue depletion and concomitant changes in white blood cell parameters, consistent with bone marrow suppression, were observed in mice, rats, and dogs and the gastrointestinal toxicity observed in rats and dogs is consistent with the known effects of JAK2/FLT3 inhibition.

The toxicities observed in nonclinical studies occurred at exposures that were significantly lower than those anticipated at the proposed therapeutic dose (Table 27). However, interpretation of the lack of safety margins must take into consideration that the toxicology studies were conducted in normal, healthy animals that do not harbor activating JAK mutations or excessive wild-type JAK

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activity. This clearly shifted the toxicological exposure/response curve leftward relative to human subjects with MF as the severe toxicities observed in the animal studies were not recapitulated in clinical trials at similar exposures. Thus, results from the toxicology studies more accurately represent the consequences of excessive JAK and/or FLT3 suppression in normal (non-disease state) animals and, presumably, what may occur in human subjects without activating JAK mutations or excessive JAK activity associated with disease. General toxicology findings are discussed in detail in Section III.13.1.3.1.

The M1 metabolite of pacritinib was identified as the predominant metabolite in mouse, rat and rabbit, a finding consistent with toxicokinetic studies and nonclinical exposure data. However, it is notable that the M2 metabolite, a principal metabolite in humans present at ~10% of the parent pacritinib, is not a predominant metabolite in any of the nonclinical species. No safety concerns were identified with the pacritinib M1 and M2 metabolites in nonclinical studies. The details regarding cross-species metabolism of pacritinib are discussed in detail in Section III.13.1.2.

Pacritinib was not carcinogenic in either a 2-year rat study or during a 26-week hemizygous Tg(HRAS) transgenic mouse study, demonstrating low carcinogenic potential secondary to inhibition of JAK2/FLT3 activity. However, a notable limitation of the carcinogenicity assessment is that pacritinib exposures achieved in rats and mice were considerably lower than the exposure observed at the recommended human dose, due to a lack of tolerability primarily from excessive JAK2/FLT3 activity at higher doses. The inability to evaluate pacritinib at multiples of clinical exposure limits the robustness of assessing carcinogenic potential from off-target kinases where pacritinib and the M1/M2 metabolites have lower inhibitory potencies than for JAK2/FLT3 (Section III.13.1.1). The details regarding the carcinogenicity assessments of pacritinib are discussed in Section III.13.1.3.3.

Reproductive toxicology was assessed in mice in two fertility and early embryonic development studies (BALB/c and CD-1), an embryo-fetal development study (CD-1) and a pre- and postnatal development study (CD-1). An embryo-fetal development study was also conducted in New Zealand white rabbits. Effects observed on developmental and reproductive parameters in mice and rabbits were considered driven by maternal toxicity and a subsequent delay in fetal development. The nonclinical data supporting pregnancy and lactation labeling are presented in Section 8.4 and the reproductive and developmental toxicity findings are discussed in detail in Section III.13.1.3.4.

Table 27. Exposure Margins (Chronic Toxicology Studies, Pivotal)

Study	NOAEL (mg/kg/day)	Nonclinical Exposure (µg.h/mL)	Exposure Margins[1] (Dose Multiples)
Six-month mouse	200 mg/kg/day	4.8 µg·h/mL	0.02×
Nine-month dog	20 mg/kg/day	11.8 µg·h/mL (males)	0.06×
		3.4 µg·h/mL (females)	0.02×

Source: Reviewer-constructed summary table of chronic toxicology studies submitted to the new drug application.
[1] Exposure margins were based on the simulated population pharmacokinetic data generated by the Clinical Pharmacology Reviewer through pharmacokinetic modeling of patient samples collected in Study PAC201, PERSIST-1, and PERSIST-2 where the proposed therapeutic dose (200 mg, BID), resulted in a systemic geometric mean exposure of 213 µg.h/mL (AUC).
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; NOAEL, no observed adverse effect level

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7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Ruxolitinib (Jakafi®) (approved for marketing on November 16, 2011, under NDA 202192) is a JAK 1 and 2 inhibitor indicated for treatment of intermediate or high risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults; polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea; and steroid refractory acute graft-versus-host disease in adult and pediatric patients 12 years and older. Fedratinib (Inrebic®) (approved for marketing on August 16, 2019, under NDA 212327) is also a JAK2 and FLT3 inhibitor also indicated for the treatment of adults with Intermediate 2 or high risk primary or secondary myelofibrosis. There is emerging safety information regarding the potential for increased risk of major adverse cardiac events, thrombosis, and increased risk of mortality and malignancy in patients who are treated with JAK inhibitors.

Relevant portions of a Memorandum to File under NDA 202192 and NDA 212327 (final signature date August 23, 2021, completed by Dr. Rosanna Setse, Deputy Director for Safety in the Division of Nonmalignant Hematology) are shown in Figure 7 for reference.

Figure 7. Excerpts From the Memorandum to File Under NDA 202192 and NDA 212327

The Agency has been informed by a sponsor of a different JAK inhibitor drug, tofacitinib, of emerging safety issues regarding major adverse cardiovascular events (MACE) (including cardiovascular death), thrombosis, and increased risk of mortality and malignancy identified from the long-term safety trial (Study A3921133) of tofacitinib in patients with rheumatoid arthritis (RA). FDA is planning to issue safety labeling changes for the JAK inhibitor class of drugs for inflammatory conditions i.e., tofacitinib, baricitinib and upadacitinib. The planned safety labeling changes for the JAK inhibitors indicated for patients with inflammatory conditions are summarized below:

Mortality:
- Sections of tofacitinib labeling are being updated to include information regarding the increased risk of mortality with both doses versus tumor necrosis factor (TNF) blockers.
- New Boxed Warning and Warnings and Precautions sections are being added to baricitinib and upadacitinib with a reference to tofacitinib as the source of the new safety information.

Malignancy and Thrombosis:
- The labeling for all three products are being updated to include information from the safety trial, highlighting the increased risk of malignancy when compared to TNF blockers and specifically referring to lymphoma and lung cancer in both Boxed Warnings and Warnings and Precautions sections.
- The tofacitinib PI will include more detailed information from the safety trial.

Major Adverse Cardiovascular Events (MACE)
- MACE will be included in the Boxed Warning and Warnings and Precautions section of the labeling for all three products.
- Tofacitinib will provide specific information based on the safety trial.
- Upadacitinib and baricitinib will refer to the information from tofacitinib as the source of the new safety information.

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To evaluate the risk of MACE, thrombosis and malignancies associated with ruxolitinib, DNH obtained safety data from four randomized trials of ruxolitinib with long-term follow-up shown in the table below.

Table: Randomized trials of ruxolitinib with long-term follow-up

STUDY	DX	N	TITLE
INCB18424-351	MF	306	A Randomized, Double-Blind, Placebo-Controlled Study of the JAK Inhibitor INCB018424 Tablets Administered Orally to Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera Myelofibrosis (PPV-MF), or Post-Essential Thrombocythemia Myelofibrosis (PET-MF)
CINC424A2352 (352)	MF	219	A randomized study of the JAK inhibitor INC424 tablets compared to best available therapy in patients with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF)
CINC424B2301	PV	222	Randomized, open label, multicenter phase III study of efficacy and safety in polycythemia vera subjects who are resistant to or intolerant of hydroxyurea: JAK inhibitor INC424 tablets versus best available care
INCB18424-357 (2302J)	PV	110	Polycythemia Vera Symptom Study Evaluating Ruxolitinib Versus Hydroxyurea in a Randomized, Multicenter, Double-Blind, Double-Dummy, Phase 3 Efficacy and Safety Study of Patient Reported Outcomes

Summary of MACE Results: With longer treatment and follow-up in the 2 MF and PV studies, exposure-adjusted analysis did not show a disproportionate increase in frequency of MACE despite prolonged treatment with ruxolitinib compared to relatively short treatment periods with control therapies (BAT, HU, or placebo). For the MF studies (INCB 18424-351 and CINC424A2352), the MACE rates are comparable to the 1.75 events per 100 patient years cumulative rate of fatal and nonfatal cardiovascular events documented in MF populations in the literature. For the PV studies (CINC424B2301 and INCB 18424-357), the rates of MACE also appear similar to or slightly lower than previously reported rates of 1.9 to 5.5 events per 100 person-years for patients with PV [4, 18, 19].

Summary of Thrombosis Results: In the 4 randomized controlled studies in subjects with MF (INCB 18424-351 and CINC424A2352) and PV (CINC424B2301 and INCB 18424-357), when adjusted for exposure duration, the incidence rates of arterial thromboembolic events (ATEs) were generally comparable in the ruxolitinib and control arms across the 4 studies as well as in the pooled population. In comparing data between the event rates demonstrated in these analyses and previously published event rates in the PV and MF populations, the risk of events appears generally lower in these studies. Adverse events of special interest in the RESPONSE trial included thromboembolic events. At the 5 year follow up in the RESPONSE trial [1], thromboembolic events were lower in the ruxolitinib arm than the best available therapy arm.

Summary of Malignancies Results: In the 4 randomized controlled studies in subjects with MF (INCB 18424-351 and CINC424A2352) and PV (CINC424B2301 and INCB 18424-357), when adjusted for exposure, the incidence rates of secondary malignancies [excluding non-melanoma skin cancer (NMSC)] in the ruxolitinib arm and control arms were generally similar across the 4 studies as well as in

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the pooled populations. The incidence rate of the control arm before or without crossover to ruxolitinib was lower across all 4 studies and the pooled populations. The exposure-adjusted incidence rates of secondary malignancies (excluding NMSC) in the crossover period were also similar in the individual studies and the pooled populations. A review of secondary malignancies (excluding NMSC) from the 4 randomized studies did not reveal any pattern for malignancies reported as second primary malignancies (SPM). The rates of secondary malignancies (excluding NMSC) appear lower in these studies than previously published literature in MPNs [20].

FDA approval of Inrebic (fedratinib) for MF in 2019 was primarily based on efficacy data from the JAKARTA study in patients with intermediate-2 to high risk primary or secondary myelofibrosis. The primary safety population was patients enrolled in JAKARTA which included 96 patients who received 400 mg and 97 patients who received 500 mg of fedratinib. Also, included in the safety analysis were 71 patients originally randomized to placebo who crossed over to receive at least 1 partial dose of fedratinib 400 mg (35 patients) or 500 mg (36 patients). Supportive safety data was obtained from the JAKARTA-2 trial which included 97 patients who received fedratinib.

In JAKARTA, death due to adverse reactions was reported in 2% of patients who received fedratinib, and 4% of patients who received placebo. Serious adverse reactions in ≥2% of patients receiving fedratinib 400 mg daily included cardiac failure (5%) and anemia (2%). MACE and/or thrombosis were not identified as risks associated with fedratinib in clinical trials. Secondary malignancies were not reported in the primary or supportive safety population at the time of approval. A safety signal of encephalopathy, including Wernicke's encephalopathy was identified during clinical trials of fedratinib. In the postmarketing setting, a safety signal for MACE, thrombosis or malignancies has not been identified for Inrebic so far.

SLC for Jakafi and Inrebic

Unlike the JAK inhibitors for inflammatory conditions, Jakafi and Inrebic do not have Boxed Warnings for serious infections, thrombosis, lymphoma, and other malignancies. Jakafi has Warnings and Precautions statements for cytopenias, the risk of infection, symptom exacerbation following interruption or discontinuation of treatment, non-melanoma skin cancer and lipid elevations. Inrebic has a Boxed Warning for serious and fatal encephalopathy, including Wernicke's encephalopathy; and has Warnings & Precautions statements for anemia and thrombocytopenia, GI toxicity, hepatic toxicity and amylase and lipase elevation.

Considering the life-threatening nature and complexity of the diseases for which ruxolitinib and fedratinib are indicated, including an inherently increased risk for thromboembolic events, cardiovascular events and malignancies, as well as the available evidence of improved survival outcomes with ruxolitinib in patients with MF and PV; different risk messaging is warranted for the JAK inhibitors approved for hematological conditions (ruxolitinib and fedratinib) than the other JAK inhibitors approved for inflammatory conditions.

(b) (5)

A summary of the planned safety labeling changes for the JAK inhibitors approved for hematological conditions (Jakafi and Inrebic) and the rationale for these recommendations are shown in the table below:

Safety issue	Labeling Recommendation	Justification/Rationale for change
Overall Survival	None	The mortality signal identified for JAK inhibitors in the RA and UC populations has not been demonstrated in patients with MPNs treated with Jakafi. On the contrary, long-term (5 years) data from 2 relatively large, randomized clinical trials (COMFORT-I, COMFORT-II), show a survival advantage in patients with intermediate-2 or high-risk PMF treated with ruxolitinib. A safety signal for mortality was not identified in clinical trials for fedratinib.
MACE	Warning and Precautions statement	The data from the 4 randomized, controlled clinical studies of Jakafi in patients with MPN do not provide evidence to support a causal association between Jakafi and increased risk of MACE. However, due to the noted limitations of the randomized trials in MPN patients, an additional MACE risk to this population due to Jakafi exposure cannot be ruled out from the available data. A safety signal for MACE was not identified in clinical trials for Inrebic. Until additional data is available to characterize this risk in patients with MPN, a Warnings & Precaution statement for MACE is recommended for the JAK inhibitors approved for hematological conditions.
Thrombosis	Warning and Precautions statement	In the 4 randomized controlled studies in subjects with MF (INCB 18424-351 and CINC424A2352) and PV, when adjusted for exposure duration, the incidence rates of arterial thromboembolic events (ATEs) were generally comparable in the Jakafi arm and control arms across studies as well as in the pooled population. A safety signal for thrombosis was not identified in clinical trials for fedratinib. The overall high risk for thrombotic events (arterial and venous) in patients with MPNs is well-known. Currently, the available safety data for ruxolitinib does not show a signal for thrombosis. The overall exposures in the randomized trials for ruxolitinib and federation are however too small to exclude an additional thrombosis risk in the MPN population due to JAK inhibitor exposure. Considering the clear dose-dependent increased risk of thrombosis (including PE, DVT, VTE, and TE) observed for tofacitinib versus TNF blockers in the long-term safety of tofacitinib in patients with RA, a Warnings & Precaution statement for thrombosis is recommended for the JAK inhibitors approved for hematological conditions.
Second primary malignancies	Warning and Precautions statement	Data from the 4 randomized, controlled clinical studies do not provide evidence to support a causal association between Jakafi and increased risk of secondary malignancies (excluding NMSC). Data on secondary malignancies (excluding NMSC) has been identified as missing information in the global risk management plan for ruxolitinib. The current safety profile concerning this missing information topic remains unchanged. Secondary malignancies were not reported in the primary or supportive safety population for Inrebic (fedratinib) at the time of approval. Until additional data is available to characterize this risk in patients with MPN, a Warnings & Precaution statement regarding the risk for secondary malignancies (excluding NMSC) is recommended for JAK inhibitors for hematological conditions.

The exact language for the Warning and Precautions statements is to be determined.

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FDA has analyzed the new safety information identified above and believes it is important to issue SLC notifications for Jakafi and Inrebic now, given the serious risks at issue.

(b) (5)

(b) (5)

Source: Memorandum to NDA 202192 and NDA 212327.
Abbreviations: AD, atopic dermatitis; ATE, arterial thromboembolic event; BAT, best available therapy; CP, compliance program; DNH, Division of Nonmalignant Hematology; DVT, deep vein thrombosis; GI, gastrointestinal; HU, hydroxyurea; JAK, Janus-associated kinase; MACE, major adverse cardiac event; MF, myelofibrosis; MPN, myeloproliferative neoplasm; NDA, new drug application; NMSC, nonmelanoma skin cancer; PE, pulmonary embolism; PI, prescribing information; PMF, primary myelofibrosis; PsA, psoriatic arthritis; PV, polycythemia vera; RA, rheumatoid arthritis; SLC, safety labeling change; SPM, second primary malignancy; TE, thromboembolism; TNF, tumor necrosis factor; VTE, venous thromboembolism

Relevant portions of a Safety Labeling Change Notification Letter (final signature date August 23, 2021, under NDA 202192 for ruxolitinib) are shown in Figure 8 for reference.

Figure 8. Excerpts From Safety Labeling Change Notification Letter for NDA 202192

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product.

Since ruxolitinib was approved on November 16, 2011, we have become aware of an increased risk of lymphoma and other malignancies (excluding non-melanoma skin cancer), thrombosis (including deep venous thrombosis, pulmonary embolism and arterial thrombosis) and major adverse cardiovascular events (MACE) associated with use of tofacitinib in patients with rheumatoid arthritis. We have determined that JAK inhibitor products represent a class of products that have the potential for the same increased risk of lymphoma and other malignancies (excluding non-melanoma skin cancer), thrombosis and MACE. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for ruxolitinib as follows:

Add the following text to section 5 of the approved labeling for JAKAFI:

    5.6   **Major Cardiovascular Events (MACE)**

        Another JAK-inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers), in patients with rheumatoid arthritis, a condition for which JAKAFI is not indicated.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with JAKAFI particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

5.7 Thrombosis

Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which JAKAFI is not indicated. In patients with myelofibrosis and polycythemia vera treated with JAKAFI in clinical trials, the rates of arterial thromboembolic events were similar in JAKAFI and control treated patients.

Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

5.8 Secondary Malignancies

Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which JAKAFI is not indicated. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with JAKAFI, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

Source: Safety Labeling Change Notification Letter for New Drug Application 202192.
Abbreviations: FDCA, Federal Food, Drug, and Cosmetic Act; JAK, Janus-associated kinase; MACE, major adverse cardiac event; NDA, new drug application; NMSC, nonmalignant skin cancer; TNF, tumor necrosis factor

It is anticipated that similar class labeling wording (Section 505(o)(4) of the Federal Food, Drug, and Cosmetics Act), regarding the potential increased risk of major adverse cardiac events, thrombosis, and secondary malignancy, will be included in Section 5 titled, "Warnings and Precautions", for the pacritinib product label under NDA 208712 because pacritinib is a JAK inhibitor that has a similar proposed indication compared to ruxolitinib, i.e., the treatment of patients with MF.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Pacritinib is not currently marketed anywhere in the world.

7.4. FDA Approach to the Safety Review

The safety analyses for pacritinib for the proposed indication, i.e., treatment of adult patients with intermediate- or high-risk primary or secondary PPV MF or PET MF with thrombocytopenia with a baseline platelet count of $<50\times10^9$/L are primarily derived from the

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safety data from PERSIST-2, which is the pivotal study evaluating the 200 mg BID dose of pacritinib that is proposed for marketing. The key design features of the PERSIST-2 study were discussed in Section II.6.2. We also assessed the safety of pacritinib 400 mg QD (from PERSIST-1 and PERSIST-2) in comparison to pacritinib 200 mg BID and BAT given that the AUC and Cmax of the pacritinib 400 mg QD regimen is only modestly higher than that with 200 mg BID.

7.5. Adequacy of Clinical Safety Database

In the PERSIST-2 study there were 311 patients enrolled (n=104 patients in the pacritinib 400 mg QD group, n=107 patients in the pacritinib 200 mg BID group and n=100 patients in the BAT group). The safety database of the PERSIST-2 study consists of data from 308 patients overall. Three patients (two in the BAT group and one in the pacritinib BID group) did not receive study treatment.

Overall, the median duration of therapy was similar between the three treatment groups: 23 weeks (range 1 to 82 weeks) in the pacritinib QD group, 25 weeks (range 1 to 84 weeks) in the pacritinib BID group and 21 weeks (1 to 56 weeks) in the BAT group. AEs led to dose modification in 49 of 104 (47%) patients in the pacritinib QD group, 35 of 106 (33%) patients in the pacritinib BID group and 22 of 98 (26%) patients in the BAT group. However, the most frequently cited reason for treatment dose modification in any pacritinib study group was reported as *Other* and consisted primarily of patients whose treatment dosing was interrupted due to our issuance of a Full Clinical Hold based on results of the PERSIST-1 study and which accounted for dose discontinuation in 174 of 210 (83%) patients in the pacritinib groups and 80 of 98 (82%) patients in the BAT group. Table 28 summarizes the duration of exposure to study treatment by treatment group.

Table 28. Duration of Treatment, Safety Population, PERSIST-2

Parameter	Pacritinib 400 mg QD N=104	Pacritinib 200 mg BID N=106	BAT N=98
Duration, n (%)			
≥1 day	104 (100%)	106 (100%)	98 (100%)
≥8 weeks	82 (79%)	90 (65%)	87 (89%)
≥12 weeks	71 (68%)	84 (79%)	77 (79%)
≥24 weeks	47 (45%)	57 (54%)	42 (43%)
≥36 weeks	30 (29%)	32 (30%)	5 (5%)
≥48 weeks	11 (11%)	19 (18%)	2 (2%)
Median duration of therapy, weeks (minimum, maximum)	22 (1, 82)	25 (1, 84)	21 (1, 56)
Mean dose intensity[1] (mg/day) (SD)	367 (62)	380 (46)	NA

Source: Reviewer table derived from the completed Study Report for PERSIST-2.
[1] Dose intensity=cumulative dose/duration of therapy.
Abbreviations: BAT, best available therapy; BID, twice daily; N, number of subjects in group; n, number of subjects with given treatment duration; NA, not applicable; QD, once daily; SD, standard deviation

The safety database obtained from the PERSIST-2 study, which is intended to support the proposed indication for pacritinib, appears to be adequate. There were 106 patients in the pacritinib 200 mg BID group and 98 patients in the BAT group; among them, 54% of patients in the pacritinib 200 mg BID group and 43% in the BAT group completed at least 24 weeks of

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therapy. In addition, in the overall ITT population across PERSIST-1, PERSIST-2, and PAC203, 185 patients received pacritinib for at least 48 weeks (150 on 400 mg QD and 35 on 200 mg BID) and 139 patients received pacritinib for at least 60 weeks (125 on 400 mg QD and 14 on 200 mg BID). These longer-term exposures are adequate in the context of this rare disease. The safety findings with the modestly higher systemic exposures with 400 mg QD compared to 200 mg BID help inform the long-term safety of pacritinib.

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns, PERSIST-2

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary

Overall, the proportion of patients reporting any AEs was highest in the pacritinib 400 mg QD group (104 of 104 [100%] patients) compared to the pacritinib 200 mg BID group (100 of 106 [94%]) and the BAT group (91 of 92 [93%] patients). Table 29 lists the proportions of patients with treatment-emergent adverse events in the PERSIST-2 study.

Table 29. Treatment-Emergent Adverse Events, PERSIST-2

Category, n (%)	Pacritinib QD (N=104)	Pacritinib BID (N=106)	BAT (N=98)
Subjects with any TEAE	104 (100)	100 (94.3)	91 (92.9)
Subjects with severe TEAE	0 (0)	0 (0)	0 (0)
Subjects with any treatment emergent SAE	49 (47.1)	50 (47.2)	38 (38.8)
Subjects with any TEAEs leading to death	15 (14.4)	8 (7.6)	15 (15.3)
Subjects with any TEAEs leading to permanent treatment discontinuation	17 (16.4)	15 (14.2)	17 (17.4)

Source: Reviewer's table derived from the completed Study Report for PERSIST-2.
No patients were reported with serious AEs.
Abbreviations: BAT, best available therapy; BID, twice daily; N, number of subjects in treatment arm; n, number of subjects in indicated category; QD, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event

The most common AEs in ≥20% of patients in the pacritinib 200 mg BID group were diarrhea, thrombocytopenia, nausea, anemia, and peripheral edema, all of which occurred at a higher incidence with pacritinib 200 mg BID than BAT. Table 30 shows the AEs reported in ≥10% of patients in the pacritinib 200 mg BID group or BAT group during randomized treatment in PERSIST-2. Patients in the pacritinib 400 mg QD group are shown for comparison.

Table 30. AEs Occurring in ≥10% of Patients Receiving Pacritinib 200 mg BID or BAT, PERSIST-2

Adverse Event[1]	Pacritinib 400 mg QD (N=104)		Pacritinib 200 mg BID (N=106)		BAT (N=98)	
	%All Grades[2]	%Grade ≥3	%All Grades[2]	%Grade ≥3	%All Grades[2]	%Grade ≥3%
Diarrhea	69	5	53	4	38	2
Thrombocytopenia	34	32	37	35	33	30
Nausea	38	1	35	1	28	1
Anemia	34	32	26	25	24	20
Peripheral edema	14	0	20	1	19	0
Vomiting	21	2	19	0	13	1
Pyrexia	14	3	15	1	7	0
Dizziness	14	1	15	1	12	0
Epistaxis	14	2	12	5	13	1
Headache	6	0	11	1	9	1
Dyspnea	14	2	10	0	9	3
Pruritus	10	0	10	2	10	0
Upper respiratory tract infection	8	5	10	0	8	0
Cough	14	0	9	2	10	0

Source: Reviewer's table derived from the completed Study Report for PERSIST-2.
[1] Medical Dictionary for Regulatory Activities Version 16.0.
[2] Grade by CTCAE Version 4.03.
Abbreviations: AE, adverse event; BAT, best available therapy; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; N, number of subjects in treatment arm; QD, once daily

Serious AEs were reported in 47% of patients in the pacritinib 200 mg BID group, 47% of patients in the 400 mg QD group, and 39% of patients in the BAT group. The most frequent serious AEs occurring in patients in the pacritinib 200 mg BID group daily (and more frequently than with BAT) were anemia (8% versus 3%), thrombocytopenia (6% versus 2%), cardiac failure (4% versus 2%), pyrexia (3% versus 2%), and squamous cell carcinoma of skin (3% versus 0%). Table 31 summarizes the SAEs occurring in ≥3% of patients receiving pacritinib 200 mg BID or BAT. Patients in the pacritinib 400 mg QD group are shown for comparison. Other serious adverse events that were reported in > 1% of patients overall in the study in the pacritinib 200 mg BID group compared to the BAT group include febrile neutropenia (1% vs 2%), and epistaxis (2% vs 1%), and acute renal failure (2% vs 2%), respectively. Serious infections may be a concern due to the potential myelosuppressive effects of pacritinib. Serious infections were reported in 15%, 9% and 10% of patients in the pacritinib 400 mg QD group, pacritinib 200 mg BID group and BAT group respectively. For additional perspective in the PAC203 study there were 54 patients who were treated with pacritinib 200 mg BID of which 46% reported at least 1 serious adverse event. Serious adverse events reported among ≥ 5% patients who were treated with pacritinib 200 mg BID in the PAC203 study were pneumonia (9%) and pyrexia (6%). No other serious adverse events were reported in at least 5% of patients.

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Table 31. SAEs Occurring in ≥3% Patients Receiving Pacritinib 200 mg BID or BAT, PERSIST-2

Serious Adverse Event[1], %	Pacritinib 400 mg QD N=104	Pacritinib 200 mg BID N=106	BAT N=98
Anemia	5	8	3
Thrombocytopenia	2	6	2
Pneumonia	5	6	4
Cardiac failure	1	4	2
Pyrexia	2	3	2
Disease progression	4	3	3
Squamous cell carcinoma of skin	0	3	0
Sepsis	1	1	5
Cellulitis	0	1	4
Cholecystitis	0	0	3

Source: Reviewer's table derived from the completed Study Report for PERSIST-2.
[1] Medical Dictionary for Regulatory Activities Version 16.0.
Abbreviations: BAT, best available therapy; BID, twice daily; N, number of subjects in treatment arm; QD, once daily; SAE, serious adverse event

Fatal AEs were reported in 8% of patients in the pacritinib 200 mg BID group, 14.4% of patients in the pacritinib 400 mg QD group and 15.3% of patients in the BAT group. There was one fatal AE each of multiorgan failure, central nervous system lesion (recognized on CT but no pathologic evaluation was performed), cerebral hemorrhage, menorrhagia, and acute myeloid leukemia reported in the pacritinib 200 mg BID group and in none of the BAT treated patients. The other fatal AEs reported with pacritinib 200 mg BID (up to week 24) were at a lower incidence (disease progression) or similar incidence (cerebral hemorrhage) compared with BAT (Table 32).

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Table 32. Proportion of Patients With Fatal AEs, PERSIST-2

| | Actual Treatment for Period 01 | | | | | | |
| | Pacritinib QD (N = 104) | | Pacritinib BID (N = 106) | | BAT (N = 98) | | |
Dictionary-Derived Term	Count	%	Count	%	Count	%	Total
Disease progression	4	3.8%	3	2.8%	4	4.1%	11
Thrombocytopenia	1	1.0%	.	.	.	.	1
Cardiac failure	.	.	.	.	2	2.0%	2
Sepsis	.	.	.	.	1	1.0%	1
Cardiac failure congestive	.	.	.	.	1	1.0%	1
Failure to thrive	1	1.0%	.	.	1	1.0%	2
Oesophageal varices haemorrhage	1	1.0%	.	.	.	.	1
Respiratory failure	.	.	.	.	1	1.0%	1
Septic shock	1	1.0%	.	.	1	1.0%	2
Acute myeloid leukaemia	.	.	1	0.9%	.	.	1
Cardiac arrest	2	1.9%	.	.	.	.	2
Cerebral haemorrhage	.	.	1	0.9%	1	1.0%	2
Lung infection	1	1.0%	.	.	.	.	1
Pulmonary embolism	1	1.0%	.	.	.	.	1
Bronchopneumonia	1	1.0%	.	.	.	.	1
Cardiac failure chronic	.	.	.	.	1	1.0%	1
Central nervous system lesion	.	.	1	0.9%	.	.	1
Circulatory collapse	1	1.0%	.	.	.	.	1
Meningorrhagia	.	.	1	0.9%	.	.	1
Multi-organ failure	.	.	1	0.9%	.	.	1
Myelofibrosis	.	.	.	.	1	1.0%	1
Neurological decompensation	.	.	.	.	1	1.0%	1
Sudden death	1	1.0%	.	.	.	.	1

Source: Reviewer's table derived from the completed Study Report for PERSIST-2 and Applicant table in NDA 208712 supporting document 76, received December 22, 2021.
Abbreviations: BAT, best available therapy; BID, twice daily; N, number of subjects in treatment arm; QD, once daily

Permanent discontinuations due to AEs were reported in 14 of 106 (14%) patients in the pacritinib 200 mg BID group, 16% of patients in the pacritinib 400 mg QD group and 17% of patients in the BAT group. Anemia was the only AE leading to permanent discontinuation in ≥2% of patients in the pacritinib 200 mg group (3%) and at a higher incidence than with BAT (0%). Table 33 summarizes the proportion of patients (≥2%) with AEs leading to permanent discontinuation of the study drug.

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Table 33. Adverse Events Leading to Permanent Discontinuation of Study Drug in ≥2% of Patients

Adverse Event, %	Pacritinib 400 mg QD N=104	Pacritinib 200 mg BID N=106	BAT N=98
Anemia	2	3	0
Thrombocytopenia	4	2	2
Neutropenia	2	1	0
Diarrhea	2	0	0
Hyponatremia	2	0	0

Source: Reviewer's table derived from the completed Study Report for PERSIST-2.
Abbreviations: BAT, best available therapy; BID, twice daily; N, number of subjects in treatment arm; QD, once daily

Drug interruptions due to AEs during the randomized treatment period occurred in 23 of 106 (23%) of patients in the pacritinib 200 mg BID group, 28/104 (26.9% of patients in the pacritinib 400 mg QD group, and 10/98 (10.2%) of patients in the BAT group. The most frequent reasons for drug interruption in ≥2% of patients in the pacritinib 200 mg BID group (and at an incidence higher than with BAT) were anemia (5%), thrombocytopenia (4%), diarrhea (3%), nausea (3%), cardiac failure (3%), and neutropenia (2%). Table 34 summarizes the proportions of patients (≥2%) with AEs leading to study drug interruption.

Table 34. Adverse Events Leading to Interruption of Study Drug in ≥2% of Patients

Adverse Event, %	Pacritinib 400 mg QD N=104	Pacritinib 200 mg BID N=106	BAT N=98
Anemia	4	5	1
Thrombocytopenia	10	4	3
Diarrhea	4	3	0
Nausea	3	3	0
Cardiac failure	1	3	1
Neutropenia	1	2	1
Pneumonia	1	2	2
Pyrexia	2	0	0
Acute renal failure	2	1	2

Source: Reviewer's table derived from the completed Study Report for PERSIST-2.
Abbreviations: BAT, best available therapy; BID, twice daily; N, number of subjects in treatment arm; QD, once daily

Study drug dosing reductions due to AEs during the randomized treatment period occurred in 8 of 106 (7.5%) patients in the pacritinib 200 mg BID group, 8/104 (7.7%) of patients in the pacritinib 400 mg QD group, and 1/98 (1.0%) of patients in the BAT group. AEs requiring study drug dosing reduction in ≥2% of patients in the pacritinib 200 mg BID group included thrombocytopenia (2%), neutropenia (2%), conjunctival hemorrhage (2%), and epistaxis (2%), all of which occurred at a slightly higher incidence than with BAT. Table 35 lists the proportions of patients (≥2%) with AEs leading to study drug dose reduction.

For additional perspective among the 54 patients who were treated with pacritinib 200 mg BID for up to 24 weeks in the PAC203 study there were 35% who had study drug interruptions, 20% who had study drug dose reductions and 17% who had study drug discontinuation due to adverse events, respectively. Grade 3/4 adverse events reported in ≥ 10% patients in the PAC203 study who were treated with pacritinib 200 mg BID (n=54) were thrombocytopenia (31%) and anemia (20%). No other grade 3/4 adverse events were reported in ≥ 10% patients in the pacritinib 200 mg BID group in the PAC203 study. The only treatment emergent adverse event reported in at least 3% of patients leading to study drug discontinuation in the PAC203 pacritinib 200 mg BID

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group was thrombocytopenia (6%). Generally, a similar safety profile for pacritinib 200mg BID was observed in the PAC203 study compared to the PERSIST-2 study.

Table 35. Adverse Events Leading to Study Drug Dose Reduction in ≥2% of Patients

Adverse Event, %	Pacritinib 400 mg QD N=104	Pacritinib 200 mg BID N=106	BAT N=98
Thrombocytopenia	7	2	1
Neutropenia	1	2	0
Conjunctival hemorrhage	0	2	0
Epistaxis	0	2	0

Source: Reviewer's table derived from the completed Study Report for PERSIST-2.
Abbreviations: BAT, best available therapy; BID, twice daily; N, number of subjects in treatment arm; QD, once daily

7.6.1.2. Deaths

The clinical hold for the pacritinib clinical development program was issued February 8, 2016. As a result of the hold, all patients on the PERSIST-1 and PERSIST-2 studies ceased study treatment (both pacritinib and BAT) within 3 weeks of the hold date. Subsequently, both studies were closed permanently. The clinical hold was removed January 4, 2017. Trial inclusion and exclusion criteria and monitoring standards were modified, and the use of 400 mg QD as a pacritinib dose was discontinued. See the Clinical Review by Dr. Bhatnagar of IND 78406 (received December 5, 2016) final signature date December 30, 2016 for additional details regarding the FDA recommendations for the sponsor to remove the Full Clinical Hold on pacritinib.

The proportion of patients who died on treatment prior to the clinical hold on PERSIST-1 and PERSIST-2 for the overall study population and for those with a baseline platelet count $<50\times10^9$/L is presented below in Table 36. These data include deaths within 30 days of the last dose of study drug. In the PERSIST-2 study, the proportion of patients who died in the pacritinib 200 mg BID group was 4.7%, compared to 10.6% in the pacritinib 400 mg QD group and 12.2% in the BAT group. The proportions of patients who died on treatment or within 30 days of the last dose of study drug were consistent in PERSIST-2 for patients with platelet counts $<50\times10^9$/L and $\geq50\times10^9$/L, i.e., the proportion of patients who died was numerically lower in the pacritinib 200 mg BID dose group compared to those treated with pacritinib 400 mg QD or BAT. In the PERSIST-2 study the proportion of patients who died on treatment or within 30 days of completion of therapy among those patients with baseline platelet counts below 50×10^9/L was 8.5% (4 of 47 patients) in the pacritinib 200 mg BID group, 16.0% (8 of 50 patients) in the pacritinib 400 mg QD group and 21.4% (9 of 42 patients) in the BAT group. Although it appears that there is a higher mortality rate among patients in the pacritinib 400 mg QD group compared to the pacritinib 200 mg BID group, the small numbers of events limit conclusions, with these differences driven by fewer than four events between treatment groups. The mortality rate of pacritinib 400 mg QD is comparable to that of BAT. AEs leading to death are shown in Table 36.

See Section 7.6.1.2 for further discussion of deaths. For additional perspective among the 54 patients in the PAC203 study who were treated with pacritinib 200 mg BID (up to week 24) there were three patients who died on therapy, i.e., due to sepsis (1 patient), respiratory failure (1 patient), and subdural hematoma (1 patients).

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Table 36. Proportion of Patients Who Died on Study or Within 30 Days of Last Dose of Study Treatment, PERSIST-2 and PERSIST-1

	PERSIST-2			PERSIST-1	
	Pacritinib 400 mg QD	Pacritinib 200 mg BID	BAT	Pacritinib 400 mg QD	BAT
Overall, N	104	106	98	220	106
Deaths On Study Treatment or within 30 days of Last Dose of Study Treatment Prior to Clinical Hold, n (%)	11 (10.6)	5 (4.7)	12 (12.2)	27 (12.3)	12 (11.3)
<50,000/mcL, N	50	47	42	35	15
Deaths On Study Treatment or within 30 days of Last Dose of Study Treatment Prior to Clinical Hold, n (%)	8 (16.0)	4 (8.5)	9 (21.4)	9 (25.7)	4 (26.7)
≥50,000/mcL, N	52	58	55	185	91
Deaths On Study Treatment or within 30 days of Last Dose of Study Treatment Prior to Clinical Hold, n (%)	3 (5.8)	1 (1.7)	3 (5.5)	18 (9.7)	8 (8.8)

Note: Includes deaths occurring within 30 days of last treatment and on or before the clinical hold date 08Feb2016.
Source NDA 208712 supporting document 76 letter date December 22, 2021 (received December 22, 2021):
Abbreviations: BAT, best available therapy; BID, twice daily; N, number of subjects; QD, once daily

7.6.1.3. Laboratory Findings

There was one patient in the BAT group in the PERSIST-2 study who had clinical hepatic function laboratory tests consistent with Hy's Law. No patients with clinical hepatic function laboratory tests that were consistent with Hy's Law were reported in the pacritinib 400 mg dose group or pacritinib 200 mg dose group.

Hemoglobin

Overall, mean baseline hemoglobin values were below the reference range but similar in all treatment arms, 9.6 g/dL for the pacritinib QD arm, 9.9 g/dL for the pacritinib BID arm, and 10 g/dL for the BAT arm. At Week 24, the mean change from baseline was 0.0 g/dL for pacritinib QD, -0.4 g/dL for pacritinib BID, and -0.1 g/dL for the BAT group. At the end-of-study visit, the mean change from baseline was -0.1 g/dL for pacritinib QD, +0.1 g/dL for pacritinib BID, and +0.2 g/L for BAT. The mean absolute decreases in hemoglobin were small. The proportion of patients with the lowest on therapy hemoglobin concentration < 7 g/dL was 25% in the pacritinib 400 mg QD group (n=104), 21% in the pacritinib 200 mg BID group (n=106) and 16% in the BAT group (n=98), respectively.

Platelets

Mean baseline platelet count values were below the reference range but similar in all treatment arms: 66×10^9/L for the pacritinib QD arm, 73×10^9/L for the pacritinib BID arm, and 72×10^9/L for the BAT arm. At Week 24, small mean changes from baseline were demonstrated in all

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treatment arms: 17×10^9/L for pacritinib QD, -8×10^9/L for pacritinib BID, and 2×10^9/L for BAT. Similarly, at the end of study, small mean changes from baseline were observed in all of the treatment arms, -13×10^9/L for pacritinib QD, -6×10^9/L for pacritinib BID, and -7×10^9/L for BAT. Changes from baseline were observed in all treatment arms at Week 24, however, the mean absolute changes were small. A detailed discussion of bleeding is included in Section 7.7.1. The proportion of patients with the lowest on therapy platelet count $< 25 \times 10^9$/L was 41% in the pacritinib 400 mg QD group (n=104), 37% in the pacritinib 200 mg BID group (n=106) and 41% in the BAT group (n=98), respectively. The proposed pacritinib product label contains Warnings and recommendations for prescribers regarding the potential risk of hemorrhage and thrombocytopenia that include increased frequency of monitoring of clinical laboratory tests and dosing adjustments.

Other Laboratory Findings

No other significant clinical laboratory or physical examination findings were identified in this review.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Major Adverse Cardiac Events

Issue

An excess of major adverse cardiac events (MACE) due to deaths was reported in PERSIST-1 with pacritinib 400 mg QD compared to BAT. An assessment of MACE and deaths using the updated safety database, including PERSIST-2, is needed.

Background

An increase in MACE was identified during the review of the PERSIST-1 study (see the Clinical Review from the first cycle review of this NDA by Dr. Vishal Bhatnagar dated February 24, 2016). Dr. Bhatnagar identified an excess number of deaths in the pacritinib 400 mg QD treatment group (58/220 [26%]) compared to the BAT group (6/106 [6%]) and any grade of heart failure to be higher in the pacritinib 400 mg QD group (16/220 [7%]) compared to the BAT group (2/106 [2%]).

Assessment

As discussed in Section 7.6.1.2, deaths occurring on study or within 30 days of the last dose of study drug were comparable between pacritinib 400 mg QD and BAT in PERSIST-1 and PERSIST-2.

In contrast, in the Applicant's prior NDA submission, overall deaths for PERSIST-1 were reported for 26% of patients treated with pacritinib 400 mg QD compared to 6% of patients treated with BAT. However, this analysis censored patients on the BAT arm when they crossed over to pacritinib; therefore, the time at risk was lower in the BAT arm than in the pacritinib arm. In the safety population for PERSIST-1, the patient-year exposure was 279.6 years for pacritinib 400 mg QD compared to 60.0 years for BAT. When adjusting the overall deaths by patient-year

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exposure, the rates of overall deaths are 9.6 per 100 patient-years for pacritinib 400 mg QD versus 5.0 per 100 patient-years for BAT. Note that the BAT arm had only 3 deaths, a very small number that limits conclusions.

We also conducted an analysis of overall deaths in PERSIST-2 and PAC203 using patient-year exposures. We did so because in PERSIST-2, there was a higher number of dropouts in the pacritinib 400 mg QD group as compared to the 200 mg BID group. Study completion rates by treatment arm over time are shown in Table 37. Notably, at Week 24, the pacritinib 200 mg BID arm had 77% of patients staying in the study but the 400 mg QD arm only had 68% patients staying in the study. In addition, few patients remained on BAT after Week 24.

Table 37. Visit Distribution of ITT Efficacy Population

Patient Visit	ITT (Efficacy) Population		
	Pacritinib 400 mg QD (N=75)	Pacritinib 200 mg BID (N=74)	BAT (N=72)
Baseline	74 (99%)	73 (98.6%)	70 (97%)
End of Week 12	60 (80%)	65 (88%)	67 (93%)
End of Week 24	51 (68%)	57 (77%)	50 (69%)
End of Week 36	34 (45.3%)	39 (53%)	4 (5.5%)
End of Week 48	18 (24%)	20 (27%)	1 (1.4%)
End of Week 60	5 (6.6%)	8 (11%)	1 (1.4%)
End of Week 72	3 (4%)	3 (4%)	0 (0%)
Termination	13 (17.3%)	18 (24.3%)	3 (4.2%)

Source: FDA analysis.
Abbreviations: BAT, best available therapy; BID, twice daily; ITT, intent-to-treat; QD, once a day

As a result, patient-year exposures in PERSIST-2 were highest for pacritinib 200 mg BID (57.7 patient-years), intermediate for pacritinib 400 mg QD (49.9 patient-years), and lowest for BAT (24.1 patient-years). In PERSIST-2, the rates of MACE in the Safety Population, when adjusted for patient-year exposures, were 30.0 per 100 patient-years (15 events) for pacritinib 400 mg QD, 10.4 per 100 patient-years (6 events) for pacritinib 200 mg BID and 24.1 (9 events) for BAT. In PAC203, the rate was 11.1 per 100 patient-years (3 events). Note that PERSIST-2 enrolled a higher-risk population than PERSIST-1, which likely explains the higher overall rates of MACE (which is predominantly due to all-cause death as discussed below) in PERSIST-2. For example, in PERSIST-2, 53% of patients were categorized as DIPSS Intermediate-2, 28% were characterized as DIPSS High, and 50% had received prior JAK inhibitor therapy compared to responding rates of 32%, 14%, and 0% in PERSIST-1.

In the subset of patients with platelet counts below 50×10^9/L, the MACE rates per 100 patient-years in PERSIST-2 were 39.3 for pacritinib 400 mg QD, 22.2 for pacritinib 200 mg BID and 54.3 for BAT.

Most of the MACE events in PERSIST-1, PERSIST-2, and PAC203 were all-cause deaths. There were only three reported nonfatal myocardial infarctions (one with pacritinib 400 mg QD in PERSIST-1, and one each with pacritinib 400 mg QD and BAT in PERSIST-2) and there were no reports of nonfatal stroke.

To further investigate MACE events, the Applicant produced Kaplan-Meier plots for time to all-cause mortality events (Figure 9). The rate of all-cause mortality events in the 200 mg BID versus 400 mg QD of PERSIST-2 was similar for the first 12 weeks (overlapping Kaplan-Meier curve). However, after approximately 12 weeks, the rate of all-cause mortality events was lower

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in 200 mg BID versus 400 mg QD (separation of Kaplan-Meier curve). A similar trend was observed in the sicker subgroup of patients who had a baseline platelet count <50,000/µL (Figure 10).

Figure 9. Time to All-Cause Death (ITT Population)
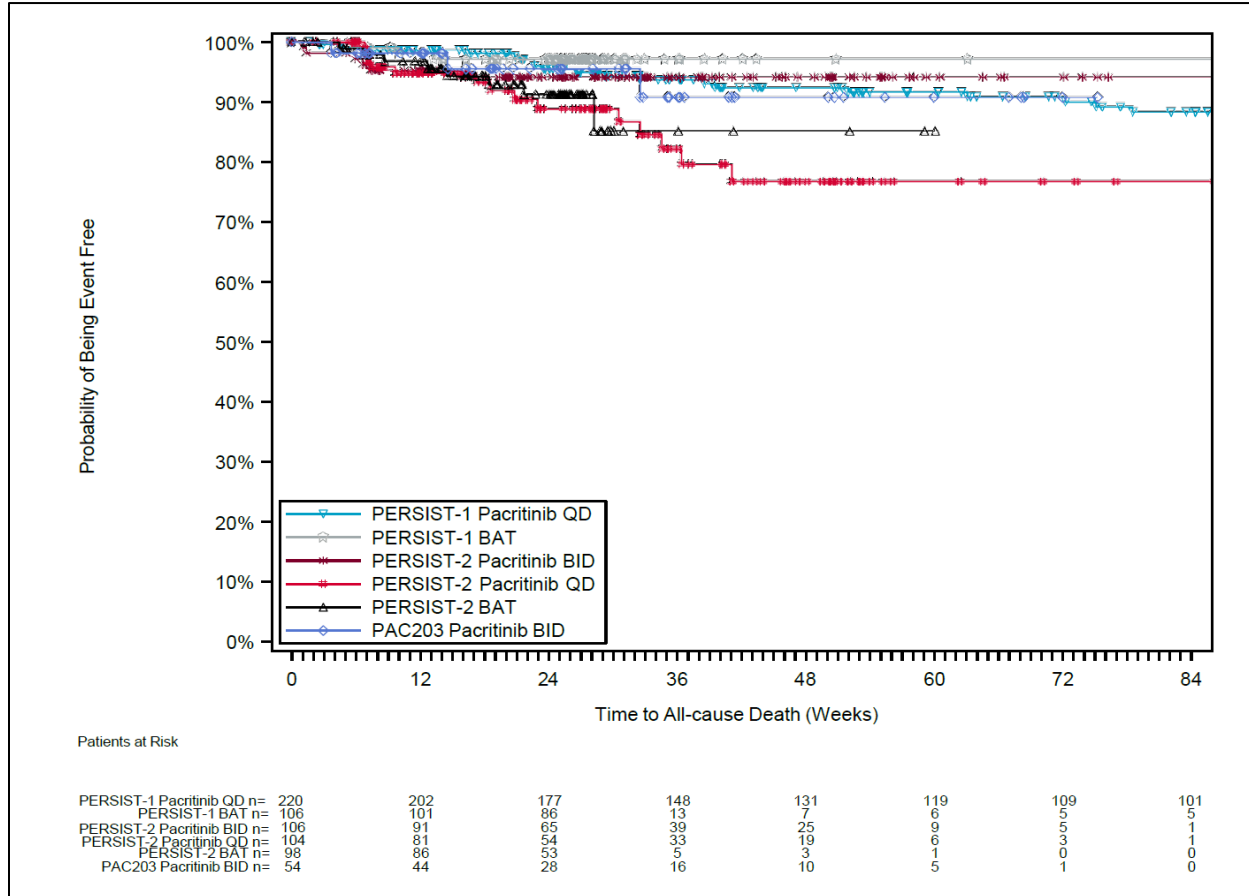
Source: Applicant's submitted response to an Information Request.
Abbreviations: BAT, best available therapy; BID, twice daily; ITT, intent-to-treat; QD, once a day

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Figure 10. Time to All-Cause Death (Population With Baseline Platelet Count <50,000/µL)
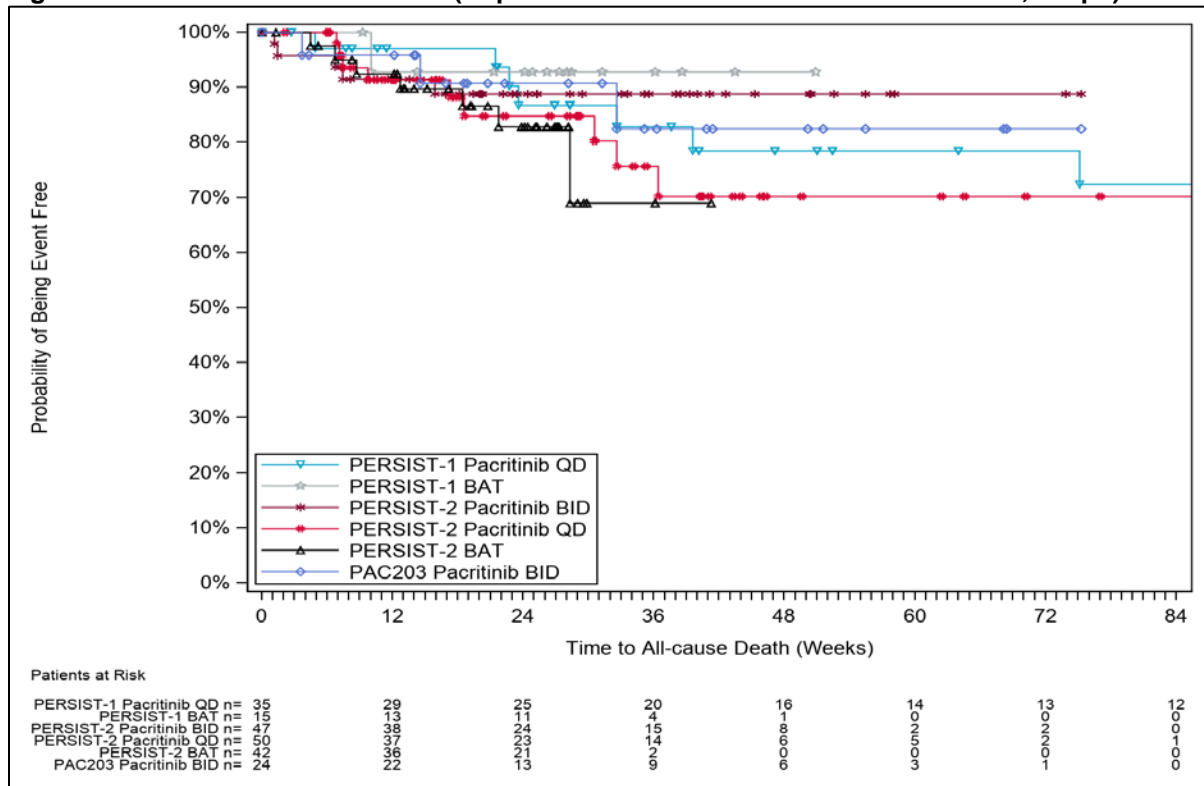
Source: Applicant's submitted response to an Information Request.
Abbreviations: BAT, best available therapy; BID, twice daily; QD, once a day

Conclusion

Virtually all of the reported MACE in PAC203, PERSIST-1, and PERSIST-2 were all-cause deaths. Because of differences in time on study drug, it is important to analyze these events based on patient-year exposure. There was a numerically lower rate of MACE with pacritinib 200 mg BID compared to BAT in PERSIST-2, and a slightly higher rate of MACE with pacritinib 400 mg QD compared to BAT in both PERSIST-1 and PERSIST-2. However, event rates are very low, particularly for the BAT arms, the studies were not designed nor powered to definitively evaluate MACE, and no formal statistical analyses were prospectively planned, limiting conclusions. Pacritinib 400 mg QD has modestly higher C_{max} and AUC compared to pacritinib 200 mg BID, but there is significant overlap in exposures between these dosing regimens, such that one would not expect these two regimens to differ substantially with regard to MACE risk. Nonetheless, given the appearance of more reassuring MACE results for 200 mg BID, the Applicant is seeking approval of the 200 mg BID dosing regimen, which is acceptable.

7.7.2. Bleeding

Issue

Pacritinib is proposed for a patient population at increased risk of bleeding. It is important to assess whether pacritinib further increases the risk of bleeding in this population.

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Background

The Applicant is proposing pacritinib for patients with MF and platelet counts below 50×10^9/L. These patients are at risk of bleeding due to thrombocytopenia. The other approved JAK inhibitors for MF studied a patient population with platelet counts above 50×10^9/L and require dose interruption for platelet counts below 50×10^9/L (ruxolitinib) or for grade 4 thrombocytopenia/grade 3 thrombocytopenia with active bleeding (fedratinib).

Assessment

Among patients with baseline platelet count below 50×10^9/L in PERSIST-2 and PAC203, about 38% had platelet counts below 25×10^9/L (79 of 210 patients), and 7% (15 of 210 patients) had baseline platelet counts below 10×10^9/L. The lowest baseline platelet count in a patient randomized to pacritinib 200 mg BID was 6×10^9/L.

Overall hemorrhagic events per 100 patient-years in PERSIST-1 and PERSIST-2 were numerically lower with pacritinib compared to BAT. The rates per 100 patient-years in PERSIST-1 were 27.5 for pacritinib 400 mg QD (64 events) and 41.3 for BAT (22 events). In PERSIST-2, the rates were 94.2 for pacritinib 400 mg QD (37 events), 110.0 for pacritinib 200 mg BID (45 events), and 139.1 for BAT (40 events). Similarly, in the subgroup of patients with baseline platelet counts below 50×10^9/L, hemorrhagic events were reported at a higher rate per 100 patient-years with BAT compared to pacritinib for both PERSIST-1 and PERSIST-2.

Hemorrhagic events with fatal outcome were rare, with only five total events across PERSIST-1 and PERSIST-2 (two events with pacritinib 400 mg QD in PERSIST-1, one event with pacritinib 400 mg QD in PERSIST-2 and two events with pacritinib 200 mg BID in PERSIST-2). Three of these events occurred in the subgroup of patients with baseline platelet counts below 50×10^9/L.

Hemorrhagic serious adverse events per 100 patient-years was 6.6 with pacritinib 400 mg QD (18 events) compared to 1.7 with BAT (one event) in PERSIST-1 and 20.1 with pacritinib 400 mg QD (10 events), 21.8 with pacritinib 200 mg BID (12 events), and 16.1 (6 events) with BAT in PERSIST-2. In the subgroup of patients with baseline platelets $<50\times10^9$/L, a similar pattern was seen but with slightly higher bleeding rates as would be expected for patients with low platelet counts. In PERSIST-2, the rates per 100 patient-years of serious hemorrhagic events in the subgroup of patients with baseline platelet counts below 50×10^9/L was 35.6 (8 events) with pacritinib 400 mg QD, 28.0 (6 events) with pacritinib 200 mg BID, and 26.8 (4 events) with BAT.

Table 38 shows the findings for bleeding AEs by pacritinib doses in Studies PAC203 and PERSIST-2 for the proposed indicated population. When considering patients in this population who had at least grade 3 bleeding (requiring a transfusion or intervention), the incidence rates were 17.0% with pacritinib 200 mg BID and 11.9% with BAT in PERSIST-2. Few patients required dose interruption, reduction or discontinuation due to adverse events of bleeding.

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Table 38. Proportion of Patients With Bleeding Events (Baseline Platelet Count <50×10^9/L)

	PERSIST-2		PAC203	Total
	Pacritinib 200 mg BID (N=47) [n (%)]	BAT (N=42) [n (%)]	Pacritinib 200 mg BID (N=24) [n (%)]	Pacritinib 200 mg BID (N=71) [n (%)]
Patients with >=1 Treatment Emergent SAE	6 (12.8)	4 (9.5)	2 (8.3)	8 (11.3)
Patients with >=1 Grade 3+ TEAE	8 (17.0)	5 (11.9)	3 (12.5)	11 (15.5)
Patients with >=1 Treatment Emergent SAE or >=1 Grade 3+ TEAE	9 (19.1)	5 (11.9)	3 (12.5)	12 (16.9)
Patients with >=1 TEAE Leading to Any Dose Adjustments (Interruptions, Reductions, Permanent Drug Discontinuations)	3 (6.4)	3 (7.1)	1 (4.2)	4 (5.6)
Patients with >=1 TEAE Leading to Dose Interruptions	1 (2.1)	0	1 (4.2)	2 (2.8)
Patients with >=1 TEAE Leading to Dose Reductions	2 (4.3)	1 (2.4)	0	2 (2.8)
Patients with >=1 TEAE Leading to Permanent Drug Discontinuations	2 (4.3)	2 (4.8)	0	2 (2.8)

Source: Applicant's table from NDA 208712 supporting document 78; received December 22, 2021.
AE Events include MedDRA SMQs: Bleeding events are defined as hematoma, hematemesis, epistaxis, subdural hematoma, muscle hemorrhage, subdural hemorrhage, post procedural hemorrhage, mouth hemorrhage, hematochezia, hemoptysis, gingival bleeding, traumatic hematoma, melaena, esophageal varices hemorrhage, rectal hemorrhage, post procedural hematoma, ecchymosis, cystitis hemorrhagic, skin hemorrhage, conjunctival hemorrhage, gastritis hemorrhagic, retinal hemorrhage, cerebral hemorrhage, small intestinal hemorrhage, abdominal wall hematoma, vessel puncture site bruise, ear hemorrhage, urethral hemorrhage.
Abbreviations: AE, adverse event; BID, twice a day; N, number of subjects in treatment arm; n, number of subjects with indicated AE; QD, once a day; Grade is according to NCI CTCAE v 4.03

A similar evaluation of the potential risk for bleeding in patients with baseline platelet counts <50×10^9/L across other clinically relevant pacritinib doses (100 mg BID and 100 mg QD for patients who have dose reductions due to adverse reactions) was performed for Studies PAC203 and PERSIST-2. There are small numbers of patients on the various pacritinib doses in Study PAC203 that limit conclusions with the 100 mg QD and 100 mg BID doses, but pharmacologically, one would not expect bleeding with these lower doses to be higher than that with the larger 200 mg BID dosing regimen.

Conclusion

While the patients with platelet counts <50×10^9/L at baseline had a higher rate of bleeding compared to the overall trial population, the pattern of bleeding rates with pacritinib versus BAT is similar to that seen for the overall trial populations of PERSIST-1 and PERSIST-2. In the subgroup of patients with platelet counts <50×10^9/L at baseline in PERSIST-2, overall bleeding events were numerically higher with BAT than pacritinib, with comparable rates of serious hemorrhagic events per 100 patient-years for pacritinib 200 mg BID (28.0) and BAT (26.8), and few patients requiring dose interruption or discontinuation due to bleeding.

Because no formal statistical analyses were prospectively planned, and the study size is small with few events, conclusions are limited. However, there does not appear to be a significant concern for worsening bleeding with pacritinib 200 mg BID compared to BAT in the patients with baseline platelet counts <50×10^9/L.

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8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

The review team recommends avoiding use of pacritinib in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 (severe renal impairment and ESRD). The impact of impaired renal function was determined by comparing the pharmacokinetics (PK) of pacritinib following administration of a single 400 mg dose in subjects with mild (eGFR 60 to 89 mL/min as estimated by the Modification of Diet in Renal Disease study equation), moderate (eGFR 30 to 59 mL/min), and severe (eGFR 15 to 29 mL/min) renal impairment and subjects with end-stage renal disease (ESRD) requiring hemodialysis to healthy subjects (eGFR ≥90 mL/min). In subjects with ESRD, PK of pacritinib was characterized on- and off-dialysis.

Compared to subjects with normal renal function, pacritinib C_{max} increased by 11% in mild and moderate renal impairment groups, by 24% in severe renal impairment group and 33% in subjects with ESRD. The AUC_{0-72h} values increased by 7%, 17%, 31% and 25% in mild, moderate, severe renal impairment and subjects with ESRD, respectively. PK of pacritinib was similar between on- and off-dialysis in subjects with ESRD suggesting that pacritinib was not removed by hemodialysis. The reason for changes in peak concentration of pacritinib with renal impairment is not clearly understood. The modest change in total systemic exposures of pacritinib in different renal impairment groups is consistent with the data that only trace amount of drug is excreted unchanged in the urine. Nevertheless, the magnitude of increase in AUC with severe renal impairment or ESRD subjects is similar to the increase in AUC with the 400 mg QD regimen compared to 200 mg BID. In light of a potential unfavorable benefit-risk observed for exposures that correspond to 400 mg QD, pacritinib should not be used in patients with eGFR <30 mL/min/1.73m^2 (severe renal impairment and ESRD).

Hepatic Impairment

A dedicated hepatic impairment study was conducted where participants with normal hepatic function (N=8), mild hepatic impairment (Child Pugh A, N=8), moderate hepatic impairment (Child Pugh B, N=8), and severe hepatic impairment (Child Pugh C, N=4) were given a single 400 mg dose of pacritinib (Study PAC105). The geometric mean AUC decreased by 8.5%, 36%, and 45% in subjects with mild, moderate, or severe hepatic impairment compared to subjects with normal hepatic function. The geometric mean C_{max} decreased by 22%, 47%, and 57% in subjects with mild, moderate, or severe hepatic impairment, compared to subjects with normal hepatic function. Plasma protein binding could not be assessed in the samples collected in the hepatic impairment study (Study PAC103) due to nonspecific binding of the drug. Comparison of PK results between the groups is shown in Table 39.

The mechanistic reason(s) for the observed lower exposures in patients with hepatic impairment is not clear. While the hepatic impairment study used a higher dose of 400 mg, it is evident that this dose is sensitive to inhibition of hepatic function as demonstrated by the clarithromycin drug interaction study (discussed in the subsequent section), also conducted using the 400 mg dose of pacritinib. Therefore, the observed lower exposures in subjects with hepatic impairment may be due to intrinsic factors in hepatically impaired subjects that alter gastrointestinal (GI) absorption.

Several publications have described that patients with hepatic impairment may have an altered gastric environment, such as with bile salts, phospholipids, or osmolality, which may influence the solubility of the drug and thus reduce absorption. Pacritinib has poor aqueous solubility and shows dissolution-limited absorption. A 400 mg dose is closer to the saturable solubility limit and it is plausible that reduced exposures in subjects with hepatic impairment could be due to altered physiological conditions in the GI tract leading to impaired absorption. That said, it is not clear whether the effect on absorption seen in subjects with hepatic impairment at a dose of 400 mg will translate to the clinically relevant dose of 200 mg. Therefore, in the absence of data with a 200 mg dose, the review team recommends avoiding use of pacritinib in patients with moderate and severe hepatic impairment. Moreover, the review team recommends a required postmarketing trial to further characterize the PK of pacritinib in subjects with hepatic impairment, including the option for a reduced design, at a clinically relevant dose of 200 mg. In addition, due to the time-dependent inhibition potential of pacritinib towards CYP3A4 (see below), the dedicated hepatic impairment study should be conducted following pacritinib 200 mg BID dosed to steady state.

Table 39. Point Estimators (LS-Means) and Two-Sided 90% CIs for PK Parameters of Pacritinib in Plasma After a Single Oral Dose of 400 mg

Parameter	Ratio of Geometric LS Means (ANOVA)	
Comparison	PE	90% CI
C_{max} (µg/mL)		
Mild versus normal	78.3	60.9, 100.7
Moderate versus normal	53.2	41.4, 68.4
Severe versus normal	43.2	31.8, 58.8
AUC_{0-t} (µg×h/mL)		
Mild versus normal	91.5	65.6, 127.8
Moderate versus normal	64.1	45.9, 89.5
Severe versus normal	54.6	36.3, 82.2
$AUC_{0-\infty}$ (µg×h/mL)		
Mild versus normal	88.7	58.3, 134.9
Moderate versus normal	54.3	33.1, 89.3
Severe versus normal	51.5	29.8, 89.2

Source: Table 8, page 41, PAC103 Report.
PE ratio and 90% CIs of the ratio of geometric LS means (ANOVA).
Abbreviations: ANOVA, analysis of variance; AUC, area under the plasma concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; LS, least-squares; PE, point estimate; PK, pharmacokinetics

Other Intrinsic Factors

No clinically significant difference in the pharmacokinetics of pacritinib was observed based on age, sex, race, and body weight. No dose adjustments are needed for these factors.

8.2. Drug Interactions

Metabolic Pathway

In vitro metabolism studies demonstrated that pacritinib is primarily metabolized by cytochrome P450 (CYP)3A4.

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Effects of Other Drugs on Pacritinib

The impact of clarithromycin, a strong CYP3A4 inhibitor on the pharmacokinetics of pacritinib was evaluated in Study PAC104. Clarithromycin was dosed at 500 mg BID for 5 days, a submaximal regimen for inhibition, before the subjects received a single dose of 400 mg pacritinib. Clarithromycin increased the AUC and C_{max} of pacritinib by 80% and 30%, respectively. As the PK of clarithromycin does not reach steady state with 5-day dosing, it is expected that the increase in pacritinib exposure could be even higher when tested following a longer treatment with clarithromycin that results in maximal CYP3A4 inhibition (i.e., worst-case scenario). Because exposures to pacritinib with strong CYP3A4 inhibitors will increase beyond the exposures seen with 400 mg QD, the benefit-risk profile of pacritinib is significantly altered. Therefore, use of pacritinib in patients concomitantly using strong CYP3A inhibitors should be contraindicated. The in vivo impact of moderate CYP3A4 inhibitors on the PK of pacritinib has not been conducted. Due to the expected increase in the risk for adverse reactions with increase in pacritinib exposure, the review team recommends 'avoid use' of pacritinib in patients concomitantly on moderate CYP3A4 inhibitors. In addition, the review team recommends physiologically based pharmacokinetic (PBPK) modeling analyses using a revised and validated PBPK model to evaluate the effect of repeat doses of strong and moderate CYP3A inhibitors and inducers on the pharmacokinetics of pacritinib 200 mg twice daily dosed to steady state as a post-marketing requirement (PMR), to support appropriate dosing recommendations. If the results from the PBPK analyses are inconclusive, a clinical pharmacokinetic study in adult healthy volunteers will be recommended.

The effect of a strong CYP3A inducer, rifampin, was also evaluated (Study PAC106). Subjects were given 600 mg QD rifampin for 10 days before taking a single dose of 400 mg pacritinib. Rifampin decreased pacritinib AUC and C_{max} by 87% and 51%, respectively. This magnitude of decrease in pacritinib exposure is expected to make the treatment ineffective, therefore, the review team recommends a contraindication of use of pacritinib in patients concomitantly on strong CYP3A inducers. The Applicant used PBPK modeling to predict the DDI effect of a moderate CYP3A inducer on the pharmacokinetics of pacritinib following a single dose of 400 mg pacritinib. Due to several limitations identified in the Applicant's PBPK analysis, such as inability to describe the pharmacokinetics of pacritinib after single or multiple doses of pacritinib across different dose levels, the Applicant's PBPK analysis was deemed inadequate. The review team recommends that concomitant use of pacritinib with moderate CYP3A4 inducers be avoided until further PBPK analysis or clinical data are available.

Refer to the section on PBPK modeling, below, for more information.

Effect of Pacritinib on Other Drugs

Results from in vitro studies showed that there could be several potential interactions involving transporter systems and CYPs in the context of pacritinib as a perpetrator.

Pacritinib is a time-dependent inhibitor for CYP1A2 and CYP3A4, with a maximal inactivation rate constant (K_{inact}) of 0.041 and 0.0096 L/min, respectively, and unbound inhibitor concentration causing half-maximal inactivation ($K_{I,u}$) of 0.95 and 1.6µM, respectively. There is a potential for in vivo CYP1A2- and CYP3A4-associated drug-drug interaction (DDI) by pacritinib, as the calculated DDI index (84 for CYP1A2 and 20 for CYP3A4) are much larger than the predefined cut-off (1.25). Pacritinib is also a reversible inhibitor of CYP1A2, CYP3A4

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and CYP2C19. Finally, pacritinib is an inducer of CYP1A2 and CYP3A4. Unlike CYP inhibition, CYP induction assay requires longer incubation of cryopreserved human hepatocytes with pacritinib. Because longer incubations with pacritinib were found to be cytotoxic, induction kinetic parameters were not able to be determined.

In addition to CYP enzymes, pacritinib also influences the activity of several transporters. In particular, pacritinib inhibits P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic cation transporter (OCT)1 with half-maximal inhibitory concentration (IC_{50}) values of 4.8μM (I_{gut}/IC_{50} 352), 5.4μM (I_{gut}/IC_{50} 313), and 0.87μM ($I_{unbound,in,max}/IC_{50}$ >0.1), respectively. Based on these in vitro studies, there is potential for in vivo DDI as the calculated DDI index (I_{gut}/IC_{50} for P-gp and BCRP) is greater than the predefined cut-off (10 for P-gp and BCRP). However, clinical drug interaction studies to investigate the effect of pacritinib as a perpetrator on other coadministered drugs have not been conducted. Because the inhibitory effects described above indicate a potential risk of increasing the concentration of concomitant substrate drugs to cause adverse responses, we recommend a clinical pharmacokinetic study to determine the DDI between pacritinib and a cocktail of substrates for CYP1A2, CYP3A4, CYP2C19, BCRP, and P-gp transporters as a postmarketing requirement. Because of the potential for interaction based on in vitro data, the review team also recommends that concomitant use of pacritinib with sensitive substrates of CYP1A2, CYP3A4, CYP2C19, P-gp, or BCRP be avoided until further clinical data are available.

PBPK Modeling

Two clinical DDI studies were conducted to evaluate the effects of a strong CYP3A inhibitor (clarithromycin, study PAC104) and a strong CYP3A inducer (rifampin, PAC106) on a single dose exposure of pacritinib. The clinical data showed an 80% increase in AUC with clarithromycin and an 87% decrease in AUC with rifampin. The Applicant noted that the clinical clarithromycin DDI study was conducted following a dose of 500 mg BID clarithromycin for 5 days. Thus, the Applicant used the PBPK modeling and simulation approach to evaluate the DDI effect of clarithromycin on pacritinib under a more conservative scenario (such as a longer clarithromycin treatment). The Applicant also used this PBPK model to predict the DDI effect with a moderate CYP3A inducer, such as efavirenz. However, the review team has concluded that the submitted PBPK modeling and simulation is inadequate to predict the effects of CYP3A inhibitors/inducers on the PK of pacritinib. Limitations of the Applicant's PBPK analysis are described below.

Key limitations of the Applicant's pacritinib PBPK model:

- First-order oral model may not be able to capture dose-dependent absorption parameters for pacritinib
  - Pacritinib is a Biopharmaceutics Classification System class II drug demonstrating low solubility (threshold 0.8 mg/mL water) over the physiological pH range (as shown in Figure 11). Population PK analysis also suggested a dose-dependent bioavailability (F) across the 100 to 400 mg QD range. Thus, the first-order oral model used in the submitted PBPK model may not be able to assess or capture the dose-dependent absorption parameters for pacritinib.

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Figure 11. pH-Dependent Solubility of Pacritinib
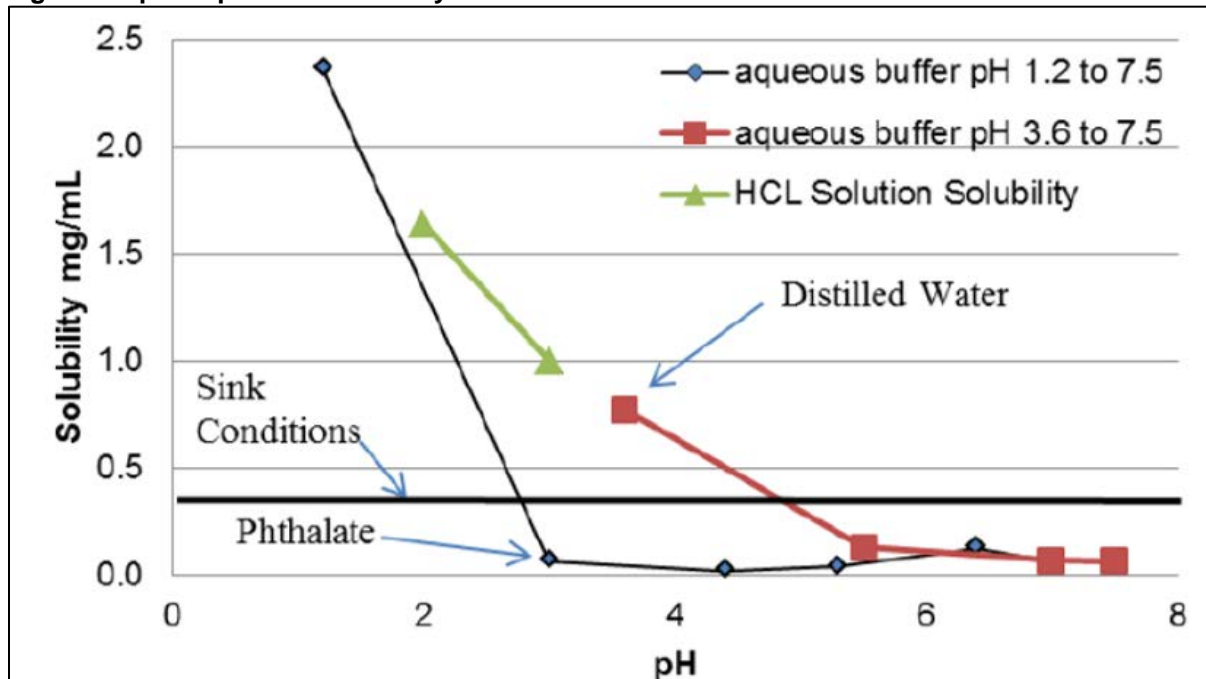
Source: Applicant's Summary of Biopharmaceutic Studies
Abbreviations: HCL, hydrochloric acid

- Lack of a clinical DDI study to inform the DDI parameter of pacritinib on the CYP3A pathway.

  — Pacritinib exhibited time-dependent inhibition (TDI) of CYP3A in vitro. The Applicant incorporated the in vitro TDI parameters in the submitted PBPK model. The Applicant also assumed that pacritinib is completely metabolized via the CYP3A pathway based on in vitro data. However, the submitted PBPK model cannot describe the observed pacritinib PK data after multiple doses, as shown in Table 40.

Table 40. Comparison of the Predicted and Observed Pacritinib PK Data, Trial SB1518-2007-001[§]

	Dose	
Parameter	**200 mg QD**	**400 mg QD**
MF patients (observed)		
C_{max} (ng/mL)		
Day 1, mean (CV)	4,999 (28)	6,275 (63)
Day 15, mean (CV)	6,696 (28)	9,770 (49)
$AUC_{(0-24h)}$ ng·h/mL		
Day 1, mean (CV)	93,283 (27)	126,608 (61)
Day 15, mean (CV)	125,115 (36)	202,878 (51)
Healthy subjects[1] (predicted[#])		
C_{max} (ng/mL)		(b) (4)
Day 1, mean (CV)		
Day 15, mean (CV)		
$AUC_{(0-24h)}$ (ng·h/mL)		
Day 1, mean (CV)		
Day 15, mean (CV)		

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Parameter	Dose	
	200 mg QD	400 mg QD
Predicted/observed ratio		
C_max		
Day 1		(b) (4)
Day 15		
AUC		
Day 1		
Day 15		

Source: Simulation output file -Reviewer's analysis; Tables 18 and 19 from SB1518-2007-001 (§: A Phase 1/2 study of pacritin b for the treatment of advanced myeloid malignancies).
[1] Simulations were conducted by Reviewer using the Healthy North European Caucasian volunteer population model to allow coverage of the age range of the clinical study (47 to 86 years).
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; CV, coefficient of variation; MF, myelof brosis; PK, pharmacokinetics; QD, once daily

- The submitted model is inadequate to predict the effect of CYP3A inhibitors/inducers on the pacritinib PK following multiple doses of pacritinib.

   — The discrepancies between the simulated and observed PK data of pacritinib could result from dose-dependent oral absorption or TDI of the CYP3A pathway. In response to FDA's information request, the Applicant proposed to revise and expand the original pacritinib PBPK model to predict pacritinib PK following multiple doses of pacritinib once the DDI parameters of pacritinib become available. To derive the appropriate DDI parameters, the review team recommends a PMR to conduct a clinical DDI study to determine the effect of pacritinib 200 mg BID dosed to steady state on the exposure of a sensitive substrate (e.g., midazolam). This assessment can be conducted as a part of the cocktail DDI study recommended earlier.

Currently, there is no information to evaluate the potential DDI effects of a moderate CYP3A inhibitor or inducer on the PK of pacritinib. It is recommended to avoid the use of pacritinib in combination with of a moderate CYP3A inhibitor or inducer. The Applicant should provide additional information to support the dosing recommendation of pacritinib when used concomitantly with moderate CYP3A inhibitors and inducers at steady state. The Applicant may use a validated PBPK model to support the DDI dosing recommendation, however, the revised PBPK model should incorporate all the up-to-date clinical PK and DDI information (i.e., a clinical DDI study with a sensitive CYP3A substrate). If the results from the revised PBPK analyses are inconclusive, the Applicant should conduct a dedicated clinical PK study to address this issue.

8.3. Plans for Pediatric Drug Development

Pacritinib was granted a full waiver from the conduct of studies in pediatric patients as MF does not occur in the pediatric population; consequently, no nonclinical juvenile toxicity studies were conducted.

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8.4. Pregnancy and Lactation

Animal Data

The following nonclinical information was used in support of the indicated labeling sections. Additional nonclinical details are located in Section III.13 and final labeling is discussed in Section III.21.

Table 41. Nonclinical Data Supporting Labeling on Pregnancy and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	The developmental toxicity study conducted in CD-1 mice resulted in maternal toxicity at the high dose (HD) (250 mg/kg/day) which resulted in post-implantation loss, a decline in body weight (decreased 7%) and a corresponding reduction in food consumption observed at this dose.
	The embryo-fetal development of CD-1 mice was affected at the HD, with lower mean fetal body weights and altered external fetal morphology (cleft palate).
	The developmental toxicity study conducted in rabbits resulted in maternal toxicity at the HD (60 mg/kg/day) evidenced by mortality, moribundity, abortion, mean body weight losses, reduced food consumption, and adverse clinical findings.
	The embryo-fetal development of rabbits was affected at the HD, with lower fetal body weights and corresponding increased litter proportions with ossification-related skeletal developmental variations at the HD.
	Embryo-fetal developmental effects observed at pacritinib high doses in mice and rabbits were considered a consequence of maternal toxicity, rather than a specific effect of pacritinib.
	The pre- and postnatal development (PPND) study conducted in CD-1 mice resulted in maternal toxicity at the HD (250 mg/kg/day) based on the single mortality and an adverse decline in body weight gain and corresponding reduction in food consumption.
	Neonatal and developmental toxicity was observed in the F1 generation from dams that received the mid-dose (MD) or HD (100 or 250 mg/kg/day), characterized by lower mean body weights (postnatal day [PND] 21) and decline in post-weaning survival. These findings were attributed to administration of pacritinib to F0 dams due to the presence of these effects during the preweaning period.
	F2 generation neonatal and developmental toxicity was observed at the HD (250 mg/kg/day) administered to dams (F0) based on the decline in postnatal survival (HD) and the presence, on PND 4, of a malformation (cheilognathopalatoschisis) in a single HD pup that presented with low body weight on PND 1.
	The findings in the F2 generation pups at the HD were considered a consequence of maternal toxicity (F0) and a subsequent delay in fetal development (F1), rather than a specific effect of pacritinib.

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Labeling Section	Nonclinical Data
8.3 Females and Males of Reproductive Potential	Pacritinib exposure was associated with an effect on male reproductive performance (lower mating and fertility indices) at the HD (300 mg/kg/day) in BALB/c mice.
	Reproductive toxicity (F0) was observed at the HD (250 mg/kg) in the presence of maternal toxicity during the CD-1 mouse PPND study and was based on the increase in F0 gestation length and dystocia.
	Reproductive toxicity was observed at the HD (250 mg/kg/day) in the F1 generation during the CD-1 mouse PPND study and was based on the reductions in male and female fertility, male copulation, and female conception indices at this dose. These findings were considered a consequence of maternal toxicity (F0) and a subsequent delay in fetal development (F1), rather than a specific effect of pacritinib.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Negative for carcinogenicity in the 2-year rat and 6-month Tg(HRAS) mouse.
	Negative for genotoxicity on the Ames, chromosome aberration, and micronucleus assays.
	Pacritinib exposure was not associated with adverse effects on male reproductive performance or early embryonic development to implantation in CD-1 mice at doses ≤250 mg/kg/day.
	Pacritinib exposure has no direct effects on the fertility of CD-1 mice at doses ≤250 mg/kg/day.

Source: Reviewer constructed summary table of reproductive toxicology studies submitted to the new drug application.
Abbreviations: HD, high dose; MD, mid dose; PND, postnatal day; PPND, pre- and postnatal development

Table 42. Reproductive Toxicity Exposure Margins/Dose Multiples

Study	NOAEL (mg/kg/day)	Nonclinical Exposure (μg.h/mL) or HED	Exposure Margins[1] (Dose Multiples[2])
Fertility BALB/c Mice	100 mg/kg/day	8.1 mg/kg/day (males)	(1×)
Fertility CD-1 Mice	250 mg/kg/day	20.3 mg/kg/day	(3×)
EFD CD-1 Mice	100 mg/kg/day	7.7 μg·h/mL (qualitative)	0.04×
EFD NZW Rabbits	30 mg/kg/day	17.9 μg·h/mL	0.08×
PPND CD-1 Mice	100 mg/kg/day (F0)	8.1 mg/kg/day	(1×)
	30 mg/kg/day (F1)	2.4 mg/kg/day	(0.04×)
	100 mg/kg/day (F2)	8.1 mg/kg/day	(1×)

Source: Reviewer constructed summary table of reproductive toxicology studies submitted to the new drug application.
[1] Exposure margins were based on the simulated population pharmacokinetic data generated by the Clinical Pharmacology Reviewer through PK modeling of patient samples collected in Study PAC201, PERSIST-1, and PERSIST-2 where the proposed therapeutic dose (200 mg, BID), resulted in a systemic geometric mean exposures of 213 μg.h/mL (AUC).
[2] Dose multiples were calculated by determining the HED at the nonclinical NOAEL and comparing to the proposed therapeutic dose (200 mg (BID), 400 mg/day, 6.7 mg/kg/day, 60 kg human).
Abbreviations: AUC, area under the plasma concentration-time curve; BID, twice daily; EFD, embryo-fetal development; HED, human equivalent dose, NOAEL, no observed adverse effect level; NZW, New Zealand white; PK, pharmacokinetics; PPND, pre- and post-natal development

9. Product Quality

Refer to the reviews by the Office of Product Quality, available in Panorama. There were no approvability issues from a product quality perspective.

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9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

The PERSIST-2 study was conducted under International Council on Harmonisation Good Clinical Practices (GCP) guidelines. A signed written Informed Consent Form was required in order to enroll in the study. The study was reviewed and monitored by an Institutional Review Board, Research Ethics Board or an Independent Ethics Committee depending on the country in which the study site was located. Review of the financial disclosure information is located in Section III.23. No investigators reported financial interests/arrangements. A summary of the results of the clinical study site inspections completed by Dr. Orencia in the Office of Scientific Investigations for this application for pacritinib is located in Section III.20.

11. Advisory Committee Summary

An Advisory Committee meeting was not convened to discuss this application because it did not raise efficacy or safety issues requiring input from outside experts.

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III. Appendices

12. Summary of Regulatory History

The investigational new drug application (IND) 078406 was submitted on December 27, 2007, to study SB1518 (also referred to as pacritinib) for the treatment of advanced chronic myeloid disease. SB1518 is a Janus-associated kinase (JAK) 2 and FMS-like tyrosine kinase 3 (FLT3) kinase inhibitor. The antitumor activity of SB1518 was demonstrated in two tumor models driven by FLT3 or JAK2 mutations. Two protocols titled *SB1518-2007-001: A Phase 1 study of SB1518 for the treatment of advanced myeloid malignancies*, and *SB1518-2007-002: A Phase 1 study of SB1518 for the treatment of advanced lymphoid malignancies* were deemed safe to proceed on February 6, 2008.

Pacritinib was granted Orphan Drug designation for the treatment of myeloproliferative disorders on March 13, 2008.

A special protocol assessment request was submitted for the proposed SB1518-2011-008 clinical study on December 21, 2020, and a no agreement letter was issued on January 21, 2011, due to the inadequate design and planned analysis.

Transfer of IND 078406 ownership from S*BIO Pte. Ltd. to CTI biopharm was made on June 15, 2012.

Another special protocol assessment request was submitted for the proposed PERSIST-2 (PAC 326) clinical study on August 16, 2013, and an agreement letter was issued on October 03, 2013. The Applicant submitted several amendments for this clinical study between August 2013, and August 2014, and modified agreement letters were issued in response to the amendments.

Two special protocol assessment requests were submitted for the proposed mouse and rat carcinogenicity studies on September 3, 2014, and May 14, 2015, respectively; agreement letters were issued October 16, 2014, and June 25, 2015.

The Applicant submitted a Fast Track designation request for pacritinib on June 11, 2014, for the treatment of Intermediate- and High-risk myelofibrosis (primary myelofibrosis [PMF], post-polycythemia vera [PPV] myelofibrosis [MF], post-essential thrombocythemia [PET] MF) including, but not limited to, patients with disease-related thrombocytopenia, patients experiencing treatment-emergent thrombocytopenia on other JAK2 inhibitor therapy, or patients who are intolerant to or whose symptoms are suboptimally managed on other JAK2 inhibitor therapy. Fast Track designation was granted on August 5, 2014.

The Applicant submitted various meeting requests to obtain feedback and guidance in preparation for submission of a marketing application for pacritinib. A pre-new drug application (NDA) meeting was held on June 3, 2015, to discuss the results of the completed Phase 3 trial (PERSIST-1), an ongoing confirmatory trial (PERSIST-2), and an NDA submission for the proposed indication of treatment of patients with Intermediate and High risk MF (PPV MF, PET MF, PMF) with disease-related thrombocytopenia. Per the Applicant's request, the indication for Orphan Drug Designation was amended to treatment of primary MF, PPV MF, and PET MF on December 3, 2015.

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NDA 208712 was submitted on December 30, 2015, based on the results of PERSIST-1 [REDACTED] [(b) (4)]. The Agency identified serious safety signals for (a) a detrimental effect on overall survival [REDACTED] [(b) (4)] in the PERSIST-1 and interim PERSIST-2 trial results, and (b) fatal and life-threatening safety issues of hemorrhage including intracranial hemorrhage, cardiac failure, and arrhythmias including sudden death. Subsequently, all clinical trial protocols under IND 078406 were placed on full clinical hold on February 8, 2016, and the NDA submission was withdrawn by the Applicant on February 10, 2016. On February 10, 2016, the Agency issued a rescind agreement letter stating the agreement on the PERSIST-2 (PAC 326) clinical study was no longer binding because a substantial scientific issue essential to determining the safety of the drug had been identified after Food and Drug Administration's (FDA's) assessment of the interim PERSIST-2 data.

In response to the Full Clinical Hold letter dated February 8, 2016, the Applicant submitted a complete response letter with a proposed Phase 2 dose finding trial PAC203, in which 100 mg QD, 100 mg twice daily (BID), and 200 mg BID was proposed. The 100 mg QD dosing associated with minimal efficacy but allowed a reasonable separation from the 200 mg BID dosing. The full clinical hold was subsequently lifted on January 3, 2017.

Another Type B pre-NDA meeting took place on September 16, 2020, during which the Agency was willing to file the application if it was complete and reminded the Applicant that the data should be convincing, and the risk mitigation plan should address issues observed with the PERSIST-1 study. The rolling submission and review of portions of the planned NDA was granted on September 30, 2020. The Agency received the last portion of the rolling submission on March 30, 2021.

The Applicant's initial proposed proprietary name, [REDACTED] [(b) (4)], was found conditionally acceptable on June 8, 2015. However, the Applicant withdrew the name on June 26, 2018. The second proposed proprietary name, [REDACTED] [(b) (4)], was submitted on May 29, 2018, and was found unacceptable on November 20, 2018. The third proposed proprietary name, Vonjo, was found conditionally acceptable on June 11, 2021.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

13.1.1. Pacritinib Pharmacology

The results of in vitro and in vivo nonclinical pharmacology studies were consistent with the expected mechanism of action of JAK2 and FLT3 inhibition and provided evidence that pacritinib can modulate JAK2/FLT3 signaling in a dose-dependent manner that results in a decrease in the level of activated signal transducers and activators of transcription (STAT) proteins that are known to be upregulated in patients with myeloproliferative diseases.

In vitro assays showed that pacritinib inhibits both wild-type JAK2 (half-maximal inhibitory concentration [IC_{50}] 1nM) and the specific JAK2 mutation, JAK2^{V617F} (IC_{50} 3nM), that is often

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present in patients with myeloproliferative neoplasms. Pacritinib has higher selectivity for JAK2 over closely-related JAK1, JAK3, and TYK2 enzymes (Table 43). Pacritinib also inhibits wild-type and mutant FLT3 receptors (IC_{50} 2.6 to 4.7nM), including those frequently mutated in acute myeloid leukemia (AML), which develops in some patients with MF. Pacritinib exhibited inhibitory activity against several other cellular kinases at therapeutic exposure levels, the clinical relevance of which is unknown.

Table 43. Pacritinib (Parent Molecule) In Vitro Kinase Inhibition Profile

Target Kinase	Pacritinib IC_{50} (nM) Parent	Human C_{max} 200 mg BID Both Fractions (19.9µM)	Human C_{max} 200 mg BID Free Fraction (240nM)[1]
JAK kinases			
JAK1	1,280nM	16×	0.2×
JAK2	1nM	19,900×	240×
JAK2 (V617F)	3nM	6633×	80×
JAK3	18.3nM	1087×	13×
TYK2	27nM	737×	9×
FMS/FLT kinases			
FLT3	3.9nM	5102×	61×
FLT3 (D835Y) mutation	4.7nM	4234×	51×
FLT3 (ITD) mutation	2.6nM	7654×	92×
FLT4/VEGFR3	86nM	231×	3×
FMS (CSF1R)	40nM	498×	6×
Other kinases			
IRAK1	13.6nM	1463×	18×
CSF1R (FMS)	39.5nM	504×	6×
c-SRC	46.7nM	426×	5×
CLK1	50nM	398×	5×
ARK5/NUAK1	53.3nM	373×	4×
ABL-1 (various mutations)	61 to 70nM	326× to 284×	4× to 3×
BRK	99.7nM	200×	2×
HIPK4	15nM	1327×	16×
ROS/ROS1	18.4nM	1082×	13×
TNK1	15nM	1327×	16×
TRKC	18.4nM	1082×	13×
c-Kit	44nM	452×	5×
CLK4	21nM	948×	11×

Source: Reviewer-constructed summary table of pharmacology studies submitted to the new drug application.
IC_{50} values were derived from Pharmacology Study Reports.
[1] Exposure multiples were based on the simulated population pharmacokinetic data generated by the Clinical Pharmacology Reviewer by PK modeling of patient samples collected in Study PAC201, PERSIST-1, and PERSIST-2 where the proposed therapeutic dose (200 mg, BID), resulted in a mean exposures of 9.394 µg/mL (C_{max}), 19.9µM. The free fraction exposures were calculated by multiplying the C_{max} by the percent unbound fraction observed in humans (1.2%), 240nM (C_{max}, free fraction).
Abbreviations: BID, twice daily; C_{max}, maximum concentration; FLT, FMS-like tyrosine; FMS, feline McDonough sarcoma; IC_{50}, half inhibitory concentration; ITD, internal tandem duplication; JAK, Janus-associated kinase; PK, pharmacokinetics

In vitro assays confirmed that the predominant metabolites of pacritinib (M1 and M2) inhibit both wild-type JAK2 (M1 and M2 IC_{50} 1 and 5nM, respectively) and the specific JAK2 mutation JAK2^{V617F} (M1 and M2 IC_{50} 5 and 23nM, respectively) that is often present in patients with myeloproliferative neoplasms. The M1 and M2 metabolites also inhibited wild-type and mutant FLT3 receptors (IC_{50} 15 to 29nM) including those frequently mutated in AML, which develops in some patients with myelofibrosis. The M1 and M2 metabolites of pacritinib exhibited

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inhibitory activity against several other cellular kinases at therapeutic exposure levels, the clinical relevance of which is unknown (Table 44 and Table 45).

Table 44. Pacritinib (M1 Metabolite) In Vitro Kinase Inhibition Profile

Target Kinase	Pacritinib M1 Metabolite IC$_{50}$	Human C$_{max}$ 200 mg BID M1 Metabolite Both Fractions (1910nM)	Human C$_{max}$ 200 mg BID M1 Metabolite Free Fraction (23nM)[1]
JAK kinases			
JAK1	135nM	14×	0.2×
JAK2	1.25nM	1,528×	18×
JAK2 (V617F)	4.52nM	423×	5×
JAK3	5.18nM	369×	4×
TYK2	11.4nM	168×	2×
FMS/FLT kinases			
FLT3	23.7nM	81×	1×
FLT3 (D835Y) mutation	28.5nM	67×	0.8×
FLT3 (ITD) mutation	14.8nM	129×	2×
FMS (CSFR1)	8.67nM	220×	3×
Other kinases			
IRAK1	10.6nM	180×	2×
CSF1R (FMS)	8.67nM	220×	3×
ROS/ROS1	13.1nM	146×	2×
TNK1	13.5nM	141×	2×

Source: Reviewer-constructed summary table of pharmacology studies submitted to the NDA.
IC$_{50}$ values were derived from the Pharmacology Study Reports.
[1] Exposure multiples were based on the simulated population pharmacokinetic data generated by the Clinical Pharmacology Reviewer through PK modeling of patient samples collected in Study PAC201, PERSIST-1, and PERSIST-2 where the proposed therapeutic dose (200 mg, BID), resulted in mean exposures of 9.394 µg/mL (C$_{max}$), 19.9µM. A human mass balance study indicated that the M1 metabolite accounted for 9.6% (1910nM) of the total drug exposure. The free fraction exposures were calculated by multiplying the C$_{max}$ by the percent unbound fraction observed in humans (1.2%), 23nM (C$_{max}$, free fraction).
Abbreviations: BID, twice daily; C$_{max}$, maximum concentration; FLT, FMS-like tyrosine; FMS, feline McDonough sarcoma; IC$_{50}$, half inh bitory concentration; ITD, internal tandem duplication; JAK, Janus-associated kinase; PK, pharmacokinetics

Table 45. Pacritinib (M2 Metabolite) In Vitro Kinase Inhibition Profile

Target Kinase	Pacritinib M2 Metabolite IC$_{50}$	Human C$_{max}$ 200 mg BID M2 Metabolite Both Fractions (2090nM)	Human C$_{max}$ 200 mg BID M2 Metabolite Free Fraction (25nM)[1]
JAK kinases			
JAK1	53nM	39×	0.5×
JAK2	5.17nM	404×	5×
JAK2 (V617F)	22.5nM	93×	1×
JAK3	20.2nM	99×	1×
TYK2	14.6nM	138×	2×
FMS/FLT kinases			
FLT3	27.1nM	77×	0.9×
FLT3 (D835Y) mutation	14.7nM	142×	2×
FLT3 (ITD) mutation	17.5nM	119×	1×
FMS (CSFR1)	16.1nM	130×	2×

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Target Kinase	Pacritinib M2 Metabolite IC$_{50}$	Human C$_{max}$ 200 mg BID M2 Metabolite Both Fractions (2090nM)	Human C$_{max}$ 200 mg BID M2 Metabolite Free Fraction (25nM)[1]
Other kinases			
IRAK1	10.8nM	194×	2×
CSF1R (FMS)	16.1nM	130×	2×
HIPK4	16.2nM	129×	2×
TRKC	12.9nM	162×	2×

Source: Reviewer constructed summary table of pharmacology studies submitted to the NDA.
IC$_{50}$ values were derived from the Pharmacology Study Reports.
[1] Exposure multiples were based on the simulated population pharmacokinetic data generated by the Clinical Pharmacology Reviewer through PK modeling of patient samples collected in Study PAC201, PERSIST-1, and PERSIST-2 where the proposed therapeutic dose (200 mg, BID), resulted in a mean exposures of 9.394 µg/mL (C$_{max}$), 19.9µM. A human mass balance study indicated that the M2 metabolite accounted for 10.5% (2,090nM) of the total drug exposure. The free fraction exposures were calculated by multiplying the C$_{max}$ by the percent unbound fraction observed in humans (1.2%), 25nM (C$_{max}$, free fraction).
Abbreviations: BID, twice daily; C$_{max}$, maximum concentration; FLT, FMS-like tyrosine; FMS, feline McDonough sarcoma; IC$_{50}$, half inhibitory concentration; ITD, internal tandem duplication; JAK, Janus-associated kinase; PK, pharmacokinetics

13.1.1.1. In Vivo and Ex Vivo Pharmacodynamic Activity

Consistent with the in vitro target kinase activity, cell lines found to be markedly sensitive to pacritinib treatment were either JAK2-dependent (i.e., 32D, SET2, BaF3-JAK2^{V617F}, and human Karpas 1106P) or expressed mutant FLT3 protein (i.e., MV4-11). See Table 46.

Table 46. Pacritinib In Vitro Inhibitory Activity in Tumor Cell Lines

Cancer Type	Cell Line	IC$_{50}$ (nM)[a]
AML	MV4-11	32
Megakaryoblastic (ET)	SET2	213
Myeloid (murine)	32D (+IL-3)	155
B-cell lymphoma	Karpas 1106P	326
AML	HL60	436
MPD-like pathology	BaF3-JAK2V617F	161-461 (depending on clone)
Prostate	PC3	540
Burkitt's lymphoma	Ramos	1000
Erythroleukemia	HEL92.1.7	1243
Colon	Colo205	1198
Colon	HCT116	1443

Source: NDA 208712 (SN 0009 - 2.6.2 - Pharmacology Written Summary, page 13).
[a] IC$_{50}$ values are averages of at least two independent experiments. CV was generally within ±30%.
Abbreviations: AML, acute myeloid leukemia; CV, coefficient of variation; ET, essential thrombocythemia; IC$_{50}$, half inhibitory concentration; MPD, myeloid proliferative disorder

Ex vivo studies of pacritinib reported in the literature described results that were consistent with those observed in vitro with regards to inhibition of STAT protein phosphorylation. Pacritinib inhibited phosphorylated STAT5 protein levels in a dose-dependent manner and reduced the viability of expanded erythroid progenitor cells derived from normal subjects expressing

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wild-type JAK2 (mean IC_{50} 260nM) and from PV patients expressing the $JAK2^{V617F}$ mutant (mean IC_{50} 230nM). Pacritinib had no effect on the $JAK2^{V617F}$ allele frequency in erythroid progenitor cells derived from PV patients, suggesting a comparable level of drug sensitivity irrespective of the presence of the JAK2 mutation (Goh et al. 2009). As genetic and protein aberrations of FLT3 are often observed in patients with AML, and this condition is known to develop in some patients with myelofibrosis, the effects of pacritinib were assessed on primary blast cells expanded from peripheral blood mononuclear cells derived from 13 patients with AML. Pacritinib inhibited the viability of blast cells (IC_{50} 470nM) and elicited a dose-dependent reduction in the phosphorylation of the FLT3 receptors, STAT5 and STAT3 proteins, that resulted in cell cycle arrest (G1 phase) and subsequent apoptosis (Hart et al. 2011).

13.1.1.2. Safety Pharmacology

Pacritinib binds to the human ether-à-go-go-related gene (hERG) potassium channel and inhibits hERG with a mean IC_{50} of 3µM. Considering the high degree of plasma protein binding observed for pacritinib in humans (98.8%), free plasma concentrations of pacritinib that might precipitate cardiac safety issues are unlikely to be achieved at clinical exposure levels (human maximum concentration [C_{max}] at 200 mg twice daily [BID], free fraction 240nM).

Cardiovascular and respiratory safety assessments of pacritinib were conducted in conscious beagle dogs after a single oral dose of 30 mg/kg (free base). No effect on the cardiovascular and respiratory systems of dogs was demonstrated, however, the single 30 mg/kg dose was poorly tolerated (emesis) and, based on postdose plasma concentrations, vomiting appeared to reduce exposure and complicated the interpretation of the study results. In addition, there were no cardiovascular effects attributed to the administration of pacritinib in the repeat-dose toxicity study in dogs dosed up to 14.2 mg/kg BID for 39 weeks. No adverse effects on respiration or the central nervous system were observed in dogs during the 39-week study.

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Table 47. Safety Pharmacology Studies

Study Details	Findings
Study Number: RPT097 Study Title: Profiling of Pacritinib (SB1518) in hERG assay Cell Line: HEK-293 Dose: 0.01, 0.1, 1, 10µM	Pacritinib binds to hERG with an IC_{50} of 3.51µM.
Study Number: RPT070 Study Title: Cardiovascular and Respiratory System Safety Pharmacology Study of Pacritinib (EX58) in Beagle Dogs Species/strain: Beagle Dogs Number/sex/group:4 Dose: 30 mg/kg/day (free base) Route of administration: Oral Frequency: Single Dose	Clinical observations: Emesis/vomit (3 of 4 dogs). No treatment related changes in cardiovascular or respiratory systems including electrocardiogram parameters, heart rate, respiratory rate, body temperature, blood pressure, or activity following a single oral dose.
Study Number: 170509.DUJ Study Title: Effects of Pacritinib on Ion Channels Expressed in Mammalian Cells Cell Lines: CHO/HEK293 Dose: 0.07, 0.20, 0.70, 2.0µM	Pacritinib inhibits hERG channel (IC_{50} 1.84µM). Effects of the other ion channels/currents were minimal. The calcium ion channel (Cav1.2) was inhibited 17.3% at 2µM. No other currents were inhibited more than 11% at 2µM.
Study Number: RPT206 Study Title: The In Vitro Investigation of Pacritinib on Agonist Induced Platelet Function using Light Transmission Aggregometry Cell Lines: Human Blood Dose: 15 and 45µM	At the highest concentration assessed (45µM, corresponding to free drug concentration of 540nM), pacritinib inhibited collagen induced platelet aggregation to an extent greater than that seen with the positive control (a combination of aspirin and a P2Y12 antagonist). A nominal effect on collagen-induced platelet aggregation was observed at 15µM (200nM, free drug). Pacritinib was minimally effective at inhibiting adenosine diphosphate or thrombin receptor activating peptide induced platelet aggregation at the HD.

Source: Reviewer-constructed summary table of safety pharmacology studies submitted to the new drug application.
Abbreviations: HD, high dose; hERG, human ether-à-go-go-related gene; IC_{50}, half inhibitory concentration

13.1.2. ADME/Pharmacokinetics

Overall, the nonclinical data characterizing the absorption, distribution, metabolism, and elimination of pacritinib in mice, rats, rabbits, and dogs allowed for interspecies exposure comparisons and provided relevant information for clinical dose selection.

Absorption

Following single-dose oral administration, pacritinib was absorbed slightly faster in mice (time to maximum concentration [T_{max}] from 0.5 to 2 hours) when compared to rats and dogs (T_{max}, 4 hours). The half-life ($t_{1/2}$) of orally administered pacritinib was 2.2, 5.7, and 4.4 hours in mice, rats, and dogs, respectively. $t_{1/2}$ of orally administered pacritinib (400 mg) was notably longer (51.5 hours) in healthy human subjects. Toxicities observed in normal (nondisease state) animals did not manifest in clinical trials at similar exposures despite the increased half-life observed in humans and suggests that animals may be more sensitive to the toxicologic effects of pacritinib and/or its metabolites. The mean Vdz of pacritinib was calculated in mice (65 L/kg), rats (13 L/kg), and dogs (10 L/kg). The CL of pacritinib in terms of liver blood flow was 8 L/h/kg in mice and 1.6 L/h/kg in rats and dogs. The terminal $t_{1/2}$ for intravenous administration of

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pacritinib was 5.6, 6, and 4.6 hours in mice, rats, and dogs, respectively. The oral bioavailability (F) of pacritinib was 39%, 10%, and 24% in mice, rats, and dogs, respectively.

Distribution

Following oral administration of 100 mg/kg radiolabeled [^{14}C]-pacritinib to BALB/c mice (RPT308), quantitative whole-body autoradiography revealed that the highest levels of drug-derived radioactivity were associated with the alimentary canal, consistent with the predominant biliary/fecal route of drug elimination. The lowest levels of drug-derived radioactivity were observed in the central nervous system, bone, and the lens of the eye. Concentrations of drug-derived radioactivity decreased rapidly, and the majority of tissues were below the level of quantitation by 24 hours postdose.

In a second mouse tissue distribution study (RPT110) that employed unlabeled pacritinib (single oral dose, 50 mg/kg), drug concentrations were measured by high-performance liquid chromatography (HPLC) with tandem mass spectrometry and pharmacokinetic parameters were determined in the plasma, brain, and lung tissues derived from BALB/c nude mice. This differs from the radiolabeled distribution study where all drug-related material was followed in all body compartments. Pacritinib exposure levels within these three tissues were highest in the lungs (increased 19-fold versus plasma, area under the concentration-time curve [AUC]) followed by the brain (increased 2-fold versus plasma, AUC) and plasma. Pacritinib plasma concentrations were below the limit of quantitation at 24 hours postdose. The higher level of pacritinib in the CNS relative to that observed in the radiolabeled study was ascribed to differences in assay methodology and design, but does indicate CNS penetrance of pacritinib in mice. Results from general toxicity studies demonstrated that pacritinib does not cause adverse or direct effects on the central nervous system or respiratory function. Effects on central nervous system and respiratory system parameters occurred only at doses at which frank toxicity was observed.

Table 48. Mean Tissue/Plasma PK Parameters of SB1518 After Oral Dosing in BALB/c Mice

Tissue PK	Plasma	Brain	Lungs
C_{max} (ng/ml or ng/g)	1108	1938	16508
T_{max} (h)	0.50	2.00	1.00
AUC_{0-last} (ng.h/ml or ng.h/g)	2439	4353	47388
AUC_{0-last} tissue to plasma ratio	-	1.78	19

Source: Applicant-constructed summary table from Study Report RPT110, submitted to the new drug application.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; PK, pharmacokinetics; T_{max}, time to maximum concentration

In Vitro Protein-Binding Determination

Plasma protein binding in the mouse, rat, dog, and rabbit ranged from 97.1% to 99.1% across species and concentrations (RPT107). The plasma protein binding of pacritinib in humans is 98.8% at clinically relevant plasma concentrations (approximately 10 μg/mL). Given the similarity across species, exposure margins are based on total drug exposure and are not corrected for free versus bound fractions.

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Metabolism

In vitro studies in recombinant microsomes expressing cytochrome P450 (CYP450) isoforms indicated that pacritinib is primarily metabolized by the CYP3A4 isozyme. No unique metabolites were identified in humans relative to nonclinical species. Moreover, the in vivo metabolites identified in mice, rats, rabbits (Figure 12), and dogs (Figure 13) were similar to those observed in humans (Figure 14), indicating that these species were appropriate and relevant for the toxicological evaluation of pacritinib.

Figure 12. Proposed Structures of Pacritinib Metabolites in Mice, Rats, and Rabbits
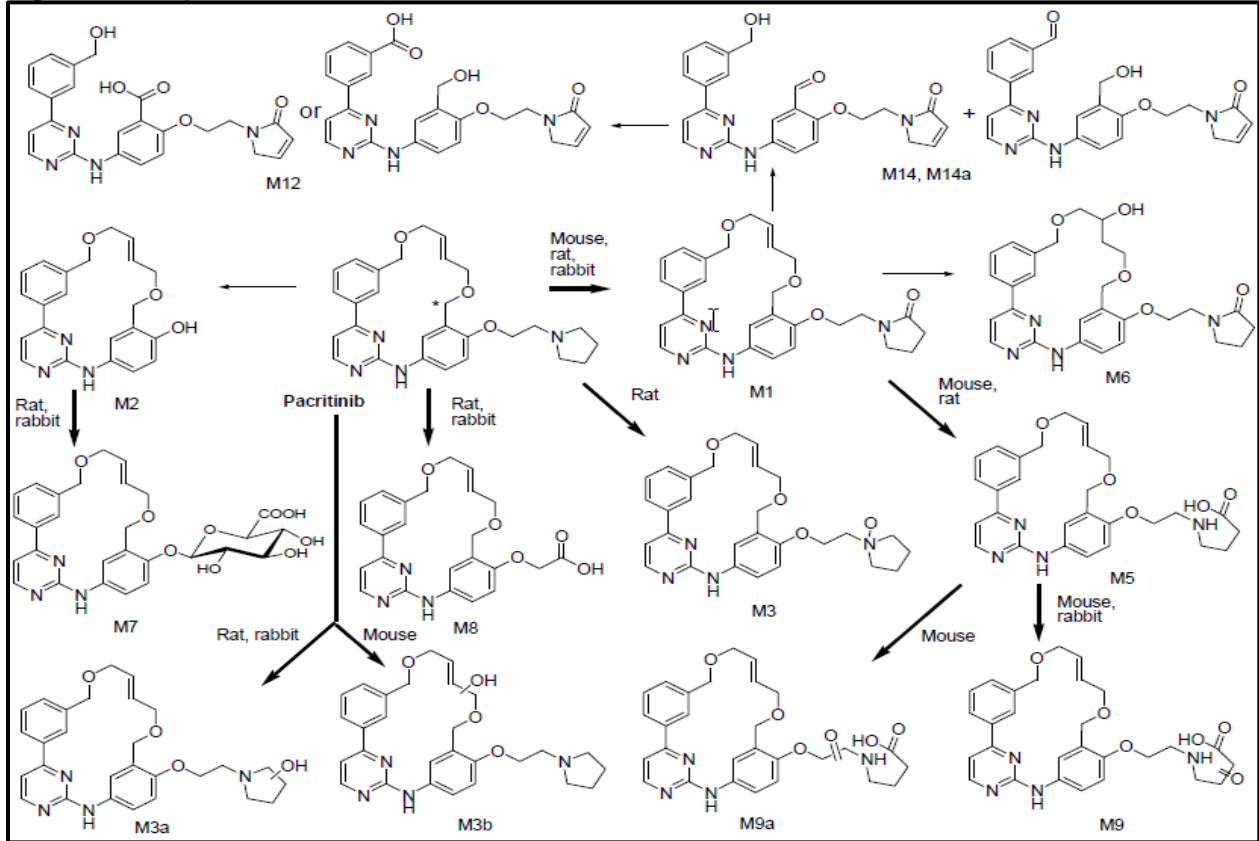
Source: Proposed Metabolic Pathways of Pacritinib in Mice, Rats, and Rabbits (RPT467N-1502).
Bold arrows indicate major metabolic pathways.

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Figure 13. Proposed Structures of Pacritinib Metabolites in Dogs
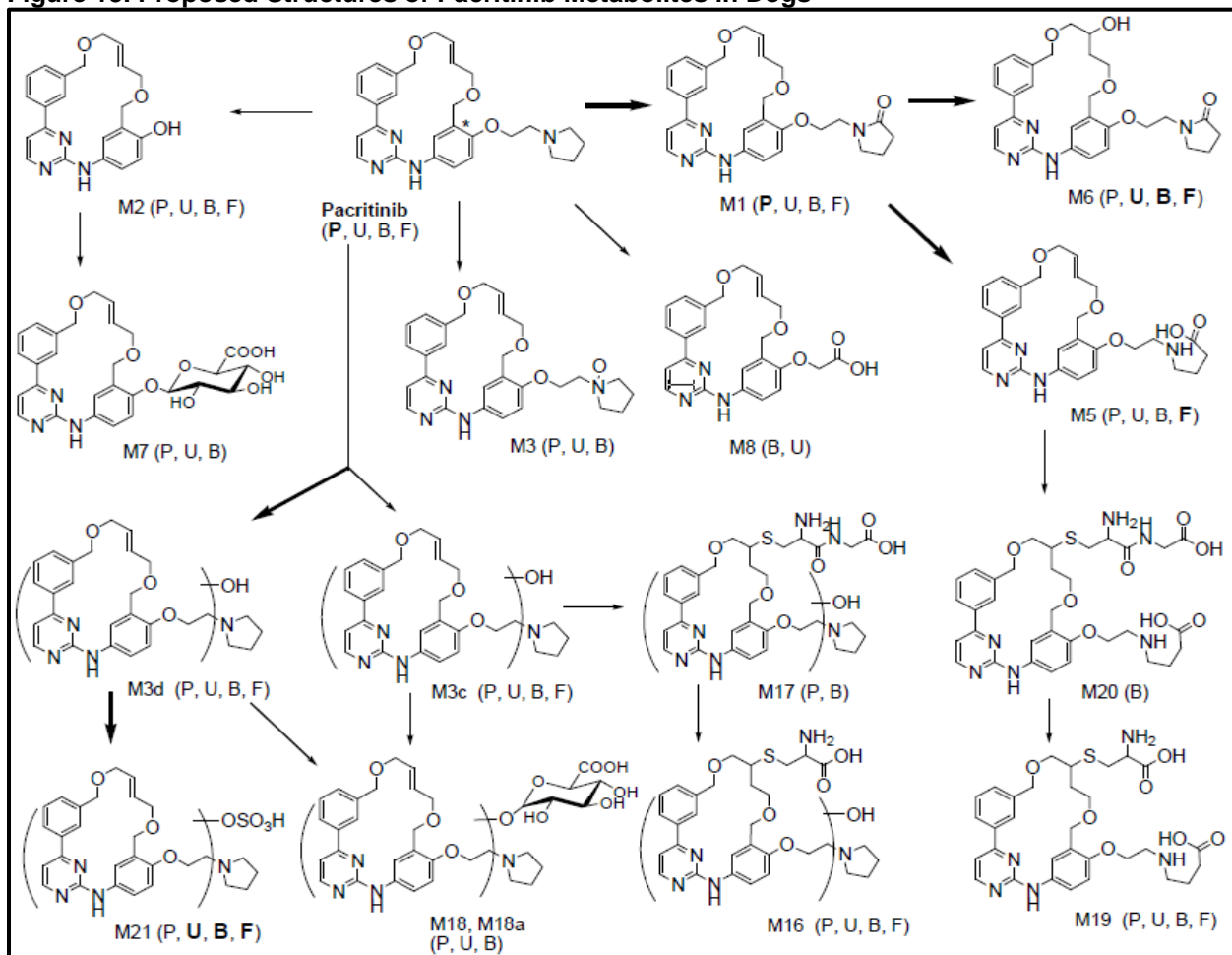
Source: Proposed Metabolic Pathways of Pacritinib in Dogs (RPT467N-1501).
Bold arrows indicate major metabolic pathways.
Bold letters (P, U, B, F) indicate the matrix in which pacritinib, or metabolite is a predominant component.
Abbreviations: B, bile; F, feces; P, plasma; U, urine

Comparative Metabolism

The M1 metabolite was identified as a predominant metabolite in the mouse, rat, and rabbit, a finding consistent with toxicokinetic studies and nonclinical exposure data. However, it is notable that the M2 metabolite, identified as a predominant metabolite in humans (M2 exposures in humans were ~10% of those observed for pacritinib) is not a predominant metabolite in any of the nonclinical species.

The Applicant contends that the M1 and M2 metabolites exhibit a fraction of the in vitro pharmacological activity of the parent molecule (50% and 20% for the M1 and M2 metabolites, respectively) and that the metabolites are unlikely to materially contribute to the pharmacological activity of pacritinib. Metabolite exposures (free fraction, unbound) at the therapeutic dose (200 mg/BID), however, do exceed the IC_{50}s for several of the JAK and FLT3 family members.

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Figure 14. Proposed Structures of Pacritinib Metabolites in Humans
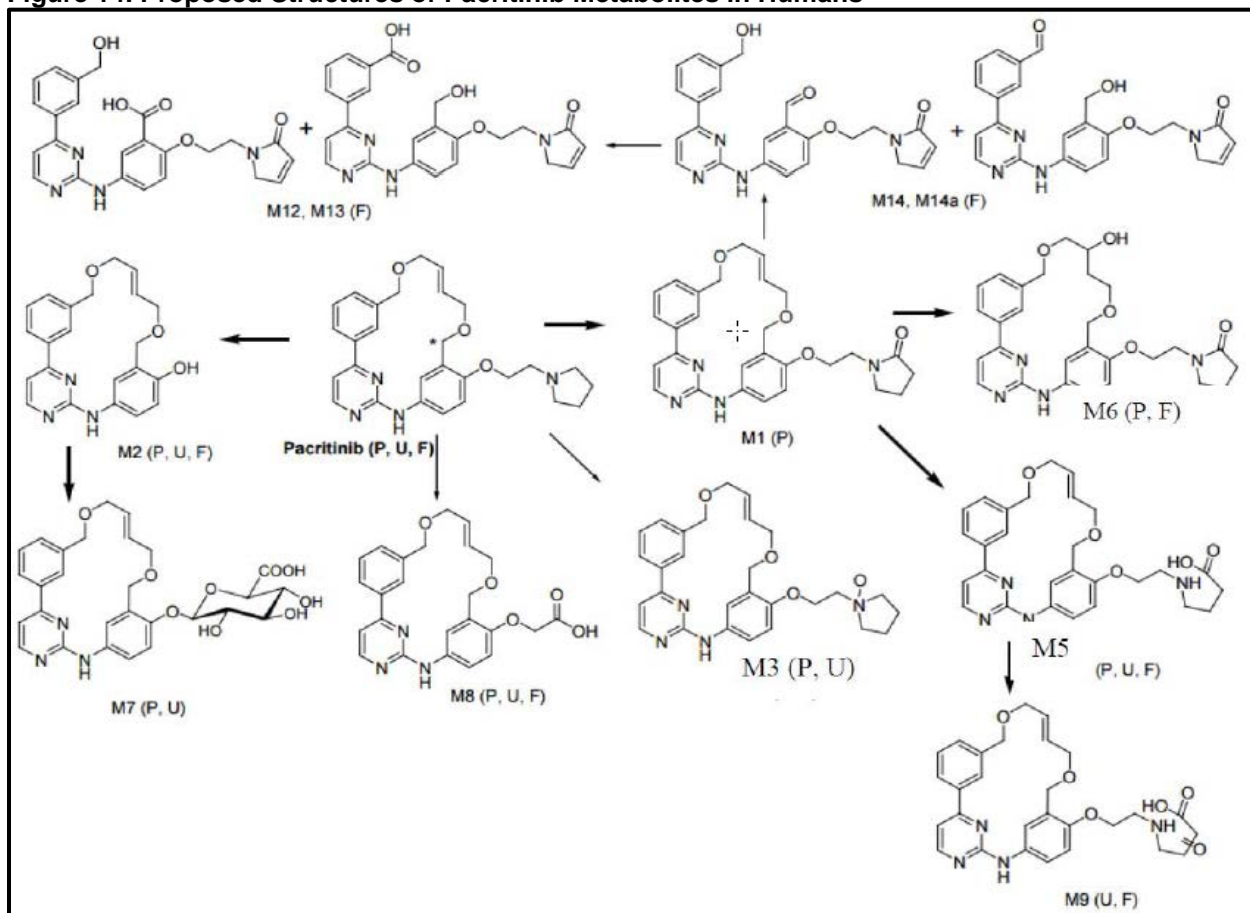
Source: Proposed Metabolic Pathways of Pacritinib in Humans (PAC102).
Bold arrows indicate major metabolic pathways.
Bold letters (P, U, F) indicate the matrix in which pacritin b, or metabolite is a predominant component.
Abbreviations: F, feces; P, plasma; U, urine

Excretion

A radiolabeled mass balance, excretion, and tissue distribution study (RPT308) was conducted in male BALB/c mice following a single dose of 71.1 mg/kg [^{14}C]-pacritinib. The recovery of dosed radioactivity over the 168-hour study period was 93%. The majority of the radioactive dose was recovered in the feces, with a recovery of 91%. Drug-derived radioactivity was widely distributed to tissues of mice through 8 hours postdose, but tissue concentrations in the majority of tissues decreased rapidly from 24 hours to 168 hours postdose. The majority of tissues reached maximal concentrations at 1 hour postdose. Elimination was nearly complete at 168 hours postdose, but radioactivity remained measurable in the liver. Overall, the highest concentrations of drug-derived radioactivity were observed in the contents of the alimentary canal and bile. Lower concentrations of drug-derived radioactivity were present in the urinary bladder contents. The human absorption, distribution, metabolism, and elimination mass-balance study showed that pacritinib was predominantly cleared via metabolism and biliary/fecal excretion (>85% of administered dose), with minimal renal clearance (no more than 0.12% of an orally administered 400 mg dose of pacritinib was excreted intact in urine) consistent with the results observed in male BALB/c mice.

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Pharmacokinetic Drug Interactions

Pacritinib did not inhibit the activity of CYP450 isozymes (IC_{50} >5µM for CYP450 1A2, 2C9, 2C19, 2D6, and 3A4) in human liver microsomes and at concentrations up to 10µM yielded no significant potential to induce CYP1A2 and CYP3A4 isozymes in cultured human hepatocytes (RPT066). In a more recent study (RPT200), pacritinib directly inhibited (dose-dependently) CYP450 enzyme probe reactions in human liver microsomes at concentrations up to 350µM. The most potent inhibition was observed towards CYP1A2 (IC_{50} 10.6µM), CYP2C19 (IC_{50} 11.6 to 13.6µM), and CYP3A4 (IC_{50} 4.7 to 86µM). Less-potent inhibition was observed towards CYP2B6, CYP2C8, CYP2C9, and CYP2D6 (IC_{50} 27 to 120µM). No notable CYP450 induction effects were observed for pacritinib in this study. These results were confirmed in another study (RPT211) that demonstrated pacritinib directly inhibited CYP1A2, CYP2C19, and CYP3A4. In addition, pacritinib was shown (RPT213) to be a strong activator of the human pregnane X receptor (PXR, 10µM) and a moderate activator of the human aryl hydrocarbon receptor (AhR, 5µM), both of which are nuclear receptors known to induce CYP450s.

Pacritinib exhibited high intestinal absorption in the Caco-2 cell model (RPT14F175CETH). The efflux ratio value (0.8) for pacritinib suggests no involvement of an active p-glycoprotein (P-gp)-mediated transport mechanism in the disposition of pacritinib. A drug transporter assay (RPT200) indicated drug interactions in vitro between pacritinib and drugs transported by P-gp (4.8µM), breast cancer resistance protein (BCRP) (5.4µM), OATP1B1 (9.4µM), OATP1B3 (74.2µM), bile salt export pump (BSEP) (>100µM), OCT1 (0.87µM), and OCT2 (19.2µM).

Pharmacokinetics

Table 49. Toxicokinetic Data From Repeat-Dose Toxicology Studies

Study Details	Major Findings
	General Toxicology Studies

Study Details	Major Findings
Study Number RPT233 Study Title: 26-Week Oral (Gavage) Toxicity Study in BALB/C Mice Sample Collection Times: Predose, 0.5, 1, 2, 4, and 8 hours postdose (Day 1). Predose, 0.5, 1, 2, 4, 8, and 24 hours postdose (Weeks 13/26). Accumulation: Minimal Dose Proportionality: Generally, greater than dose proportional. NOAEL: 200 mg/kg/day (MD) Exposure Margin: 0.02×	**Table 50. TK Parameters in BALB/C Mice**

Source: Applicant-constructed table from Study Report RPT233, submitted to the new drug application.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; TK, toxicokinetics; T_{max}, time to maximum concentration

Table 50. TK Parameters in BALB/C Mice

Day	Sex	Dose (mg/kg/day)	AUC_{0-t} (hr.ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
1	Male	60	399	292	1
		200	4569	1930	1
		400	7071	3185	1.15
	Female	60	542	342	1
		200	3914	1660	1
		400	8165	2380	1.18
91	Male	60	501	208	2
		200	3901	1177	2
		300	8117	1365	2
	Female	60	518	195	2
		200	4184	1010	1.18
		300	9591	1440	2.12
182	Male	60	734	293	1.15
		200	4167	898	2
		300	9010	2120	1.25
	Female	60	334	132	0.583
		200	5458	1407	1.22
		300	13277	2097	2

Study Details	Major Findings
Study Number: RPT241 Study Title: 39-Week Oral (Capsules) Toxicology Study in Beagle Dogs Sample Collection Times: Predose, 0.5, 1, 2, 4, and 8 hours postdose (Day 1). Predose, 0.5, 1, 2, 4, 8, and 24 hours postdose (Day 90/270). Accumulation: Exposures were comparable on Days 90 and 270. Dose Proportionality: Generally, greater than dose proportional. NOAEL: 20 mg/kg/day (MD) Exposure Margin: 0.06× (males) and 0.02× (females)	**Table 51. TK Parameters in Beagle Dog**

Table 51. TK Parameters in Beagle Dog

Day	Sex	Dose (mg/kg/day)	AUC_{0-t}^{a} (hr·ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
1	Male	6	53.1	11.5	2
		20	616	151	3
		50	1341	286	2
	Female	6	180	40.7	3
		20	338	71.9	4
		50	874	169	3
90	Male	6	620	64.1	3
		20	8401	646	3
		40	40175	2250	8
	Female	6	556	69.2	3
		20	5155	426	3
		40	27762	1695	2
270	Male	6	683	54	3
		20	11830	878	4
		40	29249	1990	4
	Female	6	533	57.2	4
		20	3434	264	4
		40	22314	1416	2

[a] For Days 90 and 270, AUC_{0-t} reflects steady state.

Source: Applicant-constructed table from Study Report RPT241, submitted to the new drug application.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; TK, toxicokinetics; T_{max}, time to maximum concentration

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Study Details	Major Findings
	Reproductive Toxicology Studies

Study Number: RPT112506

Study Title: An Oral (Gavage) Study of the Effects of Pacritinib on Embryo-Fetal Development in CD-1 Mice

NOAEL: 100 mg/kg (maternal/fetal)

Exposure Margin: 0.04× (GD15)

Note: AUC values determined in this study should not be used for human: animal AUC comparisons in labeling due to a lack of demonstrated stability between the time of collection and analysis.

Table 52. CD-1 Mouse EFD TK Parameters; GD 6 of 15

Pacritinib Dose [a] (mg/kg/day)	30	100	250
Parameter (Units)		Gestation Day 6	
AUC_{0-t} (ng·hr/mL) (SE)	342 (34.2)	6,350 (678)	22,700 (4100)
C_{max} (ng/mL) (SE)	179 (43.8)	2,660 (498)	4,350 (14.7)
T_{max} (h)	0.5	1	1
		Gestation Day 15	
AUC_{0-t} (ng·hr/mL) (SE)	760 (88.4)	7,660 (814)	23,200 (3690)
C_{max} (ng/mL) (SE)	240 (45.5)	1,730 (274)	3,080 (259)
T_{max} (h)	2	1	2

[a] = Represents the pacritinib free base based on a correction factor of 1.406 for the citrate salt.
SE = Standard error

Source: Applicant-constructed table from Study Report RPT112506, submitted to the new drug application.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; SE, standard error; TK, toxicokinetics; T_{max}, time to maximum concentration

Study Number: RPT112503

Study Title: An Oral (Gavage) Study of the Effects of Pacritinib on Embryo-Fetal Development in Rabbits

NOAEL: 30 mg/kg (maternal/fetal)

Exposure Margin: 0.08× (GD20)

Table 53. New Zealand White Rabbit EFD TK Parameters; GD 7 of 20

Dose (mg/kg/day)		15		30		60	
Day	TK Parameters	Mean	SD	Mean	SD	Mean	SD
GD 7	AUC_{0-t} (ng·hr/mL)	2,680	385	4,470[3]	113	11,400[3]	3,790
	C_{max} (ng/mL)	263	27.5	403[3]	44.7	757[3]	155
	T_{max} (hr)	3.0	1.2	4.0[3]	0.0	3.3[3]	1.2
GD 20	AUC_{0-t} (ng·hr/mL)	10,400	3,310	17,900[3]	9,790	55,500[2]	NA
	C_{max} (ng/mL)	977	323	1,490[3]	789	3,000[2]	NA
	T_{max} (hr)	4.0	0.0	4.0[3]	0.0	4.0[2]	NA

GD = gestation day, NA = Not applicable
N = 4, except where designated with †[N]

Source: Applicant-constructed table from Study Report RPT112503, submitted to the new drug application.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; EFD, embryo-fetal development; GD, gestation day; TK, toxicokinetics; SD, standard deviation; T_{max}, time to maximum concentration

Source: Reviewer-constructed summary table of reproductive toxicology studies submitted to the NDA.
Anticipated clinical dose (200 mg (BID) 213 µg.h/mL AUC_{0-24}). Source: Clinical Pharmacology Reviewer: Simulated data via PK models of patient samples collected in Studies PAC201, PERSIST-1, and PERSIST-2.
Abbreviations: AUC, area under the plasma concentration-time curve; BID, twice daily; GD, gestation day; MD, mid dose; NDA, new drug application; NOAEL, no observed adverse effect level; PK, pharmacokinetics

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13.1.3. Toxicology

13.1.3.1. General Toxicology

13.1.3.1.1. 26-Week Oral (Gavage) Toxicology Study in BALB/cAnNCrl Mice (RPT233)

Key Study Findings

- Due to the onset of severe toxicity in Week 5, the high dose ([HD], 400 mg/kg/day) was reduced to 300 mg/kg/day in Week 6 for mice scheduled to be dosed for 26 weeks and in Week 3 (staggered start) for mice scheduled to be dosed for 13 weeks.
- Five HD mice (400/300 mg/kg/day) were found dead (on Days 39, 56, 151, 153, and 165) and two HD mice were euthanized in extremis (on Days 112 and 176). The cause of the poor condition was considered the result of moderate acute inflammation involving the parotid salivary gland and mandibular lymph node in the HD female euthanized in extremis on Day 176. The cause of moribundity or death in the remaining six HD mice was not determined. Clinical signs in mice that died on study included decreased activity, eyes partially or completely closed, discolored hair, and a generalized unkempt appearance. The increased morbidity/mortality at the HD was considered directly related to the administration of pacritinib.
- Body weight gain declined significantly with increased dose in males and in mid-dose (MD) and HD females. An early decline in body weights was observed at the HD in both sexes and never fully recovered to predose levels in females.
- Spleen weight (absolute and relative) declined in both sexes at the MD and HD and correlated with a decrease in lymphoid cellularity and/or an increased proportion of lymphocytes in periarteriolar lymphoid sheaths (minimal to mild, MD and HD) and a minimal decline in red blood cell mass (HD).
- Microscopic findings in the thymus included an increase in the number or density of lymphocytes within the medullary region of the thymus resulting in decreased demarcation between the medulla and cortex (minimal to mild) and correlated with a decline in lymphocyte/leukocyte counts in both sexes at the MD and HD.
- Neutrophil counts increased in the HD in both sexes during Week 13 and progressed to the MD and HD by Week 26.

Reviewer's comment: The Reviewer agreed with the Applicant's interpretation that the no observed adverse effect level (NOAEL) was the MD (200 mg/kg/day). However, if the microscopic findings noted in the spleen and thymus at the MD are considered, the NOAEL would decline to the low dose (LD). The reversibility of findings in mice was not assessed. The NOAEL (MD) represents a 0.02× exposure margin (4.8 µg.h/mL, Day 182, sex-averaged) to the anticipated clinical dose (200 mg BID, 213 µg.h/mL AUC). Human PK data source: Clinical Pharmacology Reviewer simulated data via PK models of patient samples collected in Studies PAC201, PERSIST-1, and PERSIST-2).

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Table 54. Study Information, Study RPT233

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 30, 100, 200/150 mg/kg (BID, 8 hours apart) 0, 60, 200, 400/300 mg/kg/day (total daily doses). The HD was 400 mg/kg/day, up to study week 6 (26-Week sacrifice) or study week 3 (13-Week sacrifice) and 300 mg/kg/day for the remainder of each substudy.
Route of administration	Oral gavage
Formulation/vehicle	0.5% Methylcellulose and 0.1% Tween 80 in deionized water
Species/strain	Mouse/BALB/cAnNCrl
Number/sex/group	40
Age	8 weeks
Satellite groups/unique design	A staggered start (3 weeks) was employed for mice scheduled to be removed from the study after 13 weeks of dosing. The reversibility of findings (recovery) was not assessed.
Deviations from study protocol	None that affected the interpretation of the results.

Source: Reviewer-constructed summary table of the toxicology study (RPT233) submitted to the new drug application.
Abbreviations: BID, twice daily; GLP, good laboratory practice; HD, high dose

Table 55. Observations and Results, Study RPT233

Parameter	Major Findings
Mortality	Five HD mice (400/300 mg/kg/day) were found dead (Day 39, 56, 151, 153 and 165) and two HD mice were euthanized in extremis (Day 112 and 176). Clinical signs in these mice included decreased activity, eyes partially or completely closed, discolored hair and a generalized unkempt appearance. These deaths were considered related to the administration of pacritinib.
Clinical signs	Due to the onset of severe toxicity, the HD (400 mg/kg/day) was reduced to 300 mg/kg/day at study Week 6 for mice scheduled to be dosed for 26 weeks and at study Week 3 for mice scheduled to be dosed for 13 weeks. Clinical signs at the HD included an increased incidence of lacrimation and thinness in HD males and hair discoloration (yellow) and unkempt appearance in both sexes (HD). Yellow discoloration of the hair was also noted in MD males; however, the incidence was similar to the controls after Week 14.
Body weights	A statistically significant and dose-responsive decline in body weight gain was observed at all doses in males and in MD/HD females. Body weights at the HD in both sexes tended to decline early on and never fully recovered to predose levels in females.
Food consumption	A dose-responsive decline in food consumption was observed at all doses in males and in MD/HD females and correlated with the decrease in body weight gains.
Ophthalmoscopy	Unremarkable
Hematology	WBC: Leukocyte counts decreased in both sexes at the MD/HD (Week 13) and at the HD in females during Week 26. Lymphocytes declined with dose in both sexes at the MD/HD. Neutrophils tended to increase in both sexes at the HD only during Week 13 and progressed to the MD/HD by Week 26. RBC: Significant, albeit minimal (<10%), decreases in red cell mass (erythrocytes, hemoglobin, and hematocrit) were observed at the HD in both sexes.
Clinical chemistry	Liver parameters: Minimal decreases (4% to 13%) in protein parameters (total protein, albumin, and globulin) were observed at the HD (Week 26) and may have been related to decreases in food consumption and body weight gain. Kidney parameters: A minimal decline in blood urea nitrogen was observed in females at all doses and was likely related to the decline in food consumption and body weight gain.

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Parameter	Major Findings
Gross pathology	All macroscopic findings in mice were considered incidental and unrelated to the administration of pacritinib.
Organ weights	There were no dose-related organ weight changes observed in either sex at the LD. Spleen weight (absolute and relative) declined in both sexes at the MD/HD. A decline in absolute kidney, liver, lung/bronchi, mandibular/submandibular salivary gland, and/or thymus weight was observed in males at all doses and absolute liver and mandibular/submandibular salivary gland weight declined in HD females. These changes were likely driven by the reduced body weight gain observed in both sexes.

Histopathology
  Adequate battery:
  Yes
	Microscopic observations related to the administration of pacritinib were observed predominantly in lymphoid tissues at the HD, including the spleen and thymus, in mice. Microscopic findings in the spleen included altered cellularity characterized by decreased lymphoid cellularity and/or increased proportion of lymphocytes in periarteriolar lymphoid sheaths (minimal to mild) at the MD/HD. This condition was noted in control mice (minimal) at a lower incidence. Microscopic findings in the thymus included an increase in the number or density of lymphocytes within the medullary region of the thymus resulting in decreased demarcation between the medulla and cortex (minimal to mild). The condition was considered non-neoplastic by the study pathologist. Microscopic findings in the mesenteric lymph nodes included an increase in foamy and pigmented macrophages in MD/HD mice and were not consider adverse. Microscopic observations noted in the ileum (minimal hypertrophy and/or hyperplasia of goblet cells) were likely related to the decline in food consumption and were not considered adverse.

Source: Reviewer-constructed summary table of the toxicology study (RPT233) submitted to the new drug application.
Abbreviations: HD, high dose; LD, low dose; MD, mid dose; RBC, red blood cell; WBC, white blood cell

13.1.3.1.2. 39-Week Oral (Capsules) Toxicology Study in Beagle Dogs (RPT241)

Key Study Findings

- Due to the onset of severe toxicity on Day 8, the HD (50 mg/kg/day) was reduced to 40 mg/kg/day (20 mg/kg, BID) on Day 9 and an additional dog was added to each HD group due to the removal of two morbid dogs (one of each sex) dosed at 50 mg/kg/day (25 mg/kg, BID).
- Two HD dogs (50 mg/kg/day) were euthanized in extremis on Day 7 or 8 and one HD replacement dog that initiated dosing on Day 9 (40 mg/kg/day) was euthanized on Day 19. Two additional HD (50/40 mg/kg/day) dogs were euthanized on Days 210 and 227. Significant body weight loss and lower food consumption were observed, and clinical signs included: decreased activity, aggressive behavior, black discolored feces, cold skin, ataxia, and/or convulsions prior to euthanasia. Red discoloration of the large intestine was noted macroscopically in HD males.
- Emesis/vomitus increased at the MD/HD and were considered adverse at the HD where body weight or food consumption were notably affected and necessitated frequent anti-emetic treatments (MD/HD). Antidiarrhea treatments and subcutaneous fluids were administered to the majority of HD dogs to counteract the gastrointestinal (GI) effects (soft/watery/mucoid feces) of pacritinib.

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- Due to the onset of rapid weight loss, the majority of HD dogs received food supplementation to stabilize body weight. With the addition of supplemental food, HD females were able to maintain body weight comparable to controls while lower body weight persisted in HD males despite continuous food supplementation.
- Microscopic findings in lymphoid tissues included: Lymphoid depletion in the Peyer's patches, splenic lymphoid depletion, and thymic (medulla) lymphoid hyperplasia at the HD (both sexes). The changes in lymphoid tissues correlated with a decline in leukocyte counts in HD males, which were driven predominantly by a decrease in neutrophils and were present to a lesser extent in HD females.
- Renal tubular vacuolation increased in incidence and/or severity in HD males and MD/HD females. Calcium levels tended to decline at the MD/HD in both sexes.
- Sorbitol dehydrogenase increased significantly (increased 2.4-fold) at Week 39 and aspartate aminotransferase (AST) tended to be elevated throughout the study in HD males in the absence of microscopic liver findings. Albumin and total protein declined at the MD/HD (both sexes). These findings are conceivably related to the GI effects of pacritinib.

Reviewer's comment: The Reviewer agreed with the Applicant's interpretation that the NOAEL was the MD (20 mg/kg/day) based on the mortality, weight loss and GI toxicity observed at the HD. The reversibility of findings in dogs was not assessed. The NOAEL (MD, 11.8 μg·h/mL, and 3.4 μg·h/mL AUC_{0-24}, Day 270, in males and females) represents a $0.06\times$ (M) and $0.02\times$ (F) exposure margin to the anticipated clinical dose (200 mg BID, 213 μg·h/mL AUC). Human PK data source: Clinical Pharmacology Reviewer simulated data via PK models of patient samples collected in Studies PAC201, PERSIST-1, and PERSIST-2).

Table 56. Study Information, Study RPT241

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 3, 10 and 25/20 mg/kg (BID, 8 hours apart)
	0, 6, 20 and 50/40 mg/kg/day (total daily doses). The HD was 50 mg/kg/day, up to Day 8 and 40 mg/kg/day (Day 9 forward).
Route of administration	Oral
Formulation/vehicle	#12 Torpac Gelatin Capsules
Species/strain	Dog/Beagle
Number/sex/group	4
Age	7 to 8 Months
Satellite groups/unique design	A peripheral blood leukocyte analysis was conducted.
Deviation from study protocol	None that affected the interpretation of the results.

Source: Reviewer-constructed summary table of the toxicology study (RPT241) submitted to the new drug application.
Abbreviation: BID, twice daily; GLP, good laboratory practices; HD, high dose

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Table 57. Observations and Results, Study RPT241

Parameter	Major Findings
Mortality	Two HD dogs (one male, one female) that presented with significant body weight loss (10% to 24%), decreased food consumption and multiple clinical findings during the first 6 days of dosing were euthanized in extremis on Day 7/8. Red discoloration of the large intestine was noted macroscopically in the HD male. A single HD male that was added to the study on Day 8 and initiated dosing on Day 9 at 40 mg/kg/day, presented with a decrease in body weight (10%), decreased food consumption, and clinical observations of decreased activity, aggressive behavior, black discolored feces, and cold skin prior to euthanasia on Day 19. Consistent with the HD male sacrificed on Day 7, this male presented with red discoloration of the intestinal mucosa macroscopically. Two additional HD dogs (one male, one female) displayed significant body weight loss (18% to 26%) for 4 weeks prior to their unscheduled sacrifice. The HD male presented with cold skin and was considered moribund at termination. The HD female presented with decreased activity, ataxia, and convulsions prior to euthanasia.
Clinical signs	Due to the onset of severe toxicity, the HD (50 mg/kg/day) was reduced to 40 mg/kg/day on Day 9. One new dog/sex was added to the HD group on Day 9 due to the removal of two morbid dogs (one male, one female) dosed at 50 mg/kg/day. The incidence of emesis/vomitus increased at the MD/HD and was considered adverse at the HD where body weight or food consumption were notably affected. Frequent anti-emetic treatments were implemented at the MD/HD. Adverse finding at the HD included: fecal discoloration, an increased incidence of soft/watery/mucoid feces, loss of skin elasticity, cold skin, decreased activity, aggressive behavior, jerky head movements, ataxia, tremors, and thinness. Antidiarrhea treatment and subcutaneous fluids were administered the majority of HD dogs. There were no clinical signs observed in LD dogs that were considered related to the administration of pacritinib.
Body weight	Due to the onset of rapid weight loss, the majority of HD dogs received supplemental and/or canned food to stabilize body weights. HD females, that survived until the scheduled necropsy, maintained body weights that were similar to controls with food supplementation while body weights in HD males were notably lower than all other dosing groups despite food supplementation. At the MD, food supplementation and subcutaneous fluids were required for one male that presented with emesis/vomitus and rapid weight loss (Week 5) and over a period of 11 weeks (Week 5 to Week 16) successfully stabilized body weight gain in this dog. In females, body weight gain at the LD rapidly surpassed weight gain in all other groups, including female controls, without food supplementation. Body weight gain at the LD in males rarely exceeded the weight gain observed in male controls or at the MD.
Food consumption	Hyperphagia was observed in LD females (exceeding controls at most points during the study) and correlated with the increase in body weight gain in this group. A periodic decline in food consumption at the HD was associated with rapid body weight loss and resulted in veterinary care treatments of both canned and supplemental food.
Ophthalmoscopy	Unremarkable
Electrocardiograms	Unremarkable. In general, ECG measurements were initiated at the T_{max}/C_{max} for pacritinib.
Hematology	WBC: Leukocytes counts (relative to pretest) declined in HD males (53% decrease) at Week 39 and was driven predominantly by a decrease in neutrophil counts (45% decrease). This trend was present in HD females to a lesser extent. Platelet counts (relative to controls) increased significantly at the MD/HD in males (Week 13/39) and at the HD in females (Week 39) however platelet counts tended to be elevated in MD/HD males prior to the initiation of dosing.

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Parameter	Major Findings
Peripheral blood leukocyte analysis	Unremarkable
Clinical chemistry	Liver parameters: Total protein and albumin levels (relative to predose) declined minimally at the MD/HD (both sexes). Sorbitol dehydrogenase (relative to predose) was significantly elevated (2.4-fold) in HD males (Week 39). This trend was apparent in HD females at Week 13 and to a lesser extent at Week 39. AST levels (relative to predose) tended to increase in pacritinib-dosed males throughout the study (↑80% at the HD, Week 39). This trend was not observed in females. Kidney parameters: Calcium levels (relative to predose) tended to decline to a minimal extent (<20%) at the MD/HD in both sexes. Phosphorus levels and alkaline phosphatase levels (relative to predose) tended to decline in all groups, including no-dose controls, throughout the study in both sexes. Creatinine levels (relative to predose) increased minimally in all male groups, including no-dose controls, throughout the study. This trend was present in HD females.
Gross pathology	There were no notable macroscopic findings observed in dogs euthanized during the scheduled necropsy (Week 39). Macroscopic findings in dogs that died on study included: depleted body fat, intestinal red discoloration, and/or edema of the subcutis.
Organ weights	Absolute liver and lung weight were significantly lower in MD/HD females and slightly elevated at the LD.
Histopathology Adequate battery: Yes	Microscopic findings included lymphoid depletion in the Peyer's patch, splenic lymphoid depletion, and thymic (medulla) lymphoid hyperplasia at the HD (both sexes) and an increase in kidney tubular vacuolation in HD males and MD/HD females. Peyer's patch lymphoid depletion (minimal to mild) was noted in HD males (four of four) and HD females (three of four). These findings were either limited to the germinal centers which appeared hypocellular or affected the overall size of the Peyer's patches that were shrunken in size and/or number across various intestinal sections. Splenic lymphoid depletion (minimal to mild) was observed in all HD dogs (both sexes) and was noted intermittently in other groups, including controls. The lymphoid depletion affected predominantly the marginal zone within the periarteriolar sheaths and lymphoid follicles were decreased in size when the lymphoid depletion was graded mild. Thymic lymphoid hyperplasia (minimal) was noted at the HD in males (one of four) and females (three of four). The medulla was populated by increased numbers of cells which made the distinction between the cortex and the medulla difficult to discern. Renal tubular vacuolation increased in incidence and severity (mild) in MD/HD females and was present to a lesser extent (minimal) in LD and control females. In males, renal tubular vacuolation (mild) was confined to the HD. Kidney findings were located in the outer medulla and predominantly affected the collecting ducts and the ascending thick limb of the Henle's loop.

Source: Reviewer-constructed summary table of the toxicology study (RPT241) submitted to the new drug application.
Abbreviations: BID, twice daily; C_{max}, maximum concentration; ECG, electrocardiogram; HD, high dose; LD, low dose; MD, mid dose; T_{max}, time to maximum concentration; WBC, white blood cell

General Toxicology (Subchronic Studies)

Acute (Single-Dose) Toxicity

The single-dose toxicity of pacritinib was evaluated in the mouse as part of the in vivo micronucleus studies (RPT164 and RPT178), in a rat dose range-finding study (RPT8000742), and in an oral capsule study in the dog (RPT070).

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Mouse

Toxicology data were obtained in two murine strains in the course of conducting the in vivo micronucleus assays (Section 13.1.3.2). Following the single-dose administration of pacritinib (1,857 mg/kg, free base), mortality was observed in 10 BALB/c mice, and adverse clinical observations included decreased activity, tremors, cachexia, and a bristly coat. At a pacritinib dose of 928.5 mg/kg (free base), decreased activity was observed in two BALB/c mice on the second and third day after dose administration but no mortality occurred. There were no adverse findings in BALB/c mice dosed at ≤223.1 mg/kg, free base (RPT164). In ICR mice, mortality was observed in two mice administered a single dose of pacritinib (1422.5 mg/kg, free base). Clinical observations of lethargy (males and females) and piloerection (males only) were observed following administration of single doses ≥1066.9 mg/kg (free base). The 1066.9 mg/kg (free base) dose was not lethal. There were no adverse findings in ICR mice dosed at ≤533.4 mg/kg, free base (RPT178).

Rat

An acute and 7-day dose range-finding study (RPT8000742) was conducted in Sprague-Dawley rats to evaluate the acute toxicity of pacritinib when administered at 50, 100, 200, and 400 mg/kg (BID, free base). Pacritinib was well tolerated following single doses and there were no treatment-related mortalities. No treatment-related effects on body weight, food consumption, coagulation, clinical chemistry, or macroscopic findings were observed following a single dose. At termination, mild increases in platelet counts were observed in male rats administered a single dose at 400 mg/kg BID.

Dog

A good laboratory practice-compliant safety pharmacology study (RPT070) assessed the acute toxicity of a single oral dose of pacritinib (30 mg/kg, free base) in beagle dogs. Vomiting was observed in three of the four pacritinib-dosed dogs within 30 to 120 minutes of administration. No additional pacritinib-related effects were observed in dogs and based on the postdose plasma concentrations of pacritinib, vomiting appeared to reduce systemic exposure. Hence, a single 30 mg/kg dose was considered poorly tolerated by dogs.

Repeat-Dose Toxicity

Mouse

A comparative oral (gavage) pharmacokinetic and 7-day tolerability study of pacritinib was conducted in CD-1 and BALB/c Mice (RPT112508) at doses up to 300 mg/kg/day (free base). There were no drug-related mortalities in this study and the degree of body weight loss was slightly greater in BALB/c mice. There were no significant differences between the strains with respect to toxicity and PK characteristics and both strains of mice were considered appropriate for use in the toxicological assessment of pacritinib. The CD-1 mice were utilized in assessment of reproductive risk.

A 28-day oral (gavage) toxicity and toxicokinetic study of pacritinib was conducted in CByB6F1-Tg(HRAS)2Jic (wild-type) mice (RPT8000740) at doses up to 250 mg/kg BID. Gross pathological findings attributed to pacritinib after the 5-day pilot study included a reduction in spleen and thymus size at the HD (250 mg/kg, BID). During the 28-day phase of the study, due

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to the presence of adverse clinical observations in HD mice (two mortalities, on Day 10 or 11, sight tremors, abnormal gait, hunched posture, thin appearance, partly closed eyes, and/or dehydration), pacritinib dosing was paused on Day 10 or 11 and resumed in HD mice on Day 22 at 150 mg/kg (BID, 14 days). Microscopic findings indicated that the mortalities were likely related to a severe decrease in bone marrow hematopoiesis and lymphoid depletion (spleen and thymus). A decline in body weight and food consumption (HD); hematology and clinical chemistry changes; and histopathological changes in the bone marrow, spleen, thymus, lymph node, stomach, and kidney were observed at doses ≥100 mg/kg BID.

A 30-day oral (gavage) toxicity and toxicokinetic study of pacritinib with a 14-day recovery period was conducted in BALB/c mice (RPT121) at doses up to 278.6 mg/kg (BID, free base). The HD was reduced (Day 6) to 185.7 mg/kg (BID, free base) due to increased mortality (21 deaths at the HD occurred, predominantly between Days 5 and 10) and adverse clinical observations (tremors, hunched or huddled position, lack of motor coordination, and lethargy) in HD mice. Clinical findings tended to normalize in recovery mice. Atrophy of thymus and white pulp of spleen was observed at doses ≥139.3 mg/kg BID and bone marrow hypocellularity was observed at the HD. The decline in body weight and food consumption, hematology and clinical chemistry changes, and histopathological changes at the MD/HD indicated that the LD (46.4 mg/kg, BID) was the NOAEL.

Mouse xenograft models were used to investigate the efficacy of pacritinib. In the first model, myeloproliferative neoplasm-like symptoms were induced by inoculation of athymic BALB/c nude mice with either interleukin-3-dependent (RPT091 and RPT092) or JAK2-dependent (RPT180) hematopoietic cell lines followed by administration of pacritinib at doses up to 300 mg/kg for 6 or 14 days. Although all three studies were initially designed to assess the effects of pacritinib on Ba/F3-JAK2^{V617F} cells, it was later determined (RPT181) that the Ba/F3 clone employed in two of these studies (RPT091 and RPT092) overexpressed wild-type JAK2 and did not express JAK2^{V617F}. It was confirmed that the cells used in the third study (RPT180) expressed the JAK2^{V617F} mutation. In the second model, BALB/c nude mice were inoculated with MV4-11 cells, a cell line model of human AML with the FLT3 internal tandem duplication mutation, followed by administration of pacritinib at doses up to 100 mg/kg for 21 days (RPT073). Pacritinib was well tolerated in both mouse xenograft models and did not elicit any drug-related deaths, abnormal clinical observations, or significant changes in body weight. The disease state was allowed to develop in these mice for various durations of time in an attempt to model the effects of pacritinib treatment on the early and late stages of myeloproliferative disease. In general, results generated with these mouse models provided evidence that pacritinib can alleviate to some degree the various symptoms associated with myeloproliferative disease. The mouse models of myeloproliferative disease and the results are discussed in Section II.5.1.2.

Rat

During the 7-day dose range-finding phase of study RPT8000742 of pacritinib in Sprague-Dawley rats, no mortalities were observed when pacritinib was administered at 100, 200, and 400 mg/kg (BID, free base). Dehydration, thinness, internal firm abdominal structure, abnormal breathing sounds, hunched posture, and increased adrenal weights were observed in HD rats. Body weight loss correlated with decreased food consumption and adverse hematology and clinical chemistry findings were noted at doses ≥100 mg/kg BID. Reduced spleen and thymus weights and gastrointestinal dilatation were also noted at all doses.

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A 28-day oral (gavage) repeat-dose toxicity and toxicokinetic study (RPT8000743) of pacritinib was conducted in Sprague-Dawley rats at doses up to 150 mg/kg (BID, free base). There were no drug-related mortalities. Clinical observations included thinness, poor condition (prominent backbone), decreased muscle tone, hunched posture, and dehydration. A decline in body weight and food consumption, hematology and clinical chemistry changes, and histopathological changes (decreased bone marrow hematopoiesis and lymphoid depletion in the thymus and spleen) were observed predominantly at doses ≥75 mg/kg (BID, free base).

A 13-week oral (gavage) repeat-dose toxicity and toxicokinetic study (RPT8000744) of pacritinib (citrate salt) was conducted in Sprague-Dawley rats. Ten rats/sex/group (age 6 weeks at the start of dosing) were administered 0 (methylcellulose/Tween vehicle), 40, 75, or 125 mg/kg BID pacritinib free base, approximately 8 hours apart. Administration of pacritinib was tolerated at dose levels of 40 and 75 mg/kg BID free base (80 and 150 mg/kg/day, free base), but caused significant reductions in body weight, body weight gain, lower food consumption, and thinness when administered at 125 mg/kg BID free base (250 mg/kg/day, free base). There was minimal improvement in the condition of rats dosed at 125 mg/kg BID following a dose reduction to 100 mg/kg BID during Week 10.

There was a dose-related increase in the incidence and/or severity of microscopic changes in the bone marrow, mandibular and mesenteric lymph nodes, thymus, spleen, testes, epididymides, and small and large intestines, with or without organ weight changes and macroscopic findings. A decline in reticulocyte counts at all doses (≥40 mg/kg, BID) correlated with a dose-related decrease in hematopoiesis in the bone marrow. Increased neutrophil and platelet counts, and fibrinogen concentrations observed in rats (≥40 mg/kg, BID) were likely indicative of inflammation. Decreases in lymphocyte counts and total white blood cell counts in males at all doses (≥40 mg/kg, BID) correlated with lymphoid depletion in the spleen and thymus. Altered total bilirubin, glucose, cholesterol, albumin, globulin, total protein concentrations, and alkaline phosphatase activity were observed at all doses (≥40 mg/kg, BID) in the absence of microscopic correlates. Based on the toxicity observed at the HD in this study, the maximum tolerated dose (MTD) for 13 weeks in rats was considered less than 125/100 mg/kg BID. Day 91 exposures (AUC_{0-t}) at the 100 mg/kg BID dose were 6.1 µg.h/mL (male) and 7.5 µg.h/mL (female) and represent a 0.03× (male) and 0.04× (female) exposure margin to the anticipated clinical dose (200 mg BID, 213 µg.h/mL AUC).

Dog

An MTD oral capsule toxicity study (RPT083) of pacritinib was conducted in Beagle dogs at doses up to 80 mg/kg/day (40 mg/kg, BID, HCl salt) when administered for 2 days. No mortalities were observed, and diarrhea was noted in dogs at doses ≥30 mg/kg/day BID and a single male HD dog exhibited emesis at 1 hour postdose and was observed to be lying listless. Neutropenia was present at the HD and lactate dehydrogenase tended to increase at doses ≥25 mg/kg/day BID. Hematological parameters (red blood cells, hematocrit, hemoglobin, and white blood cells) tended to decline at doses ≥15 mg/kg/day BID. A dose of 60 mg/kg/day (30 mg/kg, BID) was considered the MTD in dogs based on the clinical observations at the HD.

A 7-day oral (capsule) dose range-finding toxicity and toxicokinetics study with a 7-day recovery period (RPT090) was conducted in Beagle dogs at a dose of 60 mg/kg/day (30 mg/kg, BID, HCl salt). Emesis and diarrhea were observed in the majority of dogs and decreased body weight was noted in a single male that presented with frequent emesis. Hematological parameters

(red blood cells, hematocrit, hemoglobin, white blood cells, and platelets) tended to decline and correlated with lymphocyte depletion in the white pulp of the spleen and intestinal Peyer's patches (accompanied by focal hemorrhage) that were observed microscopically. All findings were trending towards resolution (reversible) in dogs after the 7-day recovery period.

A 30-day oral (capsule) toxicity and toxicokinetic study (RPT120) of pacritinib with a 14-day recovery period was conducted in beagle dogs. Doses (BID, HCl salt) were titrated: Days 1/2 (10, 20, and 20 mg/kg), Days 3/4 (20, 30, and 40 mg/kg), and on Day 5 forward (20, 40, and 60 mg/kg). Due to severe emesis and diarrhea observed during the first 5 days at doses ≥40 mg/kg (BID, HCl salt) doses were reduced twice between Days 6 and 8 to final doses of 5, 10, and 20 mg/kg (BID, HCl salt). Weight loss and decreased food consumption were noted at the HD. Severe lymphadenopathy (swollen lymph nodes) manifested in three HD dogs starting on Days 9, 11, and 26. This condition led to the early termination of one HD male on Day 11 and microscopic findings in this dog included suppurative lymphadenitis (enlarged lymph nodes) and phlegmonous inflammation of the surrounding tissue and lymphocyte depletion. Mild lymphocyte depletion was observed in the left cervical lymph node, the white pulp of the spleen, and in Peyer's patches (large and small intestine) and corresponded with marked thymic atrophy. Mild hepatocellular hypertrophy was observed in the liver and cellular swelling was found in the renal parenchyma. The morbidity in the HD male that was terminated early on Day 11 was considered related to an infection spread by an inflammatory process from the mouth cavity facilitated by a decrease in immune function caused by pacritinib. The other two HD dogs that presented with lymphadenopathy (swollen lymph nodes) received antibiotic treatment and survived to scheduled termination. The edema observed in these two HD dogs did not resolve completely and macroscopic and microscopic findings at the end of the administration period were deemed related to deterioration of immune function.

The observations in this study are confounded by the toxicity of the higher doses and due to the development of severe clinical symptoms, dogs were required to be treated with antibiotics, antidiarrheal, and antinausea medications. Although the dose reduction allowed dogs to recover to some degree, emesis and diarrhea persisted at the HD. Clinical findings, decreased food consumption, and decreased body weight were dose-dependent and tended to be reversible. The NOAEL was considered 10 mg/kg BID in dogs administered pacritinib for 30 days. The mean exposure (AUC_{0-8}) on Day 30 at the 10 mg/kg BID dose was 8 μg.h/mL and represents a 0.04× exposure margin to the anticipated clinical dose (200 mg BID, 213 μg.h/mL AUC).

13.1.3.2. Genotoxicity Studies

A standard genotoxicity panel showed no mutagenic or clastogenic activity for pacritinib by in vitro and in vivo testing. The label will state that pacritinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in in vitro chromosomal aberration assay (Chinese hamster ovary cells) or in vivo in a micronucleus test in mice and is consistent with the findings here.

Table 58. Genetic Toxicology

Study/Study Number	Key Study Findings
In Vitro Reverse Mutation Assay in Bacterial cells: RPT101 GLP compliance: No Study is valid: Yes	*Salmonella typhimurium* (TA98, TA100, TA102) was treated for 48 hours at up to 3000 µg/plate with and without S-9 metabolic activation. Pacritinib did not produce any 3-fold or greater increases in revertants relative to spontaneous reversion in the solvent control (DMSO). Pacritinib was negative for mutagenicity in this bacterial reverse mutation assay. Positive controls demonstrated appropriate S-9- and strain-dependent increases in revertants. Cytotoxicity in strain TA102, with or without S9 was observed at ≥300 µg/plate.
In Vitro Reverse Mutation Assay in Bacterial cells: RPT311 GLP compliance: Yes Study is valid: Yes	*Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA102) were treated at up to 2000 µg/plate with and without S-9 metabolic activation using plate incorporation and preincubation methods. Pacritinib did not produce a ≥2-fold increases in revertants relative to spontaneous reversion in the solvent control (DMSO). Pacritinib was negative for mutagenicity in this bacterial reverse mutation assay. Positive controls demonstrated appropriate S-9- and strain-dependent increases in revertants.
Assay for Chromosomal Aberrations In Vitro in Human Peripheral Blood Lymphocytes: RP128 GLP compliance: Yes Study is valid: Yes	Human peripheral blood lymphocytes were treated with pacritinib up to 3.7 µg/mL with and without S-9 metabolic activation. There was no increase in structural chromosome aberrations in pacritinib-treated cells and pacritinib was considered negative for clastogenicity. The positive controls induced significant increases in aberrations over the solvent control (DMSO).
Assay for Micronucleus Induction in BALB/c Mouse Bone Marrow: RPT164 GLP compliance: Yes Study is valid: Yes	Mouse, single oral doses of 1000 and 2000 mg/kg, isolated bone marrow micronuclei. No effects on the proportion of polychromatic erythrocytes among total erythrocytes in the bone marrow were observed in male mice after 24 hours and in female mice after both the time points (24 hours and 48 hours). However, in male mice only, at 48 hours after dosing, there was a statistically significant increase in the mean micronuclei numbers when a parametric test (ANOVA, Dunnett's) was employed. In contrast, when employing the Kruskal-Wallis test, there was no statistically significant change in the number (median) of micronucleated cells in male mice. There were no sex-related differences in the pharmacokinetic profiles at the two dose levels (1000 mg/kg and 2000 mg/kg) and the results were considered equivocal in BALB/c mice.
Assay for Micronucleus Induction in ICR Mouse Bone Marrow RPT178 GLP compliance: Yes Study is valid: Yes	Mouse, mortality was observed at 2000 mg/kg (1422.5 mg/kg, free base) in the MTD confirmatory assay. In the definitive assay, single oral doses of less than or equal to 1500 mg/kg (1066.9 mg/kg, free base) were employed, isolated bone marrow micronuclei. No effects on the proportion of polychromatic erythrocytes among total erythrocytes in the bone marrow were observed in ICR mice at 24 or 48 hours postdose. Frequencies of micronucleated polychromatic erythrocytes for all pacritinib treated groups were similar to concurrent controls and consistent with the historical control range. The positive control induced a statistically significant increase in the incidence of micronucleated PCEs. Therefore, pacritinib was negative for clastogenicity/aneugenicity in the ICR mouse bone marrow micronucleus assay.

Source: Reviewer-constructed summary table of the genotoxicity studies submitted to the new drug application.
Abbreviations: ANOVA, analysis of variance; DMSO, dimethyl sulfoxide; GLP, good laboratory practice; MTD, maximum tolerated dose; PCE, polychromatic erythrocyte

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13.1.3.3. Carcinogenicity Studies

13.1.3.3.1. Two-Year Oral Gavage Carcinogenicity Study of Pacritinib in Rats (RPT8000745)

Table 59. Study Information, Study RPT8000745

Study Features and Methods	Details
ECAC concurrence	Yes
Dose and frequency of dosing	0, 4, 15 (M/F) and 25 mg/kg (M) or 40 mg/kg (F), BID
Route of administration	Oral
Formulation/vehicle	0.5% (w/v) Methylcellulose (4,000 cP) and 0.1% (v/v) TWEEN 80 in ultrapure water
Species/strain	Rat/Sprague-Dawley
Number/sex/group	60
Age	6 weeks
Dosing comments	Due to low survival in controls, both sexes were terminated early, when the control group reached 20. Males were terminated in Weeks 99 to 100 (D687 to D694) and females in Weeks 99 to 101 (D688 to D701).

Source: Reviewer-constructed summary table of carcinogenicity study (RPT8000745) submitted to the new drug application.
Abbreviations: BID, twice daily; cP, centipoise; ECAC, Executive Carcinogenicity Assessment Committee; F, female; M, male; v/v, volume/volume; w/v, weight/volume

The administration of pacritinib (BID) by oral gavage at 4, 15, and 25/40 mg/kg (8, 30, and 50/80 mg/kg/day) to male Sprague-Dawley rats for up to 99 weeks and female rats for up to 100 weeks did not result in any compound-related carcinogenic effects.

Tumor findings were typical of the age and strain of rats and included neoplasia of the pituitary gland, mammary gland, and hemolymphoreticular system. Tumor incidences tended to be comparable between all dosing groups, occurred independent of dose level, or were observed at a low frequency.

The FDA statistical analysis (conducted by Feng Zhou, MS, and Karl Lin, PhD) concurred with the nonclinical assessment of the tumor data and indicated that there were no statistically significant positive dose-response relationships among the pacritinib dosed groups and the vehicle control group for male and female Sprague-Dawley rats and there was no significant difference between the vehicle control group and each of the pacritinib dosed groups in terms of tumor incidence rate.

Cardiomyopathy was the most common non-neoplastic cause of death encountered on-study, particularly in males. A dose-dependent decrease in mortality was noted in MD and HD females and was driven primality by a decline in the incidence of fatal pituitary gland adenoma at these same dose levels. There were no pacritinib-related clinical signs or effects on the distribution of tumors noted during clinical observations.

Slight reductions in body weight were noted at the MD/HD in males and at all doses in females in the absence of any significant change in food consumption or effects on survival rate.

Pacritinib exposures achieved in rats (HD) were considerably lower than the exposure observed at the maximum recommended human dose (0.004× and 0.014× in males and females, respectively, AUC).

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Executive Carcinogenicity Assessment Committee Conclusions

Rat

- The Committee concluded that the carcinogenicity study was adequate.
- The Committee concluded that the study was negative and that there was no evidence of drug-related neoplasms in the 2-year rat study in either males or females.

13.1.3.3.2. 26-Week Carcinogenicity Study of Pacritinib by Oral Gavage in the Hemizygous rasH2 Transgenic (001178-T) Mouse

Table 60. Study Information, Study 001178-T

Study Features and Methods	Details
ECAC concurrence	Yes
Dose and frequency of dosing	0, 30, 50, and 80 mg/kg (BID)
Route of administration	Oral
Formulation/vehicle	0.5% (w/v) Methylcellulose (4,000 cP) and 0.1% (v/v) Tween 80 in U.S. Pharmacopeia water
Species/strain	Mouse/CByB6F1-Tg(HRAS)2Jic
Number/sex/group	25
Age	9 weeks
Dosing comments	The were no early terminations in the 26-week CByB6F1-Tg(HRAS)2Jic mouse study.

Source: Reviewer-constructed summary table of carcinogenicity study (001178-T) submitted to the NDA.
Abbreviations: BID, twice daily; cP, centipoise; ECAC, Executive Carcinogenicity Assessment Committee; v/v, volume/volume; w/v, weight/volume

There were no neoplastic changes attributed to the daily oral gavage administration of pacritinib at doses ≤80 mg/kg, BID (160 mg/kg/day) in hemizygous CByB6F1-Tg(HRAS)2Jic mice for up to 26 weeks. There was no significant or dose-related increase in the incidence of primary tumors in CByB6F1-Tg(HRAS)2Jic mice.

Tumor findings were generally typical of spontaneous tumors occurring in this strain (CByB6F1-Tg(HRAS)2Jic) and age of mice and included hemangiosarcomas in the vehicle control and pacritinib-dosed groups that occurred independent of dose level. Hemangiosarcomas were the most frequent cause of death in these groups.

The FDA statistical analysis (conducted by Feng Zhou, MS, and Karl Lin, PhD) concurred with the nonclinical assessment of the tumor data and indicated that there were no statistically significant positive dose response relationships among the pacritinib-dosed groups and the vehicle control group for male and female CByB6F1-Tg(HRAS)2Jic mice.

Pacritinib-related clinical signs included signs of dehydration, hunched posture, and prominent backbone at the MD and HD (higher incidence in males). There were no significant changes in survival, body weight, or food consumption related to the administration of pacritinib (≤160 mg/kg/day).

Decreased white blood cell counts (≤50% decrease) corresponded to a decline in neutrophils, monocytes, and lymphocytes (both sexes, all doses) and eosinophils (HD females only). The incidence of pigmented macrophages in the mesenteric lymph node (minimal to mild) increased in males (all doses) and in MD and HD females in the absence of pathological changes in the GI

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tract or corresponding clinical findings. Thymus weights were significantly decreased (≤35% decrease) in MD and HD females (consistent with the decline in lymphocytes) in the absence of histopathological correlates. A similar trend was observed in HD males (21% decrease).

Pacritinib exposures achieved in mice (HD) were considerably lower than the exposure observed at the maximum recommended human dose ($0.05\times$ and $0.02\times$ in males and females, respectively, AUC).

Executive Carcinogenicity Assessment Committee Conclusions

Mouse

- The Committee concluded that the carcinogenicity study was adequate.
- The Committee concluded that the study was negative and that there was no evidence of drug-related neoplasms in the 6-month transgenic mouse study in either males or females.

13.1.3.4. Reproductive and Developmental Toxicity

13.1.3.4.1. Fertility and Early Embryonic Development

13.1.3.4.1.1. An Oral (Gavage) Study of Fertility and Early Embryonic Development to Implantation Study of Pacritinib in Male BALB/c Mice / RPT322

Key Study Findings

- The NOAEL was considered the MD (100 mg/kg/day) based on the effects on male reproductive performance at the HD (300 mg/kg/day). A toxicokinetic evaluation was not conducted during this study and the dose multiple to the anticipated clinical dose (200 mg BID, 400 mg/day, 6.7 mg/kg/day, 60 kg human) at the NOAEL (100 mg/kg/day=8.1 mg/kg/day, human equivalent dose [HED]) is $1\times$ in male BALB/c mice.

Table 61. Methods of Oral Fertility Study in Male BALB/c Mice. Study RPT322

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 30, 100, and 300 mg/kg/day (total daily dose, citrate salt)
	0, 15, 50, and 150 mg/kg (BID, 8 hours apart, citrate salt)
	0, 10.7, 35.6, and 106.7 mg/kg (BID, 8 hours apart, free base)
Route of administration	Oral
Formulation/vehicle	0.5% methylcellulose (1,500 cP) and 0.1% Tween 80 in deionized water
Species/strain	Mouse/BALB/c
Number/sex/group	30/Males
Satellite groups	No toxicokinetic analysis was conducted
Study design	8 hours between (BID) doses. Dosing 29 days, prior to first pairing, then through 21-days of second pairing (due to low pregnancy rates in first pairing) to 1 Day prior to sacrifice). 106 to 108 doses in total.
Deviation from study protocol affecting the interpretation of results	Due to the low pregnancy rates observed in all groups (including controls) after the first pairing, dosing of the males was extended to provide for a second pairing with a second delivery of untreated females.

Source: Reviewer-constructed summary table of reproductive toxicity study (RPT322) submitted to the new drug application.
Abbreviations: BID, twice daily; cP, centipoise

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Table 62. Observations and Results, Study RPT322

Parameter	Major Findings
Mortality	The cause of the mortality (LD) and moribundity (HD) in male mice was undetermined and were considered suspect by the reviewer.
Clinical signs, body weight and food consumption	A decline in body weight and body weight gain in male mice correlated with reduced food consumption and clinical findings (decreased activity, salivation, hunched posture, and white ocular discharge) at the HD.
Sperm evaluation	The total caudal epididymal sperm concentration declined at the HD but was found to be comparable to controls when normalized to caudal tissue weight. Sperm motility, caudal epididymal concentration counts, or morphology could not be assessed in 5 males (1 control presenting with bilateral small testes, 1 LD, 1 MD, and 2 HD) that failed to impregnate females during the study. Insufficient sperm to conduct a caudal epididymal concentration count was also noted in pacritinib-dosed males (1 LD, 1 MD, and 2 HD) where only the LD male failed to impregnate a female during the study.
Reproductive performance	Effects on reproductive performance (lower mating and fertility indices) were observed at the HD (second mating). Uterine implantation data (mean number of implantations, viable embryos, litter size, resorption sites (early plus late) and pre- and post-implantation loss indices) in females mated to pacritinib-dosed males were comparable to controls.
Necropsy findings	An atypical protrusion of the penis was observed intermittently in mice administered pacritinib (at all doses) and was sufficient to prompt veterinary consultations. As this finding was transient in nature, its significance is unclear, however it is notably related to the administration of pacritinib.

Source: Reviewer-constructed summary table of reproductive toxicity study (RPT322) submitted to the new drug application.
Abbreviations: HD, high dose, LD, low dose; MD, mid dose

13.1.3.4.1.2. An Oral (Gavage) Study of Fertility and Early Embryonic Development to Implantation of Pacritinib in CD-1 Mice/RPT112504

Key Study Findings

- The NOAEL was considered the HD (250 mg/kg/day) based on the absence of adverse effects on male reproductive performance and early embryonic development to implantation in CD-1 mice. A toxicokinetic evaluation was not performed during this study and the dose multiple to the anticipated clinical dose (200 mg BID, 400 mg/day, 6.7 mg/kg/day, 60 kg human) at the NOAEL (250 mg/kg/day=20.3 mg/kg/day, HED) is 3× in CD-1 mice.

Table 63. Methods of Oral Fertility and Early Embryonic Development to Implantation Study in CD-1 Mice, Study RPT112504

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 30, 100 and 250 mg/kg (QD, free base)
Route of administration	Oral
Formulation/vehicle	0.5% methyl cellulose (4,000 cP) and 0.1% Tween 80 in deionized water
Species/strain	Mouse/CD-1
Number/sex/group	25
Satellite groups	No toxicokinetic analysis was conducted.
Study design	Males were dosed for 28 days prior to mating and throughout the mating period until 1 day prior to euthanasia (62 or 63 total doses). Females were dosed for 14 days prior to cohabitation and through GD 7 (22 to 34 total doses). Females with no evidence of mating were dosed through the day prior to euthanasia (29 total doses). Microscopic evaluations were limited to spermatogenic assessments and laparohysterectomies.
Deviations from study protocol	None that affected the interpretation of the study results.

Source: Reviewer-constructed summary table of reproductive toxicity study (RPT112504) submitted to the new drug application.
Abbreviations: cP, centipoise; GD, gestation day; QD, once daily

Table 64. Observations and Results, Study RPT112504

Parameter	Major Findings
Mortality and clinical signs	There were no mortalities or clinical signs observed in CD-1 mice related to the administration of pacritinib (≤250 mg/kg/day, free base).
Body weight and food consumption	A decline in mean body weight was noted in HD males only (↓6.5% on Day 62) in the absence of changes in food consumption.
Sperm count	Spermatogenesis parameters (motility, concentration, and morphology) were not affected by pacritinib (≤250 mg/kg/day, free base).
Reproductive performance	Male and female reproductive performance: mating, fertility, copulation, and conception, estrous cyclicity, and intrauterine survival (i.e., preimplantation loss, post implantation loss and the mean numbers of viable embryos, corpora lutea, and implantation sites) were not affected by the administration of pacritinib (≤250 mg/kg/day, free base).
Macroscopic and organ weight findings	There were no significant findings observed during macroscopic or organ weight evaluations in CD-1 mice administered pacritinib (≤250 mg/kg/day, free base).

Source: Reviewer-constructed summary table of reproductive toxicity study (RPT112504) submitted to the new drug application.
Abbreviation: HD, high dose

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13.1.3.4.2. Embryo-Fetal Development

13.1.3.4.2.1. An Oral (Gavage) Study of the Effects of Pacritinib on Embryo-Fetal Development in CD-1 Mice/RPT 112506

Key Study Findings

- The NOAEL for maternal toxicity was considered the MD (100 mg/kg/day) based on the effects on body weight and corresponding reduced food consumption at the HD (250 mg/kg/day). The NOAEL for embryo-fetal development was also considered the MD based on higher post-implantation loss, lower mean fetal body weights, and altered external fetal morphology (cleft palate) observed in the presence of maternal toxicity at the HD. The NOAEL (MD, 7.7 μg·h/mL, gestation day 15) represents a 0.04× exposure margin to the anticipated clinical dose (200 mg BID, 213 μg·h/mL AUC).

Table 65. Methods of Oral Embryo-Fetal Developmental Toxicity Study in CD-1 Mice, Study RPT 112506

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 30, 100, 250 mg/kg (QD, free base)
Route of administration	Oral gavage
Formulation/vehicle	0.5% methylcellulose (4,000 cP) and 0.1% Tween 80 in deionized water
Species/strain	Mouse/Crl:CD1 (ICR)
Number/sex/group	25/females
Satellite groups	TK, 6/females/vehicle and 42 to 43/females/pacritinib group
Study design	Daily dosing on GD 6 through GD 15 TK: 0 (predose), 0.5, 1, 2, 4, 8, and 24 hours postdose (GD 6 and 15)
Deviation from study protocol affecting the interpretation of results	AUC values determined in this study are considered qualitative due to a lack of demonstrated stability between the time of collection and analysis. Use of this data for comparisons between human exposures and animal exposures (AUC) should be considered with caution.

Source: Reviewer-constructed summary table of reproductive toxicity study (RPT112506) submitted to the new drug application.
Abbreviations: AUC, area under the plasma concentration-time curve; cP, centipoise; GD, gestation day; ICR, Institute of Cancer Research; QD, once daily; TK, toxicokinetics

Table 66. Observations and Results, Study RPT 112506

Parameter	Major Findings
Mortality	There was one maternal death at the MD (100 mg/kg/day, TK). This death occurred at 1 hour postdose with no evidence of intubation error and it is unclear if this death was related to the administration of pacritinib.
Clinical signs	One LD (30 mg/kg/day) and one MD (100 mg/kg/day) dam delivered 3 live and 8 dead pups (3 of which were partially cannibalized) and 5 live and 5 dead pups (3 of which were cannibalized), respectively, on GD 18. No remarkable clinical observations were recorded in these dams and no apparent malformations were observed in their live pups. A single HD female presented with hypoactivity, cool extremities, and a pale body during daily examinations on GD 11 and this dam was noted to have an entirely resorbed litter at necropsy.

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Parameter	Major Findings
Body weights (dams)	Reductions in mean maternal body weight on GD 18 (up to ↓8% at the HD) and a decline in body weight gain during GD 6 to 16 (up to ↓18% at the HD), and GD 12 to 16 (up to ↓22% at the HD) were observed at all doses.
Necropsy findings Cesarean section data	A higher mean litter proportion of post-implantation loss (primarily early resorptions) and corresponding slightly lower mean litter proportion of viable fetuses were observed at the HD (within historical control range). Lower mean fetal body weights (↓14%) were noted at the HD.
Necropsy findings in offspring	Reductions in maternal body weight gain during the gestation period were ↓20% at the HD, and thus malformations and variations were considered to have occurred in the presence of maternal toxicity at this dose. The external malformation cleft palate (entire length) was noted in 2(2), 2(2), 0(0) and 10(5) fetuses (litters) in the control, 30, 100, and 250 mg/kg/day groups, respectively. The incidence of cleft palate exceeded historical controls but was not statically significant at the HD. Variations in the accessory spleen (HD) and small kidney (all doses), skeletal variations of bent ribs (≥100 mg/kg/day) and reduced ossification of the skull or circular area of unossification in sternebra (≥30 mg/kg/day) were either within the historical control range or affected only a single litter.

Source: Reviewer-constructed summary table of reproductive toxicity study (RPT112506) submitted to the new drug application.
Abbreviations: GD, gestation day; HD, high dose; LD, low dose; MD, mid dose; TK, toxicokinetics

13.1.3.4.2.2. An Oral (Gavage) Study of the Effects of Pacritinib on Embryo-Fetal Development in New Zealand White Rabbits/RPT112503

Key Study Findings

- The NOAEL for maternal toxicity was considered the MD (30 mg/kg/day) based on the mortality, moribundity, abortion, mean body weight loss, reduced food consumption, and adverse clinical findings at the HD (60 mg/kg/day). The NOAEL for embryo-fetal development was also considered the MD based on the lower fetal body weights and corresponding increased litter proportions of ossification-related skeletal developmental variations at the HD. The NOAEL (MD, 17.9 μg·h/mL, GD 20) represents a 0.08× exposure margin to the anticipated clinical dose (200 mg BID, 213 μg·h/mL AUC).

Table 67. Methods of Oral Embryo-Fetal Developmental Toxicity Study in New Zealand White Rabbits, Study RPT112503

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 15, 30, 60 mg/kg/day (free base) QD
Route of administration	Oral gavage
Formulation/vehicle	0.5% methylcellulose (4,000 cP) and 0.1% Tween 80 in deionized water
Species/strain	Rabbit/Hra:(NZW)SPF
Number/sex/group	25/females
Satellite groups	TK, 2/females/vehicle and 4/females/pacritinib group
Study design	Daily dosing on gestation days (GD) 7 to 20 TK: 0 (predose), 0.5, 1, 2, 4, 8, and 24 hours postdose (GD 7 and 20)
Deviations	None that affected the interpretation of the study results.

Source: Reviewer-constructed summary table of a reproductive toxicity study (RPT112503) submitted to the new drug application.
Abbreviations: cP, centipoise; GD, gestation day; QD, once daily; TK, toxicokinetics

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Table 68. Observations and Results, Study RPT112503

Parameter	Major Findings
Mortality	At the HD (60 mg/kg/day), 7 females (6 main study, 1 TK) were found dead or were euthanized between GD 16 and GD 20. Two of these HD females had litters that were entirely composed of early resorptions. In addition, 1 female in this group aborted 3 dead fetuses on GD 26; this female also had 2 live fetuses, 3 late resorptions, and 1 placenta in utero. These females presented with body weight loss (up to 14.3% of their GD 7 body weight) and several days of reduced food consumption prior to death, euthanasia, or abortion. Clinical findings in these dams included decreased defecation, brown and red material around the anogenital and urogenital areas, red vaginal discharge, clear nasal discharge, and body cool to the touch.
Clinical signs	One LD (30 mg/kg/day) and one MD (100 mg/kg/day) dam delivered 3 live and 8 dead pups (3 of which were partially cannibalized) and 5 live and 5 dead pups (3 of which were cannibalized), respectively, on GD 18. No remarkable clinical observations were recorded in these dams and no apparent malformations were observed in their live pups. A single HD female presented with hypoactivity, cool extremities, and a pale body during daily examinations on GD 11. This dam was noted to have an entirely resorbed litter at necropsy.
Body weights (dams)	Mean body weight was reduced at the HD (60 mg/kg/day) compared to controls and was most pronounced between GD 7 to 10 and GD 10 to 13. Reduced body weight gain exceeding 10% was noted at all doses on GD 7 to 10. Differences were not present post-treatment on GD 29. Overall, body weight changes correlated with changes in food consumption.
Necropsy findings Cesarean section data	There were no definitive effects on intrauterine survival observed in rabbits administered pacritinib. However, lower mean fetal body weights were noted at the HD (60 mg/kg/day).
Necropsy findings Offspring	At 60 mg/kg/day (HD), the decline in maternal body weight exceeded 10% compared to controls (GD 7 to 10), thus variations observed in fetuses occurred in the presence of maternal toxicity. Variations likely secondary to reduced fetal body weights at the HD (60 mg/kg/day) included skeletal developmental variations (i.e., higher mean litter proportions of sternebra number 5 and/or 6 unossified, sternebrae numbers. 1, 2, 3, and/or 4 unossified, and pubis unossified). In addition, a higher number of fetuses with small spleens were noted at the HD.

Source: Reviewer-constructed summary table of a reproductive toxicity study (RPT112503) submitted to the new drug application.
Abbreviations: GD, gestation day; HD, high dose; LD, low dose; MD, mid dose; TK, toxicokinetics

13.1.3.4.3. Pre- and Post-Natal Development

13.1.3.4.3.1. An Oral (Gavage) Study of the Effects of Pacritinib on Pre- and Post-Natal Development, including Maternal Function, in CD-1 Mice /RPT112507

Key Study Findings

- The NOAEL for maternal toxicity was considered the MD (100 mg/kg/day) based on the single mortality and the adverse decline in body weight gain and corresponding reduction in food consumption at the HD (250 mg/kg/day). Based on an increase in F0 gestation

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length and dystocia (HD) the MD was also considered the NOAEL for F0 reproductive toxicity.

- The NOAEL for F1 neonatal/developmental toxicity was considered to be the LD (30 mg/kg/day) based on the lower mean body weights (postnatal day 21) and decline in post-weaning survival observed at the MD/HD. The NOAEL for F1 reproductive toxicity was considered to be the MD (100 mg/kg/day) based on the reduced male and female fertility, male copulation, and female conception indices (HD).

- The NOAEL for F2 neonatal survival and developmental toxicity was considered to be the MD (100 mg/kg/day) based on the decline in postnatal survival (HD) and the presence of a malformation (cheilognathopalatoschisis) in a single HD pup (postnatal day 4) that presented with low body weight on postnatal day 1.

- Toxicokinetics and lactational exposures were not determined during this study and dose multiples to the anticipated clinical dose (200 mg BID, 400 mg/day, 6.7 mg/kg/day, 60 kg human) at the NOAELs of 30 mg/kg/day (LD, 2.4 mg/kg/day, HED) and 100 mg/kg/day (MD, 8.1 mg/kg/day, HED) are $0.4\times$ and $1\times$, respectively, in CD-1 mice.

Table 69. Methods of Oral Pre- and Postnatal Developmental Toxicity Study in CD-1 Mice, Study RPT112507

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 30, 100, 250 mg/kg/day (free base) QD
Route of administration	Oral gavage
Formulation/vehicle	0.5% methylcellulose (4,000 cP) and 0.1% Tween 80 in deionized water
Species/strain	Mouse/CD-1
Number/sex/group	20/females
Satellite groups	No toxicokinetic analysis or lactational analysis was conducted.
Study design	Daily dosing on GD 6 to lactation day 20. Females that failed to deliver were dosed until post-mating day 23.
Deviations	None that affected the interpretation of the study results.

Source: Reviewer-constructed summary table of a reproductive toxicity study (RPT112507) submitted to the new drug application.
Abbreviations: cP, centipoise; GD, gestation day; QD, once daily

Table 70. Observations and Results, Study RPT112507

Parameter	Major Findings
Mortality (F0)	A single mortality was observed at the HD (F0 dams) on lactation day 0 (1 hour postdose) in the absence of notable clinical and macroscopic findings.
Clinical signs (F0)	The gestational length in dams (F0) was increased (HD only) and dystocia (difficulty with birth) manifested at the HD.
Body weight (F0)	Reductions in food consumption and decreased body weight at the HD (F0) were considered to be adverse during lactation.

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Parameter	Major Findings
F1 generation	The administration of pacritinib to F0 dams exceeded the maximum tolerated dose for F1 neonatal survival (total litter losses) and development (lower mean birth weights and effects on learning and memory observed during the Biel maze assessment) at the HD. Sensory function (startle response) in F1 pups was reduced at the HD (PND 20) and occurred in the presence of excessive toxicity indicative of developmental delay including significantly lower F1 pup body weights during weaning (PND 21) and a decline in post-weaning survival at the MD/HD. Sensory function and body weight tended to recover by PND 60. F1 generation male and female fertility, male copulation, and female conception indices were reduced at the HD.
F2 generation	F2 generation postnatal survival declined at the HD (PND 1 to 4) and from birth to PND 4 due to the total litter loss (PND 2) observed in 1 HD (F1) dam (total number of F1 pregnant dams at the HD, N=5). A single HD F2 generation pup observed to have a low body weight on PND 1, presented with cheilognathopalatoschisis on PND 4.

Source: Reviewer-constructed summary table of a reproductive toxicity study (RPT112507) submitted to the new drug application.
Abbreviations: F0, parental generation; F1, first filial generation; F2, second filial generation; GD, gestation day; HD, high dose; LD, low dose; MD, mid dose; PND, postnatal day

Additional Reproductive Toxicology Studies (Nonpivotal)

An oral (gavage) 7-day tolerability and toxicokinetic study of pacritinib (RPT112501) was conducted in nonpregnant New Zealand White rabbits at doses of 3, 10, 25, or 50 mg/kg (free base). There were no effects on mortality, clinical observations, body weight, body weight gain, and food consumption. No remarkable internal macroscopic findings were noted in rabbits administered pacritinib for 7 days at doses up to 50 mg/kg (free base).

An oral (gavage) dose range-finding study of the effects of pacritinib on embryo and fetal development (RPT112502) was conducted in New Zealand White rabbits at doses of 10, 25, 50, or 100 mg/kg (free base). Pacritinib was not tolerated at the HD (100 mg/kg/day), as evidenced by mortality, moribundity, excreta-related clinical findings, body weight deficits, and a corresponding reduction in food consumption. There were no remarkable effects on external fetal morphology at any dose, however only two litters were available for evaluation at the HD. Based on mortality at 100 mg/kg/day (free base), this dose level was not recommended to proceed, and dose levels of 15, 30, and 60 mg/kg/day (free base) were used in the definitive rabbit embryo-fetal development study (RPT112503).

Other Toxicology Studies (Phototoxicity)

An oral (gavage) phototoxicity evaluation of pacritinib (RPT255) was conducted in female Crl:SKH1-hr hairless mice at doses up to 300 mg/kg/day (150 mg/kg, BID, 8 hours apart, citrate salt). No skin reactions indicative of phototoxicity were observed following oral administration of pacritinib (up to 213.4 mg/kg/day, free base) for 4 consecutive days and subsequent exposure (30 minutes) to an ultraviolet radiation dose equivalent to 0.5 minimal erythema dose (an ultraviolet radiation dose adequate to elicit a minimally perceptible response from the skin).

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13.2. Individual Reviews of Studies Submitted to the NDA

All nonclinical studies submitted to the NDA were also submitted and reviewed under the IND.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Plasma Protein Binding

Study RPT107 examined plasma protein binding of pacritinib by equilibrium dialysis. In this study, plasma was spiked with a stock solution of pacritinib in methanol to obtain a final concentration of 1000 ng/mL pacritinib in plasma. Plasma samples were incubated at 37°C for 4 hours in a dialyzer cell perfused with phosphate-buffered saline (PBS). The percent of unbound (free) pacritinib in dialysate samples was measured by LC-MS/MS and calculated based on the peak area of the pacritinib standard solution. Human plasma protein binding of pacritinib was determined as 99.9%.

In Study RPT13CETHP1, protein binding of pacritinib in human plasma was measured with a Pierce rapid equilibrium dialysis (RED) device. Three concentration levels of pacritinib, 10, 25, or 50 µg/mL were tested. For each concentration, 300 µL of plasma containing pacritinib or warfarin (control compound) was loaded into three wells of the 96-well dialysis plate. Blank PBS (500 µL) was added to each corresponding receiver chamber. The device was placed into an enclosed heated rocker that was prewarmed to 37°C, and allowed to incubate for 4 hours. Plasma (50 µL) was added to the wells containing the receiver samples and 200 µL of PBS was added to the wells containing the donor samples. Samples were subjected to protein precipitation and analyzed by LC-MS/MS. Protein binding values showed a decreasing trend with increase in pacritinib concentration, with mean (n=3) plasma protein binding of 98.8%, 97.7%, and 97.1% at 10 (clinically relevant plasma concentration range), 25, and 50 µg/mL, respectively.

In Study 17CETHP1R1, binding of pacritinib and two metabolites M1 and M2 was measured with human plasma collected from healthy donors, donors with renal impairment, and donors with hepatic impairment. In addition, the percentage binding of pacritinib and M1 and M2 to human serum albumin (HSA) and α1-acid glycoprotein (AAG) was also assessed. A Pierce RED device was used for all experiments. The dosing concentration levels were 1µM, 20µM, and 100µM for pacritinib and 1µM and 50µM for each of the two metabolites. All test articles showed relatively high binding to human plasma proteins, with a rank order of M2 (99.9% at 1µM) > M1 (99.8% at 1µM) > pacritinib (99.5% at 1µM). Similar to the previous findings, test articles showed a clear concentration dependency on protein binding, with protein binding values decreasing from 99.5% (at 1µM) to 94.7% (at 100µM). The concentration dependent plasma protein binding results of pacritinib were also observed from plasma collected in subjects with renal (96.7% to 99.9% at 1 to 100µM) and hepatic (96.2% to 99.8% at 1 to 100µM) impairment. Pacritinib showed greater binding to AAG versus HSA (87.9% versus 76.9%), whereas M1 and

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M2 demonstrated greater binding to HSA versus AAG (97.9 versus 91.1% for M1 and 99.1% versus 81.4% for M2).

Metabolism Studies

Report RPT068 discussed the in vitro metabolism of pacritinib in liver microsomes of mouse, rat, dog, and human. Pacritinib (5, 10, or 50μM) was incubated with pooled liver microsomes at 37°C for specified incubation timepoints in a mixture containing potassium phosphate buffer (pH 7.4) and a nicotinamide adenine dinucleotide phosphate (NADPH) regeneration system. Following incubation, reaction mixtures were centrifuged and supernatants were analyzed by HPLC with tandem mass spectrometry to identify metabolites and measure metabolite formation. Pacritinib was most rapidly metabolized in the rat and mouse, followed by dog and human. The half-life of pacritinib in the incubations was 22, 18, 41, and >60 minutes for mouse, rat, dog, and human microsomes, respectively, and the predicted hepatic clearance was 3.11, 1.91, 0.81, and <0.5 L/h/kg for mouse, rat, dog, and human, respectively, at 5μM pacritinib. Seven metabolites (M1 to M7) were identified in this study. M1 (oxidation product) was the major metabolite in the rat and mouse, and M4 (reduction of the double bond in the linker chain) was the major metabolite in the human and dog.

The aim of Study RPT175 was to characterize the pacritinib major metabolites formed via Phase 1 metabolism in human and mouse liver microsomes and plasma samples obtained from Phase 1 clinical studies and mouse plasma from preclinical in vivo studies. The clinical plasma samples were collected from two human subjects receiving pacritinib 100 mg and 600 mg dose levels. The structure of metabolites formed in vitro and in vivo were elucidated using synthetic reference standards with a nonvalidated HPLC with tandem mass spectrometry method. Two metabolites, M1 (oxidative metabolite) and M2 (de-alkylation metabolite), were prominent metabolites in vitro and in vivo in mice and humans. Two minor metabolites were also identified, M3 (N-oxide metabolite) and M4 (reduction of the double bond in the linker chain). However, none of the identified metabolites amounted to more than 10% of the parent exposure in human plasma. Moreover, no unique in vivo metabolites were identified in humans relative to dog or mouse, indicating that mouse and dog appear to be relevant toxicological species.

In Study RPT200, the interaction potential of pacritinib with cytochrome P450 (CYP) enzymes, including direct and time-dependent inhibition and induction was investigated. The experimental details are shown in Table 71. Pacritinib was preincubated at seven concentrations for 30 minutes with human liver microsomes with or without NADPH. Then, a cocktail of substrates for seven major CYP enzymes and NADPH was added to the samples, followed by a secondary incubation of 10 minutes. The activities of these seven major CYP enzymes were determined based on formation of enzyme-specific metabolites during the secondary incubation. Inhibition in samples in pre-incubation (without NADPH) was considered as direct inhibition and increase in inhibition potency due to the presence of NADPH in preincubation was taken as a sign of time- or metabolism-dependent inhibition. For induction, cryopreserved human hepatocytes from three donors were seeded on collagen I-coated 96-well plates and incubated with pacritinib citrate at seven concentrations for 48 hours. The cell culture medium containing pacritinib was replaced after 24 hours. Cytotoxicity was evaluated based on lactate dehydrogenase release to the cell culture medium before changing the exposure medium after 24 hours of exposure. CYP induction was evaluated based on mRNA analysis after 48 hours of exposure. Time-dependent CYP enzyme inhibition results are summarized in Table 72.

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Dose-dependent direct inhibition (samples without NADPH preincubation) by pacritinib towards all CYP enzyme probe reactions was observed at the concentration range tested (up to 350μM). The most potent inhibition was observed towards CYP1A2 (IC_{50} 10.6μM), CYP2C19 (IC_{50} 11.6 to 13.6μM depending on the probe reaction) and CYP3A4 (IC_{50} 4.7 to 86μM depending on the probe reaction). Less potent direct inhibition, with IC_{50} ranging from 27 to 120μM, was observed towards CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Inhibition towards CYP1A2 was substantially more potent in the samples preincubated with NADPH than in the corresponding samples without NADPH preincubation, resulting in an approximately 100-fold shift in estimated IC_{50}, suggesting considerable time-dependent inhibition towards CYP1A2 by pacritinib. The data also suggest time-dependent inhibition towards CYP3A4 (IC_{50} shift ranging from 1.8 to 3.7-fold depending on the probe reaction) and cannot rule out minor time-dependent inhibition towards CYP2C19 (IC_{50} shift of 1.5- to 1.7-fold depending on the probe reaction) and CYP2C9 (IC_{50} shift of 1.4-fold). Inhibition of CYP2B6, CYP2C8, and CYP2D6 appeared similar in the samples with and without NADPH pre-incubation and the IC_{50} shift ranged from 0.8 to 1.2-fold, indicating no time- or metabolism-dependent inhibition at the tested concentration range. CYP gene induction results are summarized in Figure 15. Meaningful quantitative polymerase chain reaction results were not obtained at pacritinib concentrations ≥20 μM due to cytotoxicity. A minor induction signal towards CYP1A2 (>2-fold, but <5% of the positive control in the same donor) was observed in one out of three donors (SVL) at 0.3 and 1μM pacritinib. No sign of induction of CYP2B6 and CYP3A4 was observed at the concentrations tested. A potential decline in gene expression was observed in CYP1A2 at 5μM pacritinib, and in CYP2B6 and CYP3A4 at 1 to 5 μM pacritinib. Taking into consideration the cytotoxicity (lactate dehydrogenase release) results, however, the decline in CYP gene expression may reflect minor toxicity rather than specific gene repression.

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Table 71. Test Article and CYP Enzyme Assays Conducted in Study RPT200

Test article	CYP enzyme	Assay	Applied concentration range
Pacritinib citrate	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4	Direct and time dependent CYP enzyme inhibition using substrate cocktail in human liver microsomes	0.1, 0.3, 1, 5, 20, 100 and 350 μM
	CYP1A2, CYP2B6 and CYP3A4	CYP gene induction in cryopreserved primary human hepatocytes from three donors	0.1, 0.3, 1, 5, 20, 100 and 350 μM
	NA	Cytotoxicity during induction incubations as LDH release	0.1, 0.3, 1, 5, 20, 100 and 350 μM
	NA	Test article stability during induction incubations	1 μM

Source: Page 12, Table 2, RPT200 report.
Abbreviations: CYP, cytochrome P450; LDH, lactate dehydrogenase; NA, not applicable

Table 72. Test Article and CYP Enzyme Assays Conducted in Study RPT200

Enzyme	Reaction	IC_{50} (μM)		IC_{50} shift (fold)	Tentative Ki (μM)
		-NADPH in preincubation 30 min	+NADPH in preincubation 30 min		
CYP1A2	ACET	10.6	0.1*	~100	8.7
CYP2B6	OH-BUP	47.8	39.4	1.2	47
CYP2C8	OH-REPA	27.0	22.9	1.2	22
CYP2C9	OH-DICL	123	89.2	1.4	62
CYP2C19	DeM-OME	13.6	9.3	1.5	9.1
CYP2C19	5-OH-OME	11.6	6.8	1.7	7.7
CYP2D6	O-deM-DEX	35.3	44.2	0.8	29
CYP3A4	3-OH-OME	8.9	3.4	2.6	5.9
CYP3A4	SO2-OME	4.7	2.6	1.8	3.2
CYP3A4	6ß-OH-TES	86.0	23.4	3.7	78
CYP3A4	1-OH-MDZ	33.5	12.4	2.7	17

Source: Page 17, Table 4, RPT200 Report.
The lowest pacritinib test concentration (0.1μM) resulted in 47±2% inhibition of CYP1A2 after 30-minute preincubation with NADPH. The curve was fitted by fixing the *top* parameter, i.e., the upper plateau of the inhibition curve, to 100%.
Abbreviations: CYP, cytochrome P450; IC_{50}, half-inhibitory concentration; Ki, concentration of the inhibitor required to decrease the maximal rate of the reaction by half

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Figure 15. CYP mRNA Levels in the Presence of Pacritinib Citrate
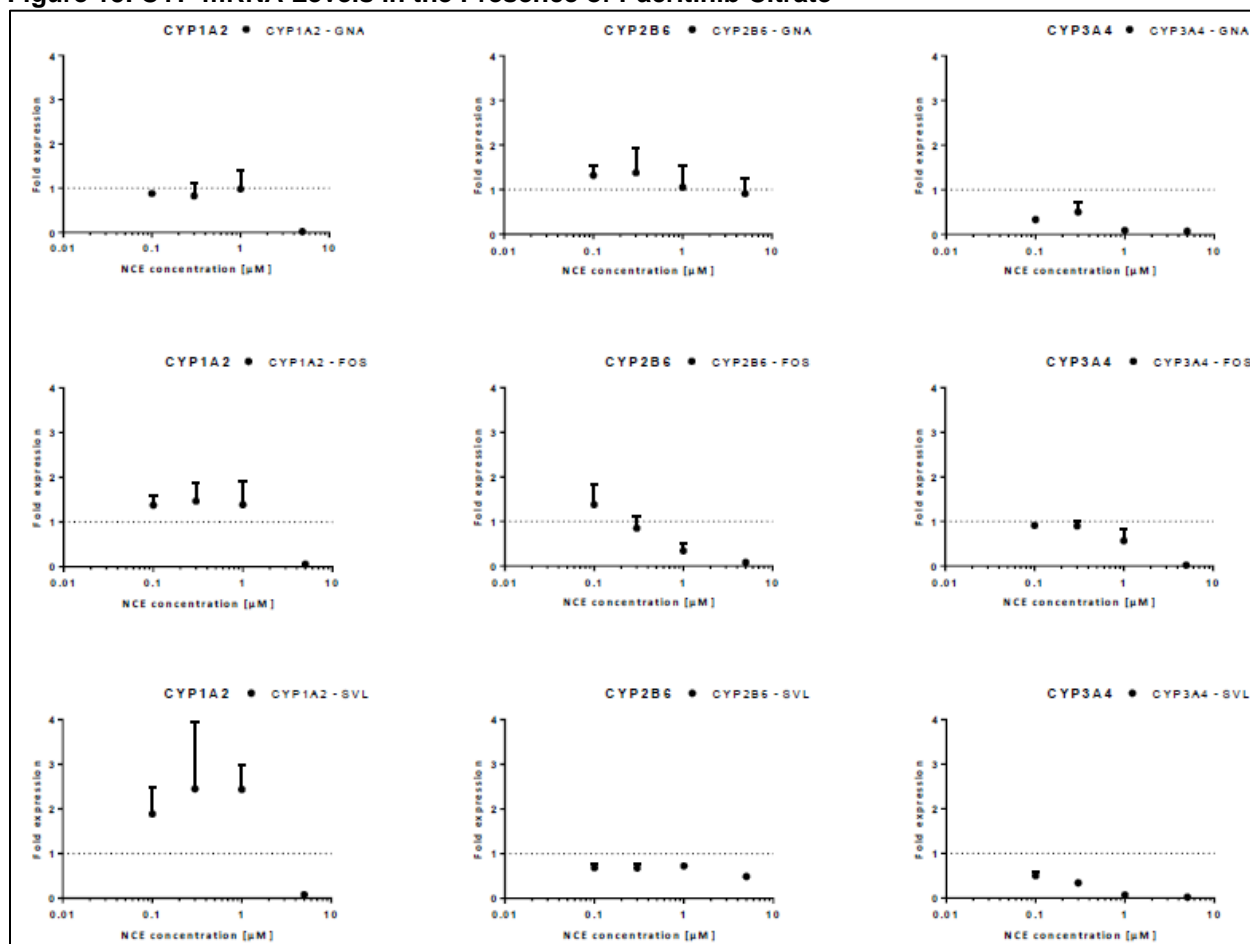
Source: Figure 17, page 62, RPT200 report.
Note: The fitted curve is omitted when the curve fit did not converge. Results at ≥20µM pacritinib citrate excluded due to toxicity.
Results are following a 48-hour exposure time. qPCR results are relative means±standard deviation.
Abbreviations: CYP, cytochrome P450; mRNA, messenger RNA; qPCR, quantitative polymerase chain reaction

Study RPT211 investigated the interaction of pacritinib with CYP enzymes, including the characterization of the time- and metabolism-dependent inhibition towards CYP1A2 and CYP3A4 and the reversible inhibition kinetics towards CYP1A2, CYP2C19, and CYP3A4. The pacritinib concentrations in this study were selected based on prior IC_{50} shift data from Study RPT200 (shown in Table 73).

Phenacetin O-deethylation (CYP1A2 probe reaction) and midazolam 1′-hydroxylation (CYP3A probe reaction) activities declined as a function of time when pacritinib was preincubated with human liver microsomes in the presence of NADPH. Increasing the pacritinib concentration in preincubation resulted in a sigmoidal increase in the observed deactivation rate, with estimated maximum inactivation rate (k_{inact}) of 0.041 1/min and K_I of 0.95µM for CYP1A2 and k_{inact} of 0.0096 1/min and K_I of 1.6µM for CYP3A4.

Direct inhibition towards phenacetin O-deethylation (CYP1A2 probe reaction) and omeprazole demethylation and 5-hydroxylation (CYP2C19 probe reactions) was consistent with competitive reversible inhibition, with estimated total incubation concentration-based K_i values of 21.7, 10.0,

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and 8.2μM, for phenacetin O-deethylation, omeprazole demethylation, and omeprazole 5-hydroxylation, respectively.

Direct inhibition towards midazolam 1′-hydroxylation (CYP3A probe reaction) was consistent with mixed model reversible inhibition with an estimated $K_{i\alpha}$ of 8.2μM and $K_{i\beta}$ of 32.1μM ($K_{i\alpha}$ referring to inhibitor affinity to the enzyme and $K_{i\beta}$ referring to inhibitor affinity to enzyme substrate complex). The unbound fraction in incubations ($f_{u,inc}$) with human liver microsomes at protein concentrations of 0.3 mg/mL (corresponding to the conditions during pre-incubation for K_I and k_{inact} determination) and 0.03 mg/mL (corresponding to the conditions during incubation for reversible K_i determination) of pacritinib were 19.8% and 69.0%, respectively.

In conclusion, the results of Study RPT211 were consistent with the previous information, suggesting that pacritinib is an inhibitor of CYP1A2, CYP2C19, and CYP3A. Furthermore, in addition to a direct (reversible) inhibition component, this study clearly demonstrated time-dependent inhibition of CYP1A2 and CYP3A by pacritinib.

Due to cytotoxicity, CYP induction could not be directly estimated with cryopreserved human hepatocytes. To address this issue, in vitro evaluation of the potential for activation of human PXR (which modulates the expression of CYP3A and CYP2C family) and AhR (which modulates the expression of the CYP1A family) by pacritinib was performed in Study RPT213.

Clear-bottom 96-well plates containing DPX2 or 1A2-DRE cells were used to assess activation of human PXR and AhR, respectively. Viability of all cell lines in the presence of the compound and the system controls was assessed in the same plate used to determine receptor activation. DPX2 and 1A2-DRE cells were seeded in 96-well plates at a density of 20,000 cells/well. Plates were maintained at 37°C, in an atmosphere of 5% CO_2 and 95% relative humidity for 24 hours to allow cell recovery. Following viability determination, 50 μL of ONE-Glo substrate (Promega) was added to each well. The plates were incubated at room temperature for 5 minutes and luminescence was read on a luminometer. The average of the duplicate luminescence measurements for each concentration of test and control compounds were divided by the average for the dimethyl sulfoxide solvent controls to determine the fold induction. In this manner, nuclear receptor activation of the CYP promoter is directly proportional to luciferase activity and is a measure of transcriptional activation of the CYP genes.

The positive control, rifampin, produced a typical dose-response curve (half-maximal effective concentration [EC_{50}] 2.6 μM and E_{max} 28.6-fold) in DPX2 cells (PXR activation). At 10μM, pacritinib elicited a 21.61-fold increase in luciferase activity, which is 90% of the activation by rifampin. The potential to activate human PXR by 20μM pacritinib could not be assessed due to cellular toxicity (only 30.2% of the cells remained viable compared to those treated with dimethyl sulfoxide). At 5μM, pacritinib produced 4.34-fold activation of PXR (15% of the 10μM rifampin response). EC_{50} and E_{max} values could not be determined for pacritinib due to cytotoxicity at 20μM.

In the human AhR assay, pacritinib was compared to a strong human AhR activator, 3-methylcholanthrene (3-MC). 3-MC produced a 31.9-fold activation of human AhR at 10μM and a typical dose-response curve from which an EC_{50} value of 2.2μM and E_{max} of 36.9-fold were derived. At 5μM, pacritinib elicited a 10.65-fold increase in luciferase activity (31% of the activation by 3-MC). The potential to activate human AhR by 20μM and 10μM pacritinib, as well as EC_{50} and E_{max} estimation could not be determined due to cytotoxicity.

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In conclusion, pacritinib was shown to be a strong activator of human PXR at 10μM and a moderate activator of human AhR at 5μM. The results suggested moderate-to-strong CYP450 induction at pacritinib concentrations of 5 to 10μM.

Table 73. Test Article and CYP Enzyme Assays in Study RPT211

Test article	CYP enzyme	Assay	Applied concentration range
	CYP1A2	K_I and k_{inact} determination, time dependent inhibition	0.03, 0.1, 0.3, 2 and 10 μM
	CYP3A4	K_I and k_{inact} determination, time dependent inhibition	1, 3, 10, 30 and 100 μM
	CYP1A2	K_i determination, reversible inhibition	1, 3, 10, 25 and 50 μM
Pacritinib citrate	CYP2C19	K_i determination, reversible inhibition	1, 3, 10, 25 and 50 μM
	CYP3A4	K_i determination, reversible inhibition	3, 10, 30, 90 and 150 μM
	NA	Free fraction in incubations	1 μM TA; 0.3 and 0.03 mg/mL HLM protein

Source: Table 1, page 9, RPT211 Report.
Abbreviations: CYP, cytochrome P450; HLM, human liver microsome; Ki, concentration of the inhibitor that is required to decrease the maximal rate of the reaction by half; NA, not applicable

Transporter Studies

In Study RPT107, the permeability classification of pacritinib and its efflux ratio was determined using Caco-2 monolayers. Pacritinib at a concentration of 5μM in Hank's balanced salt solution with maximum dimethyl sulfoxide concentration less than 1% was placed in Caco-2 monolayers that were grown to confluence (21 to 28 days). Apical and basolateral sides were both sampled at 2 hours. The concentration of pacritinib was determined by LC-MS/MS using a four-point calibration curve. The results showed that pacritinib had high permeability (apical to basolateral: $P_{app}=15.5\times10^{-6}$ cm/s; basolateral to apical: $P_{app}=12.7\times10^{-6}$ cm/s) and low efflux ratio ($P_{app,\ B\ to\ A}$ / $P_{app,\ A\ to\ B}$ =0.8), indicating that pacritinib was not actively transported by P-gp.

In Study RPT14F175CETH, the potential for pacritinib as substrate or inhibitor of transporters was investigated, including the P-gp, BCRP, and MRP2 substrate potential of pacritinib; the P-gp

and BCRP inhibition potential of pacritinib; the OATP1B1 and OATP1B3 inhibition potential of pacritinib (using transfected HEK cells); and the IC_{50} of pacritinib for inhibition of BSEP (using human BSEP-expressing vesicles). For ABC transporters including P-gp, BCRP, and MRP2, various cell monolayers were grown to confluence, then dosed on the apical side (apical to basolateral) or basolateral side (basolateral to apical) and incubated at 37°C with 5% CO_2 in a humidified incubator. Samples were taken from the donor and receiver chambers at 120 minutes.

For SLC transporters, the cells were incubated with the probe substrate in the presence and absence of the test article. All samples were assayed by LC-MS/MS assay. To determine IC_{50} for inhibition of BSEP, BSEP vesicles (50 µg) and ^{3}H-taurocholic acid (TCA, at 1µM) were incubated in the absence and presence of test article (0.041 to 10µM) or a positive control inhibitor (cyclosporin A, 10µM), and the reaction was initiated by adding 5mM adenosine 5'-triphosphate as the energy source for BSEP.

The reactions were carried out in 96-well plates incubated in a humidified incubator (37°C, 5% CO_2) for 30 minutes. After incubation, the vesicle-associated ^{3}H-TCA and free ^{3}H-TCA were separated by rapid filtration through a glass-fiber filter plate under vacuum. After extensive washing with ice-cold buffer, the radioactivity of vesicle associated ^{3}H-TCA was measured by scintillation counting. The results demonstrated that pacritinib was not a substrate of P-gp, BCRP, and MRP2. In addition, pacritinib was shown as an inhibitor of P-gp (IC_{50} 4.8µM), BCRP (IC_{50} 5.4µM), OATP1B1 (IC_{50} 9.4µM), and OATP1B3 (IC_{50} 74.2µM).

In Study RPT200, the interaction of pacritinib with OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 was explored. The assay details are shown in Table 74. The potential of pacritinib to inhibit probe substrate transport was assessed in the uptake inhibition assays. The transporter substrate assessment of pacritinib was performed by incubation of pacritinib at four concentrations and a single time point with transporter-expressing and control cells. The accumulation of the probe substrate in the presence of pacritinib citrate was measured by liquid scintillation.

Pacritinib did not inhibit the OAT1- and OAT3-mediated probe substrate accumulation at the applied concentrations (0.1 to 10µM). Pacritinib inhibited the OCT1- and OCT2-mediated probe substrate accumulation in a dose-dependent manner with a maximum inhibition of 96% (at 30µM) and 99% (at 300µM), respectively. The calculated IC_{50} was 0.87µM for OCT1 and 19.19µM for OCT2. Accumulation of pacritinib was similar in the transporter-expressing and the control cells (transporter-specific fold accumulations were <2), indicating no active accumulation of following uptake transporter substrate assays including OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2.

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Table 74. Test Article and Transporter Assays Conducted in Study RPT200

Test article	Transporter	Assay	Applied concentration range
Pacritinib citrate	OATP1B1	Substrate	0.08, 0.4, 2, and 10 µM
	OATP1B3	Substrate	
	OAT1	Inhibition and Substrate	0.1 µM and 10 µM (inhibition)
	OAT3		
	OCT1		0.08, 0.4, 2, and 10 µM (substrate)
	OCT2		
	OCT1	Inhibition	0.04 − 30 µM
	OCT2		0.41 − 300 µM

Source: Table 1, Page 11, RPT200 Report.
Abbreviations: OAT, organic anion transporter; OCT, organic cation transporter

14.2. In Vivo Studies

Study PAC101

A Phase 1, open-label, single-dose, randomized, two-period, two-treatment-sequence crossover study to assess the relative bioavailability of pacritinib following oral administration as capsule and solution formulations in healthy subjects.

Primary Objective

To determine the relative bioavailability of pacritinib following administration as either an oral capsule or an oral solution and evaluate the influence of different formulations on exposure. In addition, PK profiles of pacritinib and major human metabolites following single-dose administration as an oral capsule and an oral solution in healthy subjects was characterized.

Study Design

A total of 12 healthy subjects were randomly assigned into two sequence groups (six subjects per group) at one clinical site. Subjects were randomly assigned to two possible sequences (Sequence I: A then B, Sequence II: B then A), where Treatment A was pacritinib 400 mg (4×100 mg capsules) administered as a single oral dose and Treatment B was pacritinib 80 mg solution administered as a single 80 mg oral solution dose. All pacritinib doses were preceded by an overnight fast of at least 10 hours from food (not water) and were followed by a fast from food (not water) for at least 4 hours postdose. At least a 7-day washout separated the two treatments of study medication. Blood samples for the measurement of plasma concentrations of pacritinib were collected immediately predose (Day 1), and at 1, 2, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, and 168 hours postdose during each treatment period (Days 2 to 8). Day 8 was considered equivalent to Day 1 of the second Treatment and the 168-hour time point was equivalent to the predose (0 hour) sampling time point for the second Treatment.

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Results

The arithmetic mean plasma concentration-time profiles for pacritinib following single-dose administration (400 mg pacritinib oral capsules and 80 mg pacritinib oral solution) are presented in Figure 16. The statistical analysis of relative bioavailability for pacritinib is presented in Table 75. The effect of formulation change (capsule to solution) on pacritinib pSTAT3 inhibition is shown in Figure 17 and Table 76. The relative bioavailability for the pacritinib oral capsule formulation was approximately 58.6% as compared to the oral solution formulation. In addition, there was a modest pSTAT3 inhibition effect observed with administration of the 400 mg capsule or 80 mg oral solution formulation of pacritinib. There was also high variability observed in the pSTAT3 inhibition effect with both formulations.

Figure 16. Plasma Concentration Profiles of Pacritinib Following Single-Dose Administration (400 mg Pacritinib Oral Capsule and 80 mg Pacritinib Oral Solution)
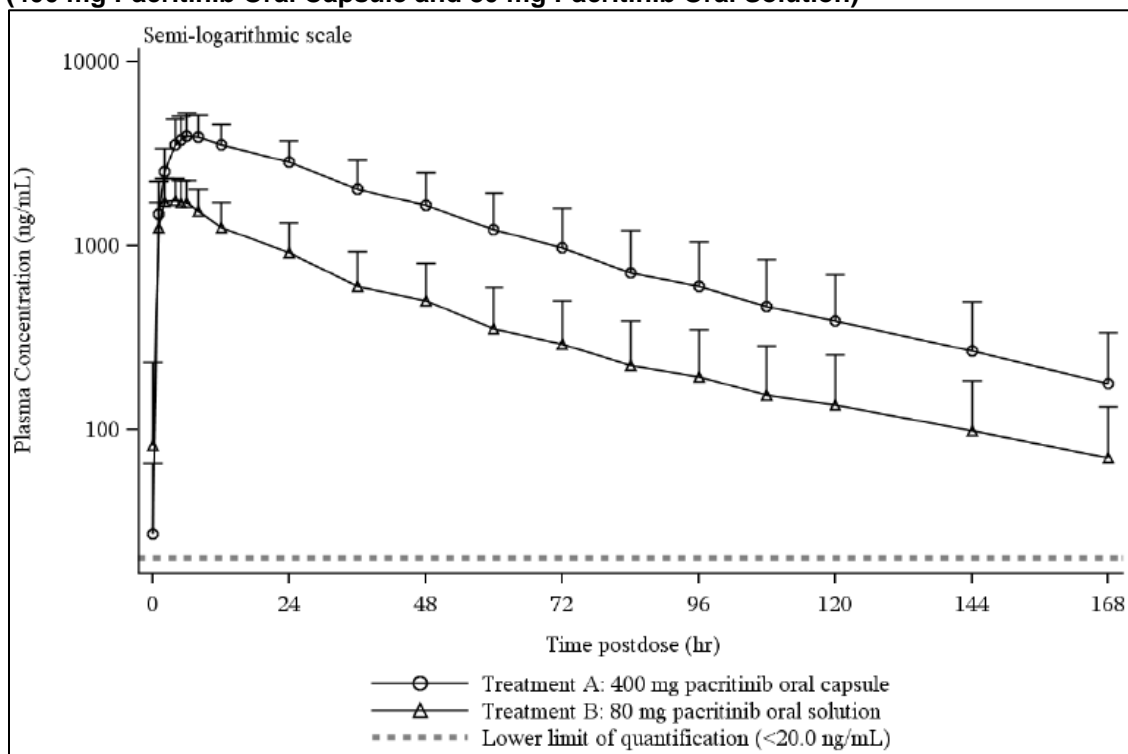
Source: Figure 11-1, page 36, PAC101 Report.
Note: Values are arithmetic means, with bars representing standard deviations.

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Table 75. Statistical Analysis of Relative Bioavailability Data: Effect of Formulation on the Pharmacokinetics of Pacritinib

Parameter	n	LSM	(90% CI)[1]	n	LSM	(90% CI)[1]	Test/ Reference Ratio[2] (%)	90% CI of the Ratio[3]	Intersubject Variability (CV%)	Intrasubject Variability (CV%)
	400 mg Pacritinib Oral Capsule (Test)			**80 mg Pacritinib Oral Solution (Reference)**						
C_{max} (ng/mL/mg)	12	9.58	(8.2, 11.2)	12	22.0	(18.8, 25.7)	43.6	(38.4, 49.6)	24.7	17.5
$AUC_{0-\infty}$ (ng·h/mL/mg)	12	482	(367.8, 630.9)	12	823	(628.1, 1077.4)	58.6	(51.8, 66.1)	51.9	16.6
AUC_{0-t} (ng·h/mL/mg)	12	461	(355.2, 597.5)	12	770	(593.7, 998.6)	59.8	(52.9, 67.7)	49.5	16.8

Source: Table 11-2, page 38, PAC101 Report.

Note: Data from subjects who completed both periods are used in the analysis. DN calculated as parameter/dose in mg.

[1] Least-squares means and the corresponding 90% confidence intervals on natural log transformed data were obtained from ANOVA and then transformed back to original scale to obtain geometric LS means and the corresponding 90% confidence intervals.

[2] Difference of LS means of natural log transformed data between test and reference was obtained by ANOVA and transformed back to the original scale to obtain ratio of Geometric LS means (expressed as a percentage).

[3] 90% confidence interval of difference of LS means was obtained by ANOVA and transformed back to the original scale to obtain the 90% confidence interval for the ratio (expressed as a percentage).

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; CI, confidence interval; CV%, coefficient of variation; DN, dose-normalized; LSM, least-squares mean; n, the number of observations in each treatment used in the model

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Figure 17. Percentage Inhibition Profiles for the Ratio of Stimulated pSTAT3/Unstimulated Total STAT3 Following Single-Dose Administration of Pacritinib (400 mg Pacritinib Oral Capsule and 80 mg Pacritinib Oral Solution)
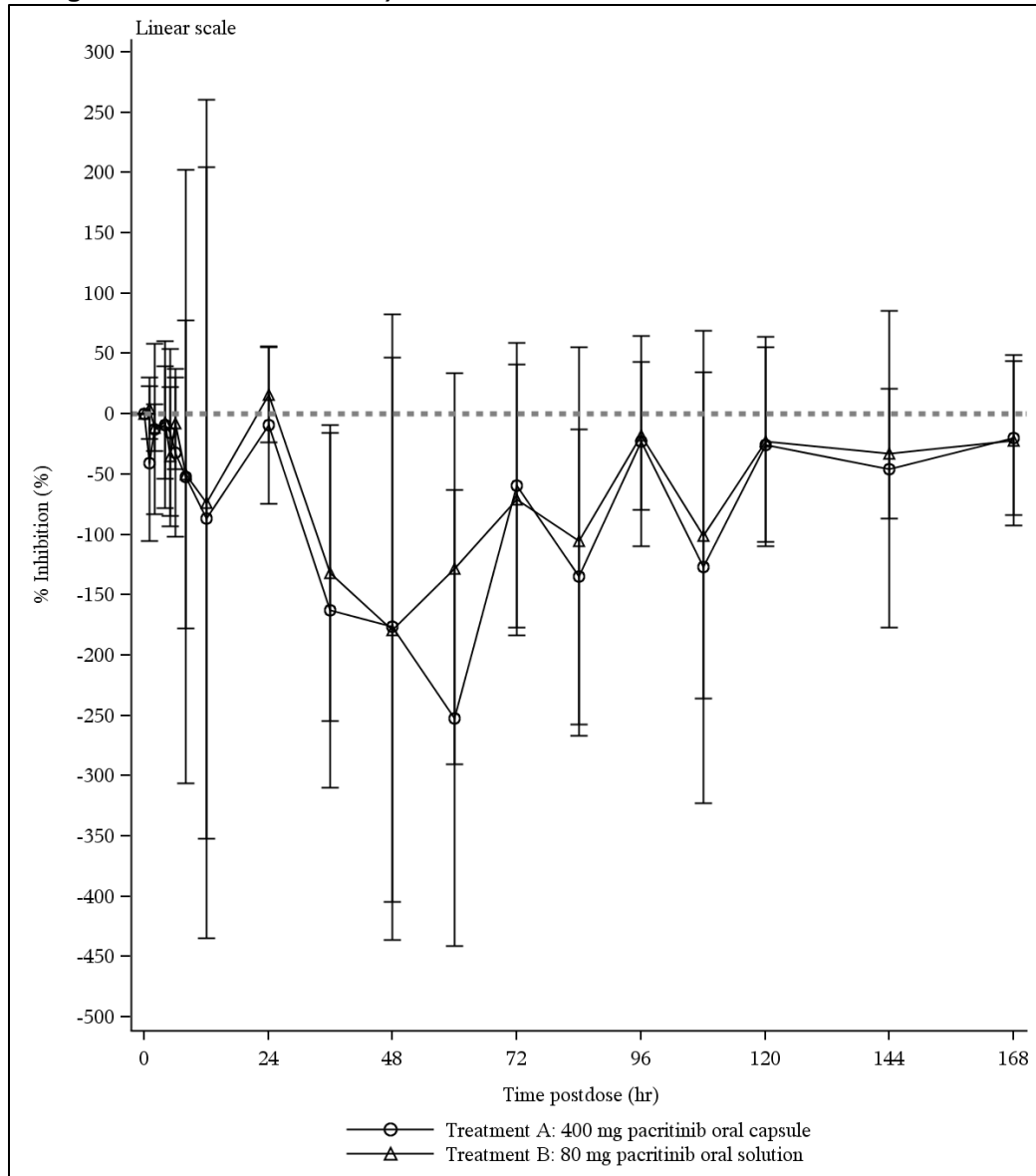
Source: Figure 11-3, page 43, PAC101 Report.
Note: Values are arithmetic means, with bars representing standard deviations.

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Table 76. Pharmacodynamic Parameters of pSTAT3 Following Single-Dose Administration of Pacritinib (400 mg Pacritinib Oral Capsule and 80 mg Pacritinib Oral Solution)

Parameter	Treatment A 400 mg Pacritinib Oral Capsule (N=12)	Treatment B 80 mg Pacritinib Oral Solution (N=12)
E_{max} (%)	1.48 (75.0)	1.41 (86.4)
TE_{max}[a] (hr)	54.0 (4.00 – 84.0)	48.0 (5.00 – 108)
$AUEC_{0-t}$ (hr*%)	85.1 (49.0)	79.9 (57.4)

Source: Table 11-4, page 44, PAC101 Report.
Note: Geometric mean (geometric CV%) data are presented.
[a] Median (minimum-maximum) presented for TE_{max}.
Abbreviations: $AUEC_{0-t}$, area under the effect-time curve from hour 0 to the last measurable activity level; E_{max}, peak effect level; CV, coefficient of variation; N, number of subjects; TE_{max}, time to peak effect level.

Study PAC102

A Phase 1, open-label study to investigate the absorption, metabolism, excretion, and mass-balance of [^{14}C]pacritinib following a single oral dose in healthy male subjects.

Primary Objective

To characterize the clearance pathways, the routes of excretion, and the recovery of total radioactivity of pacritinib and its major metabolites in healthy subjects following administration of a single oral dose of 400 mg [^{14}C]pacritinib.

Study Design

The study was conducted in six healthy male subjects. Each subject received a single oral 400 mg dose of pacritinib as four 100 mg pacritinib capsules and 100 μCi [^{14}C]pacritinib suspension. Plasma, urine, and fecal samples were collected for metabolite profiling. Plasma samples were collected at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, and 312 hours postdose; urine samples were collected at predose, 0 to 6 hours, 6 to12 hours, 12 to 24 hours, 24 to 48 hours, and at 24-hour intervals up to 312 hours postdose; and feces samples were collected at predose and at 24-hour intervals up to 312 hours postdose. Human plasma samples were prepared by protein precipitation with organic solvents. Human urine samples were concentrated by lyophilization and reconstitution. Human fecal homogenate samples were extracted with organic solvents, centrifuged to separate the pellet and supernatant, and the combined supernatants were concentrated under a nitrogen stream. LC-MS/MS coupled with a radio flow detector was used for metabolite profiling and identification. [^{14}C] pacritinib and its metabolites were separated using reverse-phase chromatography and detected using a radio flow detector and a mass spectrometer simultaneously.

Results

The mean extraction recovery of human plasma radioactivity was 90.52% for pooled samples from 0 to 120 hours postdose, the mean reconstitution recovery of human plasma extracts was 105.16%, and the overall plasma radioactivity recovery was 95.19%.

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The mean extraction recovery of radioactivity for human fecal homogenate was 85.90%, the reconstitution recovery of human feces extracts was 91.58%, and the overall fecal radioactivity recovery was 78.67%. The radioactivity recovery from human urine lyophilization and reconstitution was 100.16%.

The recovery of radioactivity from the HPLC column was 98.88%. The proposed biotransformation products and pathways of pacritinib in humans are presented in Figure 18. A summary of cumulative recovery of total radioactivity (as percent of dose) in urine and feces after administration of a mixture of dosage forms (capsules plus solution) of 400.89 mg pacritinib containing $[^{14}C]$pacritinib (94.1 μCi) to healthy male subjects is presented in Table 77. The total recovery was considered satisfactory (93.28%) with a predominant fecal excretion of 87.25% and urine excretion of 6.04% (Figure 19).

Pacritinib was the predominant radioactive component in all plasma samples from 0.5 to 120 hours postdose with mean C_{max} of 4,117.2 ng/mL. The mean C_{max} for M2, M1, M3, and M8 was 887.0, 854.5, 292.3, and 148.6 ng-equivalent/mL, respectively. M3 was present in plasma samples collected after 16 hours postdose. The mean recovery of radioactivity in human urine from 0 to 48 hours postdose for the six subjects was 3.22% of the administered dose. M7 was the predominant radioactive component in human urine and accounted for 3.03% of the administered dose (Table 78). Pacritinib and M5 accounted for 0.12% and 0.08% of the administered dose, respectively (Table 78). The mean recovery of radioactivity in human feces from 0 to 240 hours postdose for the six subjects was 85.46% of the administered dose. Pacritinib was detected by mass spectrometry in fecal samples but was not detected by radio flow detector. M2 was the predominant fecal radioactive component and accounted for a mean of 24.08% of the administered dose (Table 79). M6, M5, M9, and M8 each accounted for 15.32%, 13.54%, 10.35%, and 9.19% of the administered dose, respectively. M12, M13, and M14 each accounted for 2.99% to 4.18% of the administered dose (Table 79). M10, M11, M14a, and M15 were the minor metabolites identified in feces (<0.75% of the administered dose, Table 79).

Table 77. Pacritinib and Metabolite Concentrations From Radio-Quantitation of Individual Plasma Samples Using an HPLC Method

Name	Pacritinib	M3	P9	M8	M2	M1
Retention time (min)	11.50-13.0	13.3-14.3	15.0-15.3	16.3-16.8	16.8-18.0	18.8-19.5

Subject	Time points (h)	Concentration (ng-equivalent/mL)					
(b) (6)	0.5	1579.3	BQL	BQL	BQL	BQL	195.2
	1	3715.7	BQL	BQL	BQL	458.4	605.6
	1.5	4180.0	BQL	BQL	BQL	775.5	910.4
	2	4110.9	BQL	630.4	BQL	816.6	888.2
	3	4137.2	BQL	215.5	BQL	888.7	812.4
	4	3542.9	BQL	237.3	BQL	934.0	963.5
	6	2726.0	BQL	BQL	BQL	822.5	629.1
	8	2915.5	BQL	BQL	BQL	529.9	428.1
	12	2184.5	BQL	BQL	BQL	449.3	349.7
	16	2354.8	BQL	BQL	BQL	331.5	201.3
	24	2010.5	BQL	BQL	BQL	260.5	297.7
	36	1527.5	BQL	BQL	BQL	234.1	189.4
	48	1146.9	153.5	BQL	BQL	135.4	108.4
	72	911.3	195.3	BQL	BQL	BQL	BQL
	96	516.5	152.6	BQL	BQL	BQL	BQL
	120	396.6	BQL	BQL	BQL	BQL	BQL
	0.5	2440.4	BQL	BQL	BQL	333.6	424.4
	1	2913.6	BQL	BQL	BQL	567.2	293.2
	1.5	2987.9	BQL	BQL	BQL	441.8	336.7
	2	2752.6	BQL	BQL	BQL	629.0	576.7
	3	3063.6	BQL	BQL	BQL	519.4	605.7
	4	3191.9	BQL	BQL	BQL	540.3	556.6
	6	2708.2	BQL	BQL	BQL	445.6	463.3
	8	2738.8	BQL	BQL	BQL	391.4	279.6
	12	2180.5	BQL	BQL	BQL	272.6	311.6
	16	2057.8	BQL	BQL	BQL	277.1	257.1
	24	2145.0	BQL	BQL	BQL	BQL	174.4
	36	1417.5	BQL	BQL	BQL	BQL	BQL
	48	1072.6	BQL	BQL	BQL	BQL	321.9
	72	657.0	184.8	BQL	BQL	BQL	BQL
	96	469.5	BQL	BQL	BQL	BQL	BQL
	120	277.6	BQL	BQL	BQL	BQL	BQL

Source: Table 14-6, page 137, PAC102 Report.
Abbreviations: BQL, below the limit of quantitation; HPLC, high-performance liquid chromatography

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Table 78. Percentage of Dose for Pacritinib and Metabolites in Six Human Urine Samples

Name	M5	Pacritinib	M7	Total
Retention time (h)	8.2	12.1	12.3-12.8	
Subject		% of dose		
(b) (6)	BQL	BQL	3.05	3.05
	BQL	BQL	2.92	2.92
	BQL	BQL	3.00	3.00
	BQL	0.70	2.15	2.85
	0.49	BQL	3.76	4.25
	BQL	BQL	3.27	3.27
Mean	0.08	0.12	3.03	3.22

Source: Table 11-3, page 55, PAC102 Report.
Abbreviation: BQL, below the limit of quantitation

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Table 79. Percentage of Dose for Pacritinib and Metabolites in Six Human Fecal Samples

	M5	M9	M10	M11	M6	M12	M13	M14a	M14	M15	M8	M2	
RT (Min)	7.4 to 8.4	8.0 to 9.0	9.2 to 9.4	11.1 to 11.3	12.0 to 12.4	12.4 to 12.8	12.8 to 13.2	14.1 to 14.2	14.2 to 14.5	15.1 to 15.2	15.4 to 16.0	16.4 to 17.1	Total
Subject							% of Dose						
(b) (6)	15.69	7.34	1.78	BLQ	16.73	5.21	2.85	BLQ	2.00	BLQ	8.11	22.33	82.03
	18.08	11.39	BLQ	BLQ	19.18	2.30	BLQ	BLQ	0	BLQ	6.04	35.13	92.12
	12.91	12.44	BLQ	BLQ	10.42	0.92	1.60	BLQ	2.64	1.31	13.35	30.78	86.37
	11.55	12.50	BLQ	BLQ	14.87	7.78	BLQ	BLQ	4.04	BLQ	7.96	30.05	88.76
	13.47	8.16	1.68	0.80	10.45	8.87	5.31	1.35	8.59	2.03	11.28	16.50	88.49
	9.57	10.27	1.04	0.40	20.26	0	8.17	0.32	6.89	BLQ	8.41	9.67	75.00
Mean	13.54	10.35	0.75	0.20	15.32	4.18	2.99	0.28	4.03	0.56	9.19	24.08	85.46

Source: Table 11-4, page 56, PAC102 Report.
Abbreviations: BLQ, below the limit of quantitation; RT, retention time

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Figure 18. Proposed Biotransformation Products and Pathways of Pacritinib in Humans
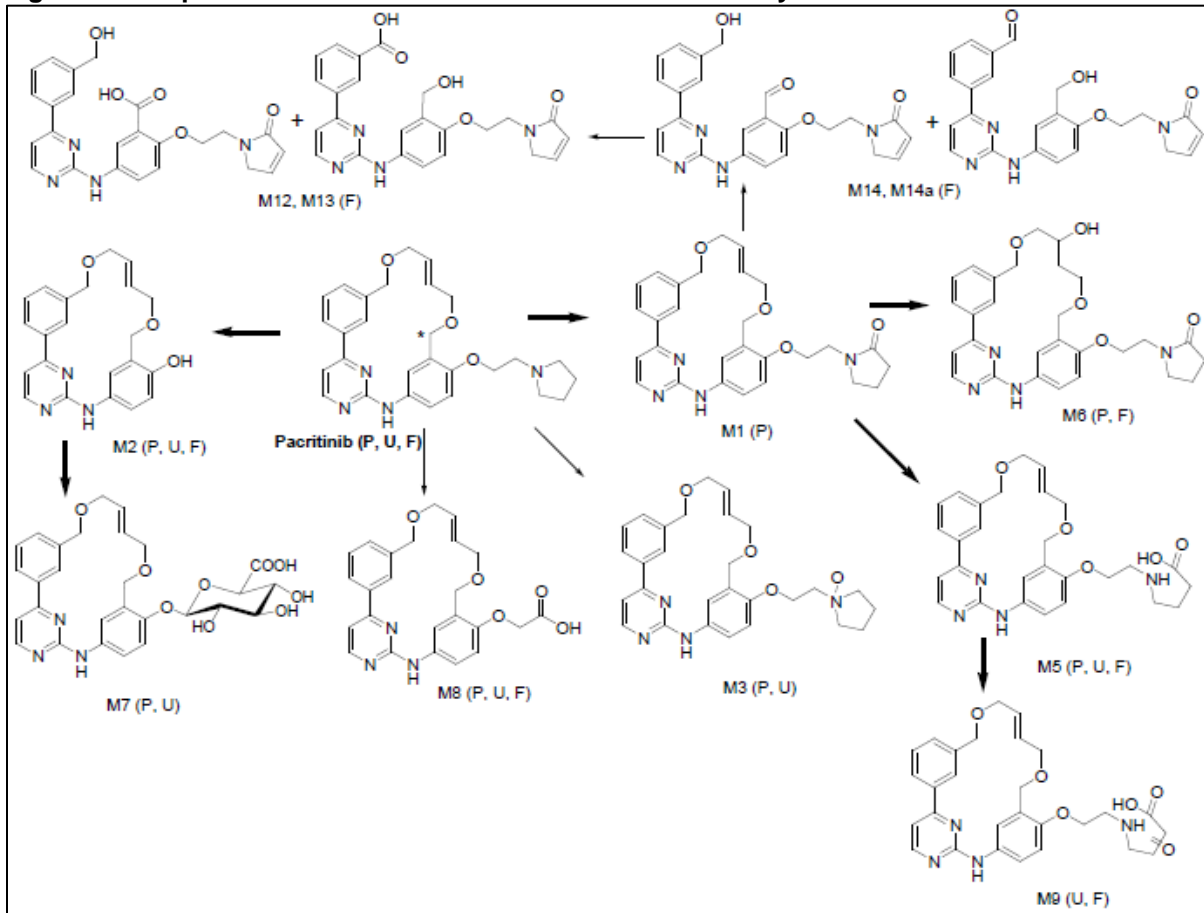
Source: Figure 14-55, page 135, PAC102 Report.
Bold arrows indicate the major metabolic pathways.
Abbreviations: F, feces; P, plasma; U, urine

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Figure 19. Mean Cumulative Excretion of Urine and Feces After Administration of 400.89 mg[1] Pacritinib as a Mixture of Dosage Forms (Capsules and Solution)
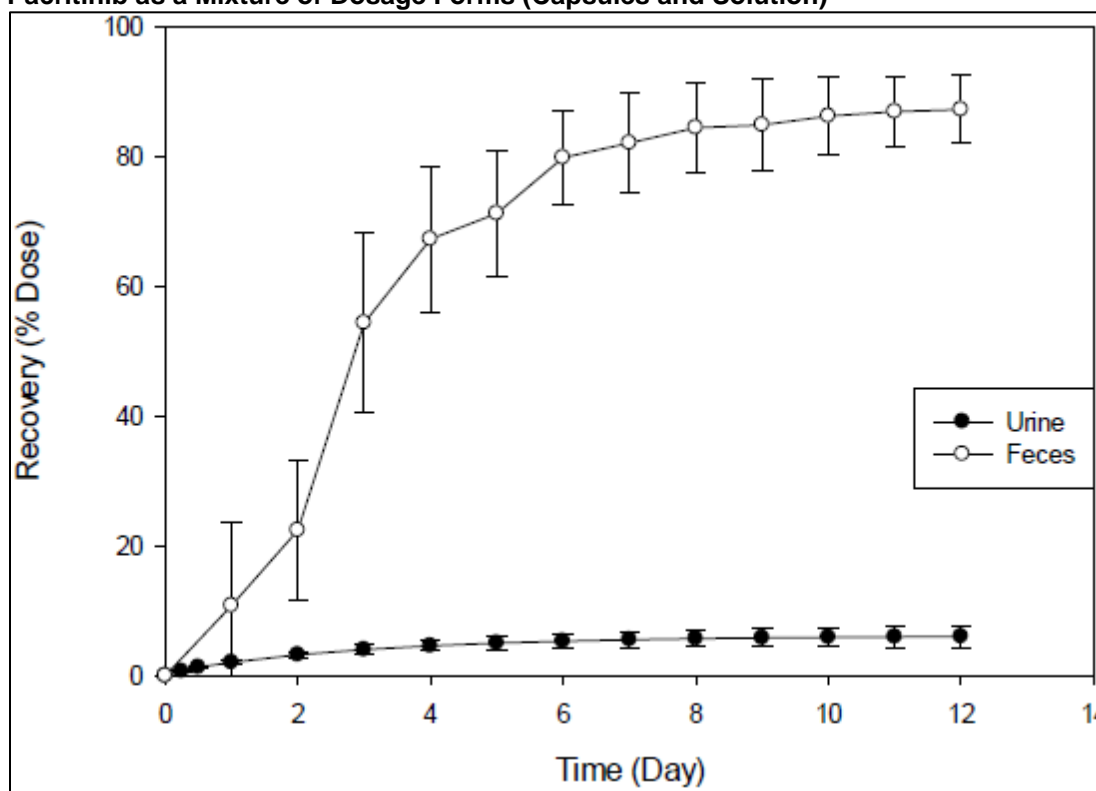
Source: Figure 11-55, page 66, PAC102 Report
[1] Subjects were administered four 100 mg pacritinib capsules first, followed immediately by a 0.89 mg pacritinib solution containing [14C]pacritin b (94.1 µCi).
Note: Values are means, with bars representing standard deviations.

Study SB1518-2010-004

A randomized, single-dose, three-treatment, six-sequence, three-period crossover study of the PK and sources of variability of pacritinib after oral administration to healthy subjects under fasted conditions.

Primary Objective

To assess the PK of pacritinib after single oral doses of 100, 200, and 400 mg.

Study Design

The study design is shown in Figure 20. A total of 24 subjects was randomly assigned into six sequence groups, with four subjects per group. Each subject received each of the treatments. Blood samples for the measurement of plasma concentrations of pacritinib were collected immediately prior to dosing, and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 18, 24, 36, 48, 60, 72, 96, 120, and 144 hours postdose during each treatment period.

Results

The plasma concentration profiles of pacritinib and PK parameters are shown in Figure 21 and Table 80, respectively. The median pacritinib T_{max} ranged from 4.5 to 5.5 hours; based on the

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ranges of individual subject values, there was no apparent change with dose. The mean pacritinib $t_{1/2}$ ranged from 33.5 to 34.5 hours and was not dose-dependent. The intersubject coefficient of variation (CV) for natural log-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} ranged from 28.28 to 45.01%, indicating relatively high variability among subjects; however, the intrasubject CVs for all three parameters were relatively low, ranging from 13.38% to 15.33%. As shown in Table 81, the geometric mean ratios were lower than the ratios between the compared dose levels and the associated 90% confidence intervals [CIs] did not include it, indicating a less than dose-proportional increase.

Figure 20. Schema of Study Design
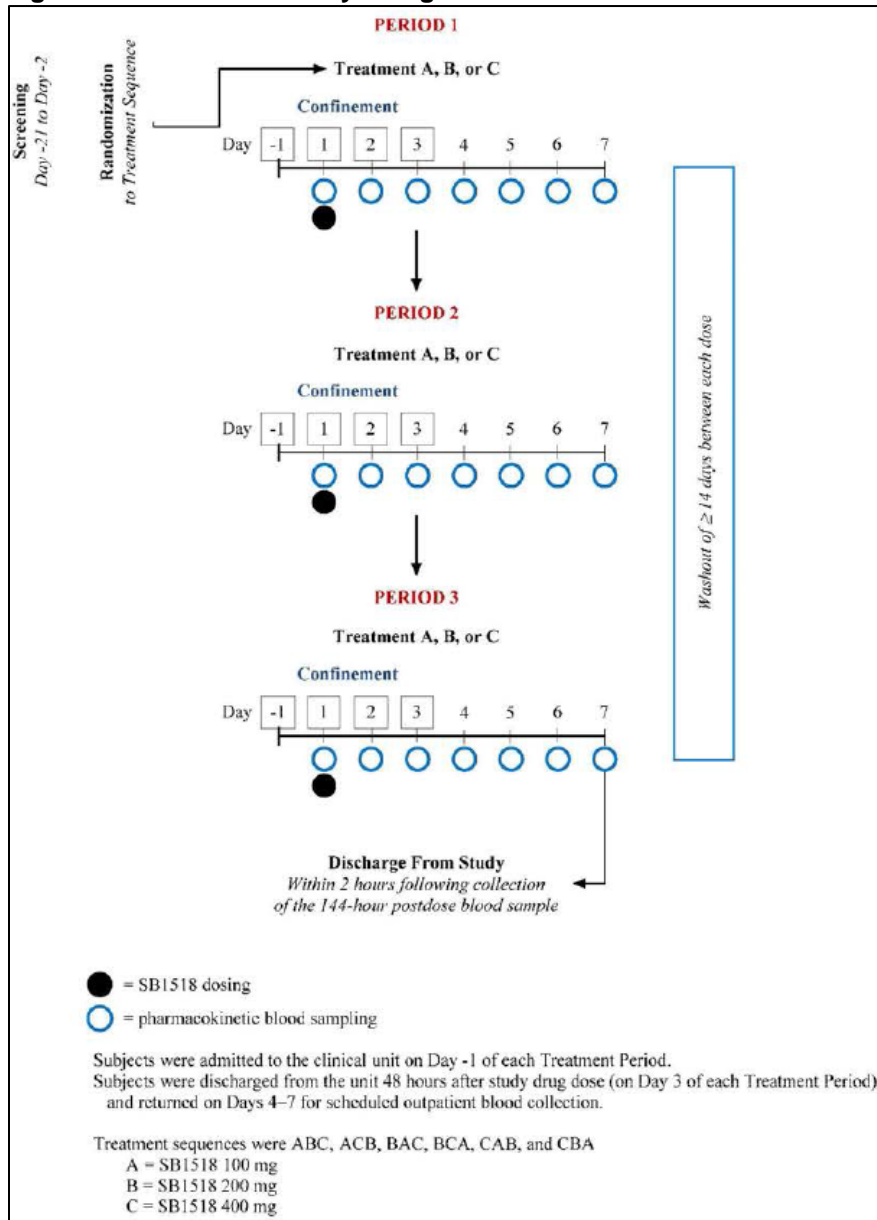
Source: Figure 9-1, page 12, SB1518-2010-004 Report.

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Figure 21. Mean Plasma Concentrations of SB1518 After Administration of Single 100 mg, 200 mg, and 400 mg Oral Doses to Healthy Subjects Under Fasted Conditions (Linear and Semi-Logarithmic Scales) (Pharmacokinetic Analysis Population)
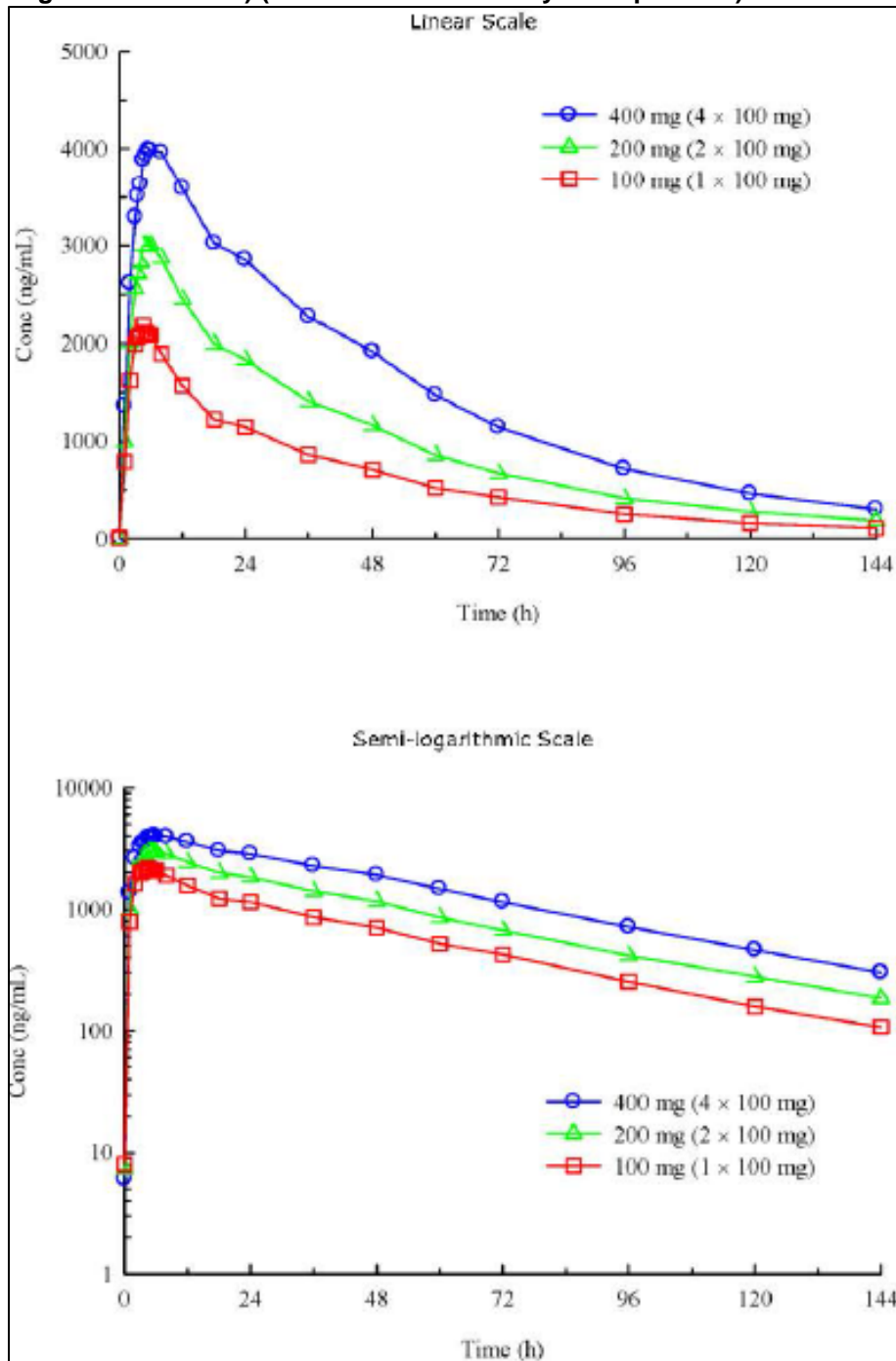
Source: Figure 11-1, page 33, SB1518-2010-004 Report.
Abbreviation: Conc; concentration

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Table 80. Summary of SB1518 Pharmacokinetic Parameters (Pharmacokinetic Analysis Population)

	SB1518		
Parameter, mean (SD)[a]	100 mg (1 × 100 mg) N=24	200 mg (2 × 100 mg) N=24	400 mg (4 × 100 mg) N=24
C_{max} (ng/mL)	2224 (616)	3106 (862)	4153 (1116)
T_{max} (hr)[a]	4.50 (2.0, 6.0)	5.00 (3.0, 8.0)	5.50 (3.0, 12.0)
AUC_{0-t} (ng*hr/mL)	86759 (29898)	137351 (62218)	214712 (86642)
AUC_{0-inf} (ng*hr/mL)	92722 (34409)	147888 (72914)	232108 (100988)
λ_z (1/hr)	0.0217 (0.0052)	0.0218 (0.0048)	0.0214 (0.0056)
$T_{1/2}$ (hr)	33.5 (7.38)	33.5 (7.83)	34.5 (8.74)
CL/F (L/h)	1.25 (0.54)	1.64 (0.69)	2.04 (0.84)
Vz (L)	56.7 (16.8)	73.5 (21.3)	94.4 (28.6)

Source: Figure 11-2, page 34, SB1518-2010-004 Report.
[a] T_{max} reported as median (minimum, maximum).
Abbreviations: AUC, area under the plasma concentration-time curve; CL/F, total clearance; C_{max}, maximum concentration; $T_{1/2}$, elimination half-life; T_{max}, time to maximum concentration; Vz, volume of distribution

Table 81. Summary of the Fit of the Power Model to C_{max} and AUC_{0-inf} Versus Dose

	Model Parameters		
Parameter	Coefficient	Exponent	P-value[a]
C_{max} (ng/mL)			
Mean (SEM)	291 (101)	0.444 (0.062)	<0.0001
95% CI	(90.6, 492)	(0.321, 0.567)	
AUC_{0-inf} (ng*hr/mL)			
Mean (SEM)	4497 (2850)	0.658 (0.111)	<0.0001
95% CI	(−1186, 10181)	(0.436, 0.881)	

Source: Figure 11-4, page 37, SB1518-2010-004 Report.
[a] P-value for the fit of the model.
Abbreviations: AUC, area under the plasma concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; SEM, standard error of the means

Study SB1518-2007-001

A dose-escalation and efficacy and safety study.

Study Overview

The PK profile of pacritinib was assessed in patients with advanced myeloid malignancies.

Study Design

This study included two parts: The Phase 1 part of the study used an open-label, dose-escalation design. Cohorts of three to six patients were enrolled at each pacritinib dose level, starting at a dose of 100 mg once daily (QD). Each patient participated in only one cohort, whereas the Phase 2 study used a multicenter, single-arm, open-label design.

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In Phase 1, pacritinib was administered orally at 100 mg, 150 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg QD without regard to food intake for 25 consecutive days of a 28-day cycle in Cycle 1 followed by 3 rest days for PK sampling.

From Cycle 2 onward, subjects were treated daily for 28 consecutive days of a 28-day cycle. The reference dose of 400 mg QD was chosen based on exposure, safety, and pharmacodynamic marker (percentage inhibition profiles for the ratio of stimulated pSTAT3/unstimulated total STAT3) data from the phase 1 study. The efficacy and safety profile of single-agent pacritinib at the reference dose in patients were investigated in the study. Efficacy was evaluated based on spleen response rate, which was defined as the proportion of subjects who achieved a $\geq 35\%$ spleen volume reduction (SVR) from baseline to Week 24 as measured by magnetic resonance imaging (MRI).

Blood samples for the measurement of plasma concentrations of pacritinib were collected immediately prior to dosing, and at 0.5, 1, 2. 3, 4, 5, 6, 8, and 24±2 hours after dosing on Days 1 and 15 (±3 days) of Cycle 1 and prior to dosing and at 2, 4, 6, and 8 hours after dosing on Day 1 of Cycle 2. Trough PK samples were drawn prior to dosing on Days 8 (±1 day) and 22 (±3 days) of Cycle 1 and at 24, 48, and 72 hours after dosing on Cycle 1 Day 25. A predose sample for PK was collected on Day 1 of Cycles 4, 7, and 10.

Results

The PK results are shown in Table 82 and Table 83. Day 1 and Day 15 PK data indicated pacritinib absorption may be dose-independent across the 100 to 600 mg QD dose range, with median T_{max} values ranging from 3 to 8 hours postdose. Day 1 mean AUC_{0-24} levels generally increased in a dose-related, but less than dose-proportional, manner up to 400 mg QD. Beyond the 400 mg QD dose level, exposures appeared to plateau. Day 15 mean exposure levels did not appear to increase in a dose-related manner in the 100 to 300 mg QD dose cohorts, with increases observed at the 400 and 500 mg QD dose levels, followed by a plateau at the 600 mg QD dose level. Relatively high interindividual coefficients of variation for C_{max} and AUC_{0-24} indicated substantial variability among patients. Overall, Day 1 pacritinib PK parameters were consistent with PK parameters determined from single-dose pacritinib studies.

Table 82. Day 1 Pharmacokinetics: Phase 1 (All Enrolled Population)

Parameter	Pacritinib Treatment						
	100 mg (N=3)	150 mg (N=6)	200 mg (N=9)[a]	300 mg (N=6)	400 mg (N=6)	500 mg (N=7)	600 mg (N=6)
C_{max}							
N	3	6	9	6	6	7	6
Mean	3699.4	3723.2	4999	5235.3	6275	7052.4	8329.3
% CV	45.8	48.6	28.0	39.4	62.6	55.7	24.8
Median	2905.6	3793.5	4571	5833	5644.2	6310	7877
Range	2548.6 - 5644.1	1667 – 6244	3153 - 7775	2116 - 7588	2023 - 13422	1211 - 12655	5981 - 11301
t_{max}							
N	2	3	6	4	6	3	3
Median	5	4	5	4	8	4	4.5
Range	3 - 5	3 – 24	3 - 24	3 - 24	5 - 24	3 - 8	2 – 5
AUC_{0-24h}							
N	3	6	9	6	6	7	6
Mean	65931.1	64716.5	93283.3	87120.7	126607.9	141152	135831
% CV	40.8	39.0	26.6	54.2	60.9	60.6	47.6
Median	56034	69156.3	87285.8	98216.75	117611	117821	128781
Range	45368.9 - 96390.4	34139.8 - 93657	61055.3 - 137843	4352.8 - 142136	35546.2 - 262181.5	22113.5 - 264974	41879.8 - 221135
C_{24h}							
N	3	6	9	6	6	7	6
Mean	2440.2	3112.7	3921.1	4213.2	5643.6	5898.7	5093
% CV	36.5	66.5	45.6	46.7	73.5	67.8	48.4
Median	2317.9	2315.5	3026	3528	4724.8	4417	4136
Range	1617.1 - 3385.6	1308 - 6244	2254 - 7775	2482 - 7588	1096 - 13422	789 - 11736	2768 - 8193

Source: Table 18, page 95, SB1518-2007-001 Report.
[a] Cohorts for HCl and citrate were pooled, because they were at the same dose. The two salt forms have been shown to be pharmaceutically equivalent.
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time zero to 24 hours; C_{max}, maximum concentration; C_{24h}, concentration at 24 hours; CV, coefficient of variation; n, number of subjects meeting prespecified criteria; N, total number of subjects; t_{max}, time to maximum concentration

Table 83. Day 15 Pharmacokinetics: Phase 1 (All Enrolled Population)

Parameter	Pacritinib Treatment						
	100 mg (N=3)	150 mg (N=6)	200 mg (N=9)	300 mg (N=6)	400 mg (N=6)	500 mg (N=7)	600 mg (N=6)
C_{max}							
N	3	6	9	6	6	7	6
Mean	6362.1	6698	6696.4	6407	9769.8	8726.1	9224.7
% CV	24.4	48.0	27.9	33.4	49.2	43.2	20.0
Median	6181	5411	6454	6855.5	11677.5	7986	8555
Range	4909.5 - 7995.7	3543 - 11236	2878 - 9227	2444 - 8726	2712 - 14820.4	2771 - 14333	7707 - 12714
t_{max}							
N	2	4	5	4	6	3	3
Median	3	2.5	5	4	341	4	4
Range	3 – 4	2 - 24	0.5 - 8	2 - 5	338 – 360	3 - 6	4 - 8
AUC_{0-24h}							
N	3	6	9	6	6	7	6
Mean	120306	139901	125115	132905	202878.1	178367	161277
% CV	26.3	53.8	35.7	37.8	51.2	49.1	45.2
Median	121364	114158.5	130082	133880	239919	160870	160968.5
Range	88134.7 - 151420	59673.3 - 235826	44131.5 - 171545	45528 - 194622	54178.2 - 318091.8	58205.5 - 323382	48272 - 276093
C_{24h}							
N	3	6	9	6	6	7	6
Mean	3944.6	5427.5	4852.1	4965	8429	6549.7	6438.8
% CV	24.4	55.6	26.5	46.1	57.4	58.2	37.4
Median	4321.7	5026	4993	4850	10168	5685	5417
Range	2849.1 - 4663	1973 - 9277	2427 - 6187	1421 - 8302	1713 - 12776.3	1994 - 12908	4410 - 10256

Source: Table 19, page 96, SB1518-2007-001 Report.
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time zero to 24 hours; C_{max}, maximum concentration; C_{24h}, concentration at 24 hours; CV, coefficient of variation; n, number of subjects meeting prespecified criteria; N, total number of subjects; t_{max}, time to maximum concentration

Study SB1518-2008-003

A dose escalation and efficacy and safety study.

Study Overview

The PK profile of pacritinib was assessed in patients with chronic idiopathic myelofibrosis.

Study Design

This study included two parts: Phase 1 was an open-label, multicenter, dose escalation study to determine the MTD and dose-limiting toxicity of pacritinib when administered orally once daily

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as a single agent in subjects with chronic idiopathic MF (including PET and PPV MF) regardless of their JAK2 mutational status. Patients were enrolled sequentially to one of five dose cohorts (100 mg, 200 mg, 400 mg, 500 mg, and 600 mg) and received pacritinib QD for 28 consecutive days (one cycle) for up to 1 year, or longer in the absence of disease progression and unacceptable toxicity. Phase 2 was a multicenter, single-arm, open-label study to evaluate the efficacy and safety profile of single-agent pacritinib at the recommended dose in patients with chronic idiopathic MF (including PET and PPV MF). The recommended dose was chosen based on exposure, safety, and spleen response data from Phase 1. Blood samples for the measurement of plasma concentrations of pacritinib were collected immediately prior to dosing, and at 0.5, 1, 2, 3, 4, 5, 6, 8, and 24±2 hours after dosing on days 1 and 15±3 of Cycle 1. Samples for a trough PK were drawn prior to dosing on day 1 of Cycle 2, Cycle 3, Cycle 4, Cycle 6, Cycle 9, and Cycle 12.

Results

The PK results are shown in Table 84 and Table 85. On Day 1 of the Phase 1 study in patients who received pacritinib 100 mg to 600 mg, comparable absorption rates were observed, with median T_{max} values ranging from 3.0 to 5.5 hours postdose. Mean C_{max}, C_{24h}, and systemic exposures (i.e., the AUC from time zero to 24 hours [AUC_{0-24}]) values did not appear to increase in a dose-related manner across the 100 mg to 600 mg QD dose cohorts; although the mean C_{24h} was not highest in the 400 mg (recommended dose) dose group, mean C_{max} and AUC were highest in the 400 mg group at Day 1. Interindividual %CV for C_{max} and AUC_{0-24} values ranged from 32% to 78%, indicating a relatively high variability among patients. Following 15 doses of pacritinib 100 mg to 600 mg QD, comparable absorption rates were observed on Day 15, with median T_{max} values ranging from 2.0 to 6.0 hours postdose. Mean C_{max}, C_{24h}, and AUC_{0-24} were higher in the 400 mg QD dose cohort. As observed on Day 1, interindividual %CV for C_{max} and AUC_{0-24} values on Day 15 ranged from 30% to 77%, indicating a relatively high variability among patients.

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Table 84. Summary of Pharmacokinetic Parameters: Day 1 (All Enrolled Population)

	100 mg (N=3)	200 mg (N=3)	400 mg (N=4)	500 mg (N=6)	600 mg (N=4)
C_{max}(ng/mL)					
N	3	3	4	6	4
Mean	2589.0	2211.3	9241.7	7646.8	6295.5
%CV	37.8	73.9	34.3	41.8	40.8
Median	2495.0	1326.0	10322.9	6677.5	5777.0
Range	1660.0 – 3612.0	1210.0 – 4098.0	4715.0 – 11606.0	4650.0 – 13861.0	3757.0 – 9871.0
AUC (ng*hr/mL)					
N	3	3	4	6	4
Mean	44577.2	40917.7	160745.0	148524.0	122238.0
%CV	33.0	78.1	31.7	43.1	33.5
Median	45421.5	23052.3	167360.5	139496.5	121593.0
Range	29485.5 – 58824.5	21878.8 – 77822.0	92892.0 – 215367.0	74169.0 – 265756.0	72945.8 – 172821.0
t_{max} (hr)					
N	2	1	2	4	4
Mean	4.7	5.0	3.8	11.0	5.5
%CV	25.5	0.0	39.5	90.9	38.2
Median	4.0	5.0	3.0	5.5	5.5
Range	4.0 – 6.0	5.0 – 5.0	3.0 – 6.0	4.0 – 24.0	3.0 – 8.0
C_{24} (ng/mL)					
N	3	3	4	6	4
Mean	1530.3	1401.0	5395.2	5777.4	4951.0
%CV	37.9	90.2	26.9	48.5	31.7
Median	1547.0	679.0	5143.9	6585.0	5289.5
Range	943.0 – 2101.0	664.0 – 2860.0	3929.0 – 7364.0	1244.0 – 9396.0	2757.0 – 6468.0

Source: Table 23, page 99, SB1518-2008-003 Report.
Abbreviations: AUC, area under the drug concentration-time curve; CV, coefficient of variation; C_{24}, concentration 24 hours postdose; C_{max}, maximum concentration; N, number of subjects; t_{max}, time to maximum concentration

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Table 85. Summary of Pharmacokinetic Parameters: Day 15 (All Enrolled Population)

	100 mg (N=3)	200 mg (N=3)	400 mg (N=4)	500 mg (N=6)	600 mg (N=4)
C_{max} (ng/mL)					
N	3	3	4	6	4
Mean	4061.0	3231.3	10631.0	7879.1	9974.8
%CV	38.1	40.5	30.7	50.2	39.7
Median	4243.0	3556.0	10482.5	7000.5	10869.0
Range	2432.0 – 5508.0	1790.0 – 4348.0	6853.0 – 14706.0	4856.0 – 15624.0	4508.0 – 13653.0
AUC (ng*hr/mL)					
N	3	3	4	6	4
Mean	59783.7	54298.9	213332.0	170505.0	186349.0
%CV	76.9	60.2	30.0	55.4	43.8
Median	42691.5	35549.0	198629.0	158185.5	226776.0
Range	24776.5 – 111883.0	35313.0 – 92034.8	155761.0 – 300308.0	78568.3 – 350410.0	92453.8 – 239817.0
t_{max} (hr)					
N	2	3	3	4	3
Mean	2.3	5.7	9.3	9.2	3.5
%CV	25.2	36.8	105.4	79.4	94.3
Median	2.0	5.0	4.5	6.0	3.0
Range	2.0 – 3.0	4.0 – 8.0	4.0 – 24.0	5.0 – 24.0	0.0 – 8.0
C_{24} (ng/mL)					
N	3	3	4	6	4
Mean	2669.5	1834.7	7106.8	6517.7	6955.0
%CV	70.4	74.5	36.9	61.9	46.7
Median	2669.5	1089.0	7050.1	6302.1	8386.0
Range	1340.0 – 3999.0	1002.0 – 3413.0	3960.0 – 10367.0	1362.0 – 13500.0	3241.0 – 9238.0

Source: Table 24, page 100, SB1518-2008-003 Report.
Abbreviations: AUC, area under the concentration-time curve; CV, coefficient of variation; C_{24}, concentration 24 hours postdose; C_{max}, maximum concentration; hr, hour; N, number of subjects; t_{max}, time to maximum concentration

Study PAC103

A Phase 1 open-label, single-dose, parallel-group study to determine the PK of pacritinib in subjects with impaired hepatic function in comparison with healthy subjects.

Primary Objectives

To characterize the PK profile of a single 400 mg dose of pacritinib and its major human metabolites in subjects with mild, moderate, and severe hepatic impairment as compared to gender-, age-, and body mass index-matched healthy subjects; to evaluate the safety and tolerability of a single 400 mg dose of pacritinib in subjects with hepatic impairment and healthy subjects.

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Study Design

This was an open-label, parallel-group, single-dose study of the PK and safety of 400 mg pacritinib administered orally to subjects with stable chronic liver disease and healthy control subjects. A total of 29 subjects was enrolled in the study, of whom one was a screen failure. Hepatic function groups and the number of subjects enrolled into each (n) were as follows: Group 1: subjects with mild hepatic impairment (n=8), Group 2: subjects with moderate hepatic impairment (n=8), Group 3: subjects with severe hepatic impairment (n=4), and Group 4: healthy subjects (n=8). Blood samples for PK analysis were collected predose (0 hour), 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, and 168 hours postdose.

Results

The PK curve is shown in Figure 22. The PK parameters are shown in Table 86. The results of the inferential statistical analysis on pacritinib PK parameters are summarized in Table 87. Although the systemic exposure of pacritinib was comparable between subjects with mild hepatic impairment and subjects with normal hepatic function, a significant difference between subjects with moderate or severe hepatic impairment and subjects with normal hepatic function was found for pacritinib peak concentration (C_{max}) and plasma exposure (AUC_{0-t} and AUC_{0-inf}). Compared to subjects with normal hepatic function, C_{max} decreased by 47% in moderately impaired subjects and by 57% in severely impaired subjects, and AUC_{0-t} decreased by 36% and 45%, respectively, and AUC_{0-inf} decreased by 46% and 48%, respectively. The average terminal half-life of pacritinib ranged between 51.5 and 74.9 hours in the four groups.

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Figure 22. Mean Pacritinib Plasma Concentration-Versus-Time Profiles
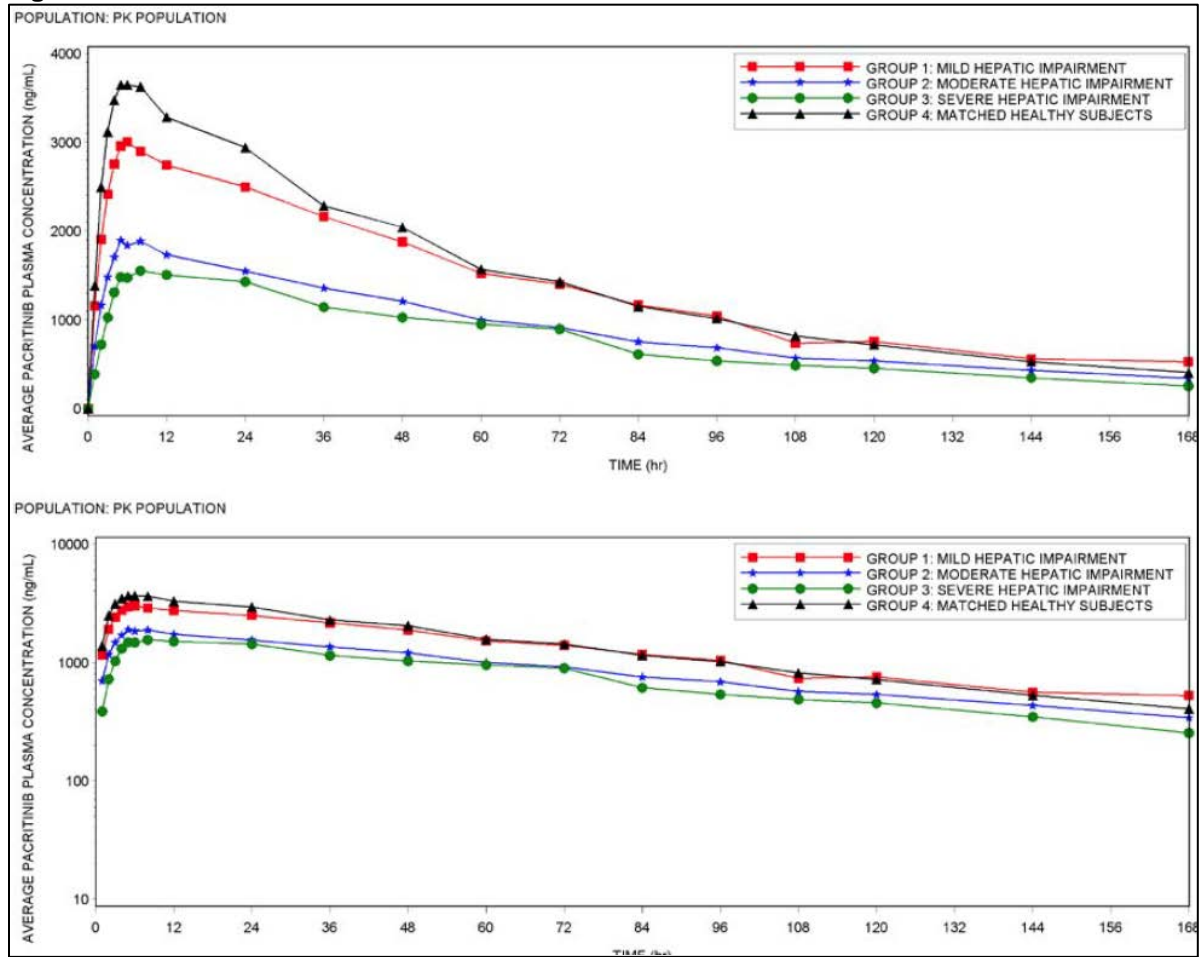
Source: Figure 1, page 39, PAC103 Report.
Abbreviation: PK, pharmacokinetic

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Table 86. Summary of Pacritinib Pharmacokinetics Parameters

PK Parameter (unit)	Pacritinib 400 mg			
	Group 1: Mild Hepatic Impairment N=8	Group 2: Moderate Hepatic Impairment N=8	Group 3: Severe Hepatic Impairment N=4	Group 4: Matched Healthy Subjects N=8
C_{max} (μg/mL)	3.07 ±1.45	1.97 ±0.412	1.58 ±0.281	3.70 ±0.832
t_{max} (h)	5.50 (4.00-8.00)	7.00 (5.00-8.00)	10.00 (8.00-24.00)	7.00 (4.00-8.00)
AUC_{0-t} (μg.h/mL)	228 ±100	150 ±38.2	127 ±34.3	245 ±103
$AUC_{0-\infty}$ (μg.h/mL)	253 ±131[a]	142 ±45.7[b]	134 ±44.2[c]	279 ±128
$t_{1/2}$ (h)	55.2 ±14.9	74.9 ±46.2	57.6 ±20.7	51.5 ±10.5
CL/F (L/h)	2.03 ±1.12[a]	3.02 ±0.893[b]	3.17 ±0.891[c]	1.76 ±0.845
Vz/F (L)	140 ±53.4[a]	193 ±67.8[b]	220 ±75.3[c]	121 ±39.1

Source: Table 7, page 40, PAC103 Report.
Note: Values are arithmetic means±SD, except median (range) for t_{max}.
[a] Seven subjects.
[b] Four subjects.
[c] Three subjects.
Abbreviations: AUC, area under the plasma concentration-time curve; CL/F, total clearance; C_{max}, maximum concentration; $t_{1/2}$, elimination half-life; t_{max}, time to maximum concentration; Vz, volume of distribution

Table 87. Summary of Inferential Statistical Analysis for Pacritinib Main PK Parameters

PK Parameter (unit)	Comparison	Ratio of Geometric LS Means (ANOVA)		
		PE	90% CI	
C_{max} (μg/mL)	Mild vs. Normal	78.31	60.91	100.69
	Moderate vs. Normal	53.21	41.39	68.41
	Severe vs. Normal	43.21	31.76	58.78
AUC_{0-t} (μg.h/mL)	Mild vs. Normal	91.53	65.57	127.78
	Moderate vs. Normal	64.10	45.92	89.48
	Severe vs. Normal	54.64	36.31	82.21
$AUC_{0-\infty}$ (μg.h/mL)	Mild vs. Normal	88.67	58.28	134.93
	Moderate vs. Normal	54.34	33.07	89.30
	Severe vs. Normal	51.52	29.75	89.21

Source: Table 8, page 41, PAC103 Report.
Point estimate (ratio) and 90% CIs of the ratio of geometric LS means (ANOVA).
Abbreviations: ANOVA, analysis of variance; AUC, area under the concentration-time curve; CI, confidence interval; LS, least-squares; PE, point estimate; PK, pharmacokinetics

Study PAC105

A Phase 1 open-label, single-dose, parallel-group study to determine the PK of pacritinib in subjects with mild, moderate, and severe renal impairment and end-stage renal disease (ESRD) compared to healthy subjects.

Primary Objective

To determine the PK of pacritinib and its major metabolites in subjects with mild, moderate, and severe renal impairment and in subjects with ESRD requiring hemodialysis as compared to

gender-, age-, and weight-matched healthy subjects following a single oral dose of 400 mg pacritinib.

Study Design

This was a Phase 1 open-label, single-dose, five-group, parallel-group study in which a single dose of 400 mg pacritinib was administered orally to subjects with mild, moderate, and severe renal impairment and subjects with ESRD requiring hemodialysis and gender-, age-, and weight-matched healthy subjects.

Subjects with ESRD received a single dose of 400 mg pacritinib during two different treatment periods: dialysis and interdialysis. A total of 39 subjects was enrolled into one of five groups based on renal function. Renal function groups and the number of subjects enrolled into each (n) were as follows: Group 1: subjects with mild renal impairment (n=8), Group 2: subjects with moderate renal impairment (n=8), Group 3: subjects with severe renal impairment (n=8), Group 4: subjects with ESRD on dialysis (n=8), and Group 5: matched healthy subjects (n=7). Renal function was evaluated based on the estimated glomerular filtration rate, calculated by the Modification of Diet in Renal Disease study equation. In Group 4, which consisted of eight subjects with ESRD requiring hemodialysis, subjects participated in two treatment periods, dialysis and interdialysis, separated by a 14-day period between two pacritinib administrations. In the dialysis treatment period, a single 400 mg dose of pacritinib was administered 4 hours prior to each subject's normally scheduled hemodialysis. In the interdialysis treatment period, a single 400 mg dose of pacritinib was administered immediately after the end of the subject's normally scheduled hemodialysis session.

Blood samples for subjects with mild, moderate, or severe renal impairment (Groups 1 to 3) and healthy subjects (Group 5) were collected at: predose (0 hour), 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, and 168 hours postdose. Two additional blood samples were obtained at 4 and 8 hours postdose for determination of the fraction of pacritinib bound to the plasma proteins. Subjects with ESRD (Group 4) had blood samples (peripheral venous blood) collected for PK analysis during the dialysis and interdialysis treatment periods at predose (0 hours), 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, and 72 hours postdose. In the dialysis treatment period, the 5, 6, and 8 hours postdose time points correspond to 1, 2, and 4 hours after start of dialysis when samples of both undialyzed (arterial line) and dialyzed (venous line) blood were collected.

Results

The plasma concentration versus time profiles are shown in Figure 23. Individual pacritinib PK plasma parameters with descriptive statistics are summarized in Table 88 and Table 89. Mean C_{max} ratio ranged from 111.18% to 132.96%, and mean AUC_{0-72} ratio ranged from 106.71% to 130.52%, for subjects with mild, moderate, or severe renal impairment, or ESRD versus healthy. Time to peak concentration was not significantly different between subjects with renal impairment and matched healthy subjects. Renal clearance was similar for subjects with mild and moderate renal impairment and matched healthy subjects, and increased by 25% for subjects with severe renal impairment compared to matched healthy subjects.

Figure 23. Mean Pacritinib Plasma Concentration-Versus-Time Profiles
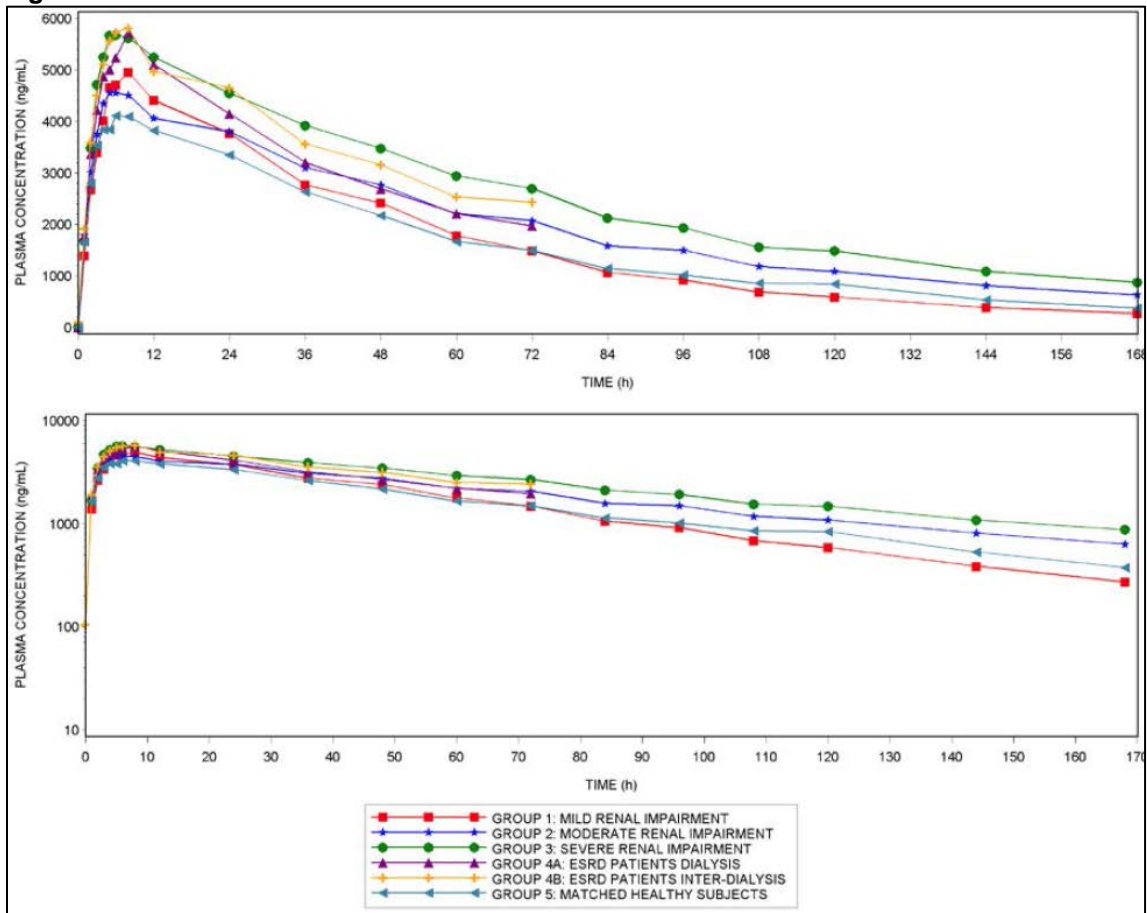
Source: Figure 1, page 53, PAC105 Report.

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Table 88. Summary of Pacritinib Pharmacokinetic Parameters

PK Parameter (unit)	Group 1: Mild Renal Impairment N=8	Group 2: Moderate Renal Impairment N=8	Group 3: Severe Renal Impairment N=8	Group 4A: Subjects With ESRD Dialysis N=8	Group 4B: Subjects With ESRD Inter-Dialysis N=8	Group 5: Matched Healthy Subjects N=7
C_{max} (μg/mL)	5.00 ±2.22	4.75 ±0.896	5.83 ±2.86	6.01 ±2.45	5.97 ±2.27	4.26 ± 0.596
t_{max} (h)	8.00 (4.00-12.00)	6.00 (5.00-24.00)	5.50 (3.00-8.00)	6.96 (4.08-12.00)	7.00 (5.00-8.00)	8.00 (3.00-24.00)
AUC_{0-t} (μg.h/mL)	274 ±106	334 ±103	430 ±287	243 ±149	267 ±136	268 ±75.5
AUC_{0-72h} (μg.h/mL)	210 ±81.4	225 ±53.9	283 ±168	243 ±149	267 ±136	191 ±40.8
$AUC_{0-\infty}$ (μg.h/mL)	290 ±112	352 ±128[a]	393 ±193[b]	148 ±51.5[c]	NC[d]	293 ±87.1
$t_{1/2}$ (h)	39.4 ±9.11	58.0 ±13.3	55.6 ±17.2	44.0 ±23.3	54.1 ±37.6	44.7 ±11.4
CL/F (L/h)	1.57 ±0.622	1.32 ±0.622[a]	1.41±1.11[b]	2.96 ±1.15[c]	NC[d]	1.58 ±0.862
Vz/F (L)	86.1 ±28.8	98.1 ±49.2[a]	90.9 ±43.8[b]	87.8 ±6.20[c]	NC[d]	99.3 ±48.9
CL_R (L/h)	0.0250 ±0.0184	0.0206 ±0.0110	0.0277 ±0.0188	NA	NA	0.0210 ±0.0118

Source: Table 12, page 55, PAC105 Report.
Note: Values are arithmetic means±SD, except median (range) for t_{max}.
[a] Six subjects.
[b] Seven subjects.
[c] Three subjects.
[d] Two subjects.

Abbreviations: AUC, area under the plasma concentration-time curve; CL/F, total clearance; CL_R, renal clearance; C_{max}, maximum concentration; ESRD, end-stage renal disease; N, number of subjects; n, number of subjects with observation; NA, not applicable; NC, not calculated; PK, pharmacokinetics; SD, standard deviation; $T_{1/2}$, elimination half-life; T_{max}, time to maximum concentration; Vz, volume of distribution

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Table 89. Summary of Inferential Statistical Analysis for Pacritinib Main PK Parameters

PK Parameter (unit)	Comparison	Ratio of Geometric LS Means (ANOVA)		
		Point Estimate	90% CI	
C_{max} (µg/mL)	Mild vs. Normal	111.18	82.23	150.32
	Moderate vs. Normal	110.92	82.04	149.98
	Severe vs. Normal	124.32	91.95	168.09
	ESRD vs. Normal	132.96	98.34	179.77
AUC_{0-t} (µg.h/mL)	Mild vs. Normal	100.94	65.08	156.57
	Moderate vs. Normal	124.50	80.26	193.10
	Severe vs. Normal	139.27	89.79	216.02
	ESRD vs. Normal	91.38	58.91	141.73
AUC_{0-72h} (µg.h/mL)	Mild vs. Normal	106.71	71.97	158.23
	Moderate vs. Normal	117.36	79.15	174.02
	Severe vs. Normal	130.52	88.02	193.54
	ESRD vs. Normal	125.29	84.49	185.77
$AUC_{0-\infty}$ (µg.h/mL)	Mild vs. Normal	98.49	65.08	149.05
	Moderate vs. Normal	118.92	76.18	185.66
	Severe vs. Normal	123.81	80.71	189.94
CL_R (L/h)	Mild vs. Normal	96.46	50.86	182.97
	Moderate vs. Normal	101.83	53.69	193.15
	Severe vs. Normal	124.90	65.85	236.90

Source: Table 13, page 56, PAC105 Report.
Point estimate and 90% CIs of the ratio of the geometric LS means (ANOVA).
Abbreviations: ANOVA, analysis of variance; AUC, area under the plasma concentration-time curve; CI, confidence interval; CL_R, renal clearance; C_{max}, maximum concentration; ESRD, end-stage renal disease; PK, pharmacokinetics

Study PAC104

A Phase 1, open-label, drug interaction study to evaluate the effect of clarithromycin, a potent CYP3A inhibitor, on the systemic exposure of pacritinib in healthy subjects.

Primary Objective

To evaluate the effect of clarithromycin, a potent CYP3A4 inhibitor, at steady-state on the systemic exposure of single dose pacritinib in healthy subjects.

Study Design

The study design is shown in Figure 24. Twenty healthy subjects entered and completed the study. All subjects were included in the safety and PK populations and received a single oral 400 mg pacritinib dose co-administered with 500 mg clarithromycin, following 4 days of 500 mg clarithromycin BID administration with a 7-day washout period separating the first administration of pacritinib and the first administration of clarithromycin.

On Day 1, subjects received a single oral 400 mg dose of pacritinib. On Day 8 through the morning of Day 12, following a 7-day washout period, 500 mg oral doses of clarithromycin were administered BID, 8 to 12 hours apart. It was anticipated that steady-state concentrations of clarithromycin would be achieved by Day 12. On Day 12, a single oral 400 mg dose of pacritinib was co-administered with the final 500 mg dose of clarithromycin. Blood samples for determination of pacritinib and any major metabolites were collected up to Day 19. Subjects were discharged on Day 19 after all study procedures were completed. Blood samples for determination of pacritinib and any major metabolites were collected predose (prior to pacritinib

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administration) and at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, and 168 hours postdose on Days 1 and 12.

Results

The PK curve is shown in Figure 25. The PK parameters of pacritinib are summarized in Table 90. The statistical analysis of the effect of clarithromycin on the PK of pacritinib is presented in Table 91. Statistical analysis of the PK parameters for pacritinib, AUC_{0-t}, and AUC_{0-inf}, showed that the 90% CIs of the ratios did not fall entirely within the 80% to 125% range. In the case of C_{max}, the 90% CIs of the ratios fell entirely outside the 80% to 125% range. Together, these results indicate a drug-drug interaction (DDI) that resulted in increased exposure of pacritinib after coadministration of a single dose of pacritinib following multiple doses of clarithromycin. Mean C_{max} and mean AUCs for pacritinib were approximately 1.3- and 1.8-fold greater, respectively, with similar mean $T_{1/2}$ following coadministration of pacritinib with clarithromycin compared to pacritinib alone.

Figure 24. Study Schematic, Study PAC104
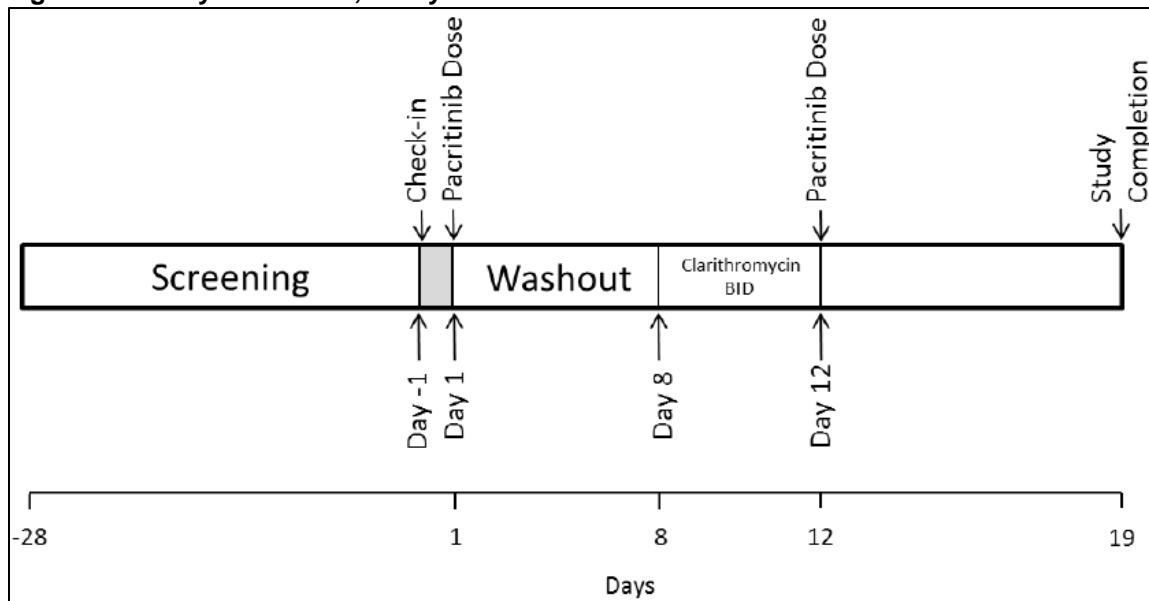
Source: Figure 9-1, page 11, PAC104 Report.
Abbreviation: BID, twice daily

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Figure 25. Plasma Concentrations of Pacritinib Following Administration Alone and Coadministration With Clarithromycin (Linear and Semi-Logarithmic Scale)
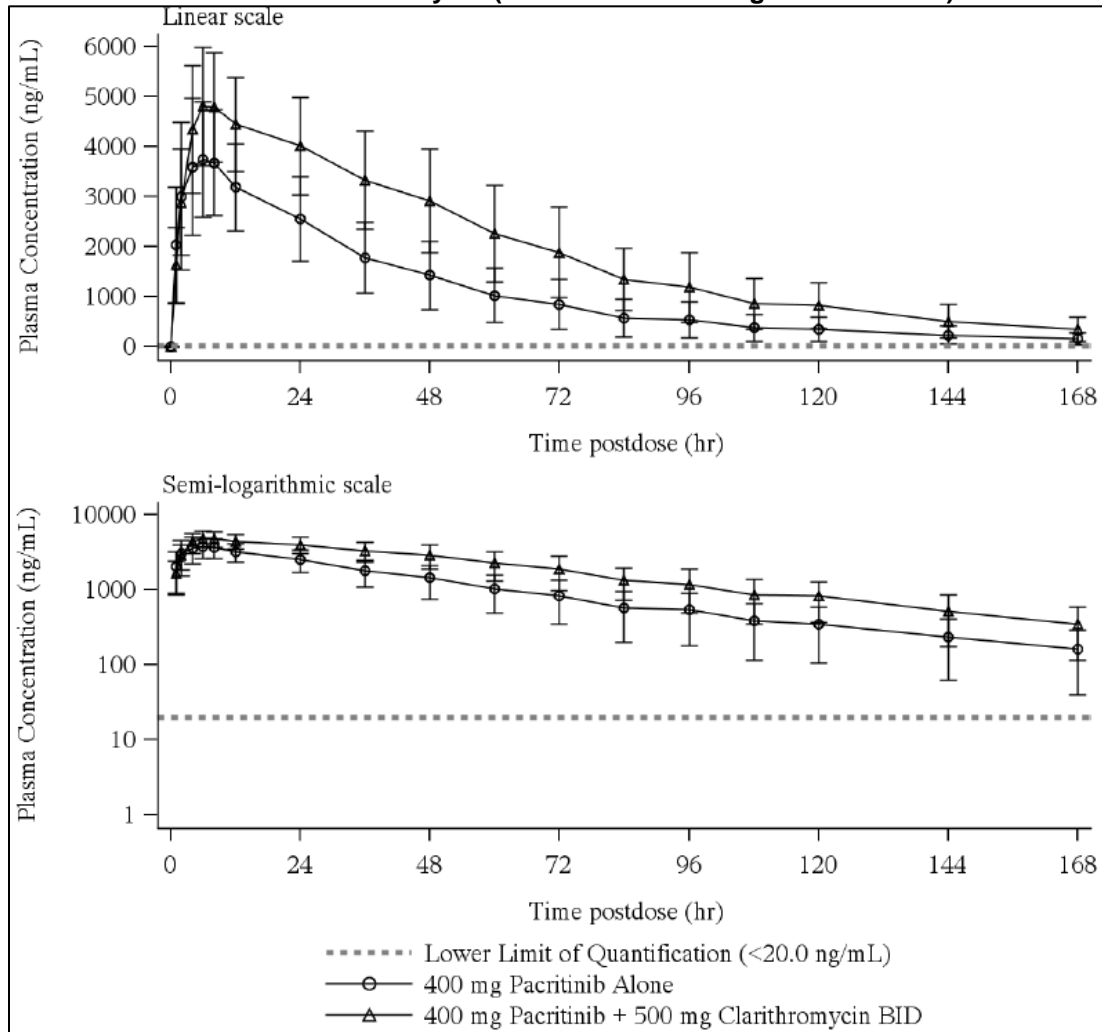
Source: Figure 11-1, page 31, PAC104 Report.
Note: Values are arithmetic means, with bars representing standard deviations.
Abbreviation: BID, twice daily

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Table 90. Summary of the Pharmacokinetic Parameters of Pacritinib Following Administration of Pacritinib Alone and Coadministration With Clarithromycin

Parameter	Pacritinib Alone (N=20)	Pacritinib + Clarithromycin (N=20)[a]
C_{max} (ng/mL)	3680 (31.4)	4790 (22.5)
$AUC_{0-\infty}$ (ng*hr/mL)	173000 (49.0)	316000 (41.9)
AUC_{0-t} (ng*hr/mL)	165000 (46.7)	297000 (39.3)
t_{max}[b] (hr)	6.00 (2.00 – 8.02)	6.03 (4.00 – 12.0)
$t_{1/2}$ (hr)	41.4 (15.1)	40.9 (18.1)
CL/F (L/hr)	2.31 (49.0)	1.27 (41.9)
V_z/F (L)	138 (47.2)	74.8 (42.4)

Source: Table 11-1, page 32, PAC104 Report.
Geometric means (CV%) are presented.
Geometric CV%=(sqrt (exp (variance for log-transformed data)−1))×100
[a] The 120-hour concentrations for Subjects 014 and 015 (pacritinib plus clarithromycin) appeared consistent with a sample switch and were excluded from PK analysis.
[b] Median (minimum−maximum).
Abbreviations: AUC, area under the plasma concentration-time curve; CL/F, total clearance; C_{max}, maximum concentration; CV, coefficient of variation; N, number of subjects; $T_{1/2}$, elimination half-life; T_{max}, time to maximum concentration; Vz/F, volume of distribution

Table 91. Statistical Analysis of Pharmacokinetic Data: Effect of Clarithromycin on the Pharmacokinetics of Pacritinib

Parameter (Unit)	n	Pacritinib Alone (Reference) LS Mean (90% CI)[a]	n	Pacritinib + Clarithromycin (Test) LS Mean (90% CI)[a]	(Test/Reference)[b] (%)	90% Confidence Interval of the Ratio[c]	Inter-subject Variability (CV%)	Intra-subject Variability (CV%)
C_{max} (ng/mL)	20	3680 (3320, 4080)	20	4790 (4320, 5310)	130.2	(122.2, 138.7)	24.5	11.6
$AUC_{0-\infty}$ (ng*hr/mL)	20	173000 (147000, 205000)	20	316000 (267000, 374000)	182.2	(169.4, 196.0)	43.1	13.4
AUC_{0-t} (ng*hr/mL)	20	165000 (141000, 194000)	20	297000 (253000, 349000)	180.0	(166.9, 194.1)	40.4	13.9

Source: Table 11-2, page 33, PAC104 Report.
[a] Least-squares means and the corresponding 90% confidence intervals on natural log transformed data were obtained from ANOVA and then transformed back to original scale to obtain geometric LS means and the corresponding 90% confidence intervals.
[b] Difference of LS means of natural log-transformed data between test and reference was obtained by ANOVA and then transformed back to the original scale to obtain the ratio of geometric LS means (expressed as a percentage).
[c] 90% confidence interval of the difference of LS means was obtained by ANOVA and transformed back to the original scale to obtain 90% confidence interval for the ratio (expressed as a percentage).
Abbreviations: ANOVA, analysis of variance; AUC_{0-t}, area under the concentration-time curve from hour 0 to the last measurable concentration; $AUC_{0-\infty}$, area under the concentration-time curve extrapolated to infinity; CI, confidence interval; C_{max}, maximum concentration; CV, coefficient of variation; LS, least-squares; n, the number of observations in each treatment used in the model

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Study PAC106

A Phase 1, open-label, drug interaction study to evaluate the effect of rifampin, a potent CYP3A inducer, on the systemic exposure of pacritinib in healthy subjects.

Primary Objective

To evaluate the effect of rifampin, a potent CYP3A inducer, at steady-state on the systemic exposure of a single dose of pacritinib in healthy subjects.

Study Design

The study design is shown in Figure 26. This was a single-center, open-label, one-way crossover, drug interaction study to evaluate the effect of a potent CYP3A4 inducer on the systemic exposure of pacritinib in healthy subjects. It was planned to study a total of 18 healthy subjects. Eighteen subjects were enrolled and 17 subjects completed the study. One subject was discontinued from the study by the Investigator. All subjects (N=18) were included in the safety and PK populations.

On Day 1, subjects received a single oral 400 mg dose of pacritinib. On Days 8 to 17, following a 7-day washout period, 600 mg oral doses of rifampin were administered QD. It was anticipated that steady-state concentrations of rifampin would be achieved by Day 17. On Day 17, a single oral 400 mg dose of pacritinib was coadministered with the final 600 mg dose of rifampin. Blood samples for determination of concentrations of pacritinib and any major metabolites were collected predose (prior to pacritinib administration) and at 1, 2, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, and 168 hours postdose on Days 1 to 17. Subjects were discharged from the clinic on Day 24 after all study procedures were completed.

Results

The plasma concentration profiles are shown in Figure 27. The PK parameters of pacritinib are summarized in Table 92. The statistical analysis of the effect of rifampin on the PK of pacritinib is presented in Table 93. Coadministration of pacritinib with rifampin resulted in reduced exposure to pacritinib (approximately 51% decrease in C_{max} and 87% decrease in AUC_{0-inf}). The T_{max} was similar for pacritinib with and without co-administration with rifampin (which occurred at approximately 5 to 6 hours and approximately 4 hours postdose, respectively). Coadministration of pacritinib with rifampin shortened the $t_{1/2}$ for pacritinib by approximately 65% (43.3 hours for pacritinib alone; 15.1 hours for pacritinib with rifampin).

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Figure 26. Study PAC106 Schematic
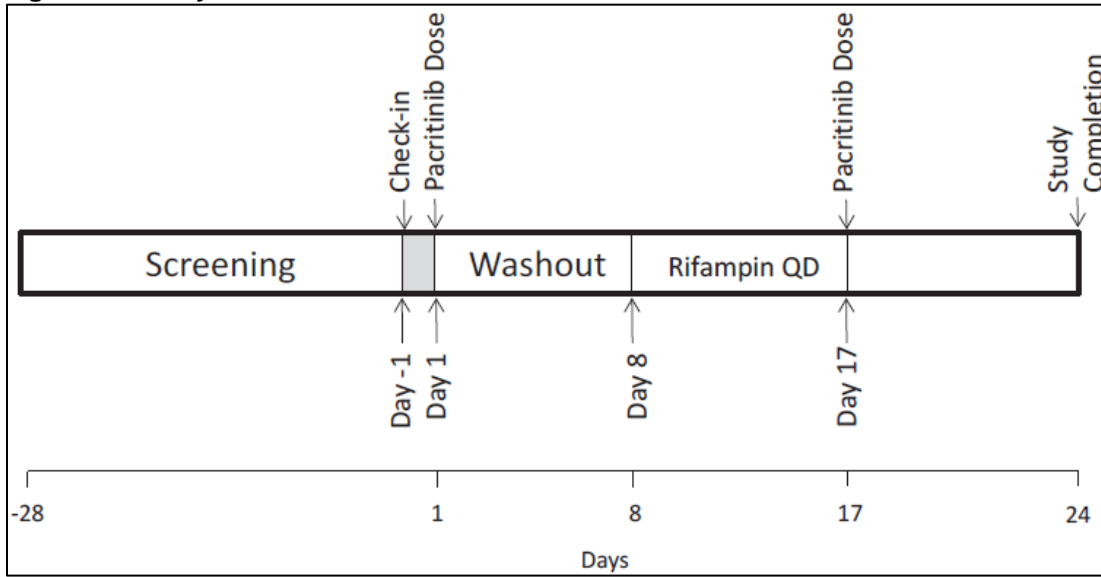
Source: Figure 9-1, page 12, PAC106 Report.
Abbreviation: QD, once daily

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Figure 27. Arithmetic Mean Plasma Concentrations of Pacritinib Following Administration Alone and Coadministration With Rifampin (Linear and Semi-Logarithmic Scales)
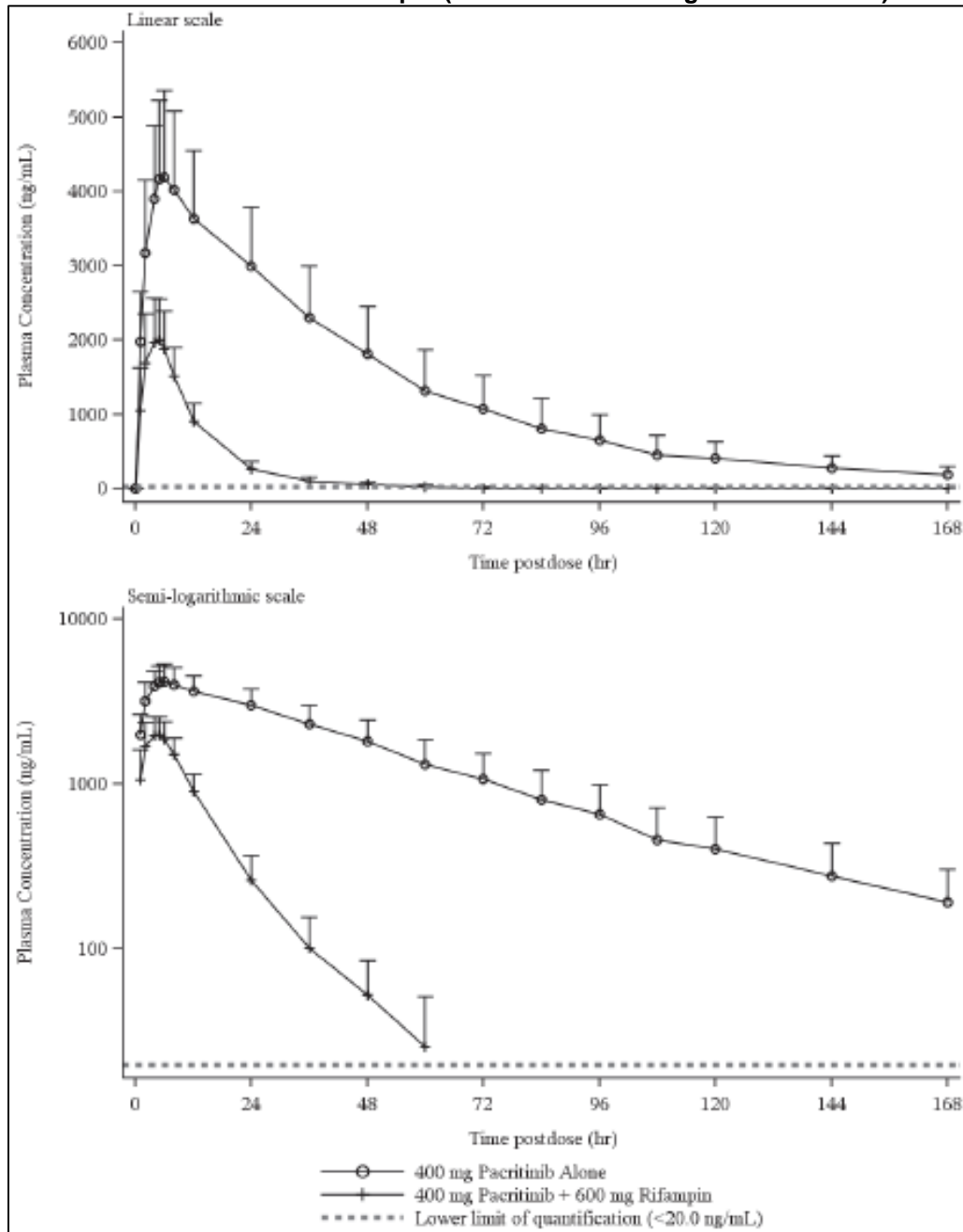
Source: Figure 11-1, page 32, PAC106 Report.

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Table 92. Summary of the Pharmacokinetic Parameters of Pacritinib Following Administration of Pacritinib Alone and Coadministration With Rifampin

Parameter	Pacritinib Alone (N=17)	Pacritinib + Rifampin (N=17)
C_{max} (ng/mL)	4120 (26.7)	2010 (31.3)
$AUC_{0-\infty}$ (ng*hr/mL)	216000 (36.9)	27000 (29.5)[b]
AUC_{0-t} (ng*hr/mL)	205000 (35.4)	26700 (29.2)
t_{max}[a] (hr)	6.00 (5.00 – 8.00)	5.00 (2.00 – 6.07)
$t_{1/2}$ (hr)	43.3 (19.6)	15.1 (76.3)[b]
CL/F (L/hr)	1.85 (36.9)	14.8 (29.5)[b]
V_z/F (L)	116 (39.1)	324 (64.5)[b]

Source: Table 11-1, page 33, PAC106 Report.
Note: Subject (b) (6) was excluded from descriptive statistics due to early termination.
Geometric mean (CV%) data are presented.
Geometric CV%=(sqrt (exp (variance for log transformed data)−1))×100.
[a] Median (minimum-maximum).
[b] N=16.
Abbreviations: AUC_{0-t}, area under the concentration-time curve from hour 0 to the last measurable concentration; $AUC_{0-\infty}$, area under the concentration-time curve extrapolated to infinity; CL/F, total clearance; C_{max}, maximum concentration; CV, coefficient of variation; N, number of subjects; $t_{1/2}$, elimination half-life; t_{max}, time to maximum concentration; Vz/F, volume of distribution

Table 93. Statistical Analysis of Pharmacokinetic Data: Effect of Rifampin on the Pharmacokinetics of Pacritinib

Parameter (Unit)	Pacritinib Alone (Reference)		Pacritinib + Rifampin (Test)		Ratio (Test/Reference)[b] (%)	90% Confidence Interval of the Ratio[c]	Inter-subject Variability (CV%)	Intra-subject Variability (CV%)
	n	LS Mean (90% CI)[a]	n	LS Mean (90% CI)[a]				
C_{max} (ng/mL)	17	4120 (3650, 4640)	17	2010 (1780, 2260)	48.7	(43.1, 55.1)	19.8	20.9
AUC_{0-t} (ng*h/mL)	17	205000 (179000, 235000)	17	26700 (23400, 30500)	13.0	(11.2, 15.1)	20.2	24.8
$AUC_{0-\infty}$ (ng*h/mL)	17	216000 (188000, 248000)	16[d]	27100 (23500, 31300)	12.5	(10.7, 14.7)	19.8	26.5

Source: Table 11-2, page 34, PAC106 Report.
Note: Subject (b) (6) was excluded from statistical analyses due to early termination.
[a] Least-squares means and the corresponding 90% CIs on natural log-transformed data were obtained by ANOVA and transformed back to the original scale to obtain geometric LS means and the corresponding 90% CIs.
[b] Difference of LS means of natural log-transformed data between test and reference was obtained by ANOVA and transformed back to the original scale to obtain the ratio of geometric LS means (expressed as a percentage).
[c] 90% CI of difference of LS means was obtained by ANOVA and transformed back to the original scale to obtain 90% CI for the ratio (expressed as a percentage).
Abbreviations: ANOVA, analysis of variance; AUC_{0-t}, area under the concentration-time curve from hour 0 to the last measurable concentration; $AUC_{0-\infty}$, area under the concentration-time curve extrapolated to infinity; CI, confidence interval; C_{max}, maximum observed concentration; CV, coefficient of variation; LS, least-squares; n, the number of observations in each treatment used in the model

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Study PAC108

A Phase 1, open-label, single-dose, randomized, two-period crossover study to assess the bioequivalence of two pacritinib drug product formulations (Phase 3 clinical trial [P3CT] formulation [Reference] and final market image [FMI] [Test] formulation) following oral administration in healthy subjects.

Primary Objective

To evaluate the bioequivalence of the P3CT (Reference) and FMI (Test) formulations in healthy subjects and to characterize the PK profile of pacritinib following single-dose administration as P3CT (Reference) and FMI (Test) formulations in healthy subjects.

Study Design

This was a single-center, open-label, randomized, crossover study to determine the bioequivalence of pacritinib following administration of two different 400 mg oral doses of four 100 mg pacritinib capsules, one dose prepared using the P3CT (Reference) formulation and the other dose prepared using the FMI (Test) formulation, and to characterize the PK of pacritinib for each formulation in a total of 28 healthy male and female subjects. A schematic of the study design is presented in Table 94.

After a screening period of up to 28 days, subjects checked into the Clinical Research Unit on Day -1 (Period 1) and were confined to the Clinical Research Unit. On Day 1 (Period 1), subjects were randomly assigned to one of two possible treatment sequences (i.e., Sequence I: A/B, Sequence II: B/A) and pacritinib was administered based on the assigned sequence. Following a 9-day washout, subjects received the second dose of pacritinib in the assigned sequence at the beginning of Period 2 on the morning of Day 10. Subjects were discharged on Day 17 after all study procedures had been completed. Blood samples for the determination of the concentration of pacritinib were collected predose and up to 168 hours post pacritinib dose on Days 1 and 10.

Results

The plasma concentration profiles are shown in Figure 28. The PK parameters of pacritinib are summarized in Table 95. The statistical analysis of the bioequivalence of the two formulations of pacritinib based on the PK data is presented in Table 96.

Table 94. Schematic of the Crossover Design Study

Number of Subjects	Sequence	Study Day 1 (Period 1)	9-Day Washout	Study Day 10 (Period 2)
14	I	Treatment A: 400-mg oral dose of pacritinib P3CT (Reference) formulation capsules	→	Treatment B: 400-mg oral dose of pacritinib FMI (Test) formulation capsules
14	II	Treatment B: 400-mg oral dose of pacritinib FMI (Test) formulation capsules	→	Treatment A: 400-mg oral dose of pacritinib P3CT (Reference) formulation capsules

Source: Table 9-1, page 12, PAC108 Report.
Abbreviations: FMI, final market image; P3CT, Phase 3 clinical trial

Table 95. Summary of the Pharmacokinetic Parameters of Pacritinib Following Administration of FMI (Test) Formulation and P3CT (Reference) Formulation

Parameter	Treatment B FMI (Test) Formulation (N=28)	Treatment A P3CT (Reference) Formulation (N=28)
C_{max} (ng/mL)	4130 (29.2)	4100 (31.4)
$AUC_{0-\infty}$ (ng*hr/mL)	216000 (57.0)	221000 (59.2)
AUC_{0-t} (ng*hr/mL)	204000 (53.7)[b]	206000 (55.6)
t_{max}[a] (hr)	6.00 (3.00 − 8.05)	6.00 (4.00 − 12.0)
$t_{1/2}$ (hr)	44.6 (27.2)	44.1 (27.4)
CL/F (L/hr)	1.85 (57.0)	1.81 (59.2)
V_z/F (L)	119 (48.9)	115 (54.0)

Source: Table 11-1, page 31, PAC108 Report.
Geometric mean (CV%) data are presented.
Geometric CV%=(sqrt (exp (variance for log transformed data)−1))×100
[a] Median (minimum−maximum).
[b] Two subjects (Subjects ____ (b) (6)) terminated the study early and their individual AUC_{0-t} parameters were excluded; therefore, AUC_{0-t} geometric mean is based on N=26.
Abbreviations: AUC_{0-t}, area under the concentration-time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$, area under the concentration-time curve from time 0 extrapolated to infinity; CL/F, total clearance; C_{max}, maximum concentration; CV, coefficient of variation; FMI, final market image; N, number of subjects; P3CT, Phase 3 clinical trial; $t_{1/2}$, elimination half-life; t_{max}, time to maximum concentration; Vz/F, volume of distribution

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Figure 28. Plasma Concentrations of Pacritinib Following Administration of FMI (Test) Formulation and P3CT (Reference) Formulation (Linear and Semi-Logarithmic Scale)
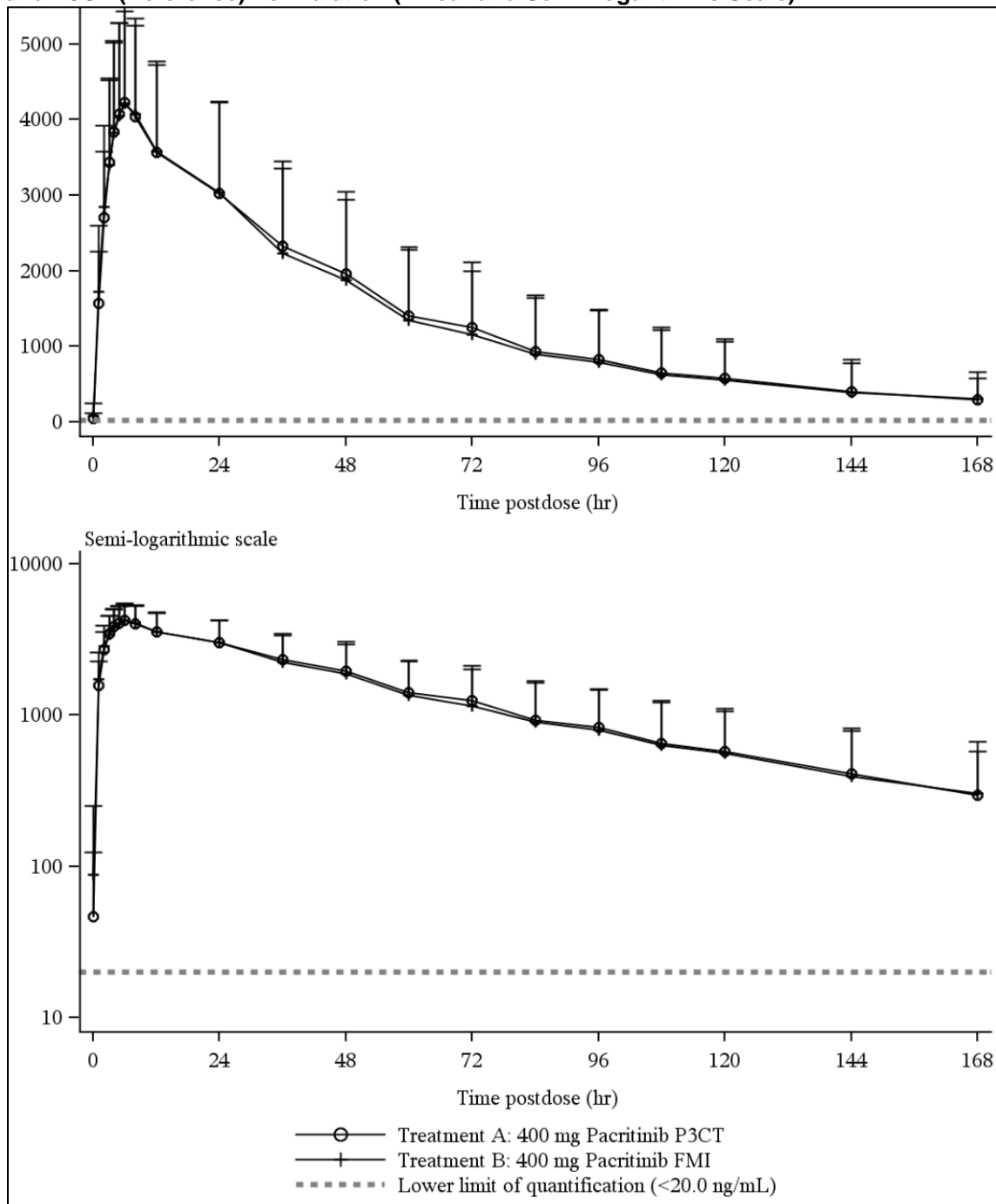
Source: Table 11-1, page 30, PAC108 Report.
Note: Values are arithmetic means, with bars representing standard deviations.
Abbreviations: FMI, final market image; P3CT, Phase 3 clinical trial

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Table 96. Statistical Analysis of Bioequivalence Data: Effect of Formulation on the Pharmacokinetics of Pacritinib

Parameter	n	Treatment B[a] LSM (90%CI)	n	Treatment A[1] LSM (90%CI)	Ratio (Test/ Reference)[2]	90% CI of the Ratio[3]	Intersubject Variability (CV%)	Intrasubject Variability (CV%)
C_{max} (µg/mL)	28	4.13 (3.76, 4.53)	28	4.10 (3.74, 4.50)	100.6	95.4, 106.1	27.1	11.8
$AUC_{0-\infty}$ (µg·h/mL)	28	216 (183, 256)	28	221 (187, 261)	97.9	91.0, 105.2	52.8	16.0
AUC_{0-t} (µg·h/mL)	26	199 (170, 234)	28	206 (176, 241)	96.9	90.1, 104.2	49.6	15.4

Source: Table 11-2, page 32, PAC108 Report.
Note: AUC_{0-t} for Subjects [(b) (6)] for Treatment B (Period 2) were excluded because the subjects terminated the study early. Treatment A: 400 mg pacritinib P3CT (Reference); Treatment B: 400 mg pacritinib FMI (Test).
[1] Least-squares means and the corresponding 90% confidence intervals on natural log-transformed data were obtained by ANOVA and transformed back to the original scale to obtain geometric LS means and the corresponding 90% confidence intervals.
[2] Difference of LS means of natural log-transformed data between test and reference was obtained by ANOVA and transformed back to the original scale to obtain the ratio of geometric LS means (expressed as percentage).
[3] 90% confidence interval of the difference of LS means was obtained by ANOVA and transformed back to the original scale to obtain the 90% confidence intervals for the ratio (expressed as a percentage).
Abbreviations: ANOVA, analysis of variance; AUC_{0-t}, area under the concentration-time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$, area under the concentration-time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum concentration; CV, coefficient of variation; FMI, final market image; LS, least-squares; LSM, least-squares mean; n, the number of observations in each treatment used in the model P3CT, Phase 3 clinical trial

14.3. Summary of Bioanalytical Method Validation

Pacritinib and its metabolite M1 in human plasma and urine were measured by validated LC-MS/MS methods. The bioanalytical methods used are adequately validated. The methods for quantification of the above mentioned moieties in human plasma were developed and validated at the contract research organization [(b) (4)]. The analyte was isolated from plasma and urine by protein precipitation after addition of stable isotope labeled internal standards. The supernatant was injected on a reversed-phase HPLC column using a gradient method. Detection was done by tandem mass spectrometry in the multiple reaction monitoring mode using the positive ion mode. The bioanalytical method and validation metrics are summarized in Table 97 and Table 98.

Table 97. Summary Review of Bioanalytical Methods Measuring Pacritinib Acid and Its Metabolite M1 in Human Urine

Parameter	Pacritinib	M1
Bioanalytical method validation report	ValRep-178-2015	ValRep-178-2015
Validation assay range (ng/mL)	20 to 20,000 ng/mL	4 to 4000 ng/mL
QCs (ng/mL)	20, 60, 1200, 10,000, 16,000, and 20,000	4, 12, 240, 2000, 3200, and 4000
Recovery (%)	99.8 to 100.5	100.6 to 101
Interday precision (% CV)	1.25 to 3.73	2.14 to 4.86
Interday accuracy (% bias)	-0.5 to 7.9	1.14 to 12.5
Intraday precision (% CV)	0.91 to 5.58	0.88 to 5.89
Intraday accuracy (% bias)	-0.1 to 9.1	2.91 to 9.51
Reference standard	Lot number: FRSBIO901	Lot number: 2123-035-3
Specificity	No interference observed in the blank matrix	No interference observed in the blank matrix

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Parameter	Pacritinib	M1
Freeze/thaw stability	3 freeze (-80°C)-thaw (ambient temperature) cycles	3 freeze (-80°C)-thaw (ambient temperature) cycles
Stock stability	156 days at 320 µg/mL in refrigerator (2 to 8°C)	84 days at approximately 400 µg/mL in refrigerator (2 to 8°C)
Bench-top stability	Working solution stability: 44 hours at room temperature Sample stability: 24 hours at ambient temperature; 24 hours in refrigerator followed 1 hour at 37°C	Working solution stability: 44 hours at room temperature Sample stability: 24 hours at ambient temperature; 24 hours in refrigerator followed 1 hour at 37°C
Processed stability	Post-preparative stability: 1 hour at 37°C Autosampler stability: 124 hours at 5°C	Post-preparative stability: 24 hours in refrigerator Autosampler stability: 124 hours at 5°C
Long-term storage stability	26 days at -70°C	83 days at -70°C

Source: Validation Report ValRep-178-2015.
Abbreviations: CV, coefficient of variation; QC, quality control

Table 98. Summary Review of Bioanalytical Methods Measuring Pacritinib Acid and Its Metabolite M1 in Human Plasma

Parameter	Pacritinib	M1
Bioanalytical method validation report	ValProt-160-2014	ValProt-160-2014
Validation assay range (ng/mL)	20 to 20,000 ng/mL	4 to 4000 ng/mL
QCs (ng/mL)	20, 60, 1200, 10,000, 16,000, and 20,000	4, 12, 240, 2000, 3200, and 4000
Recovery (%)	97.9 to 101	101 to 104
Interday precision (% CV)	0.89 to 5.12	0.80 to 4.94
Interday accuracy (% bias)	-0.5 to 4.8	-0.1 to 4.06
Intraday precision (% CV)	0.89 to 5.12	0.52 to 3.93
Intraday accuracy (% bias)	0.1 to 2.5	-0.8 to 9.2
Reference standard	Lot Number: FRSBIO901	Lot Number: 2123-035-3
Specificity	No interference observed in the blank matrix	No interference observed in the blank matrix
Freeze/thaw stability	5 freeze (≤-20°C)-thaw (ambient temperature) cycles	5 freeze (-80°C)-thaw (ambient temperature) cycles
Stock stability	84 days at approximately 320 µg/mL in refrigerator in refrigerator (2 to 8°C)	84 days at approximately 64 µg/mL in refrigerator in refrigerator (2 to 8°C)
Bench-top stability	Working solution stability: 44 hours at room temperature Sample stability: 24 hours at ambient temperature	Working solution stability: 44 hours at room temperature Sample stability: 24 hours at ambient temperature
Processed stability	Postpreparative stability: 2 hours at ambient temperature Autosampler stability: 112 hours at 5°C	Postpreparative stability: 2 hours at ambient temperature Autosampler stability: 112 hours at 5°C
Long-term storage stability	83 days at -70°C	83 days at -70°C

Source: Validation Report ValProt-160-2014.
Abbreviations: CV, coefficient of variation; QC, quality control

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14.4. Pharmacometrics Review

14.4.1. Summary of Findings

Key Review Questions

Pacritinib is proposed for primary and secondary myelofibrosis in patients with platelet counts of less than 50,000/µL. The proposed dose regimen is 200 mg orally, twice daily, with or without food for patients who tolerate it. For patients who experience intolerable adverse events, pacritinib should be stopped until the adverse event resolves ⁽ᵇ⁾ ⁽⁴⁾

However, reducing pacritinib dose to alleviate adverse events has the potential to diminish treatment effectiveness. A preliminary review of the Applicant's exposure-response analyses indicated that pacritinib exposures after a 200 mg dose were in the increasing portion of the exposure-response curve. This implied that decreased exposure as a consequence of reducing dose would be associated with a decrease in the rate of response. Therefore, the key review question was whether the proposed dose reductions would preserve efficacy while alleviating adverse events for an appreciable proportion of the patient population.

Results from Monte Carlo simulations suggest that, for subjects who are responders at 200 mg BID and experience toxicity, only 38% (95% CI 34% to 41%) would remain responders at 100 mg BID and 24% (95% CI 21% to 27%) would continue to experience adverse events. At 100 mg QD, only 15% (95% CI 13% to 17%) would remain responders while 25% (95% CI 21% to 27%) would have adverse events. It should be noted, however, that the rates of adverse events at 100 mg QD and 100 mg BID are comparable to the baseline rate of the assessed composite adverse events i.e., bleeding, or hemorrhage, or anemia, or thrombosis.

Another review question was whether the difference in exposure between 200 mg BID and 400 mg QD translates into meaningful differences in proportions of death events between these dosage regimens. See Part II [Interdisciplinary Assessment](#) for a detailed discussion of mortality with pacritinib compared to best available therapy.

The pharmacokinetic analysis indicated that despite equal total daily doses (TDDs) between the 400 mg QD and the 200 mg BID, the 400 mg QD dosing results in 33% and 25% higher mean C_{max} and AUC_{0-24}, respectively, compared to that for 200 mg BID dosing, perhaps due to greater inhibition of intestinal and hepatic metabolism. Model-based simulations indicate that the differences in exposure between the two regimens may translate to a higher probability of death (mean, 95% CI) with the 400 mg QD (6.7%, 4.8% to 9.0%) than with the 200 mg BID (3.6%, 2.2% to 5.0%) dosage. However, the following are the limitations of this analysis: (1) The exposure-response relationships could be confounded by pacritinib dose adjustments and interruptions due to intolerable adverse events. To reduce the confounding effects of dose changes, the analysis dataset was limited to the first 6 months of treatment; (2) The few deaths in the analysis dataset (i.e., 8 deaths) may not be adequate to characterize the impact of exposure on the incidences of deaths; (3) This was an exploratory analysis to assess associations but not causality of deaths.

Recommendations

The proposed pacritinib dose reductions are acceptable for preserving treatment effectiveness in an appreciable proportion of patients who respond and experience toxicity at 200 mg BID. Therefore, the proposed dose reduction strategies for patients experiencing intolerable adverse events is approvable.

Label Statements

Same as proposed by the Applicant in Section 2.5 of the label.

14.4.2. Population PK Analysis

Review Summary

The Applicant developed a two-compartment model with first-order elimination and absorption kinetics. The model was parameterized in terms of apparent clearance (CL/F), apparent volume of central compartment (V/F), apparent volume of peripheral compartment (Vp/F), apparent intercompartment clearance (Q/F), and absorption rate constant (K_a). Bioavailability (F) for 400 mg QD was fixed to 1 while relative bioavailability (RF) was estimated for other dosing regimens, e.g., doses <400 mg have RF >1, whereas twice daily dosing had RF <1 compared to QD. Pacritinib's time-dependent decrease in clearance was modeled by estimating typical maximum decrease (MAXD) and typical first-order rate constant of decrease in clearance (R).

The Applicant identified several covariates of the structural model parameters through full covariate modeling strategy. The Applicant's final model was obtained through step-wise backward elimination of less significant (p>0.001) covariate-parameter relations. Covariates of CL included the following: disease status (e.g., myelofibrosis or malignancies), renal impairment, moderate or strong CYP3A4 inhibitors, albumin, and alanine aminotransferase (ALT). Covariates of V included body weight, age, ALT, disease status (e.g., myelofibrosis or malignancies), renal impairment, hepatic impairment, moderate or strong CYP3A4 inhibitors, African race. Covariates of K_a included age, pacritinib dose, coadministration with food, and use of proton pump inhibitors (PPI). Covariates of F included: coadministration with food, and use of PPI. In addition to variances of K_a, V, CL, and V, covariances of the variances of K_a, V, and CL were also estimated.

The review of the Applicant's base and final models identified the following caveats which concern the validity of the identified covariate-parameter relations and the values of the Q and Vp. The Applicant's base model had high relative standard error (RSE) for Vp/F (50%) and high correlation between Q/F and Vp/F parameters (0.97) indicating that these parameters were unidentifiable. This is probably because of a large proportion of sparse samples (Phase 2 and 3 studies) that were used in the development of the model. The final model indicated high RSE for MAXD (51%) and high correlation between food effect on F1 and disease effect on CL. Failure to estimate MAXD with certainty can also be attributed the large proportion of sparse samples in the Phase 2 and 3 studies. The parameter could be estimated with certainty using data from richly sampled, multiple dose, Phase 1/2 studies and then fixed in later stages of model development.

To address the limitation of the Applicant's population PK model, the reviewer developed alternative base and final models. The alternative base model was developed in three steps: The

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first step aimed to estimate the Q and Vp parameters with certainty; therefore, only single-dose PK studies with PK samples collected up to 336 hours postdose were included in this analysis. The second step aimed to estimate pacritinib autoinhibition parameters (MAXD and R) with certainty, therefore richly sampled, multiple-dose and single-dose Phase 1 studies were included in this analysis. Both Q and Vp values were fixed to values estimated in step 1. The third step aimed to assess the stability of the autoinhibition parameters; therefore, all studies were included in the analysis. At the conclusion of this step the R parameter was fixed while the MAXD parameter was estimated.

The alternative final model was developed from the alternative base model by stepwise covariate modeling (guided by plots of covariate versus parameter variances (ETA) and covariate versus individual PK parameters). The final model retained the following covariate-parameter relationships with RSE >50%: covariates of CL were African race, disease status, renal impairment, moderate and unknown strength of CYP3A4 inhibition of coadministered drugs, age, albumin, ALT, and alkaline phosphatase (ALP); covariates of V were race (African and Asian), disease status, hepatic impairment, body weight, and Eastern Cooperative Oncology Group score; covariates of K_a were dose, age, malignancy, African race, and PPI use; covariates of F were dose, malignancy, renal impairment, dosing frequency (QD versus BID), PPI use, ALT, and ALP. The population average estimates of pacritinib PK parameters from the alternative final model were: CL/F=1.54 (l/h), V/F=77.4 (L), Q/F=0.151 (L/h), Vp/F=26.1 (L) and K_a=0.361 (h^{-1}). Unexplainable between-subject variability in PK parameters were estimable for CL, V, F, and K_a with estimates of 8.4%, 30.5%, 26.7%, and 39.2%, respectively; the corresponding ETA shrinkages were 19.6%, 72.3%, 22.5%, and 36.1%, respectively.

The developed alternative model can be used to support labeling of pacritinib as in Table 99.

Table 99. Reviewer's Specific Comments on the Population PK Model

Parameter	Utility of the Final Model		Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Simulations support the labeled reduction of dose from to 200 mg BID to 100 mg BID for patients who respond at 200 mg BID but experience intolerable adverse events.	A statistically and clinically meaningful relationship between pacritinib concentration versus spleen volume reduction was identified thus providing a supporting evidence of effectiveness. African race is predicted to have more than two-fold higher C_{max} and AUC compared to other races. Close treatment monitoring is recommended.
	Extrinsic factor	None	None
Derive exposure metrics for exposure-response (E-R) analyses	Predicted individual PK parameters were used in exposure-efficacy analyses		The use of predicted individual PK parameters in E-R analyses is acceptable since the model performance was reasonable as indicated by the goodness-of-fit plots and visual predictive check plots
Predict exposures at alternative dosing regimen	Not applicable		The model was not used to assess predicted exposures and response at alternative doses in subjects who cannot tolerate 200 mg BID

Source: Reviewer's analysis.
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum concentration; E-R, exposure-response; PK, pharmacokinetics

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14.4.2.1. Applicant's Population PK Model Development

Data

The analyses were based on PK data from 11 Phase 1 studies and 5 Phase 2/3 studies. The study design, study population, and timing of blood sample collection are presented in Table 100.

The final NONMEM data file for analysis contained 8674 PK observations from 630 subjects.

Table 100. Summary of Clinical Studies Used in the Population Pharmacokinetic Analysis

Study	Study ID	N	Description	Dose (mg)[a]	Nominal PK Assessments (hr)
SB1518001-Ph1	11	43	Ph1/2 for treatment of Myeloid Malignancies	100 150 200 300 400 500 600	Cycle 1: Days 1 and 15: pre-dose (0), 0.5, 1, 2, 3, 4, 5, 6, 8, and 24 hours post-dose. Day 8 and 22: pre-dose. Day 25: 24, 48 and 72 hours after dosing. Cycle 2: Days 1: pre-dose (0), 2, 4, 6, and 8 hours post-dose. Cycle 4, 7, 10: Day 1: pre-dose
SB1518001 -Ph2	12	31	Ph1/2 for treatment of Myeloid Malignancies	400	Cycle 1: Days 1 and 15: pre-dose (0), 0.5, 1, 2, 3, 4, 5, 6, 8, and 24 hours post-dose. Cycle 2: Days 1: pre-dose (0), 2, 4, 6, and 8 hours post-dose. Cycle 4, 7, 10: Day 1: pre-dose
SB1518002	2	33	Ph1 for treatment of Lymphoid Malignancies	100 200 300 400 600	Cycle 1: Days 1 and 15: pre-dose (0), 0.5, 1, 2, 3, 4, 5, 6, 8, and 24 hours post-dose. Day 8 and 22: pre-dose. Day 25: 24, 48 and 72 hours after dosing. Cycle 2: Days 1: pre-dose (0), 2, 4, 6, and 8 hours post-dose. Cycle 4, 6, 8, 10: Day 1: pre-dose
SB1518003 -Ph1	31	20	Ph1/2 in Chronic Idiopathic Myelofibrosis	100 200 400 500 600	Cycle 1: Days 1 and 15: pre-dose (0), 0.5, 1, 2, 3, 4, 5, 6, 8, and 24 hours post-dose. Cycle 2, 3, 4, 6, 9, 12: Day 1: pre-dose
SB1518003 -Ph2	32	28	Ph1/2 in Chronic Idiopathic Myelofibrosis	400	Cycle 1, 2, 3, 4: Day 1: pre-dose
SB1518004	4	24	SD, 3-period XO PK in HV (fasted)	100 200 400	Pre-dose and at 1, 2, 3, 3.5, 4, 4.5. 5, 5.5, 6, 8, 12, 18, 24, 36, 48, 60, 72, 96, 120, and 144 hours post-dose
SB1518006	6	18	SD, 2-period XO FE in HV	200	Pre-dose and at 1, 2, 3, 3.5, 4, 4.5. 5, 5.5, 6, 8, 12, 18, 24, 36, 48, 60, 72, 96, 120, and 144 hours post-dose
PAC101	101	12	SD, 2-period XO, relative bioavailability between capsule vs. solution in HV	400	Pre-dose and at 1, 2, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144 and 168 hours post-dose

Study	Study ID	N	Description	Dose (mg)[a]	Nominal PK Assessments (hr)
PAC103	103	28	SD, hepatic impairment	400	Pre-dose and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144 and 168 hours post-dose
PAC104	104	20	DDI: clarithromycin (CYP3A4 inhibitor)	400	Pre-dose and at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144 and 168 hours post-dose
PAC105	105	31	SD, renal impairment	400	Pre-dose and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144 and 168 hours post-dose
PAC106	106	18	DDI: rifampin (CYP3A4 inducer)	400	Pre-dose and at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144 and 168 hours post-dose
PAC107	107	41	3-way XO cardiac safety and PK	400	Pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144 and 168 hours post-dose
PERSIST – 1 (PAC325)	301	7	Ph3, pacritinib vs. best available therapy in MF	400	trough (pre-dose) and at 4 hr post-dose
PERSIST – 2 (PAC326)	326	159	Ph3, pacritinib vs. best available therapy in MF	200 mg BID 400 mg QD	trough (pre-dose) and at 4 hr post-dose
PAC203	203	117	Ph2, dose-finding study in MF previously treated with Ruxolitinib	100 mg QD 100 mg BID 200 mg BID	Sparse sampling (all patients): trough (pre-dose), 4 hr and 8 hr post-dose at the end of week 12 and week 24. Dense sampling (6-8 patients/group): pre-dose, 2, 4, 6, 8, and 24 hr post-dose at week 1. Pre-dose, 2, 4, 6, 8 hr post-dose at the end of week 12 and week 24.

Source: Applicant's population PK report (pages 24-25 of 150).
[a] QD dose unless otherwise specified.
Abbreviations: BID, twice daily; DDI, drug-drug interaction; FE, food effect; HV, healthy volunteer; ID, identification; MF, myelof brosis; N, number of subjects; Ph, Phase; PK, pharmacokinetics; QD, once daily; SD, single dose; XO, cross-over

Table 101 lists summary statistics of the baseline demographic and laboratory characteristics in the analysis datasets.

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Table 101. Summary of Baseline Demographic and Laboratory Characteristics

	level	HV	MF	Non-MF	Hepatic	Renal
n		148	383	55	20	24
AGE (year)		37.68 (10.93)	67.01 (8.85)	57.67 (16.86)	52.75 (9.32)	56.38 (10.71)
SEX (%)	M	105 (70.9)	231 (60.3)	38 (69.1)	17 (85.0)	8 (33.3)
	F	43 (29.1)	152 (39.7)	17 (30.9)	3 (15.0)	16 (66.7)
WT (kg)		80.69 (13.12)	74.06 (16.12)	83.08 (21.28)	94.75 (14.20)	79.73 (9.48)
RACE (%)	1	116 (78.4)	339 (88.5)	49 (89.1)	20 (100.0)	24 (100.0)
	2	28 (18.9)	4 (1.0)	4 (7.3)	0 (0.0)	0 (0.0)
	3	0 (0.0)	13 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
	4	4 (2.7)	27 (7.0)	2 (3.6)	0 (0.0)	0 (0.0)
ECOG	0	148 (100.0)	92 (24.0)	34 (61.8)	20 (100.0)	24 (100.0)
	1	0 (0.0)	229 (59.8)	16 (29.1)	0 (0.0)	0 (0.0)
	2	0 (0.0)	58 (15.1)	5 (9.1)	0 (0.0)	0 (0.0)
	3	0 (0.0)	4 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
DOSE (%)	100	8 (5.4)	88 (23.0)	4 (7.3)	0 (0.0)	0 (0.0)
	150	0 (0.0)	3 (0.8)	3 (5.5)	0 (0.0)	0 (0.0)
	200	26 (17.6)	123 (32.1)	12 (21.8)	0 (0.0)	0 (0.0)
	300	0 (0.0)	4 (1.0)	8 (14.5)	0 (0.0)	0 (0.0)
	400	114 (77.0)	148 (38.6)	11 (20.0)	20 (100.0)	24 (100.0)
	500	0 (0.0)	12 (3.1)	1 (1.8)	0 (0.0)	0 (0.0)
	600	0 (0.0)	5 (1.3)	16 (29.1)	0 (0.0)	0 (0.0)
TYPE (%)	1	148 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	272 (71.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	50 (13.1)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	39 (10.2)	0 (0.0)	0 (0.0)	0 (0.0)
	5	0 (0.0)	22 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)
	6	0 (0.0)	0 (0.0)	22 (40.0)	0 (0.0)	0 (0.0)
	7	0 (0.0)	0 (0.0)	33 (60.0)	0 (0.0)	0 (0.0)
	8	0 (0.0)	0 (0.0)	0 (0.0)	20 (100.0)	0 (0.0)
	9	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	24 (100.0)
renal impairment category (%)[†]	1	139 (93.9)	102 (26.7)	23 (41.8)	17 (85.0)	5 (20.8)
	2	9 (6.1)	164 (42.9)	20 (36.4)	3 (15.0)	8 (33.3)
	3	0 (0.0)	109 (28.5)	12 (21.8)	0 (0.0)	8 (33.3)
	4	0 (0.0)	7 (1.8)	0 (0.0)	0 (0.0)	3 (12.5)
ALB (g/dL)		42.38 (2.77)	41.34 (4.43)	40.02 (4.55)	35.13 (8.40)	42.44 (7.14)
ALP (U/L)		71.42 (19.22)	114.87 (73.33)	102.40 (43.34)	111.25 (43.76)	71.92 (18.58)
ALT (U/L)		27.21 (14.85)	21.71 (15.12)	17.84 (9.27)	63.75 (35.91)	19.12 (6.36)
AST (U/L)		21.51 (6.89)	26.96 (14.34)	27.24 (9.61)	82.25 (41.97)	19.96 (6.03)
HGB (g/dL)		146.05 (15.42)	95.60 (21.34)	115.13 (23.30)	137.70 (17.75)	130.79 (13.65)
BILI (mg/dL)		0.63 (0.30)	0.87 (0.46)	0.57 (0.32)	1.69 (1.03)	0.48 (0.15)
PLAT (10^9/L)		247.16 (52.44)	118.65 (139.76)	190.96 (129.12)	102.70 (47.82)	231.46 (47.20)
CRCL (mL/min)		124.25 (25.99)	76.16 (28.36)	93.13 (37.60)	118.74 (32.52)	63.35 (29.23)

Source: Applicant's population pharmacokinetics report (page 31 of 150).
Race categories are: 1=white, 2=black, 3=Asian, 4=all others.
Type levels are: 1=healthy volunteer not in the PKPD database, 2=myelofibrosis, 3=chronic idiopathic myelof brosis, 4=post-polycythemia vera myelofibrosis, 5=post-essential thrombocythemia myelofibrosis.
[†] Renal impairment categories are based on glomerular filtration rate: 1=normal, 2=mild, 3=moderate, 4=severe.
Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; CRCL, creatinine clearance; ECOG, Eastern Cooperative Oncology Group score; F, female; HGB, hemoglobin; HV, healthy volunteer; M, male; MF, myelofibrosis; PLAT, platelets; WT, weight

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Base Model

The Applicant's base model was a two-compartment model with first-order absorption from the gut. The model was parameterized in clearance from the central compartment (CL), volume of the central compartment (Vc), volume of the peripheral compartment (Vp), intercompartment clearance (Q), and absorption rate constant (K_a). The modeling employed the *Data Transform Both Sides* technique, in which observed and model-predicted concentrations are transformed to a natural log scale when estimating the model parameters. Residuals of log-transformed concentrations were modeled using an additive residual model, which is equivalent to a proportional residual error model in the observed scale. Residuals for studies with rich PK sampling were estimated separately from residuals for Phase 3 studies with sparse PK samples. Noncompartmental analysis identified that the relationship between dose and AUC was nonlinear and therefore the effect of dose on K_a and bioavailability (F1) was incorporated into the base model. Between-subject variabilities (BSV) for K_a, Vc, CL, and F1 were estimated, including the variance covariance between BSV K_a, BSV Vc, and BSV CL.

Parameter estimates of the base model are shown in Table 102. The PK parameters were well estimated, except for Vp and the correlation between BSV K_a and BSV CL. The precision estimate for Vp indicated high uncertainty with a relative standard error of 50%. Also, the variance-covariance matrix of the fixed effects coefficients showed a strong correlation between Q and V (0.97) implying that the two parameters were unidentifiable.

Table 102. Parameter Estimates and OFV of the Applicant's Base Model

Parameter	Estimate (RSE)
OFV	-9761.560
KA (/h)	0.2927 (5%)
Vc (L)	74.1 (4%)
CL (L/h)	1.747 (4%)
Vp (L)	209.9 (50%)
Q (L/h)	0.4021 (23%)
Q-Vp Correlation coefficient	0.97891
Proportional residual error (dense PK) (%CV)	0.2166 (5%)
Proportional residual error (sparse PK) (%CV)	0.3889 (4%)
Dose effect on KA ((DOSE/400)^DOSEKA)	-0.3929 (22%)
Dose effect on F1 ((DOSE/400)^DOSEF1)	-0.3617 (7%)
BSV KA (%CV)	0.5125 (6%)
Correlation between BSVKa and BSVVc	0.4677 (18%)
BSV Vc (%CV)	0.4544 (8%)
Correlation between BSVKA and BSVCL	-0.1171 (72%)
Correlation between BSVV2 and BSVCL	0.2032 (36%)
BSV CL (%CV)	0.4253 (8%)
BSV F1 (%CV)	0.3814 (6%)

Source: Reviewer's processing of the Applicant's results.
Abbreviations: CL, clearance from the central compartment; CV, coefficient of variation; F1, bioavailability; K_a, absorption rate constant; OFV, objective function value; PK, pharmacokinetics; Q, clearance; RSE, relative standard error; Vc, volume of the central compartment; Vp, volume of peripheral compartment

Time-dependent change in CL was evaluated using the base model, leading to a decrease in the objective function value (OFV) by 517. Therefore, the time-dependent change in clearance (Figure 29) was included in the model used for assessment of covariates.

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Figure 29. Equation for the Time-Dependent Change in Clearance

$$CL_i = \left(TVCL_{pop} + \Delta_{max} \times e^{(-\theta \times Day)} \right) \times e^{\eta}$$

Source: Reviewer.
Abbreviations: CL_i, individual predicted clearance; $TVCL_{pop}$, typical population (mean) value at baseline; Δ_{max}, maximum change in clearance over time; θ, rate constant of change in clearance over time; η, interindividual random effect

Covariate Analysis

Base model output was used for graphical evaluation of parameter versus covariate relationships. Parameter versus covariate relationships with physiological relevance or with graphical trend were tested in univariate covariate models. Statistically significant parameter versus covariate relationships or prespecified relationships of interest were included in a full model. A final model was obtained by retaining only the statistically significant (p<0.001) covariates by stepwise backward elimination. Table 103 lists the parameter versus covariate relationships tested during covariate model development.

Table 103. Covariates Tested in the Population Pharmacokinetic Analysis

Parameter	Covariates
CL/F	Age, ALB, ALP, ALT, AST, HGB, TBL, CRCL, PLAT, Weight, Sex, Race, CYP3A4 inhibitor, POP, TRT, ECOG
Vc/F	Age, ALB, ALP, ALT, AST, HGB, TBL, CRCL, PLAT, Weight, Sex, Race, CYP3A4 inhibitor, POP, TRT, ECOG
Ka or F	Age, Dose, TRT, FED, PPIs

Source: Applicant's population PK report (page 37 of 150).
Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CL, clearance; CRCL, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; F, bioavailability; FED, fed status; HGB, hemoglobin; Ka, absorption rate constant; PLAT, platelet; POP, study population; PPI, proton pump inhibitors/antacid drugs; TBL, total bilirubin; TRT, treatment (once versus twice daily); Vc, central volume

Final Model

Figure 30 shows the statistically significant parameter versus covariate relationships in the Applicant's final population PK model.

Figure 30. Covariates Tested in the Population Pharmacokinetic Analysis

$$Ka = \theta_1 * \left(\frac{Age}{50}\right)^{\theta 29} * \left(\frac{Dose}{400}\right)^{\theta 43} * \theta_{45}^{FED=99} * \theta_{49}^{PPI=99} * exp(\eta_1)$$

$$\frac{Vc}{F} = \theta_2 * \left(\frac{WT}{70}\right)^{\theta 8} * \theta_9^{MF} * \theta_{10}^{NonMF} * \theta_{11}^{HEP} * \theta_{12}^{RENAL} * \theta_{17}^{RACE2} * \theta_{24}^{CYP3A4I=2} * \left(\frac{Age}{50}\right)^{\theta 34}$$
$$* \left(\frac{ALT}{30}\right)^{\theta 37} * exp(\eta_2)$$

$$\frac{CL}{F} = \theta_3 * \theta_{13}^{MF} * \theta_{14}^{NonMF} * \theta_{16}^{RENAL} * \theta_{27}^{CYP3A4I=2} * \left(\frac{ALB}{40}\right)^{\theta 30} * \left(\frac{ALT}{30}\right)^{\theta 32} * exp(\eta_3)$$

$$\frac{Vp}{F} = \theta_4$$

$$\frac{Q}{F} = \theta_5$$

$$F = 1 * \left(\frac{Dose}{400}\right)^{\theta 44} * \theta_{46}^{FED=99} * \theta_{47}^{TRT=BID} * \theta_{50}^{PPI=1} * \theta_{51}^{PPI=99} exp(\eta_4) \qquad \text{Equation 6}$$

Source: Applicant's population PK report (page 43 of 150).
Abbreviations: ALB, albumin; ALT, alanine aminotransferase; BID, twice daily; CL, clearance; DOSE, pacritinib dose; F, bioavailability; HEP, hepatic impairment; FED, fed status; K_a, absorption rate constant; MF, myelofibrosis; PPI, proton pump inh bitor/antacid drugs; Q, intercompartmental clearance; RENAL, renal impairment; TRT, treatment (once versus twice daily); Vc, central volume; Vp, peripheral volume; WT, body weight

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The final parameter estimates of the Applicant's final population PK model are shown in
Table 104. The parameters are generally well estimated except for the parameter for maximum
clearance change from baseline (Δ_{max}) which has relative standard error (RSE) of 51%. The
parameter correlation estimates indicated that the coefficients for food effect on F and
myelofibrosis effect on CL could not be separately identified. The estimated proportional
residual error for studies with sparse PK sampling was higher than in rich PK sampling (38.7%
versus 18.5%).

Table 104. Parameter Estimates and OFV of the Applicant's Final Model

Parameter	Estimate (RSE)
OFV	-11,920.115
K_a (/h)	0.3643 (4%)
Vc (L)	90.45 (4%)
CL (L/h)	1.725 (5%)
Vp (L)	43.06 (34%)
Q (L/h)	0.1798 (11%)
Maximum clearance change	0.2846 (51%)
Rate constant of clearance change	0.5966 (15%)
Proportional residual error (dense PK) (%CV)	0.1848 (5%)
Proportional residual error (sparse PK) (%CV)	0.3865 (4%)
Weight on Vc/F	0.2924 (26%)
Myelofibrosis on Vc/F	0.06245 (14%)
Myeloid/lymphoid malignancies on Vc/F	0.06508 (14%)
Hepatic impairment on Vc/F	1.438 (8%)
Renal impairment on Vc/F	0.778 (7%)
Myelofibrosis on CL	0.1908 (13%)
Myeloid/lymphoid malignancies on CL	0.1564 (17%)
Renal impairment on CL	0.6105 (11%)
African on Vc	0.8538 (6%)
Moderate/strong CYP3A4 inhibitors on Vc/F	0.8136 (4%)
Moderate/strong CYP3A4 inhibitors on CL	0.6131 (5%)
Age on K_a	0.4153 (25%)
Albumin on CL	0.5094 (32%)
ALT on CL	0.1532 (24%)
Age on Vc	0.2702 (23%)
ALT on Vc	0.1065 (30%)
Dose effect on K_a ((DOSE/400)^DOSE K_a)	-0.3567 (24%)
Dose effect on F1 ((DOSE/400)^DOSE F1)	-0.3832 (7%)
Food effect on K_a	0.3272 (10%)
Food effect on F1	0.1911 (13%)
Dose frequency (BID versus QD) on F1	0.6438 (5%)
Unknown PPI use status on K_a	0.36 (12%)
Use of PPI on F1	0.8112 (7%)
Unknown PPI use status on F1	0.196 (16%)
BSV K_a (%CV)	0.3878 (7%)
BSV Vc (%CV)	0.1365 (24%)
BSV CL (%CV)	0.3421 (6%)
BSV F1 (%CV)	0.2942 (7%)

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Parameter	Estimate (RSE)
Correlation between BSV K$_a$ and BSV Vc	0.1027 (133%)
Correlation between BSV K$_a$ and BSV CL	-0.1551 (53%)
Correlation between BSV K$_a$ and BSV CL	-0.1551 (53%)
Food on F1 - myelofibrosis on CL correlation	0.90786

Source: Reviewer's repeated analysis of the Applicant's final population PK model.
Abbreviations: ALT, alanine aminotransferase; BID, twice daily; BSV, between-subject variability; CL, clearance from the central compartment; CV, coefficient of variation; F1, bioavailability; K$_a$, absorption rate constant; OFV, objective function value; PK, pharmacokinetics; PPI, proton pump inhibitor/antacid drugs; Q, clearance; QD, once daily; RSE, relative standard error; Vc, volume of the central compartment; Vp, volume of peripheral compartment

The goodness-of-fit plots for the Applicant's final population pharmacokinetic model are shown in Figure 31. There is good agreement between observed and model-predicted concentration as indicated by dependent variable (DV) versus individual predicted (IPRED) and DV versus population predicted (PRED) plots.

Figure 31. Goodness-of-Fit of the Applicant's Final PPK Model
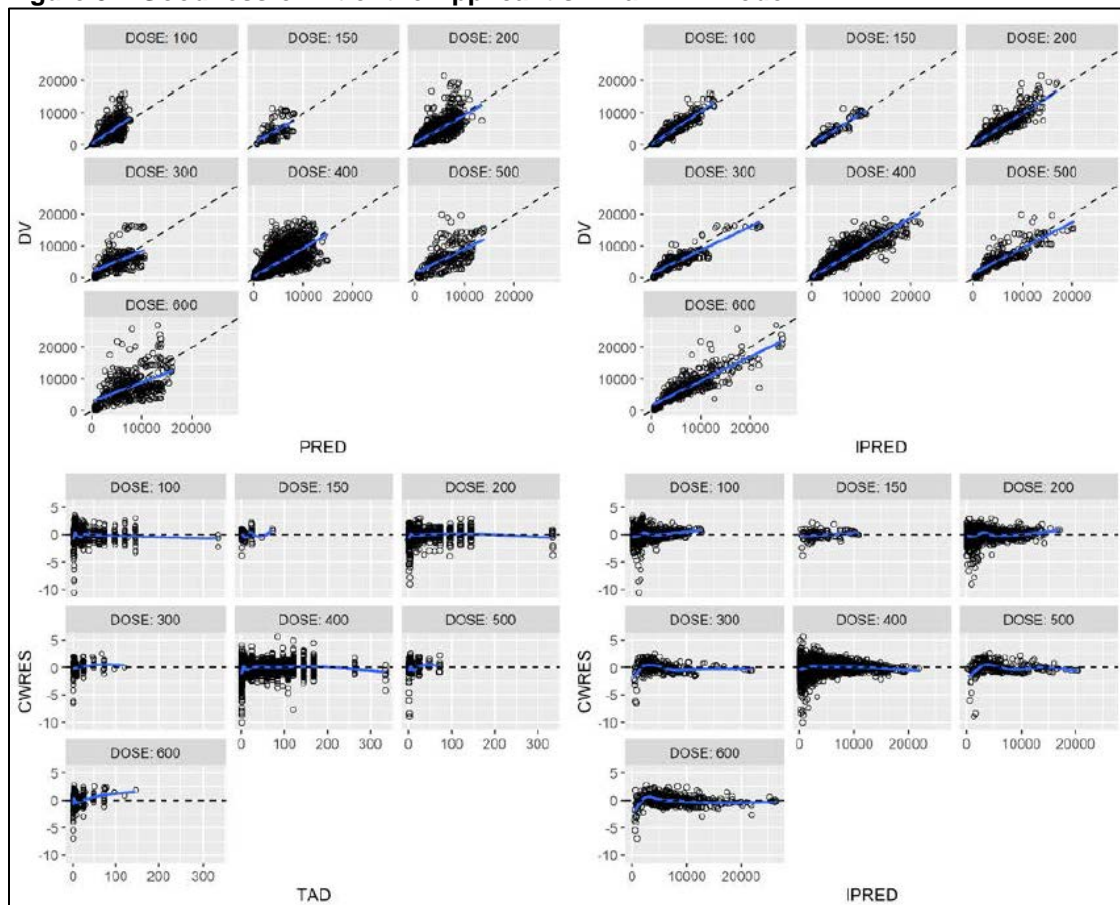
Source: Applicant's PPK report (page 45 of 150).
The open circles are observed data; the black line is the line of unity or identity, as appropriate; the blue line is a fitted linear or Loess smooth line.
TAD is shown in hours, DOSE is in milligrams.
Abbreviations: CWRES, conditional weighted residuals; DV, dependent variable; IPRED, individual predicted; PPK, population pharmacokinetics; PRED, predicted; TAD, time after dose

The Prediction-corrected Visual Predictive Check (PcVPC) plot for the Applicant's final population PK model is shown in Figure 32. The figure shows good agreement between the observed and model predicted pacritinib concentrations.

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Figure 32. PcVPC of the Applicant's Final PPK Model
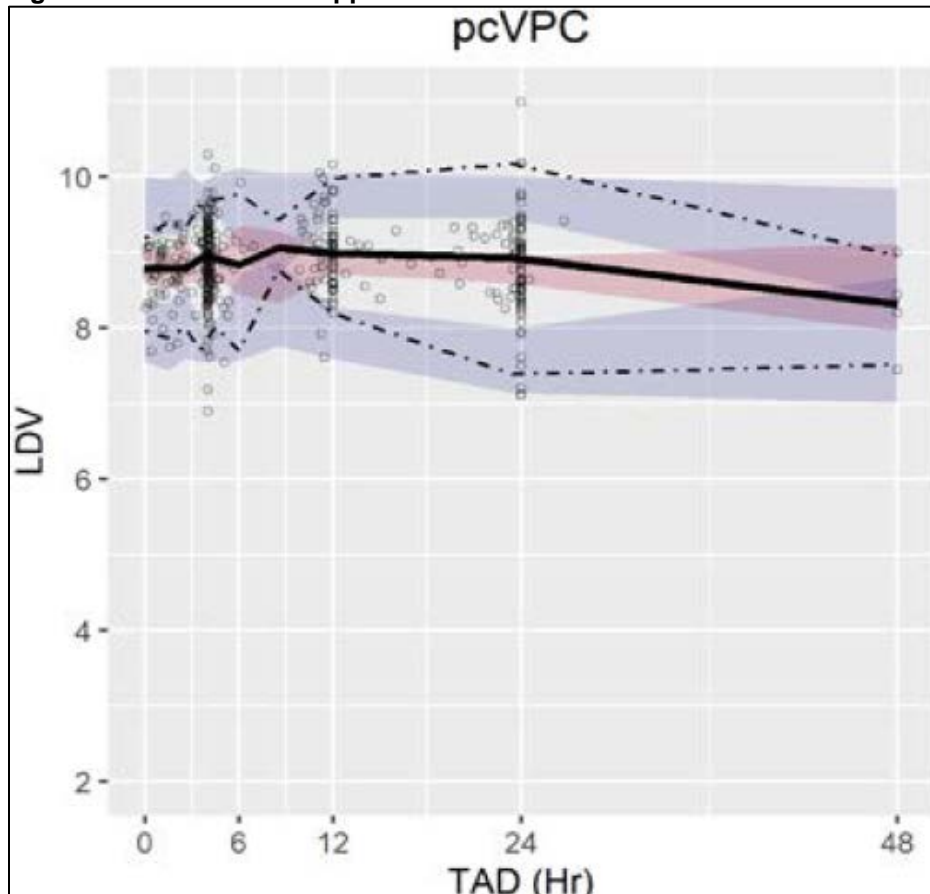
Source: Population PK report (page 53 of 150).
Abbreviations: LDV, limited dependent variable; PcVPC, prediction-corrected visual predictive check; PPK, population
pharmacokinetics; TAD, time after dose

*Reviewer's comment: Although the Applicant's final population PK model fits the observed data,
there are some limitations which concern the certainty of parameter estimates and identification
of covariates. The limitations include inability of the base model to independently estimate
parameter values for Q and V (parameter unidentifiability) and the large uncertainty of the
estimate for Vp. Similarly, in the final model, covariate coefficient for food effect on F1 and
myelofibrosis effect on CL were unidentifiable and the value of the average maximum change in
CL was uncertain (RSE 51%).*

*To have confidence in the estimated PK parameter values, the reviewer developed an alternative
population PK model, which is described in Section 14.4.2.2.*

14.4.2.2. Reviewer's Population PK Model Development

Introduction

The objective of the reviewer's independent development of an alternative population PK model
was to eliminate uncertainty in parameter values estimated in the Applicant's population PK
model and to reassess the sources of PK variability.

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Data

The same dataset as described in Section III.14.4.2.1, but with one correction, was used for alternative model development. In the submitted dataset, the dose values in the AMT column (actual dose) were not equal to the dose values in the DOSE column (covariate). This implied that the Applicant's population PK model had incorrect dose values as covariates on bioavailability (F) and absorption rate constant (K_a) parameters. Therefore, the dataset was corrected to ensure values in the DOSE column are equal to values in the AMT column.

Model Development

The alternative base model was developed in three steps:

The first step aimed to estimate the Q and Vp parameters with reasonable precision. To achieve this, only single-dose PK studies with PK samples collected up to 336 hours postdose were included in this analysis. Figure 33 shows concentration versus time profiles for subjects included in this analysis. The resulting population PK model was taken forward to the next step.

Figure 33. Individual Concentration-Time Profiles for Studies/Occasions Where Rich PK Samples Were Collected Up to 336 Hours After a Single Dose
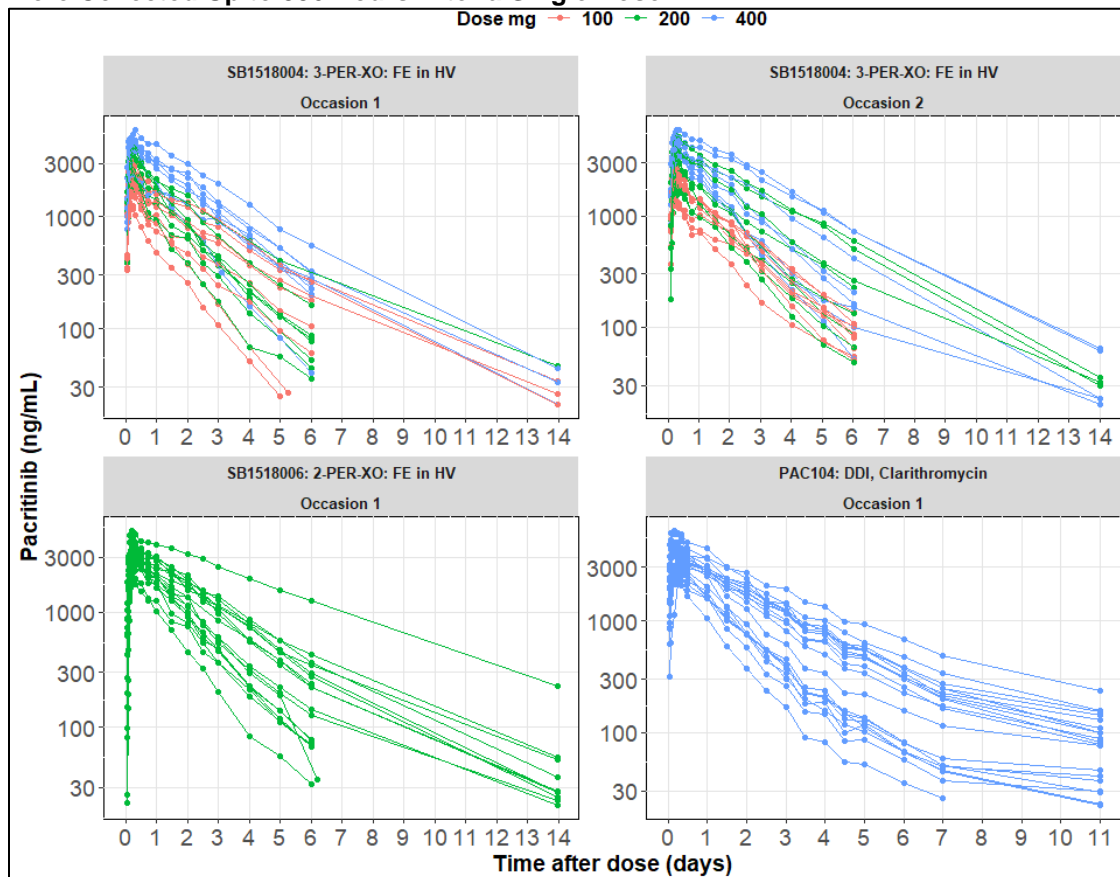
Source: Reviewer's independent analyses.
Abbreviations: DDI, drug-drug interaction; FE, food effect; HV, healthy volunteer; PK, pharmacokinetics

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The aim of the second step was to estimate with reasonable precision the pacritinib auto-inhibition parameters (MAXD and R). Multiple- and single-dose Phase 1 studies with rich PK samples were included in this analysis. Both Q/F and Vp/F values were fixed to values estimated in step 1, above. Figure 34 shows concentration versus time profiles for subjects included in this analysis. The resulting population PK model was taken forward to the next step.

Figure 34. Individual Concentration-Time Profiles for Multiple and Single Dose Studies With Rich PK Samples
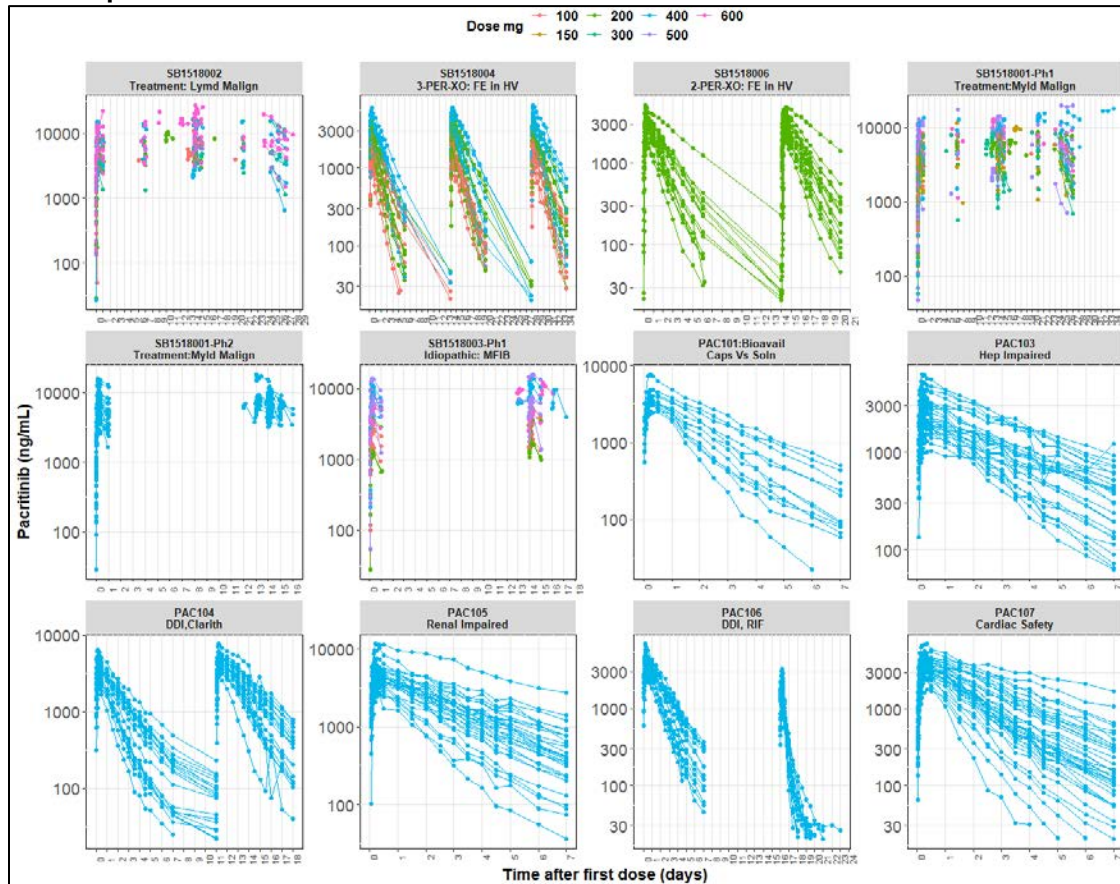
Source: Reviewer's independent analyses.
Abbreviations: Caps, capsules; DDI, drug-drug interaction; FE, food effect; Hep, hepatic; HV, healthy volunteer; Sols, solutions; PK, pharmacokinetics

The aim of the third step was to assess the stability of the autoinhibition parameters. All Phase 1, 2, and 3 studies were included in the analysis. In several iterations of this step, R was fixed while MAXD was estimated and vice versa. At the conclusion of this step the R parameter was fixed and the MAXD parameter was estimated.

Final Model

The alternative final model was developed by stepwise covariate model building guided by identification of potential covariate-parameter relationships through visual inspection of plots of ETA versus covariate or post hoc PK parameters versus covariates. The resulting full covariate model was then reduced to the final model by the elimination of covariate-parameter

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relationships with RSE >50%. Due to multiple comparisons inherent in stepwise covariate model building, there is an increased probability of false identification of covariate-parameter relationships. The final model was evaluated by assessing the conditional number, parameter identifiability, objective function value compared to the Applicant's final model, goodness-of-fit plots, and prediction corrected visual predictive checks. The final covariate-parameter relationships, the final parameter estimates, and the SCIs are given in Table 105.

Table 105. Parameter Estimates and OFV of the Reviewer's Alternative Final Model

Parameter	Estimate (RSE)
OFV	-11,935.032
K_a (/h)	0.3606 (5%)
Vc (L)	77.39 (3%)
CL (L/h)	1.536 (4%)
Vp (L)	26.1 (fixed to this value)
Q (L/h)	0.1509 (3%)
Proportional residual error (dense PK) (%CV)	0.1852 (0%)
Proportional residual error (sparse PK) (%CV)	0.3893 (1%)
Dose effect on K_a ((DOSE/400)^DOSE K_a)	-0.3558 (3%)
Dose effect on F ((DOSE/400)^DOSE F1)	-0.3854 (1%)
Maximum clearance change	0.1489 (7%)
Rate constant of clearance change	0.242 (fixed to this value)
African on CL	0.4353 (10%)
Myelofibrosis on CL	0.1978 (8%)
Myeloid/lymphoid malignancies on CL	0.2062 (13%)
Renal impairment on CL	0.7825 (8%)
Moderate/strong CYP3A4 inhibitors on CL	0.6774 (1%)
Unknown strength of CYP3A4 inhibition on CL	**0.744 (13%)**
Age on CL ((Age/50)^Age CL)	-0.3026 (26%)
Albumin on CL ((ALB/40)^ALB CL)	0.3632 (23%)
ALT on CL ((ALT/30)^ALT CL)	**0.04907 (41%)**
African on Vc	0.4176 (6%)
Asian on Vc	**0.9466 (20%)**
Myelofibrosis on Vc	0.06722 (14%)
Myeloid/lymphoid malignancies on Vc	0.06625 (23%)
Hepatic impairment on Vc	1.608 (5%)
Weight on Vc ((WT/70)^WT V)	0.2875 (28%)
Baseline ECOG score >1 on V2	**0.9867 (10%)**
Myelofibrosis on F	0.1548 (6%)
Myeloid/lymphoid malignancies on F	0.1715 (8%)
Renal impairment on F	**1.08 (6%)**
Dose frequency (BID versus QD) on F	0.6523 (6%)
Use of PPI on F	0.8067 (5%)
African on F1	0.4249 (8%)
ALT on F ((ALT/30)^ALTF)	-0.1264 (14%)
ALP on F ((ALP/30)^ALPF)	0.07557 (32%)
Age on K_a ((Age/50)^Age K_a)	0.3776 (25%)
Myelofibrosis on K_a	0.3542 (15%)

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Parameter	Estimate (RSE)
Myeloid/lymphoid malignancies on K_a	0.2814 (25%)
Unknown PPI use status on K_a	1.334 (17%)
BSV Vc (%CV)	0.08426 (fixed to this value)
BSV K_a (%CV)	0.3919 (6%)
Correlation between BSV K_a and BSV CL	-0.2195 (36%)
BSV CL (%CV)	0.3046 (5%)
Correlation between BSV K_a and BSV F	-0.06067 (164%)
Correlation between BSV CL and BSV F	-0.2127 (42%)
BSV F (%CV)	0.2669 (6%)

Source: Reviewer's independent analyses.
Bold values indicate covariates that are not statistically significant based on the simultaneous confidence interval metric.
Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; BID, twice daily; BSV, between-subject variability; CI, confidence interval; CL, clearance from the central compartment; CV, coefficient of variation; ECOG, Eastern Cooperative Oncology Group; F1, bioavailability; K_a, absorption rate constant; OFV, objective function value; PK, pharmacokinetics; PPI, proton pump inhibitor/antacid drugs; Q, clearance; QD, once daily; RSE, relative standard error; Vc, volume of the central compartment; Vp, volume of peripheral compartment; WT, weight

The final model OFV (-11,935) and condition number (180.5) were lower than the OFV (-11,920) and conditional number (513) from the Applicant's final model. The goodness-of-fit plots of the final model are shown in Figure 35 and the PcVPC are shown in Figure 36 and Figure 37. The goodness-of-fit and PcVPC plots shows that the model adequately fits the observed data and can therefore be used for exposure versus response modeling.

Figure 35. Goodness-of-Fit Plot of the Reviewer's Alternative Final Model
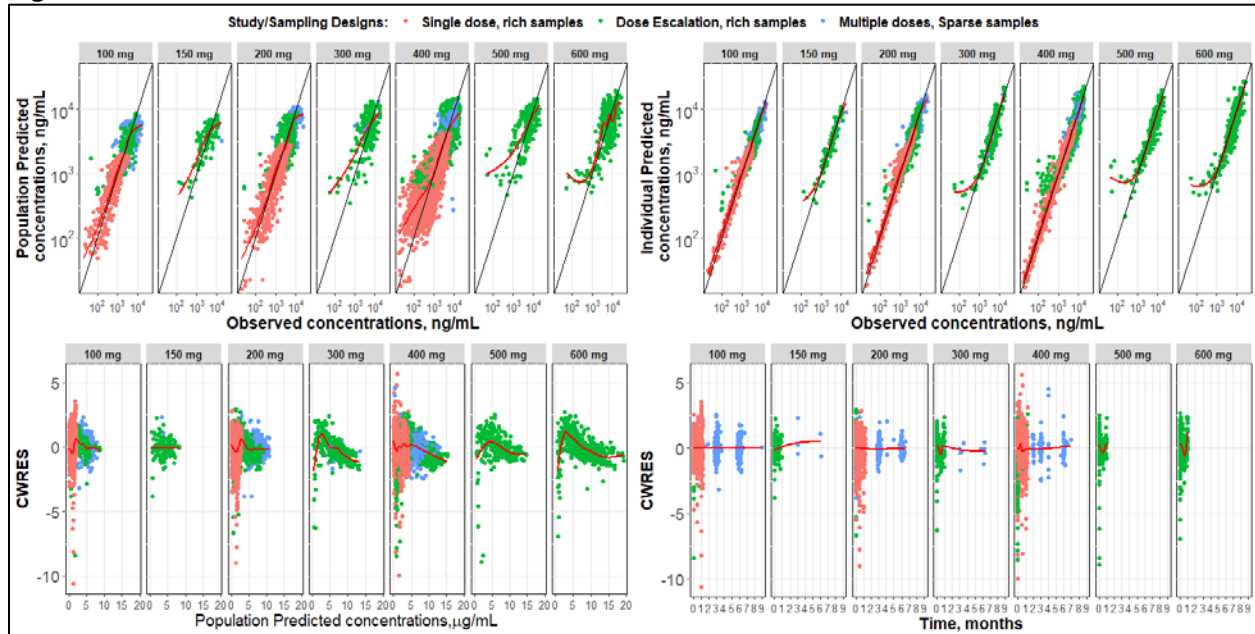
Source: Reviewer's independent analyses.
Abbreviations: CWRES, conditional weighted residuals

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Figure 36. PcVPC of the Reviewer's Alternative Final Model (Up to 336 Hours)
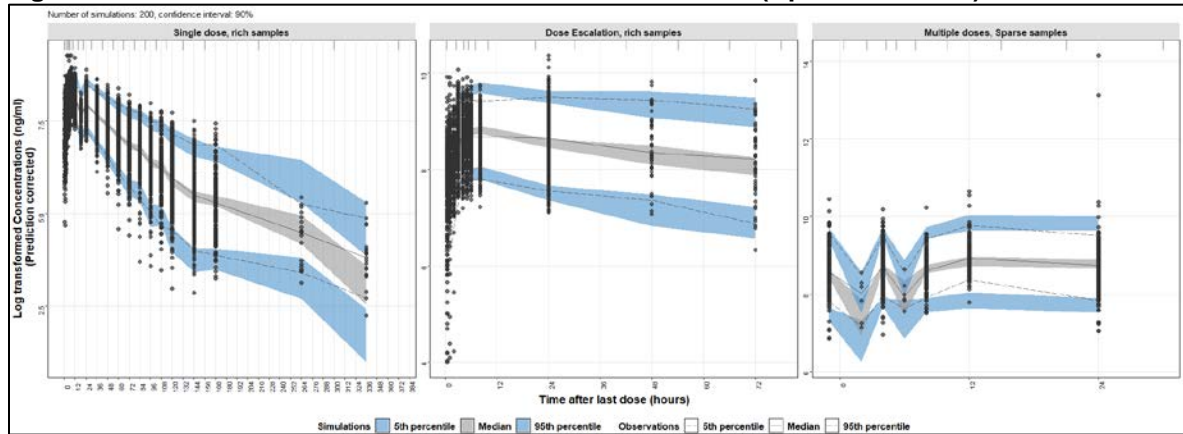
Source: Reviewer's independent analyses.
The facets represent different PK study designs and PK sampling protocols. The single dose, rich sample facet include studies SB1518004, SB1518006, PAC101, PAC103, PAC104, PAC105, PAC106, and PAC107. The dose escalation, rich samples facet includes studies SB1518002, SB1518001-Ph1, SB1518001-Ph2, and SB1518003-Ph1. The multiple doses, sparse samples facet includes studies SB1518003-Ph2, PAC203, PERSIST1, and PERSIST2.
Abbreviations: PcVPC, prediction-corrected visual predictive check; PK, pharmacokinetics

Figure 37. PcVPC of the Reviewer's Alternative Final Model (Up to 24 Hours)
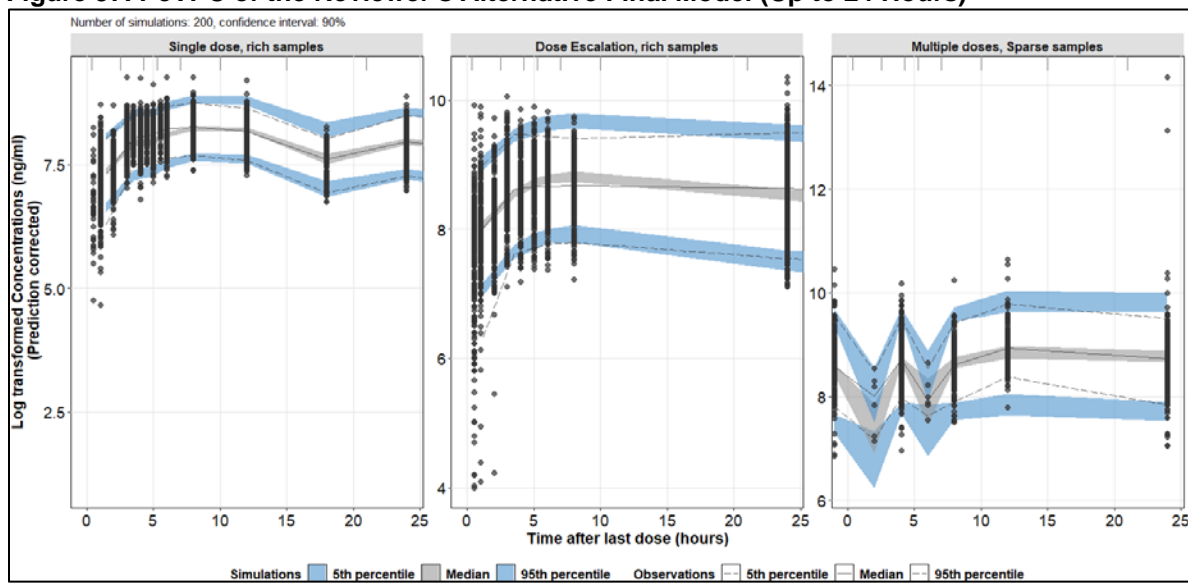
Source: Reviewer's independent analyses
The facets represent different PK study designs and PK sampling protocols. The single dose, rich samples facet includes Studies SB1518004, SB1518006, PAC101, PAC103, PAC104, PAC105, PAC106, and PAC107. The dose escalation, rich samples facet includes studies SB1518002, SB1518001-Ph1, SB1518001-Ph2, and SB1518003-Ph1. The multiple doses, sparse samples facet includes studies SB1518003-Ph2, PAC203, PERSIST1, and PERSIST2.
Abbreviations: PcVPC, prediction-corrected visual predictive check; PK, pharmacokinetics

Model-Predicted PK Parameters

The reviewer's final population PK model parameters were used to derive individual PK parameters. The derived PK parameters were subsequently used to simulate pacritinib concentration-time profiles after single-dose and at steady state. The profiles were analyzed to obtain AUC for dosing interval and C_{max} after a single dose and at steady state. Table 106 summarizes central tendency and ranges of the selected PK parameters at steady state for all subjects stratified by dose.

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Table 106. Summary Statistics of Model Estimated Individual PK Parameters for All Subjects in the Phase 2 and Phase 3 Studies Stratified by Dosing Regimen

Parameters	100 mg QD (n=40)				100 mg BID (n=48)				200 mg QD (n=6)				200 mg BID (n=107)				400 mg QD (n=67)			
	Geo Mean (CV%)	Mean (sd)	Median	Min - Max	Geo Mean (CV%)	Mean (sd)	Median	Min - Max	Geo Mean (CV%)	Mean (sd)	Median	Min - Max	Geo Mean (CV%)	Mean (sd)	Median	Min - Max	Geo Mean (CV%)	Mean (sd)	Median	Min - Max
CL/F (L/h)	0.84 (51.99)	0.96 (0.56)	0.78	0.38 - 2.61	1.41 (43.24)	1.52 (0.59)	1.51	0.61 - 2.85	1.08 (44.17)	1.16 (0.45)	1.06	0.54 - 1.85	2.09 (33.08)	2.2 (0.72)	2.08	0.87 - 5	1.65 (36.15)	1.76 (0.66)	1.67	0.77 - 4.12
VC/F (L)	17.87 (24.45)	18.41 (4.77)	17.47	11.86 - 31.93	27.85 (21.61)	28.47 (5.95)	28.57	18.1 - 41.81	22.74 (26.77)	23.41 (6.24)	21.22	15.82 - 32.61	39.16 (18.96)	39.85 (7.49)	39.02	24.1 - 62.78	31.72 (18.76)	32.26 (5.97)	32.03	20.2 - 46.38
Q/F (L/h)	0.51 (23.85)	0.53 (0.13)	0.48	0.34 - 0.94	0.8 (19.64)	0.81 (0.15)	0.84	0.54 - 1.14	0.68 (22.51)	0.69 (0.16)	0.65	0.49 - 0.96	1.13 (18.95)	1.15 (0.26)	1.1	0.76 - 3.06	0.93 (21.86)	0.95 (0.26)	0.92	0.61 - 2.63
VP/F (L)	88.37 (23.85)	90.91 (23.25)	83.85	59.25 - 163.24	138.36 (19.64)	140.89 (26.7)	144.46	93.81 - 197.29	116.77 (22.51)	119.23 (27.17)	112.91	84.5 - 165.83	195.9 (18.95)	199.71 (45.27)	190.08	132.05 - 528.58	160.75 (21.86)	165.02 (45.49)	159.19	104.87 - 454.59
KA (/h)	0.22 (10.22)	0.22 (0.02)	0.23	0.17 - 0.26	0.24 (9.23)	0.24 (0.02)	0.24	0.21 - 0.33	0.2 (9.24)	0.2 (0.02)	0.2	0.18 - 0.24	0.18 (11.36)	0.18 (0.02)	0.18	0.1 - 0.3	0.15 (13.31)	0.15 (0.02)	0.15	0.1 - 0.2
Alpha half-life (h)	8.8 (16.88)	8.91 (1.38)	9.09	5.31 - 11.42	8.46 (13.93)	8.54 (1.19)	8.22	6.25 - 11.21	8.67 (10.39)	8.71 (0.92)	8.66	7.71 - 10.21	8.17 (12.43)	8.23 (0.99)	8.17	5.26 - 10.93	8.23 (15.92)	8.33 (1.36)	8.38	5.68 - 14.09
Beta half-Life (h)	199.93 (10.16)	200.92 (19.94)	200.33	158.68 - 238.93	194.6 (9.21)	195.41 (18.32)	190.68	167.91 - 243.95	201.61 (9.29)	202.35 (19.55)	199	185.85 - 238.39	190.56 (7.76)	191.15 (15.37)	188.37	158.61 - 251.24	193.7 (10.42)	194.81 (22.79)	192.14	159.55 - 305.8
Accumulation Factor	2.21 (14.61)	2.24 (0.32)	2.23	1.53 - 2.89	3.58 (17.64)	3.64 (0.65)	3.46	2.37 - 5.27	2.22 (12)	2.23 (0.28)	2.19	1.98 - 2.74	3.86 (14.71)	3.9 (0.64)	3.8	2.81 - 7.86	2.23 (14.69)	2.26 (0.38)	2.24	1.67 - 4.03
Effective half-life (h)	27.49 (20.69)	28.03 (5.47)	28.04	15.77 - 39.16	25.34 (20.93)	25.88 (5.48)	24.39	15.16 - 39.55	27.68 (16.22)	27.99 (4.77)	27.21	23.61 - 36.58	27.68 (17.03)	28.1 (5.33)	27.23	18.91 - 61.16	27.86 (19.66)	28.43 (6.44)	28.11	18.14 - 58.39
AUCss(0-Tau) (h*mg/L)	118.3 (52.01)	131.27 (56.34)	127.28	38.3 - 263.05	71.05 (43.26)	77.43 (33.51)	66.26	35.05 - 163.47	184.85 (44.19)	199.81 (91.85)	189.66	108.09 - 369.94	95.6 (33.09)	100.71 (33.82)	96.11	39.92 - 230.14	241.6 (36.16)	256.27 (88.91)	239.48	97.11 - 519.07
CMAX (mg/L)	6.06 (47.26)	6.62 (2.64)	6.43	2.19 - 12.78	6.35 (41.89)	6.88 (2.9)	5.91	3.19 - 14.23	9.34 (41.57)	10 (4.26)	9.8	5.58 - 17.78	8.42 (32.38)	8.85 (2.91)	8.45	3.58 - 19.92	11.91 (33.68)	12.54 (4.08)	11.62	5.08 - 23.32
TMAX (h)	6.04 (5.13)	6.05 (0.32)	6	5 - 7	4 (0)	4 (0)	4	4 - 4	6.48 (8.46)	6.5 (0.55)	6.5	6 - 7	4.43 (11.2)	4.46 (0.5)	4	4 - 5	7.04 (4.52)	7.04 (0.32)	7	6 - 8

Source: Reviewer's independent analyses.
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; CL/F, total clearance; C_{max}, maximum concentration; CV, coefficient of variation; KA, absorption rate constant; PK, pharmacokinetics; Q/F, clearance; QD, once daily; T_{MAX}, time to maximum concentration; VC/F, central volume of distribution; VP/F, peripheral volume of distribution

14.4.2.3. Impact of Selected Covariates on Pacritinib Exposures

Figure 38 and Figure 39 show the predicted impact of selected covariates on AUC and C_{max} at steady state. No covariate has a clinically meaningful impact on pacritinib exposure.

Figure 38. Effects of Covariates on Pacritinib AUC$_{0-Tau}$ at Steady State
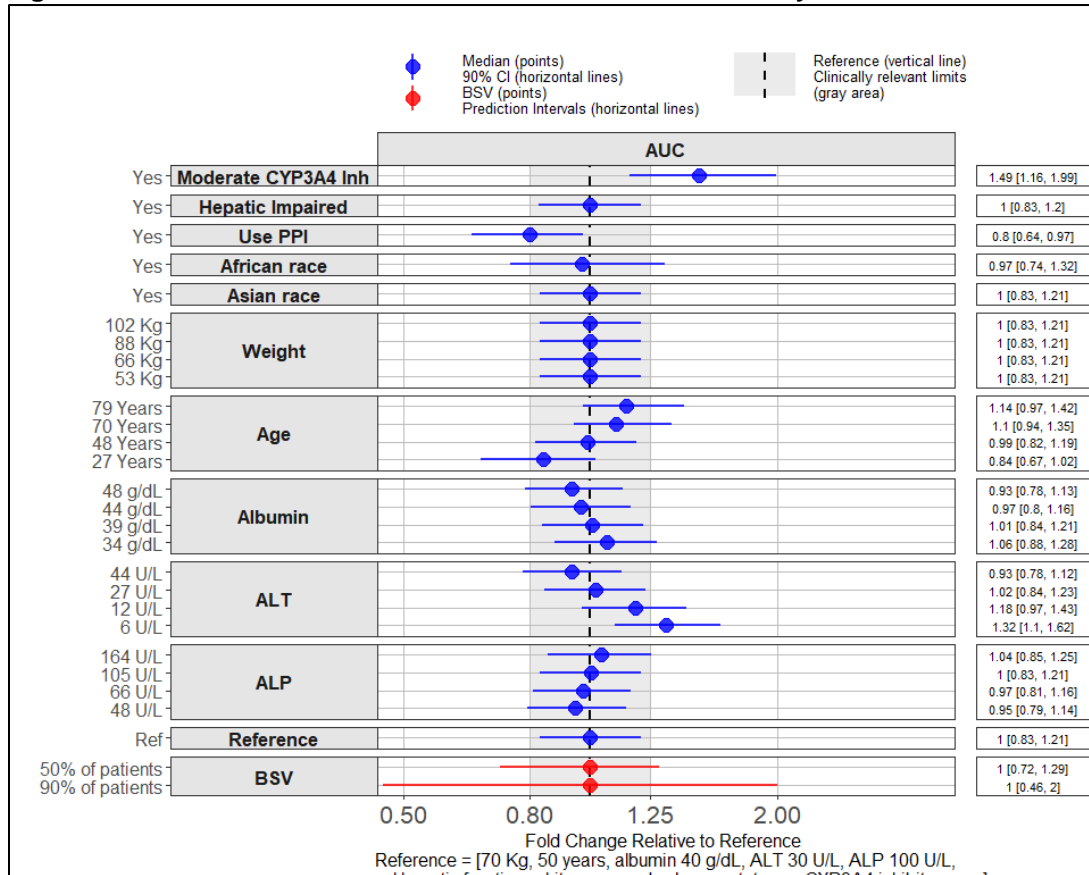
Source: Reviewer's analysis.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AUC, area under the concentration-time curve; BSV, between-subject variability; CI, confidence interval; PPI, proton pump inh bitor/antacid drugs

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Figure 39. Effects of Covariates on Pacritinib C$_{max}$ at Steady State
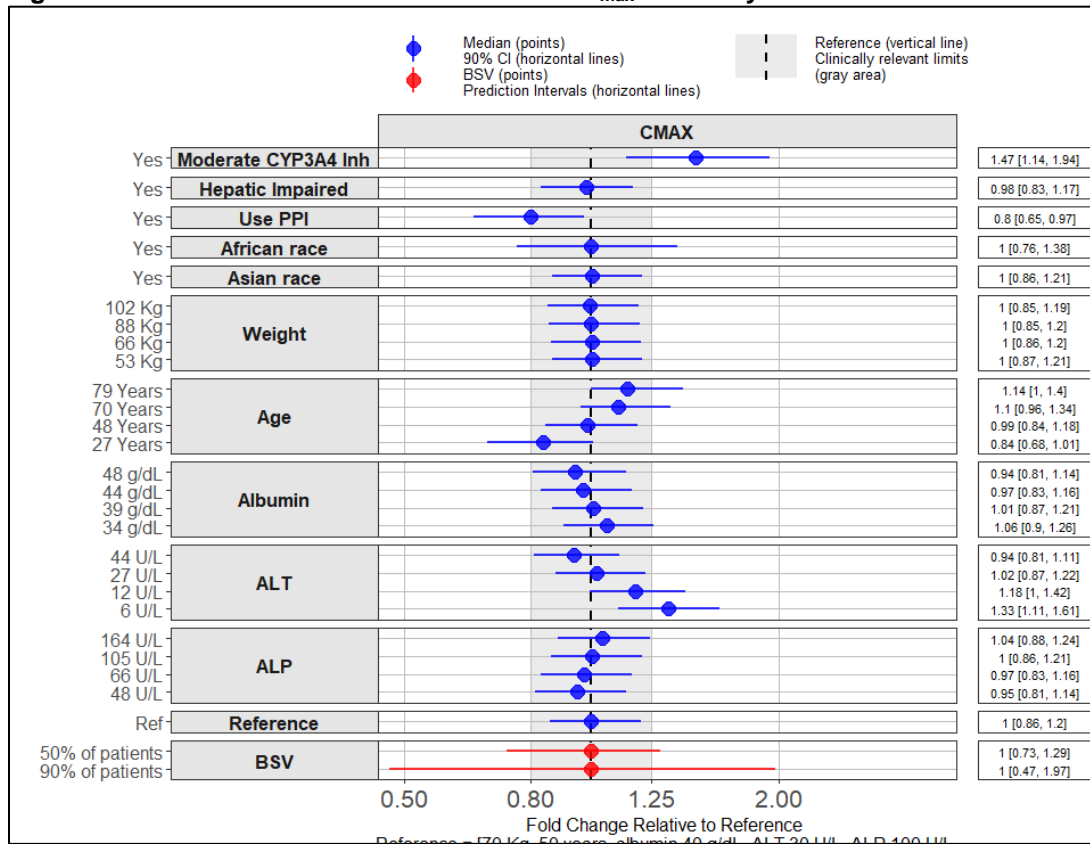
Source: Reviewer's independent analyses.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; BSV, between-subject variability; CI, confidence interval;
C$_{max}$, maximum concentration; PPI, proton pump inhibitor/antacid drugs

14.4.2.4. Comparisons of Pacritinib Exposures Between Different Dosage Regimens

The results from population PK modeling indicate that frequency of dosing is a covariate on a bioavailability parameter with relative bioavailability being lower for twice daily compared to once daily dosing. To understand the impact of frequency of dosing on pacritinib exposure, cumulative AUCs and maximum concentrations were estimated for subjects who completed follow-up until Week 22 without dose interruptions or dose reductions. Cumulative AUC was used to calculate average concentration during the 6 months of treatment ($Cavg = \frac{cumAUC\ (h\times\mu g/mL)}{3696\ (h)}$). This analysis was restricted to subjects in the PAC203, PERSIST-1, and PERSIST-2 studies. Table 107 compares average concentrations and Table 108 compares C$_{max}$ among different dosage regimens. Once daily dosing (e.g., 400 mg QD) resulted in higher pacritinib exposure compared to twice daily dosing (e.g., 200 mg BID). These results are surprising as the mechanism underlying this difference is not yet known. The suggested hypothesis is that due to the time-dependent inhibition effects of pacritinib on CYP3A4, the higher once daily dose may cause a greater inhibition of first-pass metabolism, resulting in higher bioavailability than the lower twice daily dosing.

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Table 107. Descriptive Statistics of Average Concentrations Among Subjects With No Dose Change or Dose Interruption Until Week 22 of Treatment

| Study | Dose | Average Concentration (µg/mL) | | | | Number of Subjects |
		Median	IQR	Minimum	Maximum	
PAC203	100 mg QD	4.6	3.6 to 6.2	1.5	10.7	23
PAC203	100 mg BID	4.5	3.7 to 5.4	2.9	8.8	22
PAC203	200 mg BID	6.0	5.4 to 8	3.9	12.7	20
PERSIST-1	400 mg QD	7.7	6.4 to 9.2	4.9	11.2	4
PERSIST-2	200 mg BID	7.7	6.3 to 10.3	3.3	14.3	36
PERSIST-2	400 mg QD	9.7	8 to 10.8	3.9	14.0	28

Source: Reviewer's independent analyses.
Abbreviations: BID, twice daily; IQR, interquartile range; QD, once daily

Table 108. Descriptive Statistics of Maximum Concentrations Among Subjects With No Dose Change or Dose Interruption Until Week 22 of Treatment

| Study | Dose | C_{max} (µg/mL) | | | | Number of Subjects |
		Median	IQR	Minimum	Maximum	
PAC203	100 mg QD	6.4	4.5 to 8.6	2.2	13.4	37
PAC203	100 mg BID	6.1	4.7 to 8.8	3.6	15.0	41
PAC203	200 mg BID	9.1	6.8 to 10.3	4.6	18.1	39
PERSIST-1	400 mg QD	9.9	9.3 to 12.8	6.6	24.5	6
PERSIST-2	200 mg BID	8.7	7.1 to 10.7	3.6	22.0	82
PERSIST-2	400 mg QD	12.4	10.1 to 15.6	5.1	23.1	77

Source: Reviewer's independent analyses.
Abbreviations: BID, twice daily; C_{max}, maximum concentration; IQR, interquartile range; QD, once daily

14.4.3. Population PK-PD Analyses

14.4.3.1. Applicant's Exposure vs. Spleen Volume Analyses

Data

The Applicant developed a pharmacokinetic-pharmacodynamic (PKPD) model for spleen volume reduction using data pooled from Phase 2/3 studies (PAC203, PERSIST-1, and PERSIST-3). A brief description of the studies is given in Table 100. The final PKPD dataset contained 283 patients with myelofibrosis who had PK and pharmacodynamic (PD) records. Table 109 provides summary statistics of the baseline demographic and laboratory characteristics of the patients included in the analyses.

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Table 109. Summary of Baseline Demographic and Laboratory Characteristics of the Patients With Myelofibrosis Included in the PKPD Analyses

	level	All (Pooled)	PAC203	PERSIST-1	PERSIST-2
n		283	117	7	159
AGE (years)		67.61 (8.50)	68.74 (8.05)	66.29 (7.32)	66.84 (8.82)
SEX (%)	M	163 (57.6)	71 (60.7)	5 (71.4)	87 (54.7)
	F	120 (42.4)	46 (39.3)	2 (28.6)	72 (45.3)
WT (kg)		74.63 (16.19)	76.56 (16.07)	70.61 (19.17)	73.38 (16.10)
RACE (%)	1	247 (87.3)	104 (88.9)	2 (28.6)	141 (88.7)
	2	2 (0.7)	1 (0.9)	0 (0.0)	1 (0.6)
	3	8 (2.8)	2 (1.7)	1 (14.3)	5 (3.1)
	4	26 (9.2)	10 (8.5)	4 (57.1)	12 (7.5)
ECOG (%)	0	61 (21.6)	35 (29.9)	2 (28.6)	24 (15.1)
	1	176 (62.2)	62 (53.0)	4 (57.1)	110 (69.2)
	2	42 (14.8)	20 (17.1)	1 (14.3)	21 (13.2)
	3	4 (1.4)	0 (0.0)	0 (0.0)	4 (2.5)
RUX (%)	0	94 (33.2)	0 (0.0)	7 (100.0)	87 (54.7)
	1	189 (66.8)	117 (100.0)	0 (0.0)	72 (45.3)
DOSE (%)	100	78 (27.6)	78 (66.7)	0 (0.0)	0 (0.0)
	200	122 (43.1)	39 (33.3)	0 (0.0)	83 (52.2)
	400	83 (29.3)	0 (0.0)	7 (100.0)	76 (47.8)
TYPE (%)	2	248 (87.6)	89 (76.1)	0 (0.0)	159 (100.0)
	3	6 (2.1)	0 (0.0)	6 (85.7)	0 (0.0)
	4	20 (7.1)	19 (16.2)	1 (14.3)	0 (0.0)
	5	9 (3.2)	9 (7.7)	0 (0.0)	0 (0.0)
RENAL[a]	1	75 (26.5)	29 (24.8)	2 (28.6)	44 (27.7)
	2	121 (42.8)	52 (44.4)	2 (28.6)	67 (42.1)
	3	81 (28.6)	33 (28.2)	3 (42.9)	45 (28.3)
	4	5 (1.8)	3 (2.6)	0 (0.0)	2 (1.3)
ALB (g/dL)		41.95 (4.28)	41.93 (4.11)	43.86 (4.41)	41.88 (4.40)
ALP (U/L)		105.41 (61.21)	100.93 (54.64)	151.29 (91.71)	106.69 (63.77)
ALT (U/L)		21.65 (16.02)	22.78 (17.01)	16.86 (5.98)	21.04 (15.55)
AST (U/L)		25.04 (13.74)	27.15 (13.23)	24.29 (14.50)	23.52 (13.95)
BILI (mg/dL)		0.91 (0.49)	0.90 (0.43)	0.97 (0.32)	0.91 (0.54)
HGB (g/dL)		97.00 (20.45)	92.02 (16.79)	117.00 (30.38)	99.79 (21.45)
PLAT (10^9/L)		84.89 (83.52)	87.38 (81.57)	185.00 (123.64)	78.66 (80.61)
CRCL (mL/min)		75.48 (27.19)	73.75 (24.78)	83.45 (50.96)	76.40 (27.64)

Source: Applicant's pharmacokinetic-pharmacodynamic analysis report (page 25 of 102).
Race categories are: 1=white, 2=black, 3=Asian, 4=all others.
Type levels are: 1=healthy volunteer not in the PKPD database, 2=myelofibrosis, 3=chronic idiopathic myelof brosis, 4=post-polycythemia vera myelofibrosis, 5=post-essential thrombocythemia myelofibrosis.
Rux categories are: 0=not previously treated with ruxolitin b, 1=previously treated with ruxolitinib.
[a] Renal impairment categories are based on glomerular filtration rate: 1=normal, 2=mild, 3=moderate, 4=severe.
Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; CRCL, creatinine clearance; ECOG, Eastern Cooperative Oncology Group score; F, female; HGB, hemoglobin; HV, healthy volunteer; M, male; MF, myelofibrosis; PKPD, pharmacokinetics/pharmacodynamics; PLAT, platelets; RUX, ruxolitin b; WT, weight

Base Model

The Applicant used a sequential approach to develop the PKPD model for spleen volume reduction. With this approach, estimated PK parameters from the final population PK model were included in the PKPD dataset and used to predict concentrations at the observation times for spleen volume. The schematic presentation of the structural PKPD model is depicted in Figure 40. In this model, the spleen volume trajectory is assumed to follow one-compartment

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kinetics, where the increase in spleen volume is driven by a constant rate parameter (K_{in}) and the decrease is by first order kinetics driven by a rate constant (K_{out}). The model assumes that pacritinib works by reducing K_{in} and the magnitude of effect is a function of pacritinib plasma concentration. The Applicant investigated three drug effect models, namely, the simple E_{max} model, sigmoid-E_{max} model, and the linear model. The linear model was selected as it had lower OFV and successful covariance step than the other models. Therefore, the pharmacodynamic model was parameterized in K_{in}, K_{out}, SLOPE (coefficient for linear relationship between concentration and spleen volume), and BASE (population average spleen volume). In addition, a dropout model was developed jointly with the PKPD model. In the dropout model, time to dropout was adequately described by a Weibull hazard model. The Weibull hazard model was parameterized in λ and α parameters ($HAZARD_0 = \lambda \times \alpha \times TIME^{(\alpha-1)}$). All the parameters were assumed to follow a log-normal distribution and therefore their interindividual variabilities were modeled using exponential variance models ($P_i | \sim | P_{TV} \times e^{(\eta p,i)}$). P_i is the value of parameter P for the ith individual, P_{TV} is the typical value of parameter P, and $\eta p,i \sim N(0\omega_p^2)$ is a realization of a normally distributed random variable with a mean of zero and variance ω_p^2. Spleen volume was transformed to natural logarithm scale before analysis and therefore residual variabilities in spleen volume were modeled using a log additive residual error model.

Figure 40. Spleen Volume PKPD Model Structure
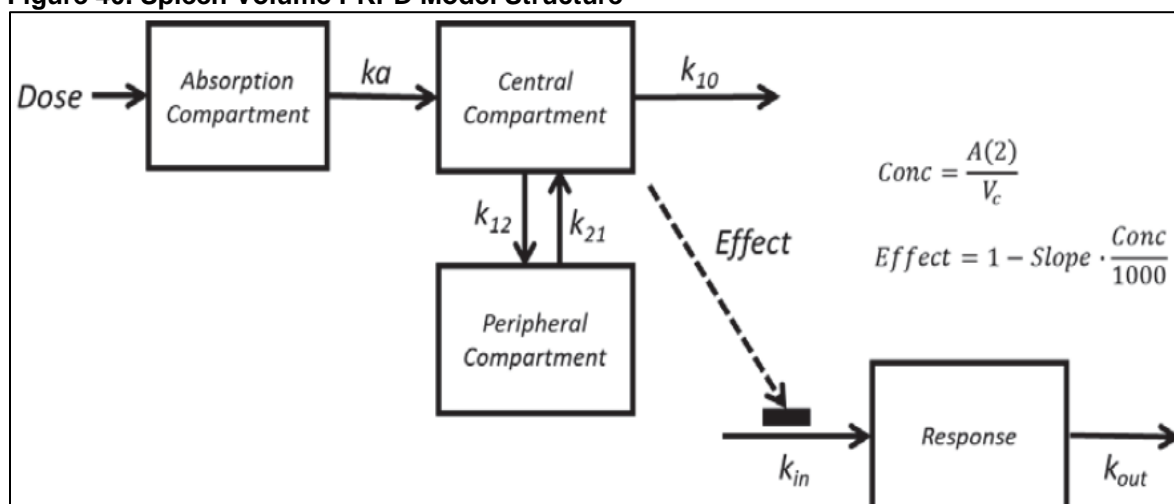
Source: Applicant's pharmacokinetic-pharmacodynamic analysis report (page 28 of 102).
Response=SPV or TSS
Abbreviations: A(x), amount in compartment (x); Conc; concentration; DOSE, pacritinib dose; k, rate constant; k_a, absorption rate; k_{in}, synthesis rate; PKPD, pharmacokinetics/pharmacodynamics; SPV, spleen volume; TSS, total symptom score; Vc, central volume

Covariate Model

The covariate model was developed by testing one covariate at a time on the SLOPE parameter and the Weibull hazard function. The tested covariates on the SLOPE parameter included age, sex, race, frequency of dosing (BID versus QD), platelet, baseline Eastern Cooperative Oncology Group score, and previous treatment with ruxolitinib (Jakafi). Only previous treatment with ruxolitinib was identified as a significant covariate of the SLOPE parameter. Albumin levels classified as <35 g/dL was identified as a covariate on the hazard function i.e., ($HAZARD_0 = \lambda \times \alpha \times TIME^{(\alpha-1)} \times e^{(\beta \times ALBFL)}$), where ALBFL took a value of 1 if ALB <35 g/dL or 0 otherwise. Spleen volume change overtime was not tested as a covariate on any of the hazard

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parameters. Therefore, the final model did not include spleen volume response as a predictor of dropout.

Final Model

The final parameter estimates of the spleen volume PKPD model are listed in Table 110.

Table 110. Parameter Estimates of the Applicant's Final Spleen Volume PKPD Model

Parameter (Units)		Indirect SLOP model (OBJ= -1170.645)	
		estimate	RSE (%) or IIV shrinkage (%)
BASE (cm³)	θ1	2270	3.4
SLOP (cm³/(ng/mL))	θ2	0.0166	16.7
Kin (/hr)	θ3	58.6	62.5
Baseline SPV on SLOP†	θ7	0.353	164.3
Ruxolitinib (RUX=1)	θ8	0.475	20.5
Residual Error	θ9	0.138	1.8
IIV BASE (CV)	η1	0.529	2.4
IIV SLOP (CV)	η2	0.875	27.9
Correlation IIV (BASE-SLOP)		-0.462	--
dropout model (Weibull)			
λ	θ10	-17.7	9.7
α	θ11	0.679	14.7
β₁ (coefficient for ALB≤35)	θ12	1.88	25.3

Source: Applicant's pharmacokinetic-pharmacodynamic analysis report (page 29 of 102).
Abbreviations: ALB, albumin; CV, coefficient of variation; kin, synthesis rate; IIV, interindividual variation; PKPD, pharmacokinetics/pharmacodynamics; RSE, relative standard error

The diagnostic goodness-of-fit plots and the visual predictive check plot of the final spleen volume PKPD model are given in Figure 41 and Figure 42, respectively. The plot of population prediction (PRED) versus observed (DV) spleen volume (SPV) indicate that the structural model is inadequate in describing the observed data. But the individual predictions are in good agreement with the observed SPV. Similarly, the visual predictive check (VPC) shows that the final SPV PKPD model adequately predicts the observed data.

Figure 41. Goodness-of-Fit Plots of the Applicant's Final Spleen Volume PKPD Model
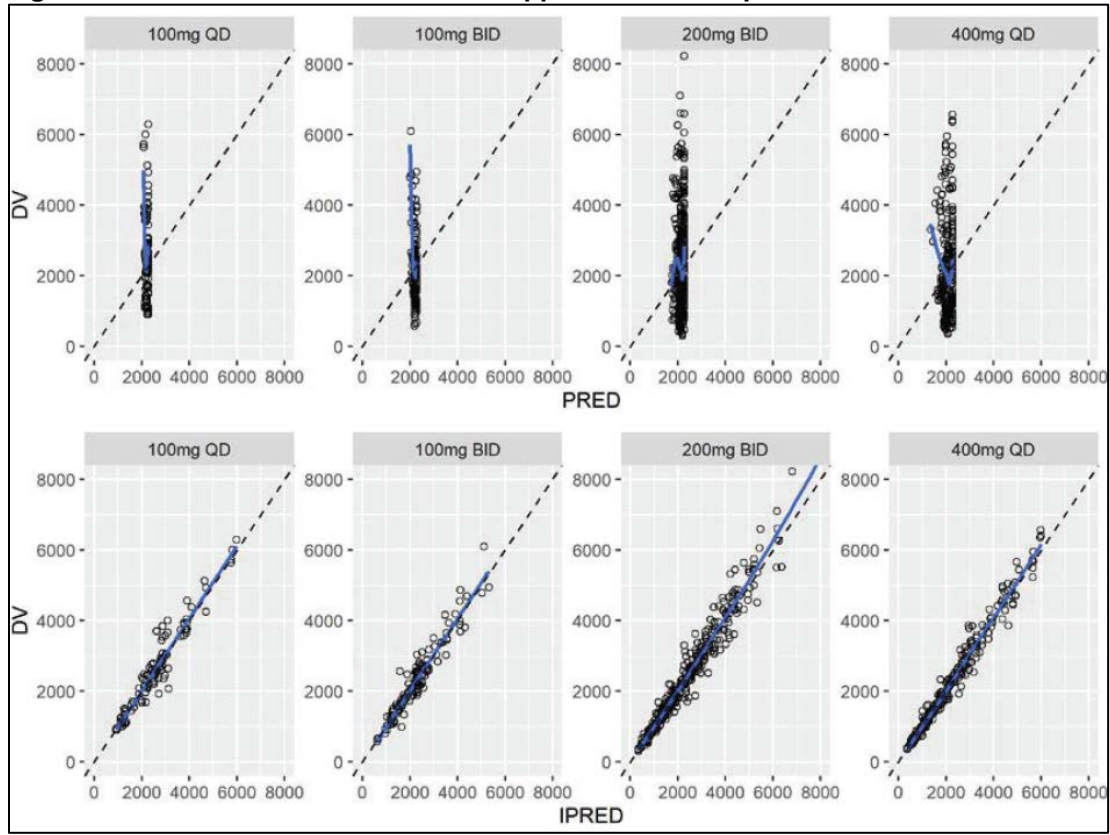
Source: Applicant's pharmacokinetic-pharmacodynamic analysis report (page 30 of 102).
Abbreviations: BID, twice daily; DV, dependent variable; IPRED, individual predicted; PKPD, pharmacokinetics/pharmacodynamics; PRED, predicted; QD, once daily

Figure 42. Visual Predictive Checks of the Applicant's Final Spleen Volume PKPD Model
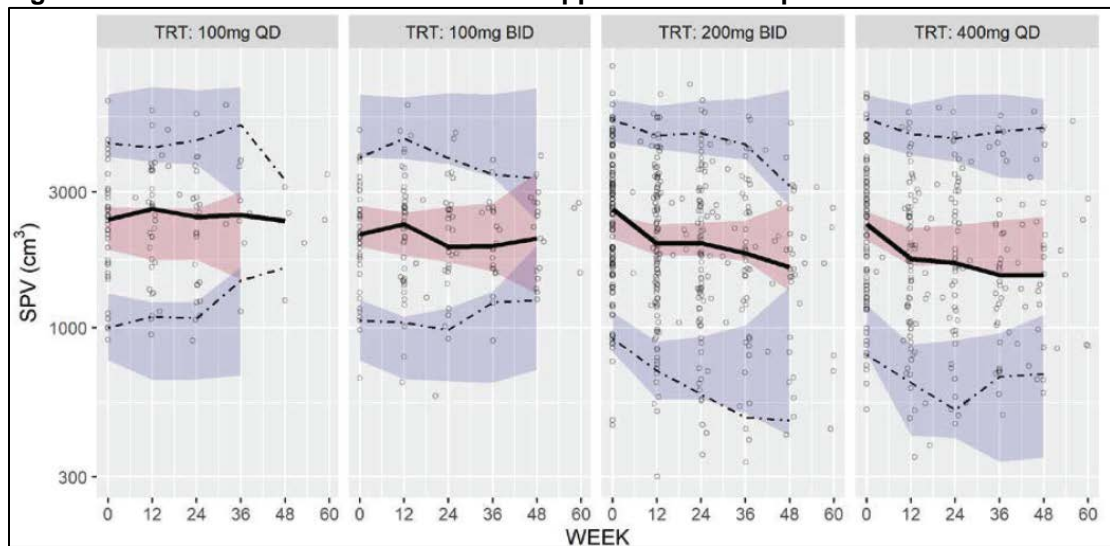
Source: Applicant's pharmacokinetic-pharmacodynamic analysis report (page 32 of 102).
Abbreviations: BID, twice daily; PKPD, pharmacokinetics/pharmacodynamics; QD, once daily; SPV, spleen volume

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Simulation of Spleen Volume Reductions

The Applicant used the final spleen volume PKPD model to simulate profiles of spleen volume reductions after 24 weeks of treatment with different dosing regimens. In these simulations, a typical population (N=500) of patients with myelofibrosis (covariates set to median) was used. Previous ruxolitinib treatment was set to 1 (with) or 0 (without) during simulation to visualize the magnitude of prior ruxolitinib treatment on spleen volume reduction. Figure 43 shows the simulated spleen volume profile for a typical patient. The figure shows dose-dependent increase in magnitude of change from baseline with maximum decrease observed by Week 6 of treatment. Subjects on prior ruxolitinib treatment had lesser spleen volume reduction than treatment-naïve patients.

Figure 43. Visual Predictive Checks of the Applicant's Final Spleen Volume PKPD Model

Source: Applicant's pharmacokinetic-pharmacodynamic analysis report (page 34 of 102).
Abbreviations: BID, twice daily; PKPD, pharmacokinetics/pharmacodynamics; QD, once daily; RUX, ruxolitin b; SPV, spleen volume; TRT, treatment

14.4.3.2. Applicant's Exposure vs. Total Symptom Score Analyses

The Applicant developed the total symptom score (TSS) PKPD model using the same patient population used for SPV PKPD modeling. The TSS PKPD model was developed in a similar manner as how the SPV PKPD model was developed, i.e., similar base, covariate, and final model. Dropout modeling was not implemented in the TSS PKPD model. Therefore, TSS was not tested as a predictor of dropout. Parameter estimates of the final TSS PKPD model are given in Table 111. The estimate of the SLOP parameter shows a statistically significant inverse relationship between pacritinib concentration and TSS. These results indicate that the higher the pacritinib exposure the lower the TSS.

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Table 111. Parameter Estimates of the Applicant's Final TSS PKPD Model

Parameter (Units)		Indirect SLOP model (OBJ= -3922.00)	
		estimate	RSE (%) or IIV shrinkage (%)
BASE (score)	θ1	23.5	6.3
SLOP (score/(ng/mL))	θ2	0.0297	7.7
Kin (/hr)	θ3	8.29	8.0
Ruxolitinib (RUX=1)	θ8	0.916	6.0
Residual Error	θ9	0.293	0.4
IIV BASE (CV)	η1	0.705	29.4
IIV SLOP (CV)	η2	0.768	26.0
Correlation IIV (BASE-SLOP)		NE	--

Source: Applicant's pharmacokinetic-pharmacodynamic analysis report (page 29 of 102).
Abbreviations: CV, coefficient of variation; Kin, synthesis rate; IIV, interindividual variation; NE, not estimated; PKPD, pharmacokinetics/pharmacodynamics; RSE, relative standard error; TSS, total symptom score

The diagnostic goodness-of-fit plots and the visual predictive check plot of the final TSS PKPD model are given in Figure 44 and Figure 45, respectively.

Figure 44. Goodness-of-Fit Plots of the Applicant's Final TSS PKPD Model
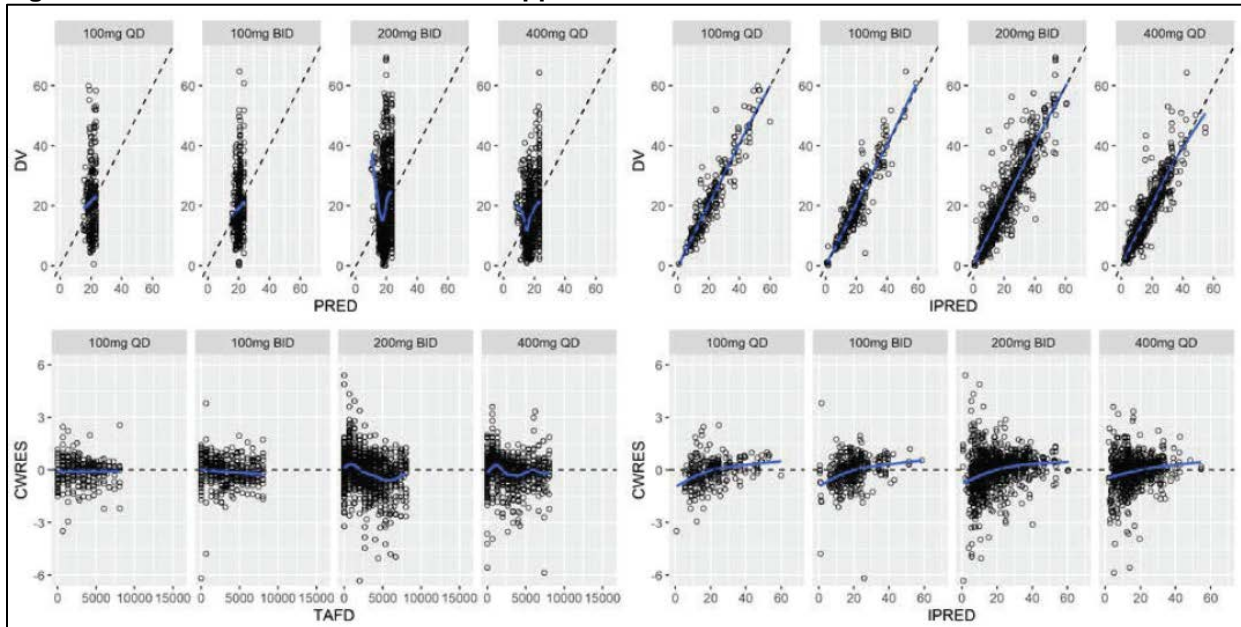
Source: Applicant's pharmacokinetic-pharmacodynamic analysis report (page 31 of 102).
Abbreviations: BID, twice daily; CWRES, conditional weighted residuals; DV, dependent variable; IPRED, individual predicted; PKPD, pharmacokinetics/pharmacodynamics; PRED, predicted; QD, once daily; TAFD, time after first dose; TSS, total symptom score

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Figure 45. Visual Predictive Checks of the Applicant's Final TSS PKPD Model

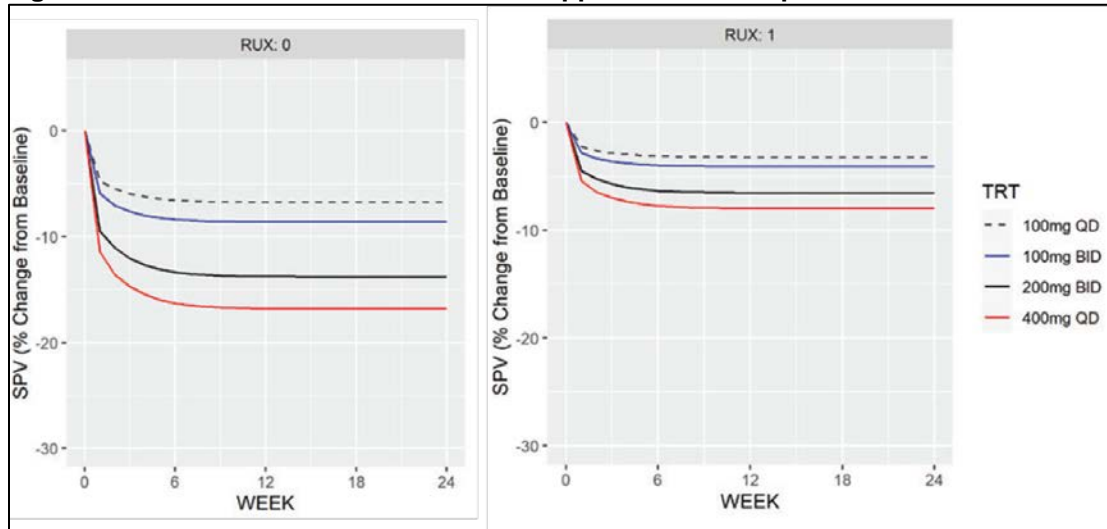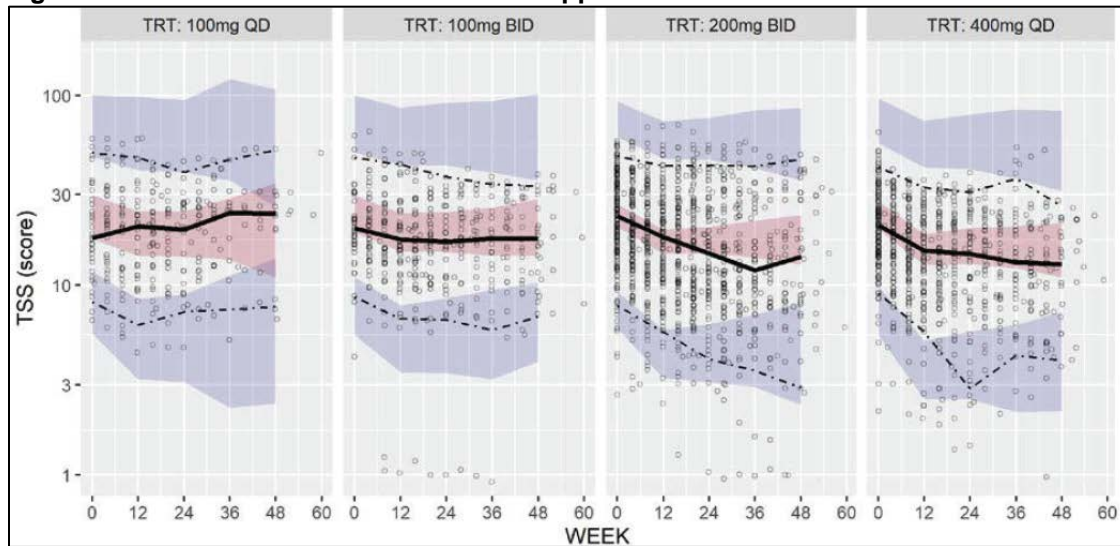Source: Applicant's pharmacokinetic-pharmacodynamic analysis report (page 33 of 102).
Abbreviations: BID, twice daily; PKPD, pharmacokinetics/pharmacodynamics; QD, once daily; TRT, treatment; TSS, total symptom score

14.4.3.3. Applicant's Exposure vs. Spleen Volume Responder Rate Analyses

The Applicant investigated the relationship between different metrics of pacritinib exposure (i.e., AUC, C_{max}, and C_{min}) and spleen volume response rate using pooled data from Phase 2 and 3 studies. A subject was a spleen volume responder (SPVr) if at the time of evaluation, spleen volume had decreased by ≥35%. The metrics of exposure were calculated from estimated PK parameters and time-averaged dose computed up to the time of event or last administered dose. The relationships between SPVr and the exposure metrics or other limited covariates were investigated through univariate logistic regression analyses. The final multivariate models were developed using significant univariate predictors of SPVr. The Applicant included 182 patients with SPV data at Week 24. Subjects who dropped from the study or who had no SPV data at Week 24 were excluded from these analyses.

Figure 46 shows the parameter estimates of the AUC versus SPVr model. Only AUC and prior ruxolitinib use were significant predictors of SPVr.

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Figure 46. Analysis Output of the Multivariate Logistic Regression Model for Spleen Volume Responder Rates

```
-----SPV-----

--- full model ---

Call:
glm(formula = SPV ~ AUC + RUX + PLATFL + ALBB, family = binomial(link = "logit"),
    data = d)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.5359  -0.6084  -0.4029  -0.2910   2.5523

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.388419   2.591086  -0.536   0.5921
AUC          0.008202   0.003368   2.435   0.0149 *
RUX         -1.139242   0.461460  -2.469   0.0136 *
PLATFL       0.498332   0.443371   1.124   0.2610
ALBB        -0.037008   0.054126  -0.684   0.4941
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 155.94  on 180  degrees of freedom
Residual deviance: 136.15  on 176  degrees of freedom
  (1 observation deleted due to missingness)
AIC: 146.15
```

Source: Applicant's exposure-response analysis report (page 77 of 85).
Abbreviations: ALBB, albumin; AUC, area under the concentration-time curve; glm, general linear model; Max, maximum; Min, minimum; PLATFL, platelets; 1Q, first quartile; 3Q, third quartile; RUX, ruxolitinib; SPV, spleen volume

Figure 47 shows the probability of SPVr versus AUC stratified by prior ruxolitinib use. The logistic regression model predicts a >50% probability of response for subjects with an AUC >350 h·µg/mL.

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Figure 47. Model-Predicted Probability of Spleen Volume Response (≥35% SPV Reduction by Week 24) by AUC Stratified by Prior Ruxolitinib Treatment
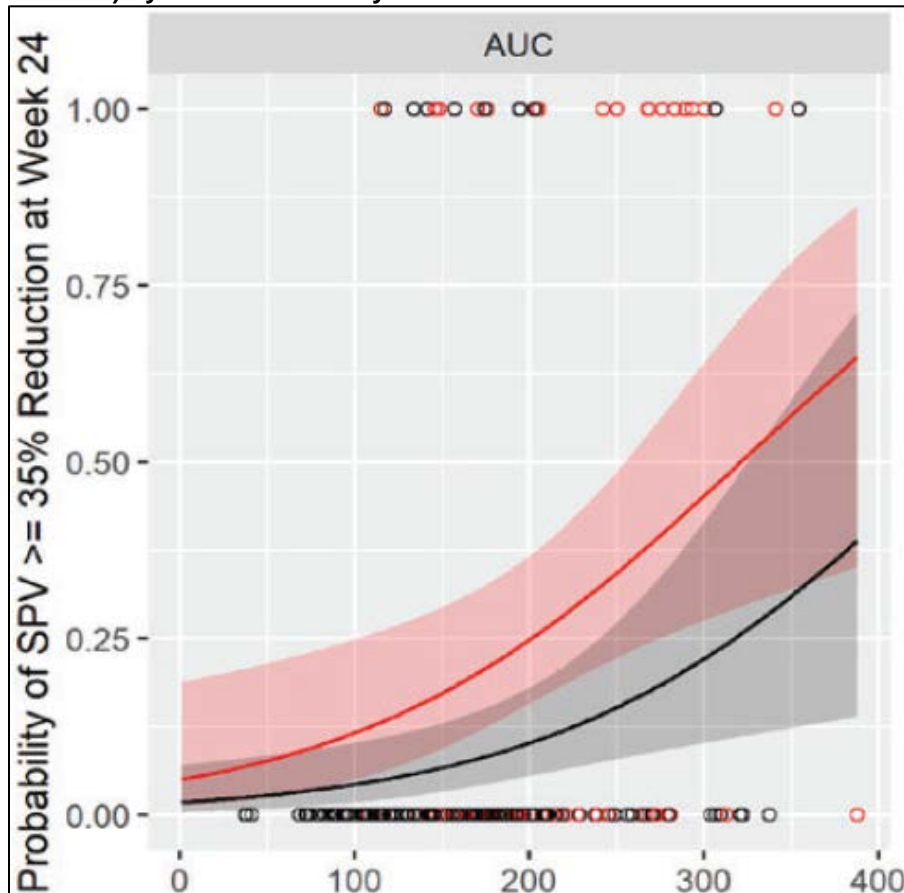
Source: Applicant's exposure-response analysis report (page 47 of 85).
The red line and shaded area show the predicted mean probability of SPV ≥35% and 95% confidence intervals for ruxolitinib naïve patients; the black line and shaded area show corresponding predictions for ruxolitinib-experienced patients. Open circles represent observed categorical data taking values of 0 for SPV <35% and 1 for SPV ≥35%. The red and black open circles are for ruxolitinib-naïve and -experienced patients, respectively.
Abbreviations: AUC, area under the concentration-time curve; SPV, spleen volume

14.4.3.4. Applicant's Exposure vs. Safety Analyses

The Applicant investigated relationships between different exposure metrics (AUC and C_{max}) versus different safety metrics. The exposure metrics were computed as described in Section III.14.4.3.3. The safety metrics included, but were not limited to, cardiovascular adverse events grade ≥3; bleeding grade ≥3 (BLEED); hemorrhage adverse event (AE) grade ≥3 (HMRG); thrombocytopenia toxicity grade ≥2 (THROM); anemia toxicity grade ≥2 (ANEM); gastrointestinal disorders and AEs including nausea, vomiting, and diarrhea grade ≥2 (GIAE); platelet ≤50,000/mL grade ≥3; and drug interruption due to AE.

The relationships between exposure metrics (AUC, C_{max}, and C_{min}) and AEs of interest were evaluated from the pooled PKPD dataset (N=433) using a logistic regression (binomial) model. ANEM, BLEED, GIAE, HMRG, and THROM indicated a significant positive correlation with pacritinib exposure metrics (AUC, C_{max}). Figure 48 shows model-predicted probabilities of different safety metrics by AUC or C_{max}. The figure shows steep exposure versus safety relationships.

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Figure 48. Model-Predicted Probabilities of Safety Metrics by AUC and C_{max}
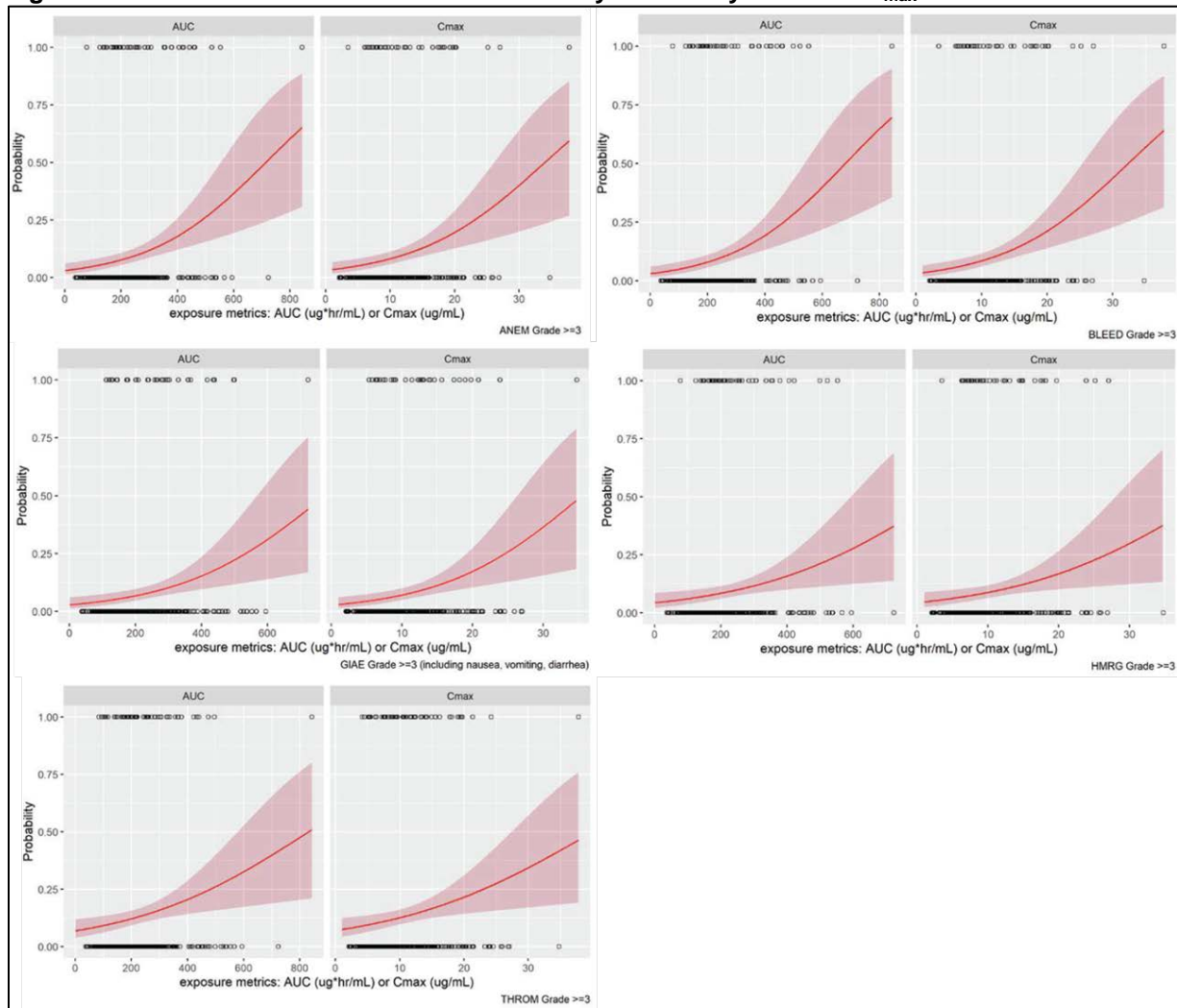
Source: Applicant's exposure-response analysis report (pages 33-37 of 85).
Solid red line is model predicted median, shaded pink area is 95% confidence intervals for the model predictions. Black circles are observed Adverse Events=1 (Yes) or 0 (No).
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration

Reviewer's comment: Although the Applicant's final SPV PKPD model appears to have adequate fit to the data, it has the following limitations concerning accuracy of parameter estimates and the use of the model to predict treatment response at alternative dose regimens:

(1) *The SPV PKPD model uses estimated PK parameters from the Applicant's final population PK model which itself had limitations as stated in Section* III.14.4.2.1.
The Applicant's SPV PKPD model simulations are not consistent with the observed SPV response rates. Although results from PERSIST-2 indicate that subjects on 400 mg QD pacritinib had a numerically lower (although statistically comparable) response rate than subjects on 200 mg BID pacritinib, the SPV PKPD model simulated higher reduction of SPV by 400 mg QD pacritinib than by 200 mg BID pacritinib.
The Applicant's SPV PKPD model estimates the influence of baseline SPV on drug effect (SLOPE) with large uncertainty.

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To have confidence in the estimated PKPD parameter values, the reviewer developed an alternative population PKPD model for SPV as described in Section 14.4.3.5.

The Applicant's logistic regression model for exposure versus spleen volume response (Section 14.4.3.3) also has limitations concerning simulation of response at alternative dose regimens. Figure 49 shows the probability of response curve (predicted by logistic regression models for SPV response and hemorrhage) overlaid over the range of exposures after 100 mg BID, 200 mg BID, and 400 mg QD pacritinib. The SPVr predictions are for typical patients without prior ruxolitinib treatment, baseline albumin of 40 g/mL, and baseline platelet count of <50,000/mL. As shown in this figure, contrary to the observed response rates, the logistic regression model for SPV response predicts higher response rates. The model predicts a higher response rate at 400 mg QD compared to 200 mg BID pacritinib.

Figure 49. Probability of SPV Response and Hemorrhage Versus AUC, Predicted by the Applicant's Logistic Regression Models for SPV Reduction and Hemorrhage
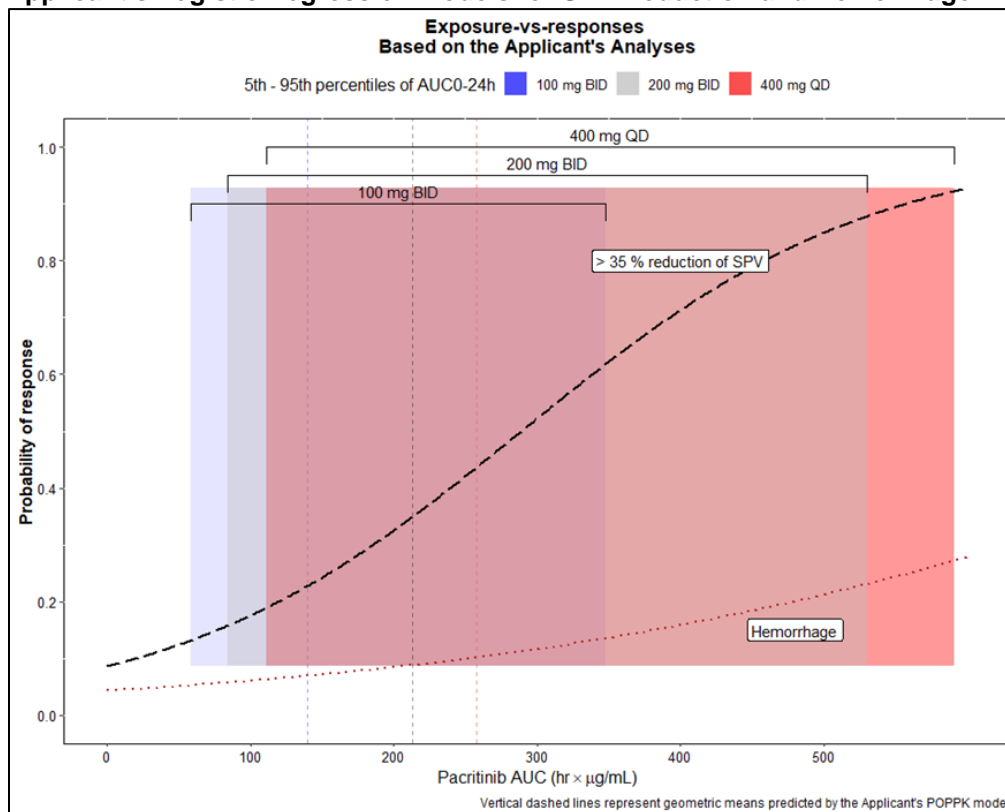
Source: Reviewer's independent analysis.
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; POPPK, population pharmacokinetics; QD, once daily; SPV, spleen volume

14.4.3.5. Reviewer's PKPD Model Development

Data

The reviewer's alternative SPV PKPD model was developed using the same dataset used to develop the Applicant's PKPD model except for the individual PK parameters which were derived from the reviewer's alternative population PK model.

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Base PKPD Model

The reviewer's alternative structural PKPD model was developed by the following steps:

(2) The Applicant's final SPV PKPD model was fit to the new dataset with individual PK parameters derived from the reviewer's alternative population PK model. The OFV of this fit (-1334.5) was 168 units lower than the OFV of the fit using the old dataset with PK parameters derived from the Applicant's final population PK model (-1166.0). However, both fits did not converge successfully. The fit with the new dataset terminated due to proximity of the next iteration estimate to a value at which the OFV is infinite. The fit with the original dataset terminated due to rounding errors.

Method 2 (B2) of handling pharmacodynamic baseline responses was implemented ([Dansirikul et al. 2008](#)). With this method, true baseline is assumed to deviate from individual observed baseline by a random component that is derived from a residual error model ($BL_i \sim |BL_O \times e^{(\eta \times res)}$). Using the B2 method significantly improved model fit ($\Delta OFV = -738.4$) and was retained for further model developments. Method 2 (B2) of handling pharmacodynamic baseline responses was implemented ([Dansirikul et al. 2008](#)). With this method, true baseline is assumed to deviate from individual observed baseline by a random component that is derived from a residual error model ($BL_i \sim |BL_O \times e^{(\eta \times res)}$). Using the B2 method significantly improved model fit ($\Delta OFV = -738.4$) and was retained for further model developments.

In addition to E_{max} and linear drug-effect models, other drug-effect models that were tested were: the "hockey stick model" and the "Brain's hormesis model." The reason for testing the hormesis model was the biphasic (bell shaped) exposure-response relationship observed after plotting observed SPVr versus average concentration (C_{avg}, calculated in Section [14.4.2.4](#)). [Figure 50](#) shows the observed SPV responder rates at different septiles of C_{avg}, overlaid over the range of 5th to 95th percentiles of C_{avg} after 100 mg BID, 200 mg BID, and 400 mg QD pacritinib exposure. The hormesis model fit the data better than the other models but was unstable due to some parameters being unidentifiable.

Figure 50. Observed SPV Responder Rates Versus AUCs
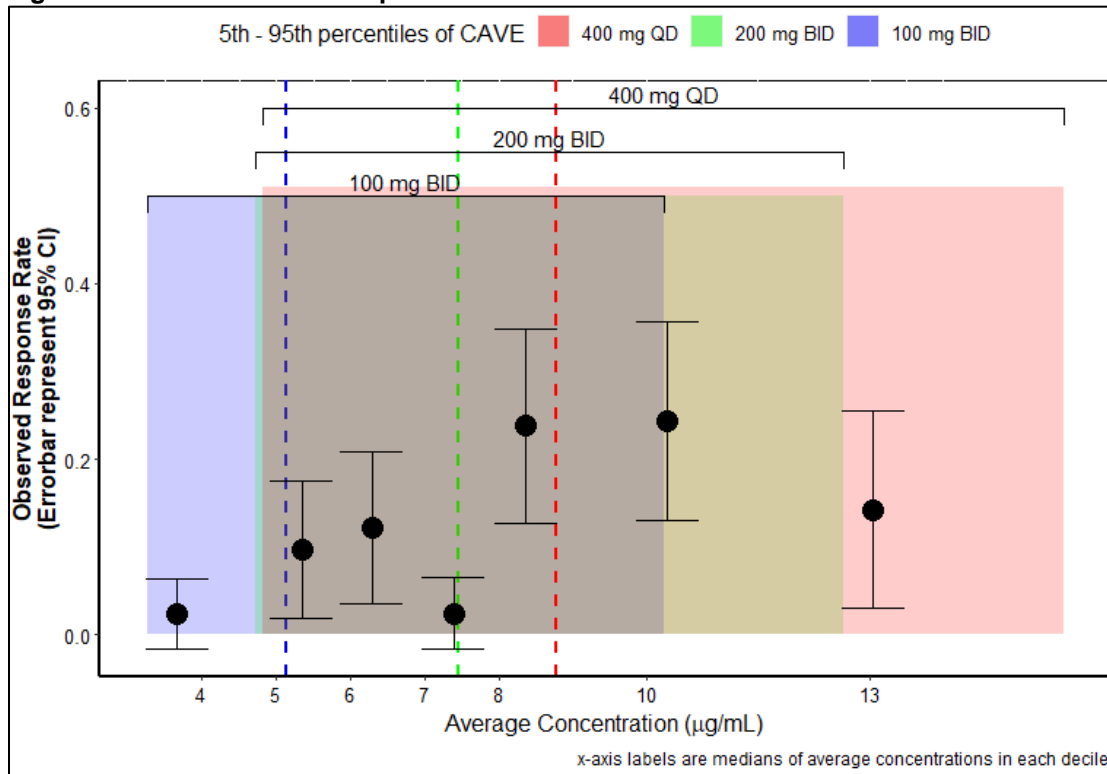
Source: Reviewer's independent analysis.
The colors pale red, blue, and green color represent concentration ranges for 400 mg QD, 100 mg BID, and 200 mg BID respectively. The colors greying green, and tea green represent overlap of exposures. The black points and error-bars represent observed response rates and 95 confidence intervals, respectively.
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; CAVE, average concentration; CI, confidence interval; QD, once daily; SPV, spleen volume.

The fourth step involved identifying hormesis model parameters that could be identifiable. This was done through sensitivity analysis where the impact on OFV of varying one parameter while fixing the others was assessed. Parameters that led to a large change in OFV when changed by more than two-fold were estimated and the others were fixed to reasonable values. The hormesis drug effect model is defined as $EFF =$

$$\left(INT_{MAX} - \frac{(INT_{MAX} - INT_0 + (SLOPE \times CONC))}{\left(1 + \frac{CONC}{EC50}^{HILL}\right)} \right) / 100.$$

*Where EFF is the fractional change in rate of SPV increase (K_{in}), CONC is pacritinib concentration, INT_0 is EFF when CONC=0, INT_{MAX} is EFF at infinite CONC, SLOPE is the concentration coefficient, EC_{50} and HILL have no biological meaning (*Nweke and Ogbonna 2017*). Where EFF is the fractional change in rate of SPV increase (K_{in}), CONC is pacritinib concentration, INT_0 is EFF when CONC=0, INT_{MAX} is EFF at infinite CONC, SLOPE is the concentration coefficient, EC_{50} and HILL have no biological meaning (*Nweke and Ogbonna 2017*).*

Covariate PKPD Model

Candidate covariates of the PD parameters were explored by covariate versus ETA and covariate versus parameter plots. The final covariate model identified the following relationships: prior

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ruxolitinib use on hormesis SLOPE, Study PAC203 on baseline SPV residuals, dropout on SLOPE, and Study PAC203 on hormesis INT_{MAX}.

Reviewer's Final SPV PKPD Model

Parameter estimates of the alternative final SPV PKPD model are given in Table 112. The INT_0 and HILL parameters were fixed to 100% and 2.26, respectively, and other hormesis parameters were estimated. Dropout model parameters were fixed to the parameters estimated in the Applicant's final SPV PKPD model. The goodness-of-fit plots and visual predictive check of the final model are shown in Figure 51 and Figure 52, respectively.

Table 112. Parameter Estimates of the Reviewer's Final SPV PKPD Model

Parameter	Estimate (RSE)
OFV	-2449.826
INT_{MAX} (cm³)	78.31 (3%)
HILL	2.26 (fixed to this value)
EC_{50} (µg/mL)	4.024 (8%)
SLOPE (cm³/µg/mL)	2.731 (23%)
Rate of SPV increase (K_{in}, /hour)	79.99 (39%)
Weibull's LAMDA	-17.2 (fixed to this value)
Weibull's ALPHA	0.65 (fixed to this value)
Fractional change in dropout HAZARD for albumin <35 g/mL	1.77 (fixed to this value)
Ruxolitinib coefficient on hormesis SLOPE	0.5144 (24%)
Fractional change in baseline SPV residuals for study PAC203	0.5523 (16%)
Fractional change in hormesis SLOPE for dropouts	0.661 (26%)
Fractional change in hormesis INT_{MAX} for study PAC203	1.317 (4%)
SPV residual variability (%CV)	0.09225 (2%)
Intersubject variability for SLOPE (%CV)	0.9508 (fixed to this value)
Intersubject variability for INT_{MAX} (%CV)	0.281 (7%)
Intersubject variability for EC_{50} (%CV)	0.296 (17%)

Source: Reviewer's independent analysis.

Abbreviations: CV, coefficient of variation; EC_{50}, half effective concentration; OFV, objective function value; RSE, relative standard error; SPV, spleen volume

Figure 51. Goodness-of-Fit Plot of the Reviewer's Final SPV PKPD Model
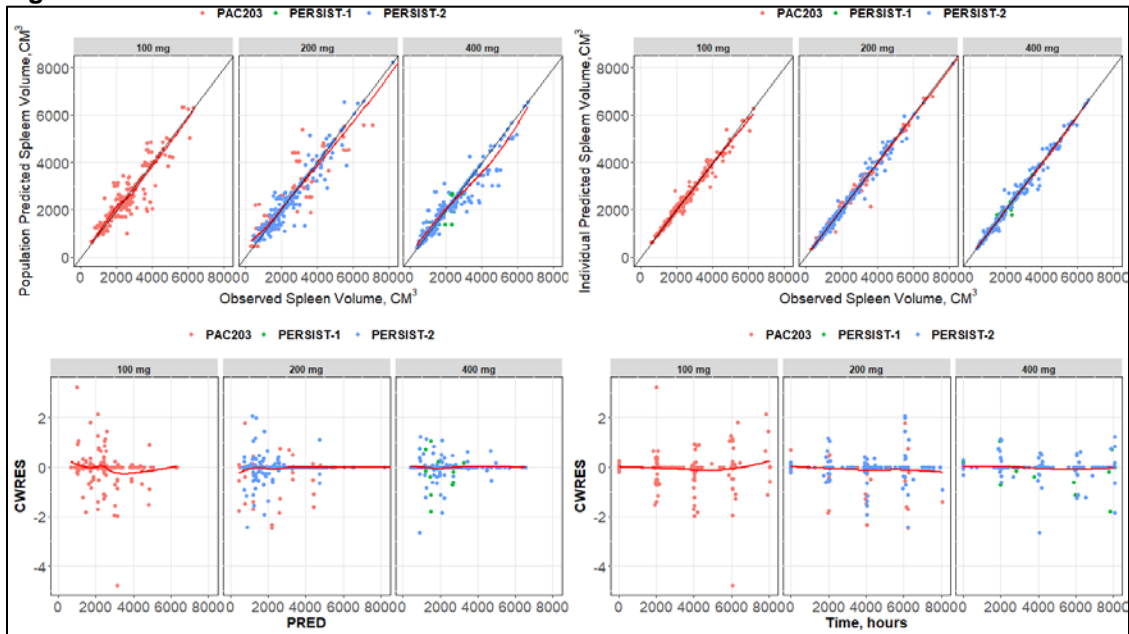
Source: Reviewer's independent analysis.
Abbreviations: CWRES, conditional weighted residuals; PKPD, pharmacokinetics/pharmacodynamics; PRED, predicted; SPV, spleen volume

Figure 52. Visual Predictive Check of the Reviewer's Final SPV PKPD Model
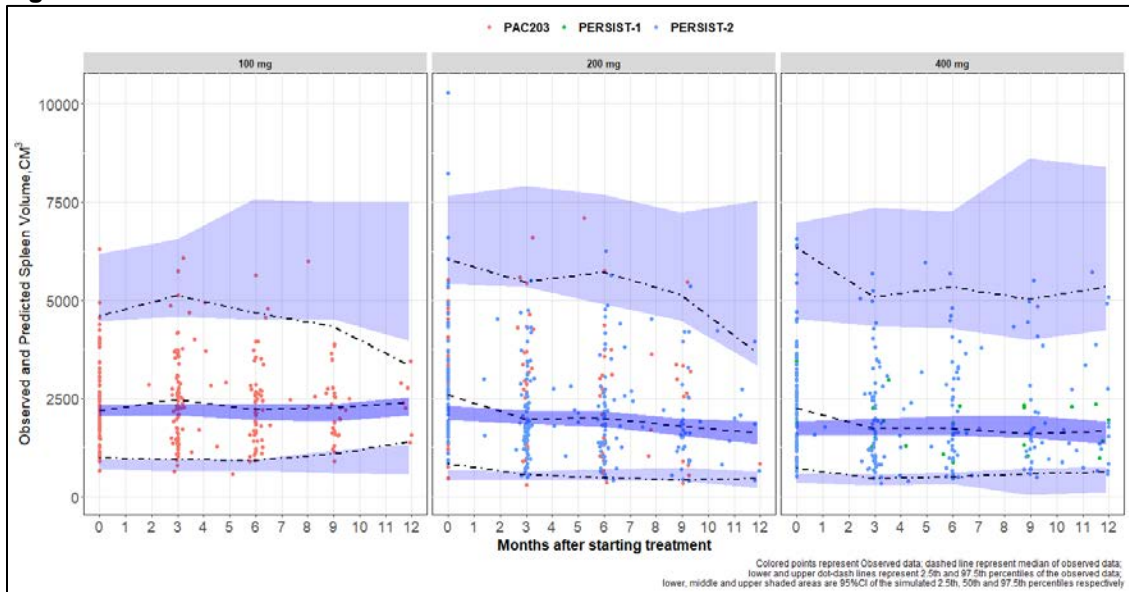
Source: Reviewer's independent analysis.
Abbreviations: PKPD, pharmacokinetics/pharmacodynamics; SPV, spleen volume

Validation of the Reviewer's Final SPV PKPD Model for Prediction of SPV Responders

Graphical explorations were conducted to determine if the reviewer's alternative SPV PKPD model was suitable for simulation of SPV responder rate at different dose regimens.

The first graphical exploration compared response rates from Monte Carlo simulations (VPC data) with observed response rates at 100 mg BID and 200 mg BID pacritinib. In this analysis,

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Monte Carlo simulations, using the final SPV PKPD model and dataset, were used to generate simulated SPV until the sixth month. The individual simulated SPV at baseline and at 6 months were used to calculate change from baseline and hence SPV response (i.e., >35% reduction in SPV). Five-hundred datasets were simulated. Figure 53 shows good agreement between observed and model-simulated response rates.

Figure 53. Observed and Simulated Proportions of Responders at 100 mg BID and 200 mg BID
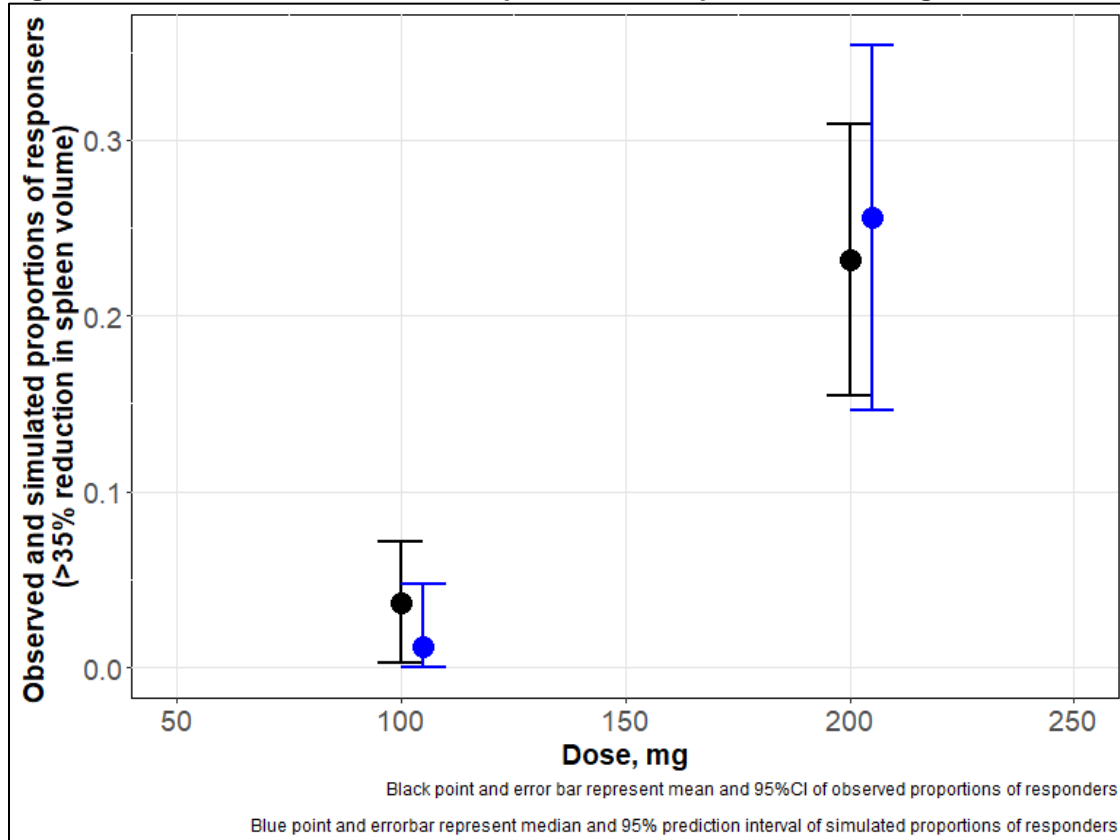
Source: Reviewer's independent analysis.
Abbreviations: BID, twice daily; CI, confidence interval

The second graphical exploration compared response rates from Monte Carlo simulations (VPC data) with observed response rates at different deciles of AUC. In this analysis, data generated for VPC were used to calculate change from baseline at dropout or at the sixth month. Response was defined as a >35% reduction in SPV. AUC was calculated from dose and individual estimated clearance and relative bioavailability. For each subject, the first dose was used for computation of AUC. The simulated response rates (and 95% prediction interval) was plotted and overlaid on observed response rates in each decile of AUC. Figure 54 shows good agreement between observed and Monte Carlo-simulated response rates.

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Figure 54. Observed Proportions of Responders in AUC Deciles Overlaid on the Monte Carlo Simulated Proportion of Responders
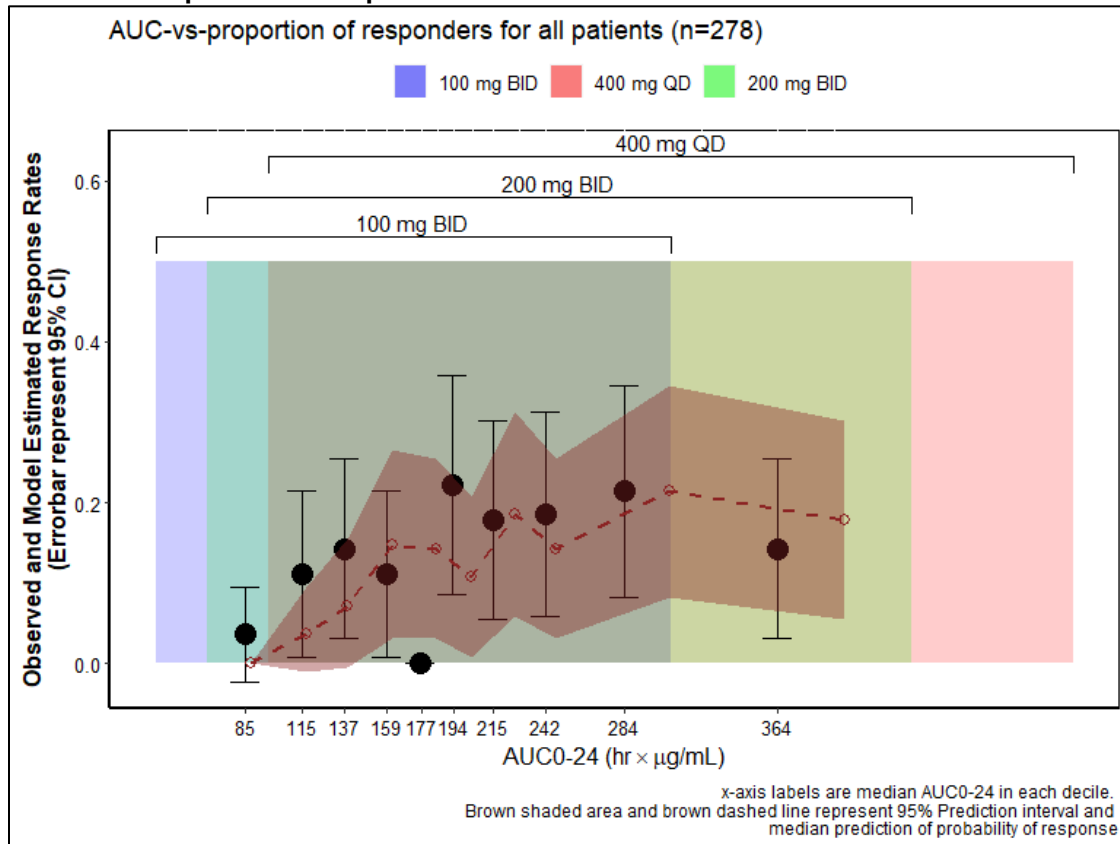
Source: Reviewer's independent analysis.
Black points and error bars represent observed response rates and 95% confidence intervals, respectively.
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; CI, confidence interval; QD, once daily

14.4.3.6. Reviewer's Exposure vs. Safety Modeling

Data

The models for exposure versus safety events were developed using the adverse-event dataset used by the Applicant to develop exposure-versus-safety models. However, the metrics of exposures (C_{max}, C_{avg}, AUC, and cumulative AUC) were computed using individual PK parameters estimated from the reviewer's final population PK model. For each subject, the average dose received until Week 24 (dose intensity) was used for computation of AUC_{0-24}.

Definition of Adverse Events

Adverse events were graded from 0 to 5 (0=no adverse events). For logistic regression analysis, the adverse events were converted from ordinal to binary variables where subjects with grade <3 adverse events were considered to have no adverse events in the logistic regression analysis.

Logistic Regression Modeling

Univariate logistic regression modeling was conducted to assess the relationships between pacritinib AUC and proportions of adverse events. The adverse events considered for analyses

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were hemorrhage, bleeding, diarrhea, thrombocytopenia, and cardiovascular adverse events (CAVE). In addition, a composite adverse event termed hematological disorders was created. Any subject experiencing grade ≥3 bleeding, hemorrhage, thrombosis, or anemia was categorized to have experienced a hematological disorder.

Results from the logistic regression analyses of exposures versus hemorrhage, bleeding, diarrhea, thrombocytopenia, and cardiovascular adverse events (CAVE) are summarized in Figure 55. Pacritinib exposure is statistically significantly associated with thrombocytopenia, bleeding, and hemorrhage but not with diarrhea or CAVE.

Figure 55. Model-Predicted Probability of Adverse Events Versus AUC
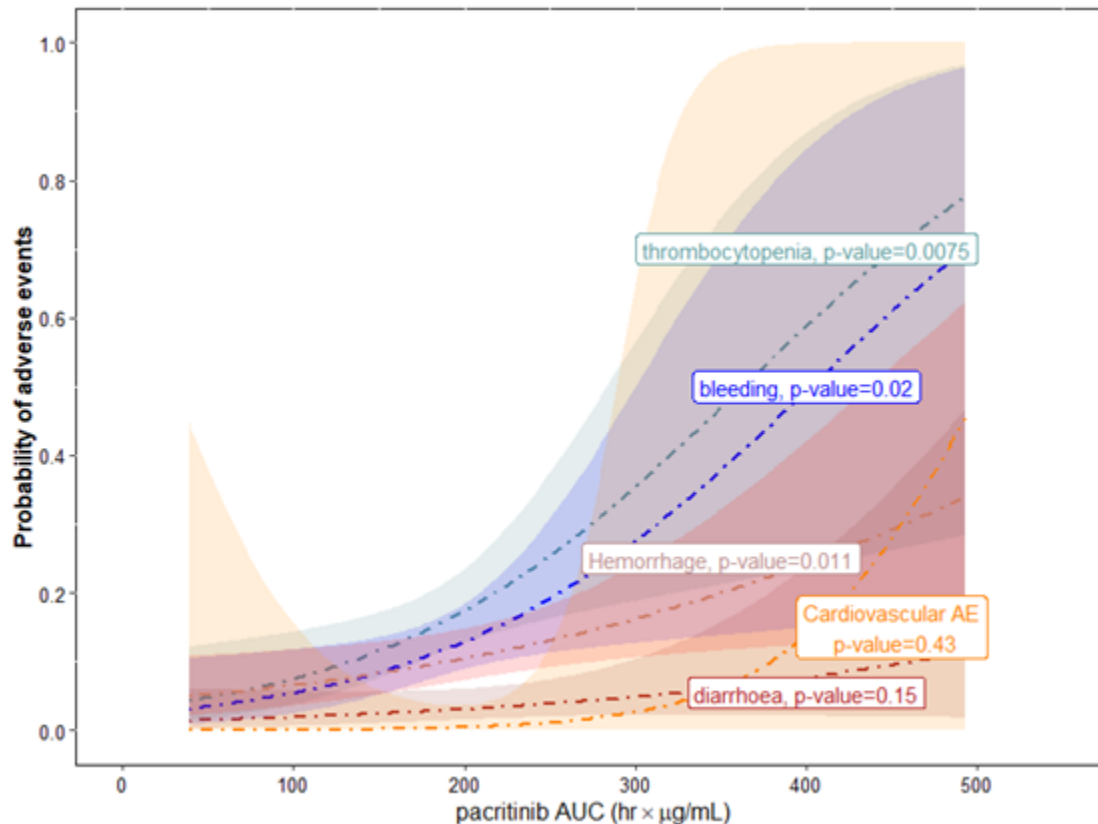
Source: Reviewer's independent analysis.
Note: p-values are nominal and are from the logistic regression model fit.
Abbreviations: AE, adverse event; AUC, area under the concentration-time curve

Figure 56 shows the observed proportions of hematological disorders (as defined above) in different deciles of pacritinib AUC. The figure shows increasing proportions of hematological disorders until the eighth decile. To avoid the impact of undocumented dose reductions or interruptions on frequency of adverse events, the logistic regression analysis of exposure versus hematological disorders excluded subjects with pacritinib AUC >280 µg/mL.

Figure 56. Proportions of Hematological Disorders According to AUC Decile
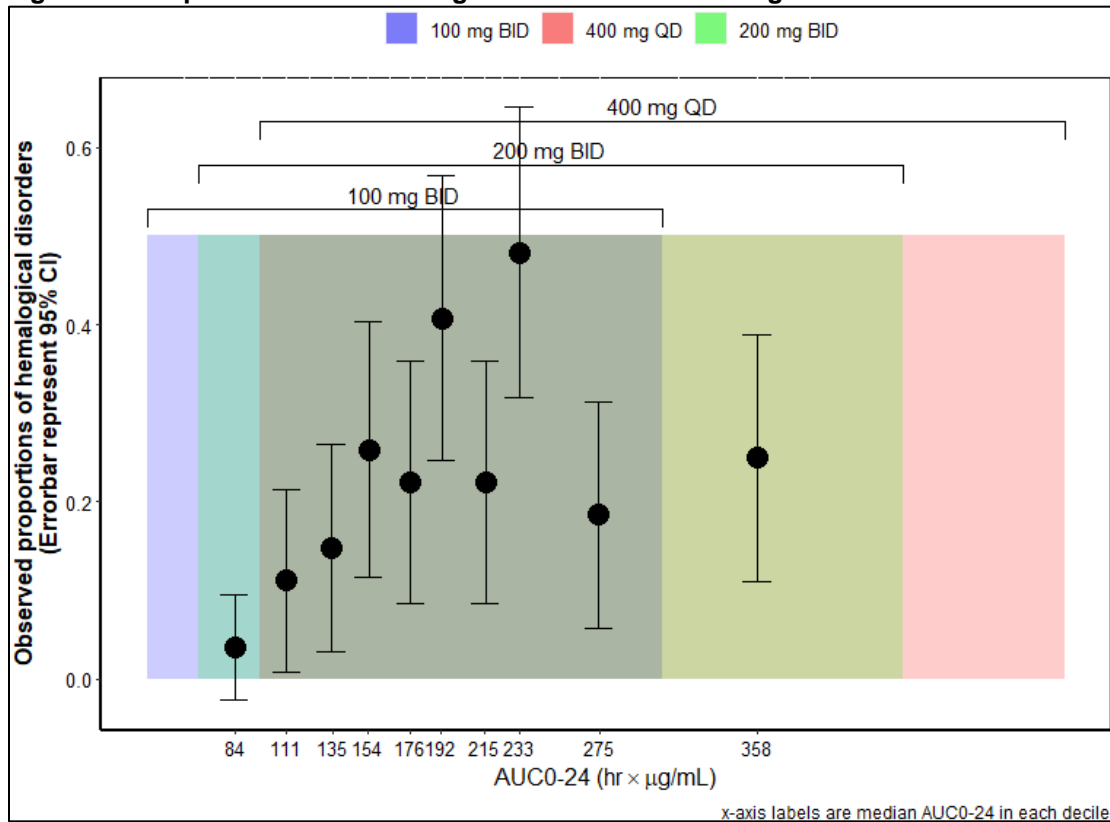
Source: Reviewer's independent analysis.
Note: Hematological disorder is defined as hemorrhage, bleeding, thrombosis, or anemia.
Black points and error-bars represent observed and 95 confidence intervals, respectively.
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; CI, confidence interval; QD, once daily

Logistic regression modeling identified pacritinib AUC to be significantly associated with frequency of hematological disorders. Figure 57 shows that there was good agreement between observed and predicted proportions of hematological disorders.

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Figure 57. Observed Proportions of Hematological Disorders Overlaid on Model-Predicted Median Proportions and 95% Prediction Intervals
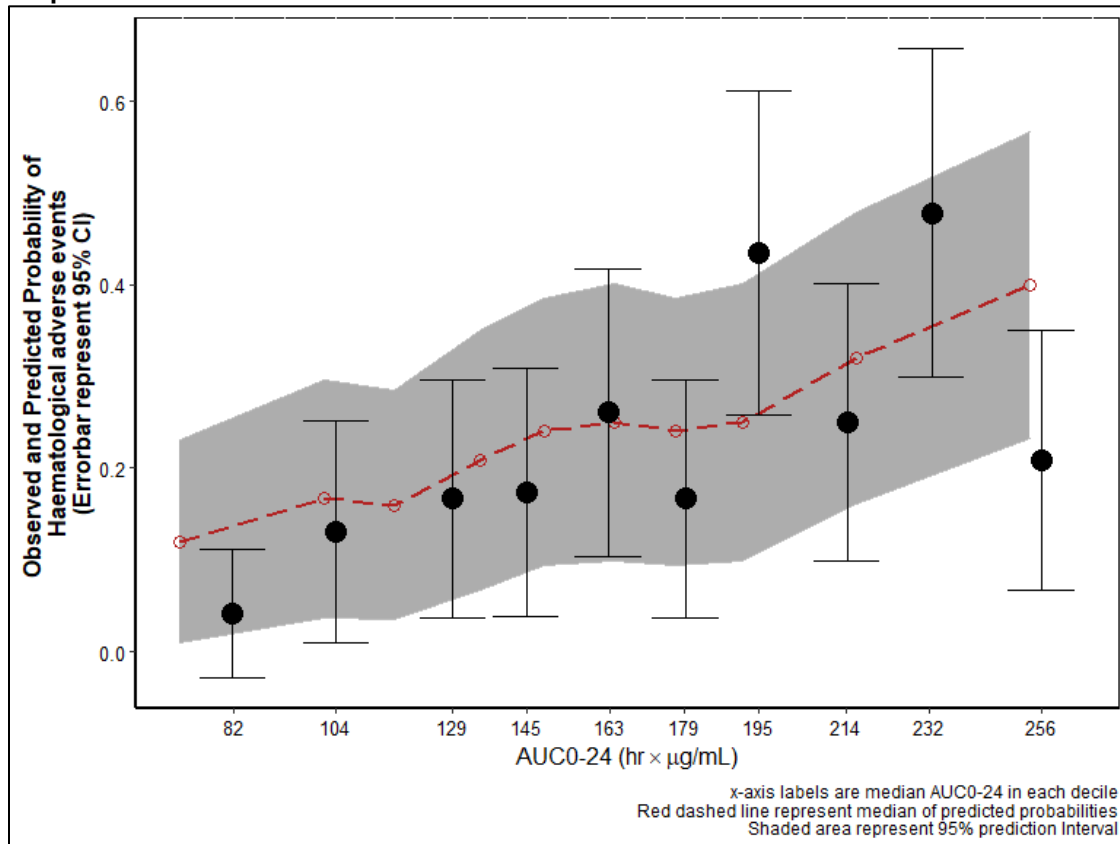
Source: Reviewer's independent analysis.
Black points and error bars represent observed and 95 confidence intervals, respectively. Open circles joined by red dashed lines and the grey-shaded area represent the medians of predicted probabilities and 95% prediction intervals, respectively.
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval

14.4.3.7. Assessment of the Impact of Dose Reduction on Spleen Volume Response

Introduction

Dosing instructions in the PERSIST-2 study recommended dose interruption if patients experienced intolerable adverse events and restarting treatment after resolution of symptoms. For patients in whom adverse reactions reoccur after reinitiation of treatment, it was recommended to reduce the pacritinib dose by 50%. These dosing recommendations have been proposed in the pacritinib label. Therefore, for a patient initiated at 200 mg BID, the dose could be reduced, in steps, to 100 mg BID and finally to 100 mg QD. A patient who cannot tolerate 100 mg QD will terminate pacritinib treatment and continue with best available therapy.

The review of the Applicant's exposure versus SPVr and exposure versus safety analyses indicated that exposure (AUC) after 200 mg BID pacritinib was at the steep part of the exposure-response curve and therefore dose reduction to 100 mg would be associated with significant loss of efficacy with little benefit on alleviation of hemorrhagic adverse events (see Figure 49). However, the observed big overlap in exposure between 100 mg BID and 200 mg BID implies that some patients on 100 mg BID pacritinib could still benefit from the dose

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reduction. For these reasons, independent Monte Carlo simulations were conducted to determine if dose reductions could still preserve efficacy in an appreciable proportion of subjects while alleviating toxicity in the majority of patients.

Simulation Models

Monte Carlo simulations for SPV and hematological disorder responses were conducted using the reviewer's final SPV PKPD model (Section III.14.4.3.5) and the logistic regression model for hematological disorders (Section III.14.4.3.6). The performance of these two models in prediction of SPVr and hematological disorders is illustrated in Figure 58. The medians of AUC_{0-24} after 200 mg BID or 400 mg QD pacritinib are at the plateau of the exposure versus SPVr relationship.

Figure 58. Predicted Probabilities of SPV Reduction and Hematological Disorders at the Expected Range of Pacritinib AUC (i.e., 0 to 600 µg/mL)
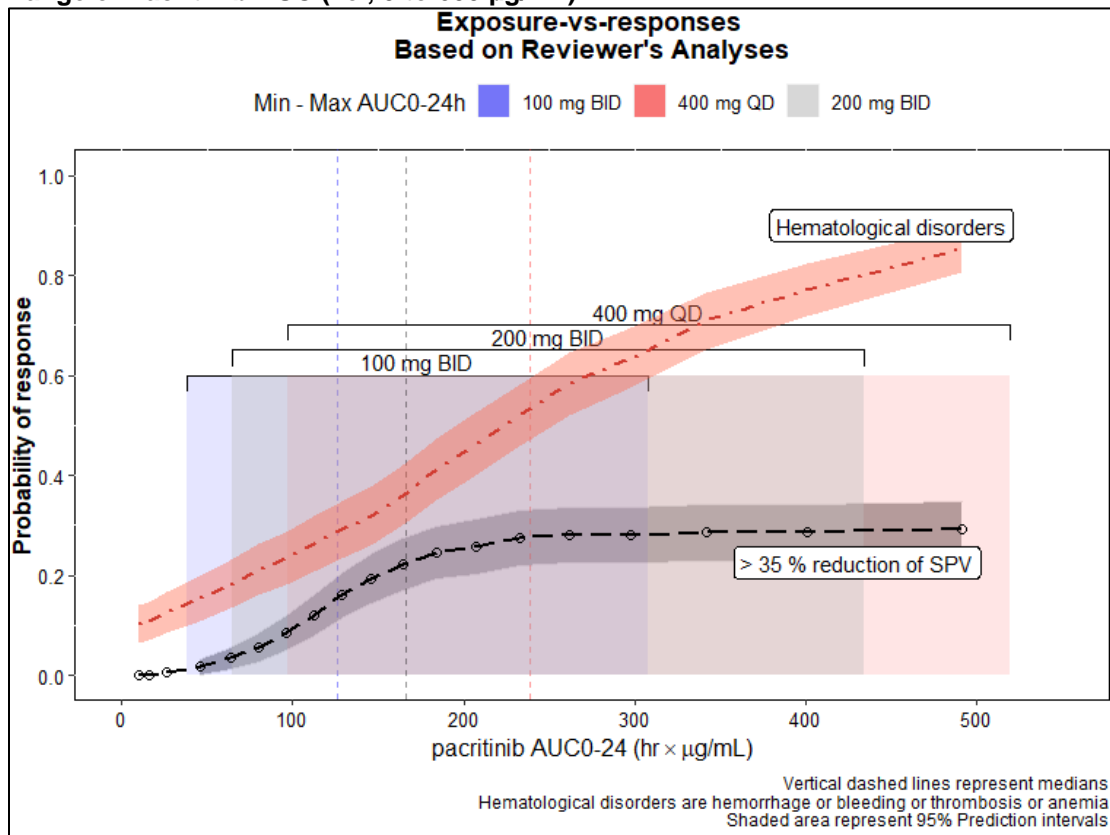
Source: Reviewer's independent analysis.
Prediction intervals are based on stochastic simulations which did not account for uncertainty in predictions. They span the 2.5th to 97.5th percentiles of 200 stochastic simulations.
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; QD, once daily; SPV, spleen volume

Simulation Strategy

A virtual population (n=10,000) with similar distribution of demographic, laboratory, and clinical characteristics as patients with myelofibrosis in the Phase 2/3 studies was created through bootstrap resampling of the SPV PKPD dataset (with replacement). The virtual patients had their individual PKPD parameters derived from Monte Carlo simulations.

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Two simulation steps were performed: First, the patients received 200 mg BID pacritinib for 6 months and daily SPV and hematological disorders were simulated. The simulated SPVs were used to determine SPVr (>35% reduction in SPV). Subjects were considered to be SPV responders or to have hematological disorders if any of the daily records indicated so. Second, patients who were SPVr and had hematological disorders were identified and used to populate a new dataset for simulation with 200 mg QD, 100 mg BID, or 100 mg QD pacritinib. The simulations at lower doses did not involve Monte Carlo simulation but the individual PK parameters derived during simulation with 200 mg BID were used for simulation with any of the reduced doses. After simulations with reduced doses, the proportions of subjects with SPVr and those with hematological disorders were calculated. Each step was repeated 200 times to obtain 95% prediction intervals (PI) of the responder and hematological disorder rates.

Probability of Effectiveness and Safety After Dose Reductions

The simulated proportions of response and hematological disorders after 200 mg BID for 6 months were 23.5% (95% PI, 23.0% to 24.3%), and 34.5% (95% PI, 33.4% to 35.3%). For subjects who were SPVr but experienced hematological disorders at 200 mg BID, when they received 100 mg BID for 6 months, proportion of SPVr was 38.0% (95% PI, 34.0% to 41%) indicating 60% reduction in efficacy. In the same patients, the proportion of hematological disorders was 24% (95% PI, 21% to 27%), indicating 75% reduction in hematological disorders.

Figure 58 shows probabilities of SPVr and hematological disorders at reduced doses in patients who are responders and have hematological disorders at 200 mg BID (Reference). Despite comparable response rates, the 200 mg QD dose regimen is associated with higher rates of hematological disorders than 100 mg BID. By contrast, 100 mg QD results in lower SPVr than 100 mg BID, but the same rate of hematological disorders. Deducing from Figure 58 and Figure 59, it appears that changing from 400 mg QD to 200 mg BID would alleviate hematological disorders without impacting efficacy.

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Figure 59. Probabilities of SPV Reduction and Hematological Disorders After Dose Reductions
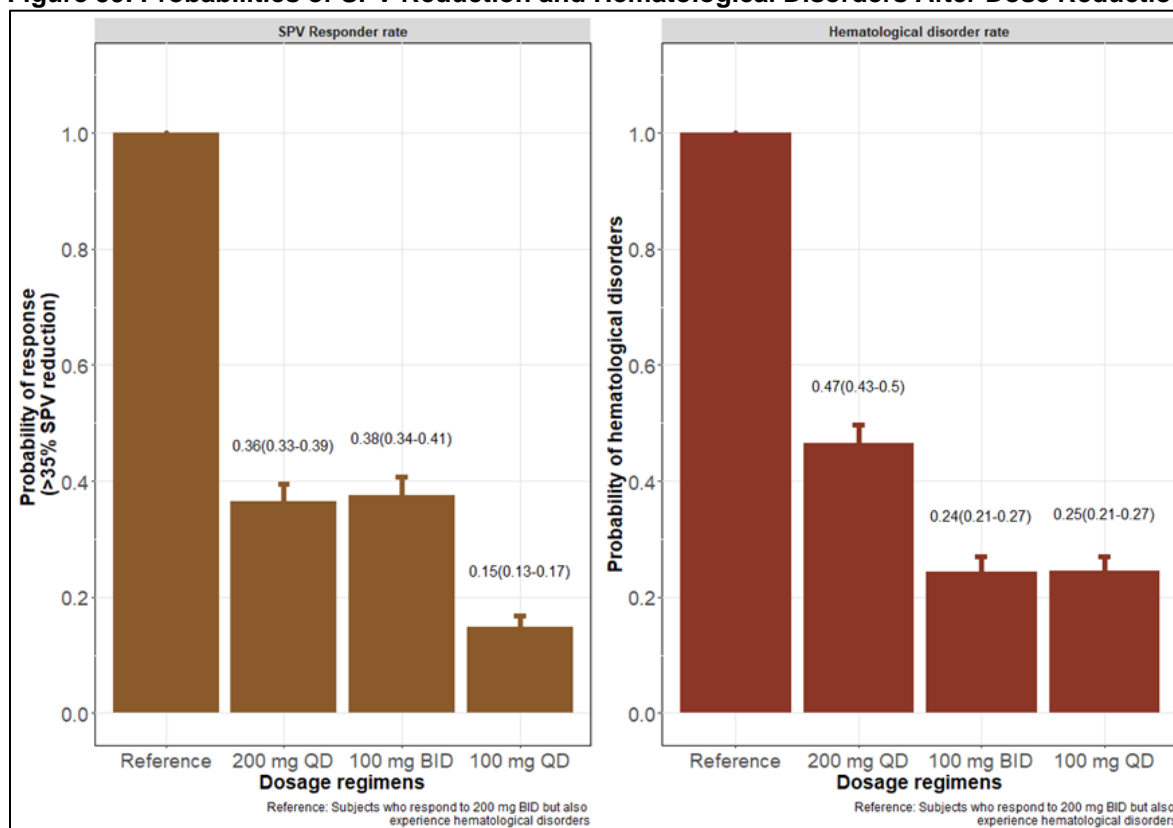
Source: Reviewer's independent analysis.
Note: Reference is subjects who respond to 200 mg BID but also experience hematological disorder.
Abbreviations: BID, twice daily; QD, once daily; SPV, spleen volume

14.4.3.8. Predicted Probabilities of Death Events at 200 mg BID and 400 mg QD

Introduction

Survival data from a study (PERSIST-1) comparing efficacy and safety of 400 mg QD versus best available therapy (BAT) indicated that the 400 mg QD dosing was associated with more death (26%) compared to BAT (6%). However, survival data from another study (PERSIST-2) indicated that proportions of death with 400 mg QD (14.4%) was comparable to that with BAT (15.3%), but higher than that with 200 mg BID dosing (7.6%). The lower death risk for the 200 mg BID dosing is surprising considering that the total daily dose (TDD) of 200 mg BID is equal to TDD of 400 mg QD. The following analyses compares the 200 mg BID to 400 mg QD in the following aspects: (1) estimated C_{max} and AUC_{0-24} among patients in PAC203, PERSIST-1 and PERSIST-2 studies with PK and adverse outcome information (n=276) (2) model predicted probabilities of death events.

Comparisons of Exposures Among Dosage Regimens in the PAC203, PERSIST-1, and PERSIST-2 Studies

As indicated in Table 113, the mean C_{max} and AUC_{0-24} are about 33% and 25% higher for 400 mg QD compared to 200 mg BID. With 400 mg QD dosing, about 19% and 11% subjects

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have C_{max} and AUC_{0-24}, respectively, higher than the 97.5th percentiles of the C_{max} and AUC_{0-24} of the 200 mg BID dosing.

Table 113. Descriptive Statistics of C_{max} (µg/mL) and AUC_{0-24} (hr×µg/mL) Among Subjects With PK and Adverse Events Data in Studies PAC203, PERSIST-1 and PERSIST-2

Pacritinib Dosage	N	Mean		95% CI		Proportions >97.5th Percentile of C_{max} or AUC_{0-24} in 200 mg BID (%)	
		AUC	C_{max}	AUC	C_{max}	AUC	C_{max}
100 mg BID	40	163	6	81-460	3-11	5.00	0.00
100 mg QD	36	124	6	40-211	2-10	0.00	0.00
200 mg BID	121	200	9	92-357	4-15	2.48	2.48
400 mg QD	79	254	12	111-488	5-20	11.39	18.99

Source: Reviewer's independent analysis.
Abbreviations: BID, twice daily; QD, once daily; AUC, area under the concentration-time curve; Cmax, maximum concentration.

Predicted Probabilities of Death Events

To predict death events at different pacritinib doses, an exposure-response model for death events was developed. Only death events occurring during the first 6 months of treatment were considered for this analysis. Table 114 shows the number/proportion of death by the sixth month of treatment stratified by study and treatment groups.

Table 114. Proportions of Deaths in Pacritinib Dosage Groups After 6 Months of Treatment

Study	Pacritinib Dosage	N	Number of Deaths by Month 6	Proportions of Death by Month 6 (%)
PAC203	100 mg BID	40	1	2.50
PAC203	100 mg QD	36	0	0.00
PAC203	200 mg BID	39	1	2.56
PERSIST-1	400 mg QD	6	0	0.00
PERSIST-2	200 mg BID	82	2	2.44
PERSIST-2	400 mg QD	73	4	5.48

Source: Reviewer's independent analysis.
Abbreviations: BID, twice daily; QD, once daily

Logistic regression modeling was used to assess the association between pacritinib exposures (C_{max} and AUC_{0-24}) and probability of death within 6 months of treatment. Table 115 shows the parameter estimates of the logistic regression model of AUC_{0-24} versus death. Figure 60 is a visual predictive check showing good agreement between observed and model-predicted probability of death during the first 6 months of treatment with pacritinib.

Table 115. Parameter Estimates of Logistic Regression Model of AUC_{0-24} Versus Death

Predictors	Estimate	P-Value	Odds Ratio
Intercept	-4.932	0.00	-
AUC_{0-24}	0.006	0.02	1.006

Source: Reviewer's independent analysis.
Abbreviation: AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours

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Figure 60. Observed Proportions of Death Overlaid on Predicted Probability of Death (AUC$_{0-24}$ Versus Death Model)
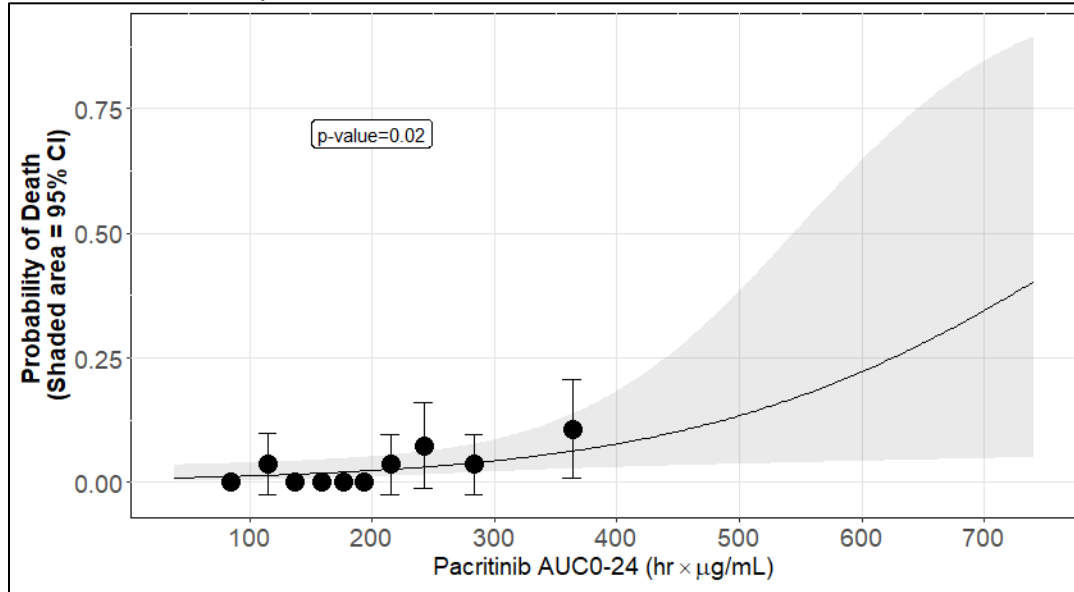
Source: Reviewer's independent analysis.
Abbreviation: AUC$_{0-24}$, area under the concentration-time curve from 0 to 24 hours

Table 116 shows the parameter estimates of the logistic regression model of C$_{max}$ versus death. Figure 61 is a visual predictive check showing good agreement between observed and predicted probability of death by the C$_{max}$-death model.

Table 116. Parameter Estimates of Logistic Regression Model for C$_{max}$(µg/mL) Versus Death

Predictors	Estimate	P-Value	Odds Ratio
Intercept	-5.403	0.000	-
C$_{max}$	0.186	0.015	1.205

Source: Reviewer's independent analysis.
Abbreviation: C$_{max}$, maximum concentration

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Figure 61. Observed Proportions of Death Overlaid on Predicted Probability of Death (C_{max} Versus Death Model)
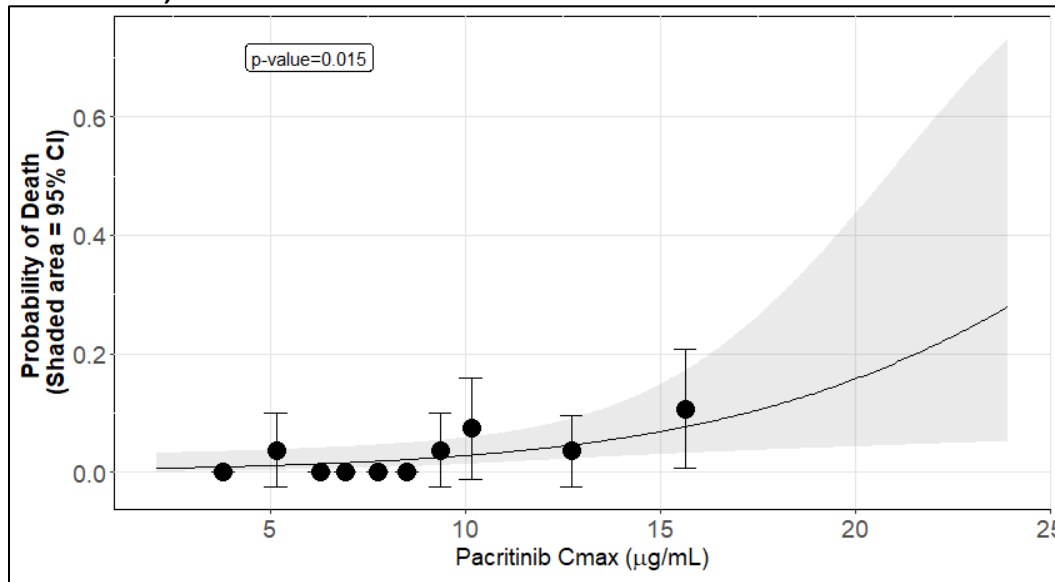
Source: Reviewer's independent analysis.
Abbreviation: C_{max}, maximum concentration

Table 117 shows the predicted probabilities of death by the sixth month of treatment with pacritinib 200 mg BID and 400 mg BID. Due to the higher exposure with 400 mg QD compared to 200 mg BID dosing, the predicted probability of death associated with 400 mg QD is higher by about 3% compared to that associated with 200 mg BID. However, the following are the limitations of this analysis: (1) The exposure-response relationships could be confounded by pacritinib dose adjustments and interruptions due to intolerable adverse events. To reduce the confounding effects of dose changes, the analysis dataset was limited to the first 6 months of treatment; (2) The few deaths in the analysis dataset (i.e., 8 deaths) may not be adequate to characterize the impact of exposure on the incidences of deaths; (3) This was an exploratory analysis to assess associations but not causality of deaths.

Table 117. Predicted Probabilities of Death at 200 mg BID and 400 mg QD

Pacritinib Dosage	Predicted Probability of Death	95% CI
200 mg BID	3.57%	2.2-5.01%
400 mg QD	6.7%	4.8-9.0%

Source: Reviewer's independent analysis.
Abbreviations: BID, twice daily; QD, once daily

15. Trial Design: Additional Information and Assessment

Not applicable.

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16. Efficacy: Additional Information and Assessment

Not applicable.

17. Clinical Safety: Additional Information and Assessment

Not applicable.

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Not applicable.

19. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

A Clinical Inspection Summary was completed by Dr. Anthony Orencia (Medical Officer) in the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations with a final signature date of August 11, 2021, for NDA 208712 supporting document 10 letter date October 9, 2020 (received October 13, 2020) for the marketing application for pacritinib for the MF indication. Dr. Orencia's summary review states that two clinical investigators (John Mascarenhas, M.D., and Huong Nguyen, M.D. [currently Moshe Talpaz, M.D.]) and the Applicant (CTI Biopharma Corp.) were inspected for PERSIST-2. The deficiencies included inadequate or inaccurate record maintenance of study records at the Dr. Mascarenhas study site (three subjects with adverse events were under reported; four subjects with concomitant medications not accurately reported and eCRF not maintained at study site). At the Dr. Talpaz study site, participants did not receive updated informed consent and re-consent after the application was placed on clinical-hold due to the results of the PERSIST-1 study. The OSI review states that Dr. Talpaz provided an adequate response to the violation on July 8, 2021. Dr. Orencia's summary review states that, although regulatory deficiencies were observed at the two investigator sites, the deficiencies appear unlikely to have significant impact on the efficacy and safety results. CTI Biopharma Corp.'s oversight of Studies PAC325 and PAC326 appears to be adequate. Dr. Orencia's review states that, based on these inspections, the data from the two

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studies submitted to the Agency appear acceptable in support of this NDA for the proposed indication.

Reviewer's comment: I agree with Dr. Orencia's summary review and recommendations (final signature date August 11, 2021). The OSI review identified a small number of clinically relevant violations, i.e., three subjects with adverse events were under reported; four subjects with concomitant medications not accurately reported and eCRF not maintained at study site (Dr. Mascarenhas study site). The impact of the identified study site violations overall is expected to be minimal given the low number of violations.

21. Labeling Summary of Considerations and Key Additional Information

The reviewer's table below summarizes the key labeling changes and incorporates recommendations from the various review disciplines. Final wording of the proposed pacritinib product label is also based on agreement with the Applicant.

Table 118. High-Level Labeling Changes

Section	Applicant-Proposed Labeling	FDA Proposed Labeling
Highlights		

(b) (4)

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

(b) (4)

22. Postmarketing Requirements and Commitments

We are requesting the following postmarketing requirements (PMR) for pacritinib. The final wording of the PMRs and timelines for completion of the PMRs are described in the accelerated approval letter.

(3) To verify the clinical benefit of pacritinib, a confirmatory trial will be required to show that pacritinib improves the proportion of patients achieving a ≥50% reduction in TSS after 24 weeks compared to best available therapy in treatment-naïve adult patients with intermediate- or high-risk MF, including PMF, PPV MF, and PET MF, who have severe thrombocytopenia (platelet count less than 50,000/µL). Completion and submission of the results of the ongoing PACIFICA trial will be acceptable to address this PMR, although fulfillment of the PMR will be a review issue. This is an open-label randomized comparison of pacritinib versus physicians' choice with SVR (assessed with MRI or CT) and mTSS as coprimary endpoints. These are the same coprimary endpoints used for approval of roxulitinib and fedratinib for MF. The Applicant is also required to evaluate long-terms safety outcomes, e.g., risks for bleeding, thrombosis, infections, cardiac events, secondary malignancies, and mortality.

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Although the trial is open-label, the radiographic readers will be blinded to treatment assignment when assessing SVR. Use of a placebo comparator design is not feasible in this advanced stage of disease. A double-blinded trial design for the Physicians' Choice (which involves four different therapies) is logistically difficult and subject to unblinding due to the different patterns of side effects with the drugs with the Physicians' Choice comparator (danazol, hydroxyurea, low dose ruxolitinib and steroids). Although mTSS could be susceptible to bias in an open-label trial, the coprimary mTSS endpoint requires large improvements (≥50% improvement from baseline), which should be less susceptible to bias than if the endpoint was looking for modest improvements. A more objective endpoint (e.g., mortality) would be desirable in an open-label trial, but we do not consider mortality to be a feasible choice here given that neither of the approved JAK inhibitors for MF have established a mortality benefit in the intermediate/advanced patient population.

(4) A dedicated hepatic impairment study was conducted and submitted to the NDA. However, the study was conducted with a 400 mg dose of pacritinib, which is higher than the approved 200 mg dose. The reason for a decrease in exposure in subjects with hepatic impairment is not entirely clear but may be due to 400 mg being closer to the saturable solubility limit and subjects with hepatic impairment having an altered gastric environment that reduces the solubility of the drug. For these reasons, we are not able to extrapolate the findings observed with the pacritinib 400 mg dose to the clinically relevant dose of 200 mg. Therefore, the Applicant must conduct a dedicated hepatic impairment study at a dose of 200 mg to determine the pharmacokinetics of pacritinib in subjects with hepatic impairment patients relative to healthy controls.

(5) The Applicant must conduct a clinical pharmacokinetic study to determine the effect of repeat doses of pacritinib on the exposure of a sensitive CYP3A substrate. We recommend this study be conducted in accordance with the FDA Guidance for Industry titled, *"Clinical Drug Interaction Studies: Study Design, Data Analysis, and Clinical Implications"* (February 2012).

(6) The Applicant must conduct physiologically based pharmacokinetic (PBPK) modeling analyses to evaluate the effect of repeat doses of strong and moderate CYP3A inhibitors and inducers on the repeat dose pharmacokinetics of pacritinib and to determine appropriate dosing recommendations. If the results from the PBPK analyses are inconclusive, the Applicant must conduct clinical pharmacokinetic studies to address these issues. We recommend that the in silico and in vivo trials be designed and conducted in accordance with the FDA Guidance for Industry titled, *"Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry"* (September 2018) and/or *"Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations"* (February 2012).

(7) The Applicant must conduct a clinical pharmacokinetic study to determine the drug-drug interaction between pacritinib and a cocktail of substrates for CYP1A2, CYP2C19, BCRP, OCT, and P-gp transporters. We recommend this study be conducted in accordance with the FDA Guidance for Industry titled, *"Clinical Drug Interaction Studies: Study Design, Data Analysis, and Clinical Implications."*

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23. Financial Disclosure

Table 119. Covered Clinical Studies: PERSIST-2

Was a list of clinical investigators provided:	Yes ☒☐	No ☐ (Request list from Applicant)
Total number of investigators identified: 123		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): *Reviewer comment: No investigators reported financial interests/arrangements.*
   Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here.
   Significant payments of other sorts: Enter text here.
   Proprietary interest in the product tested held by investigator: Enter text here.
   Significant equity interest held by investigator: Enter text here.
   Sponsor of covered study: Enter text here.		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 123		
Is an attachment provided with the reason:	Yes	No ☐ (Request explanation from Applicant)

24. References

Goh, KC, S Hart, YC Tan, A Chithra, KH Ong, and J Wood, 2009, The Effects of SB1518, a Novel Oral JAK2 Inhibitor, On Ex Vivo Expanded PV Erythroid Progenitors Correlate with Clinical Observations, Blood, 114(22):2913-2913.

Hart, S, KC Goh, V Novotny-Diermayr, CY Hu, H Hentze, YC Tan, B Madan, C Amalini, YK Loh, LC Ong, AD William, A Lee, A Poulsen, R Jayaraman, KH Ong, K Ethirajulu, BW Dymock, and JW Wood, 2011, SB1518, a novel macrocyclic pyrimidine-based JAK2 inhibitor for the treatment of myeloid and lymphoid malignancies, Leukemia, 25(11):1751-1759.

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25. Review Team

Table 120. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Caden Brennen
Nonclinical Reviewer	Jeffrey Quinn
Nonclinical Team Leader	Pedro DelValle
Office of Clinical Pharmacology Reviewer(s)	Li Wang, Eliford Kitabi, Guansheng Liu
Office of Clinical Pharmacology Team Leader(s)	Sudharshan Hariharan, Justin Earp, Yuching Yang
Clinical Reviewer	Andrew Dmytrijuk
Clinical Team Leader	Albert Deisseroth
Statistical Reviewer	Sarabdeep Singh
Statistical Team Leader	Yeh-Fong Chen
Cross-Disciplinary Team Leader	Albert Deisseroth
Division Director (pharm/tox)	Todd Bourcier
Division Director (OCP)	Shirley Seo
Division Director (OB)	Thomas Gwise
Division Director (clinical)	Albert Deisseroth
Office Director (or designated signatory authority)	Hylton Joffe

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 121. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Dhanalakshmi Kasi, Nancy Waites, Daniel Obrzut, Joan Zhao, Poonam Delvadia, Joseph Leginus, Suong Tran; Ee-Sunn Chia
OPDP	Rebecca Falter
OSI	Anthony Orencia, Min Lu
OSE/DEPI	Kate Gelperin, Steve Bird
OSE/DMEPA	Niloofar Rezvani, Hina Mehta
OSE/DRISK	Brad Moriyama, Naomi Boston
Other	Sharon Mills, Barbara Fuller, Mallika Mundkur

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

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Table 122 Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Andrew Dmytrijuk, MD	OND/DNH	I , II.3, II.4, II.6, II.7, III.19, III.20, III.21, III.22, III.23., III.24 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Andrew Dmytrijuk -S	Digitally signed by Andrew Dmytrijuk -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300233348, cn=Andrew Dmytrijuk -S Date: 2022.02.25 12:04:34 -05'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved1
Clinical	Albert Deisseroth, MD, PhD	OND/DNH	I , II.3, II.4, II.6, II.7, III.19, III.20, III.21, III.22, III.23., III.24 ☐ Authored ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Albert B. Deisseroth -S	Digitally signed by Albert B. Deisseroth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000589069, cn=Albert B. Deisseroth -S Date: 2022.02.23 14:24:32 -05'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Albert Deisseroth, MD, PhD	OND/DNH	All Sections ☐ Authored ☐ Contributed ☒ Approved
Deputy Division Director	**Signature:** Albert B. Deisseroth -S	Digitally signed by Albert B. Deisseroth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000589069, cn=Albert B. Deisseroth -S Date: 2022.02.23 14:25:45 -05'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Jeffrey Quinn, PhD	OND/DPTCHEN	5, 5.1, 7.1, 8.3, 8.4, 13, 13.1,13.2 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Jeffrey A. Quinn -S	Digitally signed by Jeffrey A. Quinn -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000364377, cn=Jeffrey A. Quinn -S Date: 2022.02.23 08:15:40 -05'00'	

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 122. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Pedro Del Valle, MS, PhD, FATS	OND/DPTCHEN	5, 5.1, 7.1, 8.3, 8.4, 13 ☐ Authored ☒ Contributed ☒ Approved
Supervisor	**Signature:** Pedro L. Del Valle -A		Digitally signed by Pedro L. Del Valle -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001000884, cn=Pedro L. Del Valle -A Date: 2022.02.23 08:29:25 -05'00'

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Todd Bourcier, PhD	OND/DPTCHEN	5, 5.1, 7.1, 8.3, 8.4, 13 ☐ Authored ☒ Contributed ☒ Approved
Division Director	**Signature:** Todd M. Bourcier - S		Digitally signed by Todd M. Bourcier -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235462, cn=Todd M. Bourcier -S Date: 2022.02.23 08:22:09 -05'00'

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Li Wang, PhD	OTS/OCP/DCEP	5 (Table 11), 6.1, 8.1, 8.2, 14 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Li Wang -S (Affiliate)		Digitally signed by Li Wang -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002641068, cn=Li Wang -S (Affiliate) Date: 2022.02.22 13:06:56 -05'00'

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Eliford Kitabi, PhD	OTS/OCP/DPM	5 (Table 11), 6.1, 14 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Eliford N. Kitabi -S		Digitally signed by Eliford N. Kitabi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002641767, cn=Eliford N. Kitabi -S Date: 2022.02.22 12:45:47 -05'00'

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
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Continued: Table 122. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Guansheng Liu, PhD	OTS/OCP/DPM	8.2 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Guansheng Liu -S	Digitally signed by Guansheng Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Guansheng Liu -S, 0.9.2342.19200300.100.1.1=2003130570 Date: 2022.02.22 14:17:13 -05'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Yuching Yang, PhD	OTS/OCP/DPM	8.2 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Yuching Yang -S	Digitally signed by Yuching Yang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuching Yang -S, 0.9.2342.19200300.100.1.1=2000846164 Date: 2022.02.22 12:33:47 -05'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Justin Earp, PhD	OTS/OCP/DPM	5 (Table 11), 6.1, 14 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Justin C. Earp -S	Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2022.02.23 16:06:15 -05'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Sudharshan Hariharan, PhD	OTS/OCP/DCEP	5 (Table 11), 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Sudharshan Hariharan -S	Digitally signed by Sudharshan Hariharan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000394743, cn=Sudharshan Hariharan -S Date: 2022.02.22 13:55:13 -05'00'	

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
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Continued: Table 122. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Shirley Seo, PhD	OTS/OCP/DCEP	5 (Table 11), 6.1, 8.1, 8.2, 14 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Shirley K. Seo -S		Digitally signed by Shirley K. Seo -S Date: 2022.02.22 14:06:30 -05'00'

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Sarabdeep Singh, PhD	OB/DBIX	Section 1 and Section 6 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Sarabdeep Singh -S		Digitally signed by Sarabdeep Singh -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001109770, cn=Sarabdeep Singh -S Date: 2022.02.23 09:14:09 -05'00'

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Yeh-Fong Chen, PhD	OB/DBIX	Section 1 and Section 6 ☒ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Yeh Fong Chen -S		Digitally signed by Yeh Fong Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yeh Fong Chen -S, 0.9.2342.19200300.100.1.1=1300157970 Date: 2022.02.23 08:41:38 -05'00'

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Thomas Gwise, PhD	OB/DBIX	Section 1 and Section 6 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Thomas E. Gwise -S		Digitally signed by Thomas E. Gwise -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300369224, cn=Thomas E. Gwise -S Date: 2022.02.22 19:48:50 -05'00'

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 122. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Caden Brennen, MS	ORO/DROCHEN	Section 12 ☒ Authored ☐ Contributed ☐ Approved
Regulatory Project Manager	**Signature:** Caden Brennen Digitally signed by Caden Brennen DN: cn=Caden Brennen, o=FDA, ou, email=Caden.Brennen@fda.hhs.gov, c=US Date: 2022.02.22 12:25:13 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Charlene Wheeler, MSHS	ORO/DROCHEN	Section 12 ☐ Authored ☒ Contributed ☒ Approved
Chief, Project Management Staff	**Signature:** Charlene N. Wheeler -S Digitally signed by Charlene N. Wheeler -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000621384, cn=Charlene N. Wheeler -S Date: 2022.02.23 09:33:13 -05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA208712 (IND78406)
Drug Name:	Pacritinib (SB1518 Citrate)
Indication(s):	The treatment of adults with intermediate or high-risk myelofibrosis, including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF).
Applicant:	CTI BioPharma Corp.
	3101 Western Ave. Ste 800
	Seattle, Washington 98121, USA
	Laboratory: (b) (4)
	(b) (4) (b) (4)
Date(s):	Received 4/8/2021
Documents Reviewed:	Study 8000745 (rats) and the electronic tumor.xpt datasets were submitted on 10/12/2020 (via NDA 208712/S-0009) and study 8000741 (mice) was submitted on 11/19/2015 (via NDA 208712/S-0000) and the electronic tumor.xpt datasets was submitted late.
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Feng Zhou, MS
Concurring Reviewers:	Karl Lin, Ph. D., Team Leader
Medical Division:	CDER/OCHEN/DNH
Nonclinical Team:	Jeffrey Quinn, Ph.D
Project Manager:	Caden Brennen, RPM
Keywords:	Carcinogenicity, Dose response

Table of Contents

File Name: NDA208712Carcin.doc

1   Summary

This review evaluates statistically the data of the 2-year oral carcinogenicity study in Sprague-Dawley rats and 26-weeks oral carcinogenicity study in Hemizygous rasH2 Transgenic (001178-T) Mouse. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality). The analyses showed that Pacritinib (SB1518 Citrate) had no effects on survival or tumor incidence in either species.

Rat Study: Rats (60/sex/group) were dosed by oral gavage with SB1518 twice daily for up to 98 weeks. The respective SB1518 doses in the vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 8, 30, and 50 mg/kg/day for male rats and 0, 8, 30, and 80 mg/kg/day for female rats.

The survival analyses didn't show any statistically significant dose response relationship in mortality in both males and females. All rats were terminated at Week 99 due to low survival in vehicle control group. The respective survival rates in the VC, LD, MD, or HD groups at the time they were terminated were 33%, 28%, 30%, and 38% in males and 35%, 35%, 40%, and 58% in females.

Tumor analysis results showed that there were no statistically significant positive dose response relationships among the SB1518 treated groups and the vehicle control group for male and female rats. There was no significant difference between the vehicle control group and each of the SB1518 treated groups in term of tumor incidence rates.

Mouse Study: Mice (25/sex/group) were dosed by oral gavage with SB1518 twice daily for up to 26 weeks. The respective SB1518 doses in the vehicle control (VC), low (LD), mid (MD), high-dose (HD) groups were 0, 6, 100, 160 mg/kg/day for both male and female mice. The positive control group received intraperitoneal injection of 75 mg/kg of NM N-Methyl-N-nitrosourea (MNU) at Day 1.

Excluding the positive control group, the survival analyses didn't show any statistically significant dose response relationship in mortality in males and females. The respective survival rates in the VC, LD, MD, HD, and PC groups at the time they were terminated were 96%, 96%, 88%, 96%, and 8% in males and 84%, 92%, 92%, 96%, and 4% in females. The mortality rates for the positive control group were statistically significantly higher than that for the VC group for both male and female mice.

Excluding the positive control group, the tumor analysis showed that there were no statistically significant positive dose response relationships among the SB1518 treated groups and the vehicle control group for male and female mice. However, the incidence rates of the following tumor types were statistically significantly higher for positive control group compared to vehicle control group: malignant lymphoma in hemolymphoreticular tissue, bronchioloalveolar adenoma in lung, carcinoma and papilloma in stomach in male mice; lymphoma in hemolymphoreticular tissue, bronchioloalveolar adenoma in lung, papilloma in skin, carcinoma and papilloma in stomach, and adenocarcinoma in small intestine jejunum in female mice.

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2   Background

The sponsor, CTI BioPharma Corp., is submitting a New Drug Application (NDA) for Pacritinib (SB1518 Citrate). The proposed indication is for the treatment of adults with intermediate or high-risk myelofibrosis, including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). The sponsor submitted two carcinogenicity study reports: Study 8000745: "A 2-Year Oral Gavage Carcinogenicity Study of Pacritinib in Rats" and Study 8000741: "A 26-Week Carcinogenicity Study of Pacritinib by Oral Gavage in the Hemizygous rasH2 Transgenic (001178-T) Mouse". Study report of 8000745 and the electronic tumor.xpt datasets were submitted on 10/12/2020 (via NDA 208712/S-0009) and the study report of 8000741was submitted on 11/19/2015 (via NDA 208712/S-0000) and the electronic tumor.xpt datasets was submitted late.

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases. Results of this review have been discussed with the nonclinical team.

3   Rat Study- 8000745

Study Report: **8000745.pdf (statistical report on page 1241)**
SAS data: **Tumor.xpt**

The objective of this study was to determine the carcinogenic potential of the test item, Pacritinib (SB1518), a JAK2/FLT3 tyrosine kinase inhibitor, when given twice daily by oral gavage for 104 consecutive weeks to Sprague-Dawley rats. However, due to deteriorating survival rates (when the vehicle control group size reached 20 animals), all groups were terminated prior to the completion of 104 weeks. The respective SB1518 doses in the vehicle control (VC), low (LD), mid (MD), high-dose (HD) groups were displayed in following table:

Group No.	Test Material / Group Assignment	Dose Level (mg/kg BID)[a]	Dose Level (mg/kg/day)[a]	Dose Concentration (mg/mL)[a]	Number of Animals			
					Main Study		TK	
					M	F	M	F
1	Reference Item [b]	0	0	0	60	60	9	9
2	Pacritinib	4	8	0.4	60	60	9	9
3	Pacritinib	15	30	1.5	60	60	9	9
4	Pacritinib	25 (M) 40 (F)	50 (M) 80 (F)	2.5 (M) 4.0 (F)	60	60	9	9
5	Health Screen	-	-	-	10	10	-	-

F= female; M= male; TK= toxicokinetic
[a]: Represents the pacritinib free base based on a correction factor of 1.406 for the citrate salt
[b]: Control group: administered with reference item (0.5%[w/v] methylcellulose [4000 cP], and 0.1% [v/v] Tween 80 in ultra pure water)

Assessment of carcinogenicity was based on anatomic pathology to include incidences of masses or tumors and possible effects on survival. Mortality, clinical observations, body weight, and food consumption were also monitored and evaluated.

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3.1   Sponsor's Analyses

3.1.1   Survival Analysis

Intercurrent mortality data were analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test[12]. Any animal with accidental injury that caused death or unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. If this overall test was significant (p <0.05) and there were more than two groups, then a follow up analysis was done where each treatment group was compared to the vehicle control group using a log-rank test. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's concluded results: There were no effects on survival that would have a negative impact on the objectives of the study.

3.1.2   Tumor Data Analysis

The statistical evaluation of tumor data was done separately for each sex and was limited to all non-secondary neoplastic lesions found in study plan-required tissues/sites, subcutis and hemolymphoreticular tissue using all study animals and to the combination of hemangiosarcoma findings across whole body.

When tumor combinations of interest were required for statistical analysis, the list of these combinations was detailed in a signed study note provided by the study pathologist and approved by the Sponsor prior to the statistical analysis.

Palpable neoplastic lesions found under study plan-required glands were statistically analyzed in a "mortality independent" context according to Peto's onset rate using all study animals. Whereas, non-palpable neoplastic findings were statistically analyzed in a "mortality dependent" context according to Peto's prevalence and death rate methods. Animal deaths occurring after the experimental period were classified as incidental.

For each dataset of interest, Peto's one-sided test was conducted, using dose level scores, in order to assess significance of tumor rate increase across all groups and in each Test Item-treated group when compared to the Reference Item group.

As per Lin (1997), the discrete permutation distribution was used for each statistical test involving a dataset with 10 or less tumor bearing animals.

All statistical tests were performed at the 5% significance level and, as recommended by FDA, significance was reported according to the tumor prevalence classification (common or rare). As per FDA guidance, the processing of incidental tumors was done by creating a single separate interval for the time period following the experimental period and by dividing the experimental period into the following fixed intervals: Days 1-350, Days 351-560, and Days 561-686 for the males, and Days 1-350, Days 351-560, and Days 561-687 for the

females. For each dataset of interest, the significance of a linear dose-related increase in tumor incidence rates, across all groups, was evaluated via Peto's survival-adjusted one-tailed trend test, using the corresponding arithmetic dose level scores.

Sponsor's concluded results: No pacritinib-related effects were seen in the incidence of any neoplastic lesion in male or female rats in this study.

3.2   Reviewer's Analyses

3.2.1   Data Quality

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of this study received on 10/12/2020 via NDA 208712/S-0009. The sponsor only submitted tumor.xpt file. The data quality was acceptable.

3.2.2   Survival Analysis

The survival distributions of rates in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions were tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 3A and 3B in the appendix for male and female rats, respectively.

Reviewer's findings: All rats were terminated at Week 99. This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 40 (67%), 43 (72%), 42 (70%), or 37 (62%) in male rats and 39 (65%), 39 (65%), 36 (60%), or 25 (42%) in female rats in the VC, LD, MD, or HD groups, respectively. The survival analyses didn't show any statistically significant dose response relationship in mortality in males and females.

3.2.3   Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the papers of Bailer and Portier [2] and Bieler and Williams [3]. In this method an animal that lives the full study period (w_{max}) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of $s_h = 1$. An animal that dies at week w_h without developing the tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{max}}\right)^k < 1$. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each

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animal that dies before the terminal sacrifice develops at least one tumor of the tumor type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

The adjusted levels of significance for testing a positive dose response in the 2-year rat study are 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparison in the 2-year rat study are 0.01 and 0.05 for a common tumor and a rare tumor, respectively. A rare tumor is defined as one in which the tumor rate is less than 1% in the vehicle control group. The tumor rates and the p-values of the tested tumor types are listed in Tables 5A, and 5B in the appendix for male and female rats, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of treated groups and control.

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Male Rats

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	8 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	50 mg/kg/day High (H) P - C vs. H
Gland, Thyroid	Follicular Cell Adenoma	0/60 (35)	0/60 (34)	1/60 (34)	3/60 (37)
		0.0215	NS	0.4928	0.1303
	Follicular Cell Carcinoma	0/60 (35)	2/60 (34)	0/60 (34)	1/60 (37)
		0.5133	0.2391	NS	0.5139
	C_Follicular Cell_A+C	0/60 (35)	2/60 (34)	1/60 (34)	4/60 (37)
		0.0494	0.2391	0.4928	0.0642

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, there were no statistically significant positive dose response relationships among the SB1518 treated groups and the vehicle control group for male and female rats. There was no significant difference between the vehicle control group and each of the SB1518 treated groups in term of tumor incidence rates.

4   Mouse Study- 8000741

Study Report: 8000741.pdf (statistical report on page 467)
SAS data: Tumor.xpt

The objective of this study was to determine the carcinogenic potential of the test item, Pacritinib (SB1518), a JAK2/FLT3 tyrosine kinase inhibitor, when given twice daily by oral

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gavage for 26 consecutive weeks to Hemizygous rasH2 Transgenic (001178-T) Mouse. The respective SB1518 doses in the vehicle control (VC), low (LD), mid (MD), high-dose (HD), and positive control (PC) groups were displayed in following table:

| Group No. | No. of Toxicity Animals Main Study | | Test Material | Dose Level (mg/kg BID) | Dose Level (mg/kg/day) |
	M	F			
1	25	25	Vehicle Control	0	0
2	25	25	Positive Control	-	75
3	25	25	Pacritinib	30	60
4	25	25	Pacritinib	50	100
5	25	25	Pacritinib	80	160

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

4.1   Sponsor's Analyses

4.1.1   Survival Analysis

The sponsor used the same survival analysis methods for the rat study in this mouse study.

Sponsor's concluded results: SB1518 administered orally to mice for up to 26 weeks had no effect on survival.

4.1.2   Tumor Data Analysis

The sponsor used the same tumor data analysis methods for the rat study in this mouse study.

 Sponsor's findings: There were no neoplastic findings attributed to SB1518.

4.2   Reviewer's Analyses

4.2.1   Data Quality

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of this study received late. The sponsor only submitted tumor.xpt file. The data quality was acceptable.

4.2.2   Survival Analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 2A and 2B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals

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for VC, LD, MD, HD, and PC groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 1 (4%), 1 (4%), 3 (12%), 1 (4%), or 23 (92%) in male mice and 4 (16%), 2 (8%), 2 (8%), 1 (4%), or 24 (96%) in female mice in the VC, LD, MD, HD or PC groups, respectively. The survival analyses didn't show any statistically significant dose response relationship in mortality in males and females when data of the PC group were excluded. The mortality rates for the PC group were statistically significantly higher than that for the VC group for both male and female mice.

4.2.3   *Tumor Data Analysis*

The tumor data were analyzed for dose response relationships and pairwise comparisons of the vehicle control group separately with each of the treated groups using the same method that was used for the rat study. The adjusted levels of significance for testing a positive dose response in the 6-month mice study are 0.05 and 0.05 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparison in the 6-month mice study are 0.05 and 0.05 for a common tumor and a rare tumor, respectively. A rare tumor is defined as one in which the tumor rate is less than 1% in the vehicle control group. The tumor rates and the p-values of the tested tumor types are listed in Tables 6A, and 6B in the appendix for male and female mice, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of positive control group and vehicle control group.

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Mice

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle Control	75 mg Positive (PC) P - VC vs. PC
Male	Hemolymphoreticular Tissue	Lymphoma, Malignant	0/25 (24)	21/25 (22) 0.0001 **
	Lung	Bronchioloalveolar Adenoma	1/25 (24)	4/25 (12) 0.0336 **
	Stomach	Carcinoma	0/25 (24)	8/25 (15) 0.0001 **
		Papilloma	0/25 (24)	19/25 (22) 0.0001 **
Female	Hemolymphoreticular Tissue	Lymphoma, Malignant	0/25 (23)	21/25 (23) 0.0001 **
	Lung	Bronchioloalveolar Adenoma	2/25 (23)	5/25 (11) 0.0238 **
	Skin	Papilloma	0/25 (23)	4/25 (10) 0.0051 **
	Small Intestine, Jejunum	Adenocarcinoma	0/24 (23)	4/25 (11) 0.0071 **
	Stomach	Carcinoma	0/25 (23)	4/25 (12) 0.0095 **

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Sex	Organ name	Tumor name	0 mg/kg/day Vehicle Control	75 mg Positive (PC) P - VC vs. PC
		Papilloma	0/25 (23)	23/25 (23) 0.0001 **

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for both a common tumor and a rare tumor.

Based on the criteria of adjustment for multiple testing discussed above, there were no statistically significant positive dose response relationships among the SB1518 treated groups and vehicle control group for male and female mice when data of the positive control group were excluded. However, the incidence rates of tumor types listed in above table were statistically significantly higher for positive control group compared to vehicle control group.

5   Conclusion

This review evaluates statistically the data of the 2-year oral carcinogenicity study in Sprague-Dawley rats and 26-weeks oral carcinogenicity study in Hemizygous rasH2 Transgenic (001178-T) Mouse. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality). The analyses showed that Pacritinib (SB1518 Citrate) had no effects on survival or tumor incidence in either species.

Rat Study: Rats (60/sex/group) were dosed by oral gavage with SB1518 twice daily for up to 98 weeks. The respective SB1518 doses in the vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 8, 30, and 50 mg/kg/day for male rats and 0, 8, 30, and 80 mg/kg/day for female rats.

The survival analyses didn't show any statistically significant dose response relationship in mortality in both males and females. All rats were terminated at Week 99 due to low survival in vehicle control group. The respective survival rates in the VC, LD, MD, or HD groups at the time they were terminated were 33%, 28%, 30%, and 38% in males and 35%, 35%, 40%, and 58% in females.

Tumor analysis results showed that there were no statistically significant positive dose response relationships among the SB1518 treated groups and the vehicle control group for male and female rats. There was no significant difference between the vehicle control group and each of the SB1518 treated groups in term of tumor incidence rates.

Mouse Study: Mice (25/sex/group) were dosed by oral gavage with SB1518 twice daily for up to 26 weeks. The respective SB1518 doses in the vehicle control (VC), low (LD), mid (MD), high-dose (HD) groups were 0, 6, 100, 160 mg/kg/day for both male and female mice. The positive control group received intraperitoneal injection of 75 mg/kg of NM N-Methyl-N-nitrosourea (MNU) at Day 1.

Excluding the positive control group, the survival analyses didn't show any statistically significant dose response relationship in mortality in males and females. The respective survival

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rates in the VC, LD, MD, HD, and PC groups at the time they were terminated were 96%, 96%, 88%, 96%, and 8% in males and 84%, 92%, 92%, 96%, and 4% in females. The mortality rates for the positive control group were statistically significantly higher than that for the VC group for both male and female mice.

Excluding the positive control group, the tumor analysis showed that there were no statistically significant positive dose response relationships among the SB1518 treated groups and the vehicle control group for male and female mice. However, the incidence rates of the following tumor types were statistically significantly higher for positive control group compared to vehicle control group: malignant lymphoma in hemolymphoreticular tissue, bronchioloalveolar adenoma in lung, carcinoma and papilloma in stomach in male mice; lymphoma in hemolymphoreticular tissue, bronchioloalveolar adenoma in lung, papilloma in skin, carcinoma and papilloma in stomach, and adenocarcinoma in small intestine jejunum in female mice.

Feng Zhou
Mathematical Statistician

Concurring Reviewer: Karl Lin, Ph.D., Team Leader, Biometrics-6
cc:
Dr. Jeffrey Quinn
Dr. Yi Tsong
Dr. Karl Lin

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6   Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

Week / Type of Death	Vehicle Control No. of Death	Cum %	Low Dose No. of Death	Cum %	Mid Dose No. of Death	Cum %	High Dose No. of Death	Cum %
0 - 50	7	11.67	2	3.33	4	6.67	4	6.67
51 - 80	10	28.33	21	38.33	19	38.33	16	33.33
81 - 98	22	65.00	19	70.00	18	68.33	17	61.67
Accidental Death	1	1.67	1	1.67	1	1.67		
Terminal sacrifice	20	33.33	17	28.33	18	30.00	23	38.33
Total	60		60		60		60	

Table 1B: Intercurrent Mortality Rate in Female Rats

Week / Type of Death	Vehicle Control No. of Death	Cum %	Low Dose No. of Death	Cum %	Mid Dose No. of Death	Cum %	High Dose No. of Death	Cum %
0 - 50	2	3.33					2	3.33
51 - 80	19	35.00	13	21.67	16	26.67	7	15.00
81 - 98	17	63.33	26	65.00	20	60.00	16	41.67
Accidental Death	1	1.67						
Terminal sacrifice	21	35.00	21	35.00	24	40.00	35	58.33
Total	60		60		60		60	

Table 2A: Intercurrent Mortality Rate in Male Mice

Week / Type of Death	Vehicle Control No. of Death	Cum %	Low Dose No. of Death	Cum %	Mid Dose No. of Death	Cum %	High Dose No. of Death	Cum %	Positive C No. of Death	Cum %
0 - 13	.	.	.	.	.	.	.	.	4	16.00
14 - 26	1	4.00	1	4.00	.	.	1	4.00	19	92.00
Accidental Death	.	.	.	.	3	12.00	.	.	.	.
Terminal sacrifice	24	96.00	24	96.00	22	88.00	24	96.00	2	8.00
Total	25	.	25	.	25	.	25	.	25	.

Table 2B: Intercurrent Mortality Rate in Female Mice

Week / Type of Death	Vehicle Control No. of Death	Cum %	Low Dose No. of Death	Cum %	Mid Dose No. of Death	Cum %	High Dose No. of Death	Cum %	Positive C No. of Death	Cum %
0 - 13	1	4.00	1	4.00	2	8.00	.	.	6	24.00
14 - 26	3	16.00	1	8.00	.	.	1	4.00	18	96.00
Terminal sacrifice	21	84.00	23	92.00	23	92.00	24	96.00	1	4.00
Total	25	.	25	.	25	.	25	.	25	.

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Table 3A: Intercurrent Mortality Comparison in Male Rats

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High
Dose-Response (Likelihood Ratio)	0.4774	0.5213	0.6938	0.5772
Homogeneity (Log-Rank)	0.6960	0.5155	0.6905	0.5737

Table 3B: Intercurrent Mortality Comparison in Female Rats

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High
Dose-Response (Likelihood Ratio)	0.0053	0.5887	0.4581	0.0116
Homogeneity (Log-Rank)	0.0530	0.5830	0.4531	0.0107

Table 4A: Intercurrent Mortality Comparison in Male Mice

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. PC
Dose-Response (Likelihood Ratio)	0.8486	0.9885	0.2534	0.9885	<.0001
Homogeneity (Log-Rank)	0.8208	0.9885	0.3375	0.9885	<.0001

Table 4B: Intercurrent Mortality Comparison in Female Mice

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. PC
Dose-Response (Likelihood Ratio)	0.1569	0.3897	0.4238	0.1489	<.0001
Homogeneity (Log-Rank)	0.5294	0.3921	0.4285	0.1618	<.0001

Table 5A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats Compared with Control

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	8 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	50 mg/kg/day High (H) P - C vs. H
Body Cavity, Nasal	Chondroma	0/60 (35) 0.2643	0/60 (34) NS	0/60 (34) NS	1/60 (37) 0.5139
Bone	Osteosarcoma	1/1 (1) 0.8000	1/3 (2) 1.0000	1/2 (2) 1.0000	1/3 (2) 1.0000
Brain	Astrocytoma, Benign	0/60 (35) 0.2643	0/60 (34) NS	0/60 (34) NS	1/60 (37) 0.5139
	Astrocytoma, Malignant	1/60 (35) 0.6939	1/60 (35) 0.7536	2/60 (35) 0.5000	0/60 (37) 1.0000
	C_Astrocytoma_B+M	1/60 (35) 0.4586	1/60 (35) 0.7536	2/60 (35) 0.5000	1/60 (37) 0.7672
	Granular Cell Tumor, Benign	0/60 (35) 0.2643	0/60 (34) NS	0/60 (34) NS	1/60 (37) 0.5139
	Granular Cell Tumor, Malignant	0/60 (35) 0.5071	0/60 (34) NS	1/60 (34) 0.4928	0/60 (37) NS
	C_Granular Cell Tumor_B+M	0/60 (35) 0.1977	0/60 (34) NS	1/60 (34) 0.4928	1/60 (37) 0.5139

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Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	8 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	50 mg/kg/day High (H) P - C vs. H
	Oligodendroglioma, Malignant	0/60 (35) 0.2031	0/60 (34) NS	1/60 (35) 0.5000	1/60 (38) 0.5205
Epididymis	Mesothelioma, Malignant	1/60 (35) 1.0000	0/60 (34) 1.0000	0/60 (34) 1.0000	0/60 (37) 1.0000
Gland, Adrenal	Cortical Adenoma	3/60 (36) 0.9448	0/60 (34) 1.0000	1/60 (34) 0.9358	0/60 (37) 1.0000
	Pheochromocytoma, Benign	5/60 (36) 0.1937	6/60 (36) 0.5000	4/60 (34) 0.7315	9/60 (39) 0.2356
	Pheochromocytoma, Malignant	2/60 (35) 0.7047	0/60 (34) 1.0000	0/60 (34) 1.0000	1/60 (37) 0.8903
	C_Pheochromocytoma_B+M	6/60 (36) 0.1855	6/60 (36) 0.6235	4/60 (34) 0.8226	10/60 (39) 0.2537
Gland, Mammary	Adenocarcinoma	1/7 (5) 0.8901	1/4 (3) 0.6429	0/4 (3) 1.0000	0/4 (3) 1.0000
	Fibroadenoma	3/7 (6) 0.6504	1/4 (3) 0.8810	2/4 (4) 0.7381	1/4 (3) 0.8810
Gland, Parathyroid	Adenoma	1/55 (33) 0.3842	1/55 (31) 0.7381	0/57 (32) 1.0000	2/58 (36) 0.5331
Gland, Pituitary	Adenoma, Pars Distalis	35/60 (47) 0.9577	29/60 (47) 0.9396	25/60 (43) 0.9692	25/60 (45) 0.9834
Gland, Prostate	Adenocarcinoma	0/59 (34) 0.7554	1/60 (34) 0.5000	0/60 (34) NS	0/60 (37) NS
	Adenoma	0/59 (34) 0.5108	0/60 (34) NS	1/60 (34) 0.5000	0/60 (37) NS
	Schwannoma, Malignant	0/59 (34) 0.5108	0/60 (34) NS	1/60 (34) 0.5000	0/60 (37) NS
Gland, Seminal Vesicle	Adenoma	0/59 (34) 0.2662	0/60 (34) NS	0/60 (34) NS	1/60 (37) 0.5211
Gland, Thyroid	C-Cell Adenoma	9/60 (38) 0.4776	5/60 (36) 0.9159	7/60 (35) 0.7455	8/60 (39) 0.7288
	C-Cell Carcinoma	0/60 (35) 0.2643	0/60 (34) NS	0/60 (34) NS	1/60 (37) 0.5139
	C_C-Cell_A+C	9/60 (38) 0.4776	5/60 (36) 0.9159	7/60 (35) 0.7455	8/60 (39) 0.7288
	Follicular Cell Adenoma	0/60 (35) 0.0215	0/60 (34) NS	1/60 (34) 0.4928	3/60 (37) 0.1303
	Follicular Cell Carcinoma	0/60 (35) 0.5133	2/60 (34) 0.2391	0/60 (34) NS	1/60 (37) 0.5139
	C_Follicular Cell_A+C	0/60 (35) 0.0494	2/60 (34) 0.2391	1/60 (34) 0.4928	4/60 (37) 0.0642
Heart	Leiomyoma	1/60 (35) 1.0000	0/60 (34) 1.0000	0/60 (34) 1.0000	0/60 (37) 1.0000
Hemolymphoreticular Tissue	Histiocytic Sarcoma	1/60 (35) 0.5701	3/60 (35) 0.3069	4/60 (36) 0.1873	1/60 (38) 0.7736

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Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	8 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	50 mg/kg/day High (H) P - C vs. H
	Leukemia, Granulocytic	0/60 (35) 0.2695	0/60 (34) NS	0/60 (34) NS	1/60 (38) 0.5205
	Leukemia, Large Granular Lymphocytic	0/60 (35) 0.2695	0/60 (34) NS	0/60 (34) NS	1/60 (38) 0.5205
	Lymphoma, Malignant	1/60 (35) 0.2544	2/60 (35) 0.5000	1/60 (34) 0.7464	3/60 (38) 0.3391
Kidney	Amphophilic Vacuolar Tubular Adenoma	1/60 (35) 0.3178	2/60 (36) 0.5107	3/60 (36) 0.3178	2/60 (37) 0.5211
	Amphophilic Vacuolar Tubular Carcinoma	1/60 (35) 0.4586	1/60 (35) 0.7536	2/60 (35) 0.5000	1/60 (37) 0.7672
	C_Amphophilic Vacuolar Tubular_C+A	1/60 (35) 0.3178	2/60 (36) 0.5107	3/60 (36) 0.3178	2/60 (37) 0.5211
Large Intestine, Cecum	Hemangiosarcoma	0/60 (35) 0.2643	0/60 (34) NS	0/60 (34) NS	1/60 (37) 0.5139
Large Intestine, Rectum	Adenocarcinoma	0/60 (35) 0.7500	1/60 (34) 0.4928	0/60 (34) NS	0/60 (37) NS
Liver	Hemangiosarcoma	1/60 (35) 0.9397	1/60 (35) 0.7536	0/60 (34) 1.0000	0/60 (37) 1.0000
	Hepatocellular Adenoma	2/60 (35) 0.4518	2/60 (35) 0.6931	0/60 (34) 1.0000	3/60 (38) 0.5396
	Hepatocellular Carcinoma	2/60 (35) 0.8829	0/60 (34) 1.0000	1/60 (34) 0.8751	0/60 (37) 1.0000
	C_Hepatocellular_A+C	4/60 (35) 0.6853	2/60 (35) 0.9010	1/60 (34) 0.9711	3/60 (38) 0.8180
Lung	Bronchioloalveolar Adenoma	2/60 (35) 0.9857	1/60 (35) 0.8804	0/60 (34) 1.0000	0/60 (37) 1.0000
	Bronchioloalveolar Carcinoma	0/60 (35) 0.2643	0/60 (34) NS	0/60 (34) NS	1/60 (37) 0.5139
	C_Bronchioloalveolar_A+C	2/60 (35) 0.8086	1/60 (35) 0.8804	0/60 (34) 1.0000	1/60 (37) 0.8903
	Hemangiosarcoma	0/60 (35) 0.7518	1/60 (35) 0.5000	0/60 (34) NS	0/60 (37) NS
Lymph Node	Hemangiosarcoma	1/13 (10) 0.8810	1/6 (5) 0.5714	0/11 (7) 1.0000	0/10 (6) 1.0000
Lymph Node, Mesenteric	Hemangioma	1/60 (35) 0.7589	0/60 (34) 1.0000	1/60 (34) 0.7464	0/60 (37) 1.0000
	Hemangiosarcoma	1/60 (35) 0.5757	2/60 (35) 0.5000	2/60 (34) 0.4890	1/60 (37) 0.7672
Muscle, Skeletal	Fibrosarcoma	1/60 (35) 1.0000	0/60 (34) 1.0000	0/60 (34) 1.0000	0/60 (37) 1.0000
	Hemangiosarcoma	0/60 (35) 0.6348	1/60 (35) 0.5000	1/60 (34) 0.4928	0/60 (37) NS
Pancreas	Acinar Adenoma	3/60 (35) 0.6825	2/60 (34) 0.8127	2/60 (34) 0.8127	2/60 (37) 0.8383
	Acinar Carcinoma	0/60 (35) 0.5071	0/60 (34) NS	1/60 (34) 0.4928	0/60 (37) NS

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Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	8 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	50 mg/kg/day High (H) P - C vs. H
	Acinar-Islet Cell Adenoma	0/60 (35) 0.2021	0/60 (34) NS	1/60 (34) 0.4928	1/60 (38) 0.5205
	Hemangiosarcoma	0/60 (35) 0.2643	0/60 (34) NS	0/60 (34) NS	1/60 (37) 0.5139
	Islet Cell Adenoma	12/60 (37) 0.7518	12/60 (37) 0.5979	8/60 (36) 0.8929	11/60 (39) 0.7423
	Islet Cell Carcinoma	1/60 (35) 0.6555	1/60 (34) 0.7464	0/60 (34) 1.0000	1/60 (37) 0.7672
Skin	Basal Cell Tumor, Benign	1/60 (35) 0.2698	1/60 (35) 0.7536	2/60 (34) 0.4890	2/60 (38) 0.5312
	Basal Cell Tumor, Malignant	1/60 (35) 1.0000	0/60 (34) 1.0000	0/60 (34) 1.0000	0/60 (37) 1.0000
	Hair Follicle Tumor, Benign	2/60 (35) 1.0000	0/60 (34) 1.0000	0/60 (34) 1.0000	0/60 (37) 1.0000
	Keratoacanthoma	6/60 (36) 0.5915	5/60 (35) 0.7264	3/60 (35) 0.9178	6/60 (38) 0.6618
	Papilloma	2/60 (35) 0.3555	0/60 (34) 1.0000	1/60 (34) 0.8751	2/60 (37) 0.7137
	Sebaceous Cell Adenoma	1/60 (35) 0.9388	1/60 (34) 0.7464	0/60 (34) 1.0000	0/60 (37) 1.0000
	Squamous Cell Carcinoma	1/60 (35) 0.9388	1/60 (34) 0.7464	0/60 (34) 1.0000	0/60 (37) 1.0000
Small Intestine, Jejunum	Adenoma	0/60 (35) 0.7518	1/60 (35) 0.5000	0/60 (34) NS	0/60 (37) NS
Spinal Cord, Cervical	Astrocytoma, Malignant	0/60 (35) 0.7518	1/60 (35) 0.5000	0/60 (34) NS	0/60 (37) NS
Spleen	Hemangiosarcoma	1/60 (35) 0.7386	2/60 (35) 0.5000	0/60 (34) 1.0000	1/60 (37) 0.7672
Subcutis	Fibroma	7/15 (11) 0.7821	12/17 (15) 0.3130	8/14 (12) 0.6111	7/16 (12) 0.7532
	Fibrosarcoma	4/15 (11) 0.4083	2/17 (13) 0.9519	2/14 (10) 0.9063	4/16 (12) 0.7221
	Hemangiosarcoma	0/15 (9) 0.2500	0/17 (12) NS	0/14 (9) NS	1/16 (10) 0.5263
	Lipoma	0/15 (9) 0.0622	2/17 (13) 0.3377	2/14 (9) 0.2353	3/16 (10) 0.1238
	Osteoma	0/15 (9) 0.4878	0/17 (12) NS	1/14 (10) 0.5263	0/16 (10) NS
	Osteosarcoma	0/15 (9) 0.2192	0/17 (12) NS	2/14 (9) 0.2353	0/16 (10) NS
	Sarcoma	2/15 (11) 1.0000	0/17 (12) 1.0000	0/14 (9) 1.0000	0/16 (10) 1.0000
	Schwannoma, Malignant	0/15 (9) 0.2683	0/17 (12) NS	0/14 (9) NS	1/16 (11) 0.5500
Testis	Hemangioma	0/60 (35) 0.3830	1/60 (35) 0.5000	0/60 (34) NS	1/60 (37) 0.5139
	Interstitial (Leydig) Cell Adenoma	0/60 (35) 0.2643	0/60 (34) NS	0/60 (34) NS	1/60 (37) 0.5139

File Name: NDA208712Carcin.doc

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	8 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	50 mg/kg/day High (H) P - C vs. H
Thymus	Hemangiosarcoma	0/58 (33) 0.5109	0/59 (34) NS	1/59 (34) 0.5075	0/59 (36) NS
	Thymoma, Malignant	1/58 (34) 1.0000	0/59 (34) 1.0000	0/59 (33) 1.0000	0/59 (36) 1.0000
Urinary Bladder	Lipoma	0/59 (34) 0.2662	0/60 (34) NS	0/60 (34) NS	1/60 (37) 0.5211
	Papilloma	0/59 (34) 0.5108	0/60 (34) NS	1/60 (34) 0.5000	0/60 (37) NS
Whole body	Hemangioma	1/60 (35) 0.5622	1/60 (35) 0.7536	1/60 (34) 0.7464	1/60 (37) 0.7672
	Hemangioma/Hemangiosarcoma	3/60 (35) 0.2412	4/60 (36) 0.5161	6/60 (36) 0.2534	5/60 (38) 0.4031
	Hemangiosarcoma	2/60 (35) 0.1266	3/60 (35) 0.5000	5/60 (35) 0.2141	5/60 (38) 0.2503

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.   The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 5B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats Compared with Control

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	8 mg/kg/day Low (L) P - L vs. C	30 mg/kg/day Mid (M) P - M vs. C	80 mg/kg/day High (H) P - H vs. C
Body Cavity, Abdominal	Fibrosarcoma	0/1 (0) 1.0000	1/1 (1) NS	0/1 (1) NS	0/1 (1) NS
Brain	Astrocytoma, Malignant	1/60 (36) 0.7249	0/60 (40) 1.0000	2/60 (40) 0.5400	0/60 (44) 1.0000
	Granular Cell Tumor, Benign	0/60 (36) 0.7750	1/60 (40) 0 5263	0/60 (40) NS	0/60 (44) NS
	Medulloblastoma	1/60 (36) 1.0000	0/60 (40) 1.0000	0/60 (40) 1.0000	0/60 (44) 1.0000
Cervix	Granular Cell Tumor, Benign	1/60 (36) 0.4193	0/60 (40) 1.0000	2/60 (40) 0.5400	1/60 (44) 0.8006
Gland, Adrenal	Cortical Adenoma	2/60 (36) 0.5721	2/60 (41) 0.7402	2/60 (40) 0.7315	2/60 (44) 0.7641
	Pheochromocytoma, Benign	1/60 (36) 0.6685	2/60 (41) 0 5493	1/60 (40) 0.7789	1/60 (44) 0.8006
Gland, Mammary	Adenocarcinoma	21/60 (42) 0.9402	30/60 (50) 0 2264	21/60 (47) 0.7624	20/60 (49) 0.8619
	Adenoma	1/60 (36) 0.6145	4/60 (42) 0 2312	3/60 (40) 0.3485	2/60 (44) 0.5757
	Adenosquamous Carcinoma	0/60 (36) 0.7750	1/60 (40) 0 5263	0/60 (40) NS	0/60 (44) NS
	Carcinosarcoma	2/60 (36) 0.6734	3/60 (41) 0 5624	0/60 (40) 1.0000	2/60 (45) 0.7715

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Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	8 mg/kg/day Low (L) P - L vs. C	30 mg/kg/day Mid (M) P - M vs. C	80 mg/kg/day High (H) P - H vs. C
	Fibroadenoma	34/60 (47) 0.9995	44/60 (53) 0 1481	31/60 (49) 0.8789	25/60 (50) 0.9934
	Mixed Tumor, Benign	0/60 (36) 0.2750	0/60 (40) NS	0/60 (40) NS	1/60 (44) 0.5500
Gland, Parathyroid	Adenoma	1/56 (34) 0.8534	1/54 (36) 0.7677	1/57 (38) 0.7805	0/54 (39) 1.0000
Gland, Pituitary	Adenoma, Pars Distalis	40/60 (50) 0.8972	38/60 (53) 0.8876	38/60 (52) 0.8549	34/60 (51) 0.9595
	Carcinoma, Pars Distalis	0/60 (36) 0.1317	1/60 (41) 0 5325	0/60 (40) NS	2/60 (44) 0.2994
Gland, Thyroid	C-Cell Adenoma	5/60 (37) 0.7055	11/60 (43) 0 1433	10/60 (42) 0.1909	7/60 (46) 0.5408
	C-Cell Carcinoma	0/60 (36) 0.5250	0/60 (40) NS	1/60 (40) 0.5263	0/60 (44) NS
	C_C-Cell_A+C	5/60 (37) 0.7055	11/60 (43) 0 1433	10/60 (42) 0.1909	7/60 (46) 0.5408
	Carcinoma	1/60 (36) 1.0000	0/60 (40) 1.0000	0/60 (40) 1.0000	0/60 (44) 1.0000
	Follicular Cell Carcinoma	0/60 (36) 0.5369	0/60 (40) NS	2/60 (40) 0.2737	0/60 (44) NS
Hemolymphoreticular Tissue	Histiocytic Sarcoma	3/60 (37) 1.0000	0/60 (40) 1.0000	0/60 (40) 1.0000	0/60 (44) 1.0000
	Leukemia, Granulocytic	0/60 (36) 0.7750	1/60 (40) 0 5263	0/60 (40) NS	0/60 (44) NS
	Lymphoma, Malignant	2/60 (36) 0.9607	2/60 (40) 0.7315	1/60 (40) 0.8984	0/60 (44) 1.0000
Kidney	Amphophilic Vacuolar Tubular Adenoma	1/60 (36) 0.7759	0/60 (40) 1.0000	1/60 (40) 0.7789	0/60 (44) 1.0000
	Amphophilic Vacuolar Tubular Carcinoma	0/60 (36) 0.5369	0/60 (40) NS	2/60 (40) 0.2737	0/60 (44) NS
	C_Amphophilic Vacuolar Tubular_A+C	1/60 (36) 0.7249	0/60 (40) 1.0000	2/60 (40) 0.5400	0/60 (44) 1.0000
	Lipoma	0/60 (36) 0.2750	0/60 (40) NS	0/60 (40) NS	1/60 (44) 0.5500
Liver	Hemangiosarcoma	0/60 (36) 0.7764	1/60 (41) 0 5325	0/60 (40) NS	0/60 (44) NS
	Hepatocellular Adenoma	6/60 (37) 0.6350	4/60 (41) 0.8833	5/60 (41) 0.7980	5/60 (45) 0.8413
Lung	Bronchioloalveolar Adenoma	0/60 (36) 0.5250	0/60 (40) NS	1/60 (40) 0.5263	0/60 (44) NS
Ovary	Granulosa Cell Tumor, Malignant	0/60 (36) 0.5250	0/60 (40) NS	1/60 (40) 0.5263	0/60 (44) NS
	Hemangioma	0/60 (36) 0.5250	0/60 (40) NS	1/60 (40) 0.5263	0/60 (44) NS
Pancreas	Acinar Adenoma	1/60 (36)	2/60 (41)	0/60 (40)	1/60 (44)

File Name: NDA208712Carcin.doc

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	8 mg/kg/day Low (L) P - L vs. C	30 mg/kg/day Mid (M) P - M vs. C	80 mg/kg/day High (H) P - H vs. C
		0.6897	0 5493	1.0000	0.8006
	Acinar-Islet Cell Adenoma	0/60 (36)	1/60 (41)	0/60 (40)	0/60 (44)
		0.7764	0 5325	NS	NS
	Hemangiosarcoma	0/60 (36)	0/60 (40)	0/60 (40)	1/60 (45)
		0.2795	NS	NS	0.5556
	Islet Cell Adenoma	5/60 (37)	1/60 (40)	4/60 (40)	0/60 (44)
		0.9789	0 9902	0.7975	1.0000
	Islet Cell Carcinoma	1/60 (36)	1/60 (40)	0/60 (40)	3/60 (44)
		0.1294	0.7789	1.0000	0.3873
	C_Islet Cell_A+C	5/60 (37)	2/60 (40)	4/60 (40)	3/60 (44)
		0.7035	0 9570	0.7975	0.9163
Skin	Basal Cell Tumor, Benign	0/60 (36)	1/60 (41)	0/60 (40)	0/60 (44)
		0.7764	0 5325	NS	NS
	Papilloma	1/60 (36)	1/60 (40)	0/60 (40)	1/60 (44)
		0.5950	0.7789	1.0000	0.8006
	Squamous Cell Carcinoma	0/60 (36)	0/60 (40)	1/60 (40)	1/60 (44)
		0.2127	NS	0.5263	0.5500
Small Intestine, Duodenum	Leiomyoma	0/60 (36)	0/60 (40)	0/60 (40)	1/60 (44)
		0.2750	NS	NS	0.5500
Spleen	Hemangiosarcoma	0/60 (36)	0/60 (40)	1/60 (40)	0/60 (44)
		0.5250	NS	0.5263	NS
Stomach	Leiomyosarcoma	0/60 (36)	1/60 (40)	0/60 (40)	0/60 (44)
		0.7750	0 5263	NS	NS
	Papilloma	2/60 (36)	0/60 (40)	0/60 (40)	0/60 (44)
		1.0000	1.0000	1.0000	1.0000
Subcutis	Fibroma	4/7 (6)	3/5 (5)	1/8 (5)	2/6 (5)
		0.8329	0.8030	0.9870	0.9329
	Fibrosarcoma	0/7 (4)	1/5 (3)	2/8 (5)	1/6 (5)
		0.4139	0.4286	0.2778	0.5556
	Hemangiosarcoma	0/7 (4)	0/5 (3)	1/8 (6)	0/6 (5)
		0.6111	NS	0.6000	NS
	Lipoma	1/7 (4)	1/5 (3)	3/8 (6)	1/6 (5)
		0.6550	0.7143	0.4524	0.8333
	Schwannoma, Malignant	0/7 (4)	0/5 (3)	1/8 (6)	1/6 (5)
		0.2614	NS	0.6000	0.5556
Thymus	Thymoma, Benign	0/59 (35)	0/58 (39)	0/57 (37)	1/57 (41)
		0.2697	NS	NS	0.5395
Urinary Bladder	Transitional Cell Carcinoma	1/60 (36)	0/60 (40)	0/60 (40)	0/60 (44)
		1.0000	1.0000	1.0000	1.0000
Uterus	Endometrial Adenocarcinoma	0/60 (36)	0/60 (40)	0/60 (40)	1/60 (44)
		0.2750	NS	NS	0.5500
	Endometrial Stromal Polyp	4/60 (37)	3/60 (41)	4/60 (41)	2/60 (44)
		0.8229	0.8247	0.7009	0.9337
	Endometrial Stromal Sarcoma	1/60 (36)	1/60 (41)	0/60 (40)	0/60 (44)
		0.9511	0.7847	1.0000	1.0000
	Leiomyoma	1/60 (36)	0/60 (40)	1/60 (40)	0/60 (44)

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Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	8 mg/kg/day Low (L) P - L vs. C	30 mg/kg/day Mid (M) P - M vs. C	80 mg/kg/day High (H) P - H vs. C
		0.7759	1.0000	0.7789	1.0000
	Schwannoma, Malignant	1/60 (36)	0/60 (40)	1/60 (40)	0/60 (44)
		0.7759	1.0000	0.7789	1.0000
Vagina	Granular Cell Tumor, Benign	1/60 (36)	0/60 (40)	0/60 (40)	1/60 (44)
		0.4756	1.0000	1.0000	0.8006
Whole body	Hemangioma	0/60 (36)	0/60 (40)	1/60 (40)	0/60 (44)
		0.5250	NS	0.5263	NS
	Hemangioma/Hemangiosarcoma	0/60 (36)	1/60 (41)	3/60 (41)	1/60 (45)
		0.3810	0 5325	0.1457	0.5556
	Hemangiosarcoma	0/60 (36)	1/60 (41)	2/60 (41)	1/60 (45)
		0.3758	0 5325	0.2802	0.5556

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.   The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 6A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice Compared with Control

Organ name	Tumor name	0 mg/kg/day Control P - Trend	60 mg/kg/day Low (L) P - C vs. L	100 mg/kg/day Mid (M) P - C vs. M	160 mg/kg/day High (H) P - C vs. H	75 mg Positive (PC) P - C vs. PC
Body Cavity, Nasal	Adenoma	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	1/25 (11) 0.3143
	Papilloma	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	1/25 (11) 0.3143
Epididymis	Hemangioma	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	1/25 (11) 0.3143
	Hemangiosarcoma	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	1/25 (11) 0.3143
Gland, Harderian	Adenoma	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	2/25 (11) 0.0924
Hemolymphoreticular Tissue	Lymphoma, Malignant	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	21/25 (22) 0.0000 **
Large Intestine, Cecum	Adenocarcinoma	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	2/23 (10) 0.0802
Larynx	Papilloma	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	1/25 (10) 0.2941
Liver	Hepatocellular Adenoma	0/25 (24) 0.4948	0/25 (25) NS	1/25 (23) 0.4894	0/25 (25) NS	0/25 (10) NS
Lung	Bronchioloalveolar Adenoma	1/25 (24) 0.5019	0/25 (25) 1.0000	1/25 (23) 0.7447	1/25 (25) 0.7653	4/25 (12) 0.0336 **
	Bronchioloalveolar Carcinoma	0/25 (24) 0.2577	0/25 (25) NS	0/25 (23) NS	1/25 (25) 0.5102	1/25 (11) 0.3143
	C_Bronchioloalveolar_	1/25 (24)	0/25 (25)	1/25 (23)	2/25 (25)	5/25 (13)

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Organ name	Tumor name	0 mg/kg/day Control P - Trend	60 mg/kg/day Low (L) P - C vs. L	100 mg/kg/day Mid (M) P - C vs. M	160 mg/kg/day High (H) P - C vs. H	75 mg Positive (PC) P - C vs. PC
	A+C	0.2553	1.0000	0.7447	0.5156	0.0140 **
Skin	Papilloma	0/24 (23) NS	0/25 (25) NS	0/24 (22) NS	0/25 (25) NS	2/25 (10) 0.0852
	Squamous Cell Carcinoma	0/24 (23) NS	0/25 (25) NS	0/24 (22) NS	0/25 (25) NS	1/25 (10) 0.3030
Small Intestine, Duodenum	Adenocarcinoma	0/25 (24) NS	0/25 (25) NS	0/24 (22) NS	0/25 (25) NS	2/16 (8) 0.0565
Small Intestine, Jejunum	Adenocarcinoma	0/24 (24) NS	0/25 (25) NS	0/25 (23) NS	0/24 (24) NS	2/23 (11) 0.0924
Spleen	Hemangiosarcoma	1/25 (25) 0.3914	2/25 (25) 0.5000	0/25 (23) 1.0000	2/25 (25) 0.5000	0/25 (10) 1.0000
Stomach	Adenoma	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	1/25 (11) 0.3143
	Carcinoma	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	8/25 (15) 0.0001 **
	Papilloma	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	19/25 (22) 0.0001 **
Thymus	Thymoma, Malignant	0/25 (24) 0.7526	1/25 (25) 0.5102	0/25 (23) NS	0/25 (25) NS	0/25 (10) NS
Whole body	Hemangioma	0/25 (24) NS	0/25 (25) NS	0/25 (23) NS	0/25 (25) NS	1/25 (11) 0.3143
	Hemangiosarcoma	1/25 (25) 0.3914	2/25 (25) 0.5000	0/25 (23) 1.0000	2/25 (25) 0.5000	1/25 (11) 0.5238
	Hemangioma /Hemangiosarcoma	1/25 (25) 0.3914	2/25 (25) 0.5000	0/25 (23) 1.0000	2/25 (25) 0.5000	2/25 (11) 0.2157

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.05 for both common tumor and rare tumor. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for both common tumor and a rare tumor.

Table 6B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice Compared with Control

Organ name	Tumor name	0 mg/kg/day Control P - Trend	60 mg/kg/day Low (L) P - C vs. L	100 mg/kg/day Mid (M) P - C vs. M	160 mg/kg/day High (H) P - C vs. H	75 mg Positive (PC) P - C vs. PC
Body Cavity, Nasal	Polyp	0/25 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	2/25 (10) 0.0852
Cervix	Papilloma	0/25 (23) NS	0/25 (24) NS	0/25 (23) NS	0/24 (23) NS	1/24 (9) 0.2813
Esophagus	Papilloma	0/25 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	2/24 (10) 0.0852
Gland, Harderian	Adenoma	0/25 (23)	0/25 (24)	1/25 (23)	0/25 (24)	1/25 (10)

File Name: NDA208712Carcin.doc

Organ name	Tumor name	0 mg/kg/day Control P - Trend	60 mg/kg/day Low (L) P - C vs. L	100 mg/kg/day Mid (M) P - C vs. M	160 mg/kg/day High (H) P - C vs. H	75 mg Positive (PC) P - C vs. PC
		0.5000	NS	0.5000	NS	0.3030
Gland, Mammary	Adenocarcinoma	0/25 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	1/25 (9) 0.2813
Hemolymphoreticular Tissue	Lymphoma, Malignant	0/25 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	21/25 (23) 0.0000 **
Large Intestine, Cecum	Hemangiosarcoma	0/24 (22) 0.5106	0/25 (24) NS	1/25 (24) 0.5217	0/25 (24) NS	0/24 (9) NS
Lung	Bronchioloalveolar Adenoma	2/25 (23) 1.0000	0/25 (24) 1.0000	0/25 (23) 1.0000	0/25 (24) 1.0000	5/25 (11) 0.0238 **
	Bronchioloalveolar Carcinoma	0/25 (23) 0.7553	1/25 (24) 0.5106	0/25 (23) NS	0/25 (24) NS	0/25 (9) NS
	C_Bronchioloalveolar _A+C	2/25 (23) 0.9415	1/25 (24) 0.8908	0/25 (23) 1.0000	0/25 (24) 1.0000	5/25 (11) 0.0238 **
Muscle, Skeletal	Osteosarcoma	0/25 (23) 0.7579	1/25 (25) 0.5208	0/25 (23) NS	0/25 (24) NS	0/24 (9) NS
Skin	Keratoacanthoma	0/25 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	1/25 (9) 0.2813
	Papilloma	0/25 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	4/25 (10) 0.0051 **
	Squamous Cell Carcinoma	0/25 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	1/25 (9) 0.2813
Small Intestine, Duodenum	Adenoma	0/23 (21) NS	0/25 (24) NS	0/24 (23) NS	0/25 (24) NS	1/22 (9) 0.3000
Small Intestine, Ileum	Adenocarcinoma	0/24 (22) NS	0/24 (23) NS	0/24 (23) NS	0/25 (24) NS	1/24 (9) 0.2903
	Adenoma	0/24 (22) NS	0/24 (23) NS	0/24 (23) NS	0/25 (24) NS	1/24 (9) 0.2903
Small Intestine, Jejunum	Adenocarcinoma	0/24 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	4/25 (11) 0.0071 **
	Leiomyosarcoma	0/24 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	1/25 (10) 0.3030
Spleen	Hemangiosarcoma	2/25 (24) 0.8425	1/25 (24) 0.8830	0/25 (23) 1.0000	1/25 (24) 0.8830	3/25 (11) 0.1661
Stomach	Carcinoma	0/25 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	4/25 (12) 0.0095 **
	Papilloma	0/25 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	23/25 (23) 0.0000 **
Thymus	Thymoma, Malignant	1/25 (23) 1.0000	0/25 (24) 1.0000	0/24 (22) 1.0000	0/25 (24) 1.0000	0/25 (9) 1.0000
Tongue	Papilloma	0/25 (23) NS	0/25 (24) NS	0/25 (23) NS	0/25 (24) NS	1/25 (10) 0.3030
Uterus	Carcinoma	0/25 (23)	1/25 (24)	0/25 (23)	0/25 (24)	0/24 (9)

File Name: NDA208712Carcin.doc

Organ name	Tumor name	0 mg/kg/day Control P - Trend	60 mg/kg/day Low (L) P - C vs. L	100 mg/kg/day Mid (M) P - C vs. M	160 mg/kg/day High (H) P - C vs. H	75 mg Positive (PC) P - C vs. PC
		0.7553	0.5106	NS	NS	NS
	Hemangiosarcoma	0/25 (23)	1/25 (24)	0/25 (23)	1/25 (24)	1/24 (9)
		0.3212	0.5106	NS	0.5106	0.2813
	Polyp	0/25 (23)	0/25 (24)	0/25 (23)	0/25 (24)	1/24 (9)
		NS	NS	NS	NS	0.2813
Whole body	Hemangioma	0/25 (23)	0/25 (24)	0/25 (23)	1/25 (24)	0/25 (9)
		0.2553	NS	NS	0.5106	NS
	Hemangiosarcoma	3/25 (25)	2/25 (24)	2/25 (25)	3/25 (25)	3/25 (11)
		0.4709	0.8129	0.8257	0.6664	0.2518
	Hemangioma	3/25 (25)	2/25 (24)	2/25 (25)	3/25 (25)	3/25 (11)
	/Hemangiosarcoma	0.4709	0.8129	0.8257	0.6664	0.2518

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.05 for both common tumor and rare tumor. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for both common tumor and a rare tumor.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats
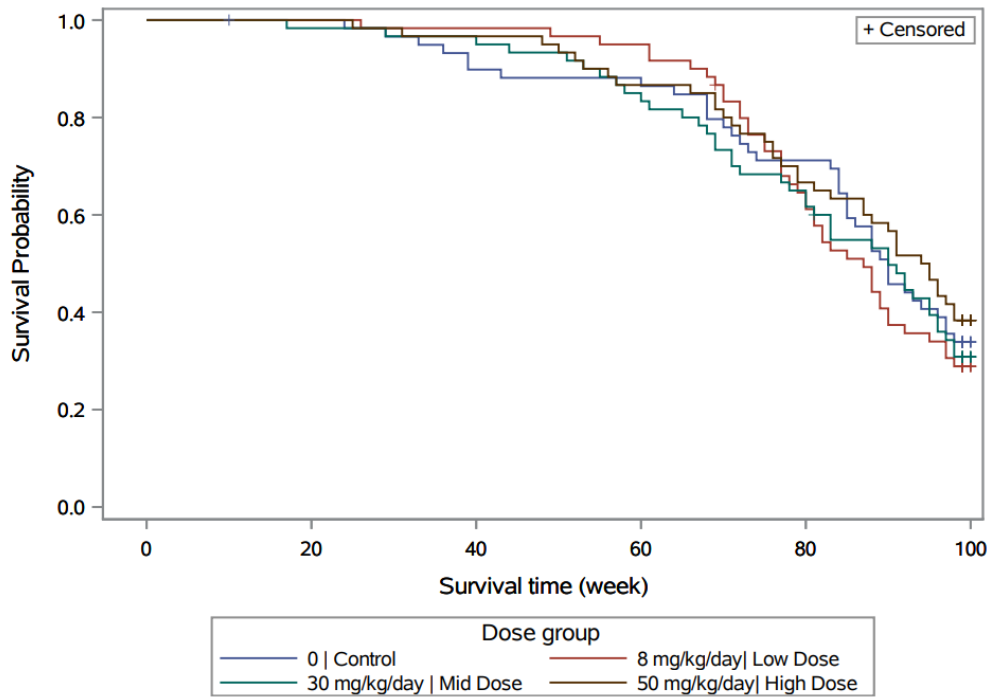
Figure 1B: Kaplan-Meier Survival Functions for Female Rats
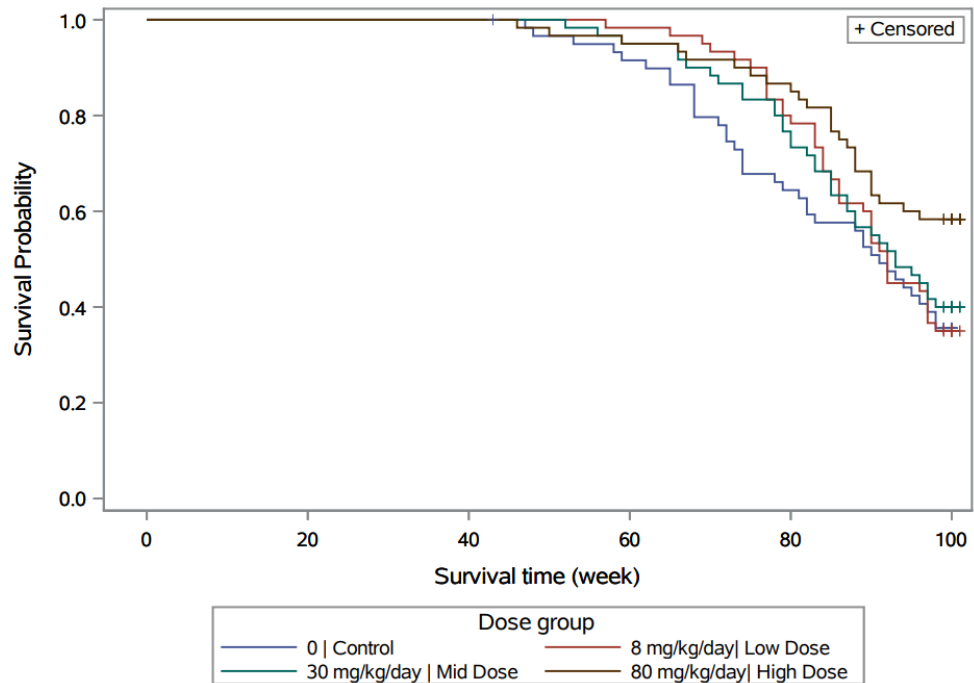

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Figure 2A: Kaplan-Meier Survival Functions for Male Mice
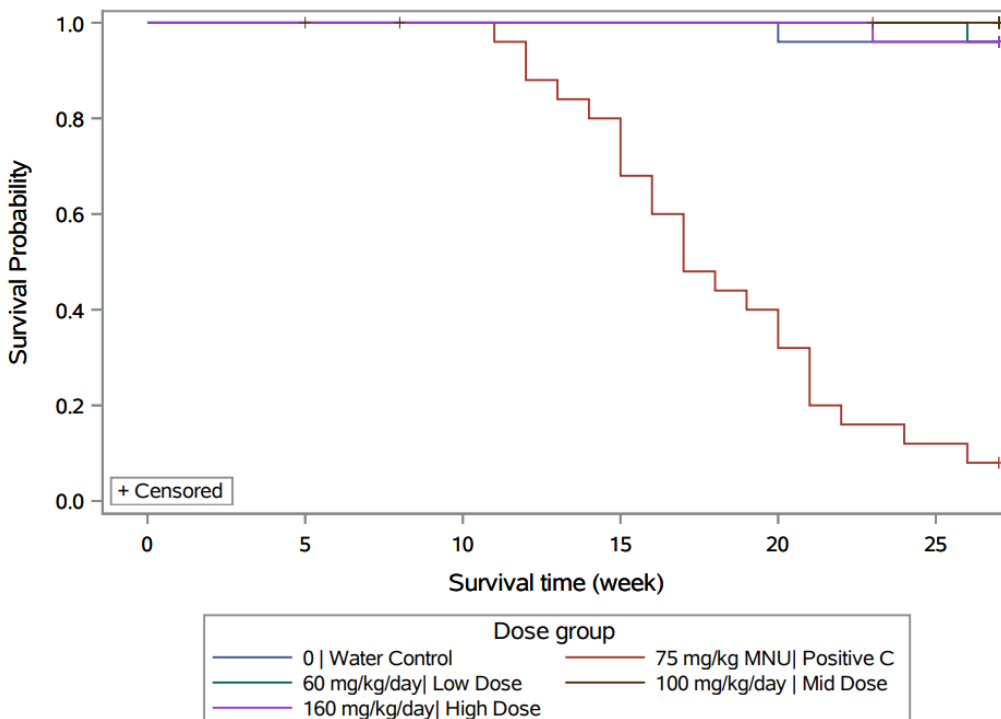
Figure 2B: Kaplan-Meier Survival Functions for Female Mice

File Name: NDA208712Carcin.doc
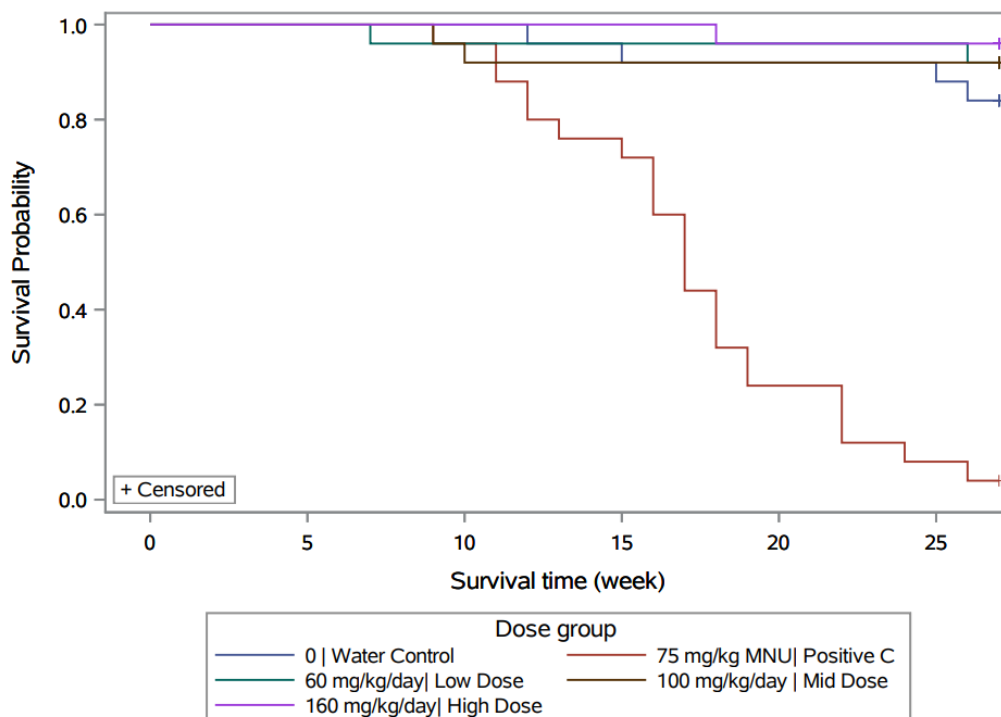
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/s/

FENG ZHOU
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KARL K LIN
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Concur with review.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION MEMO

CLINICAL STUDIES

NDA/BLA #:	NDA 208-712
Supplement #:	000
Drug Name:	(b) (4) (Pacritinib) (b) (4) Capsule
Indication(s):	treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post essential thrombocythemia myelofibrosis, with thrombocytopenia (platelet counts <50,000/μL)
Applicant:	Cti Biopharma
Submission Date:	12/30/2015
PDUFA Date:	8/30/2016
Review Priority:	Priority
Biometrics Division:	DBV
Statistical Reviewer:	Cindy Gao, Ph.D.
Concurring Reviewers:	Yuan-Li Shen, Dr. P.H
	Rajeshwari Sridhara, Ph.D.
Medical Division:	DHP
Clinical Reviewer:	Vishal Bhatnagar, M.D.
Clinical Team Leader:	Angelo De Claro, M.D.
Project Manager:	Alycia Anderson

Keywords: Survival analysis; Kapan-Meier curve, Cross-over

Overview and Summary

The applicant submitted a NDA to seek an accelerated approval of pacritinib for the treatment of patients with intermediate and high risk myelofibrosis and with disease-related thrombocytopenia (baseline platelet counts < 50,000/μL). The application was supported by the pivotal study PERSIST-1, which was a multicenter, randomized, controlled, phase III study comparing the efficacy and safety of pacritinib with that of best available therapy (BAT) in subjects with intermediate and high risk myelofibrosis, including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF) and with thrombocytopenia (platelet counts <50,000/μL) . Due to the concern of detrimental treatment effect observed on the overall survival data in PERSIST-1, the Agency requests submission of the data from PERSIST-2 an ongoing randomized controlled Phase 3 study of oral pacritinib versus BAT in the same population as in PERSIST-1.

Based on results from PERSIST-1 and PERSIST-2, the results indicated higher risk of mortality (the hazard ratio was 1.29, 95% CI [0.80, 2.09] with the ITT population for PERSIST-1 and 1.75, 95% CI [0.79, 3.87]) with the ITT population for PERSIST-2). The original IDMC (Independent Data Safety Monitoring Committee) recommends termination of the PERSIST-1 study due to higher toxicity and incidence of deaths, while the sponsor did not follow the original IDMC's recommendation citing several experts' opinions. Due to the concern of higher risk of mortality, the clinical team recommended a full clinical hold for both trials (refer to the clinical review). The sponsor withdrew the NDA on February 10, 2016 subsequently. This statistical memo will document an evaluation of the overall survival and IDMC's recommendation.

Study PERSIST-1

The application was mainly based on the efficacy and safety findings from the pivotal study PERSIST-1, which was a multicenter, randomized, controlled, phase III study comparing the efficacy and safety of pacritinib with that of best available therapy (BAT) in subjects with intermediate and high risk myelofibrosis including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF) and with thrombocytopenia. Subjects randomized to the BAT arm were allowed to crossover to pacritinib at week 24 without disease progression or earlier if a subject experienced disease progression. An Independent Data Monitoring Committee (IDMC) was implemented to evaluate the safety of pacritinib. No interim efficacy analysis was planned.

The primary efficacy endpoint was the proportion of patients achieving ≥ 35% reduction in spleen volume at week 24. Overall survival was an exploratory endpoint with data cut-off date of January 17, 2015. The applicant also submitted the data of overall survival with data cut-off date of October 31, 2015 responding to the Agency's information request.

Overall, 327 patients were randomized in a 2:1 ratio to receive pacritinib (capsules administered orally at 400 mg per day) or the BAT. The analysis showed that the hazard ratio was 1.21 (95% CI [0.65, 2.26]) based on data cut-off date of January 2015 and 1.29 (95% CI [0.80, 2.09]) based

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on the data cut-off date of October 2015 for the ITT population. All the hazards ratio estimates or survival probability estimates, either based on Jan 2015 or October, 2015 cut-off dates, or based on both ITT population or censored patients at cross-over, indicate higher risk of deaths against the pacritinib treated arm (see Table 1 and Kaplan-Meier plots below).

Table 1 Overall Survival of Study PERSIST-1

Overall Survival	Pacritinib (N = 220)	BAT (N = 107)	p-value	Hazard Ratio (95% CI)
Number (%) event [death] Median (95% CI): weeks Cut-off: Jan 2015, ITT	33 (15.0%) NA (NA, NA)	15 (14.0%) 101 (NA, NA)	0.55	1.21 (0.65, 2.26)
Number (%) event [death] Median (95% CI): weeks Cut-off: Jan 2015, censoring at crossover	33 (15.0%) NA (NA, NA)	4 (3.7%) NA (NA, NA)	0.16	2.10 (0.72, 6.07)
Number (%) event [death] Median (95% CI): weeks Cut-off: Oct 2015, ITT	58 (26.4%) NA (NA, NA)	23 (21.5%) NA (NA, NA)	0.30	1.29 (0.80, 2.09)
Number (%) event [death] Median (95% CI): weeks Cut-off: Oct 2015, censoring at crossover	58 (26.4%) NA (NA, NA)	6 (5.6%) 111.6 (111.6, NA)	0.26	1.65 (0.69, 3.94)

Figure 1 Kaplan-Meier Plot with ITT Population and Cut-off Date of January 2015 for Study PERSIST-1
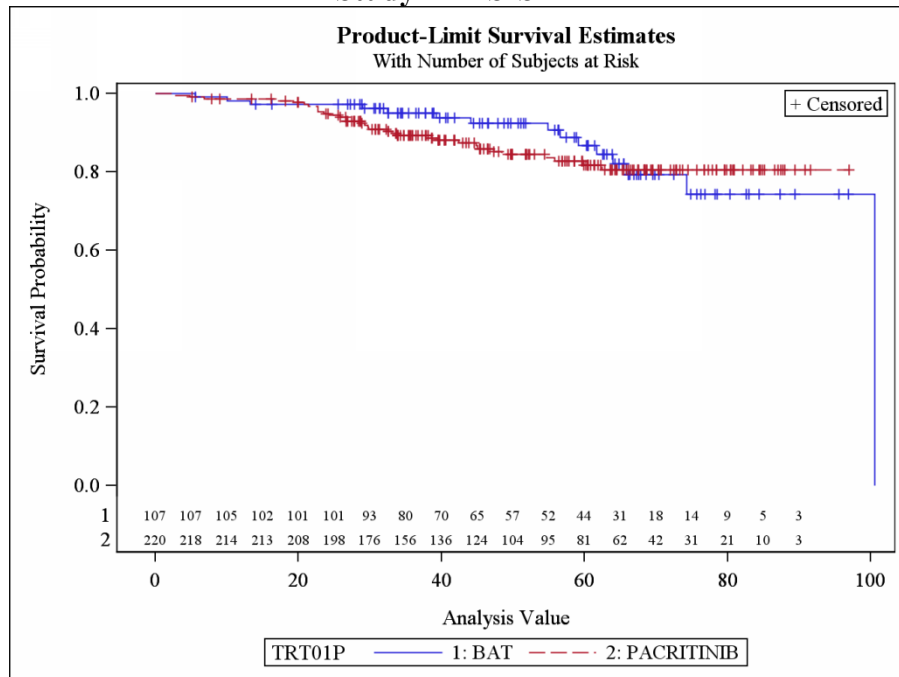
Figure 2 Kaplan-Meier Plot with Patients Censored at Crossover and Cut-off Date of January 2015 for Study PERSIST-1
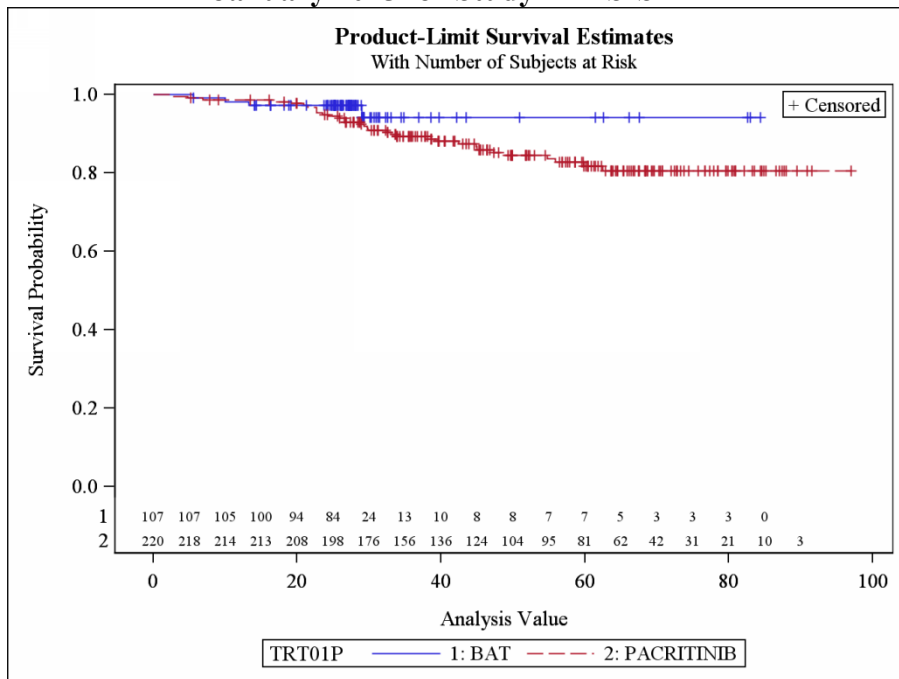
Figure 3 Kaplan-Meier Plot with ITT Population and Cut-off Date of October 2015 for Study PERSIST-1

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Figure 4 Kaplan-Meier Plot with Patients Censored at Crossover and Cut-off date of October 2015 for Study PERSIST-1

Study PERSIST-2

PERSIST-2 study was a confirmatory study of pacritinib, which was designed as a randomized controlled Phase 3 study of oral pacritinib versus BAT in patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis. A total of 300 eligible patients was pl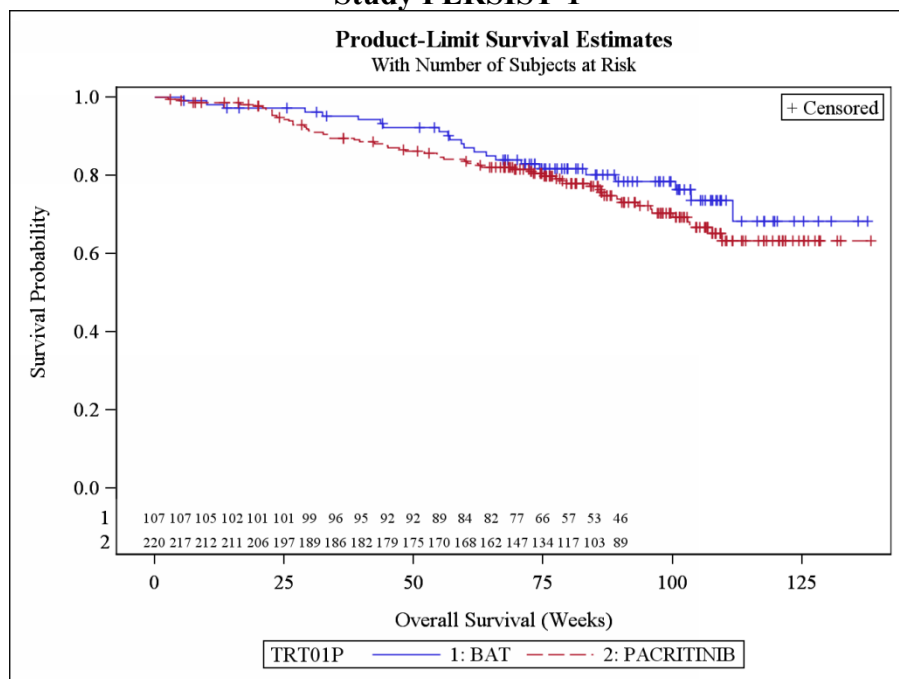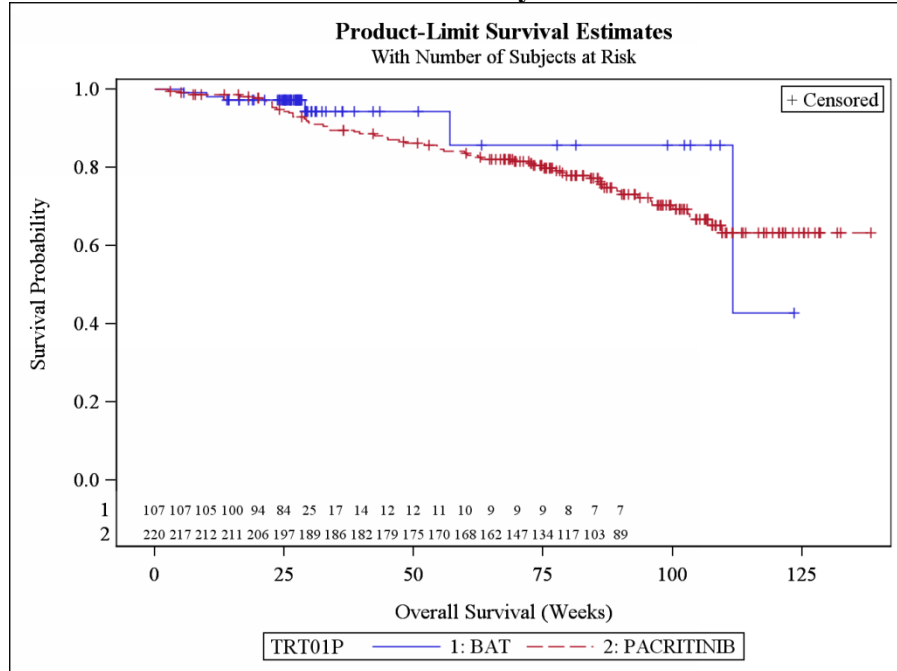anned to be randomized in a 1:1:1 allocation to pacritinib 400 mg dosed QD, pacritinib 200 mg dosed BID, or BAT: Subjects randomized to the BAT arm were allowed to crossover to pacritinib at week 24 without disease progression or earlier if a subject experienced disease progression. An IDMC was planned to evaluate the safety of pacritinib. No interim efficacy analysis is planned.

The efficacy co-endpoints are the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging (MRl) or computed tomography (CT) scan and the proportion of patients achieving a ≥ 50% reduction in total symptom score (TSS) from baseline to Week 24 as measured by the Myeloproliferative Neoplasm Symptom Assessment Form 2.0 (MPN-SAF TSS 2.0). Overall survival was an exploratory efficacy endpoint.

The overall survival analysis showed that the hazard ratio was 1.75 (95% CI [0.79, 3.87]) comparing pacritinib QD arm with BAT arm with the ITT population. Based on the pacritinib QD arm, the results also indicate an excess risk of deaths against the pacritinib treated arm which appears to support the OS finding from study PERSISIT-1.

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Table 2 Overall Survival in PERSIST-2

	Pacritinib (BID) (N = 106)	Pacritinib (QD) (N = 103)	BAT (N = 98)
Number of Events Median time (95% CI) HR (95% CI) p-value ITT Analysis	9 (8.5%) NA (NA, NA) 0.88 (0.36, 2.16) 0.77	16 (15.5%) NA (NA, NA) 1.75 (0.79, 3.87) 0.16	10 (10.2%) NA (NA, NA)
Number of Events Median time (95% CI) HR (95% CI) p-value Censor at Crossover Number of Events	9 (8.5%) NA (NA, NA) 0.94 (0.34, 2.60) 0.91	16 (15.5%) NA (NA, NA) 1.36 (0.54, 3.42) 0.51	7 (7.1%) NA (41.4, NA)

Figure 5 Kaplan-Meier Plot with ITT population for Study PERSIST-2
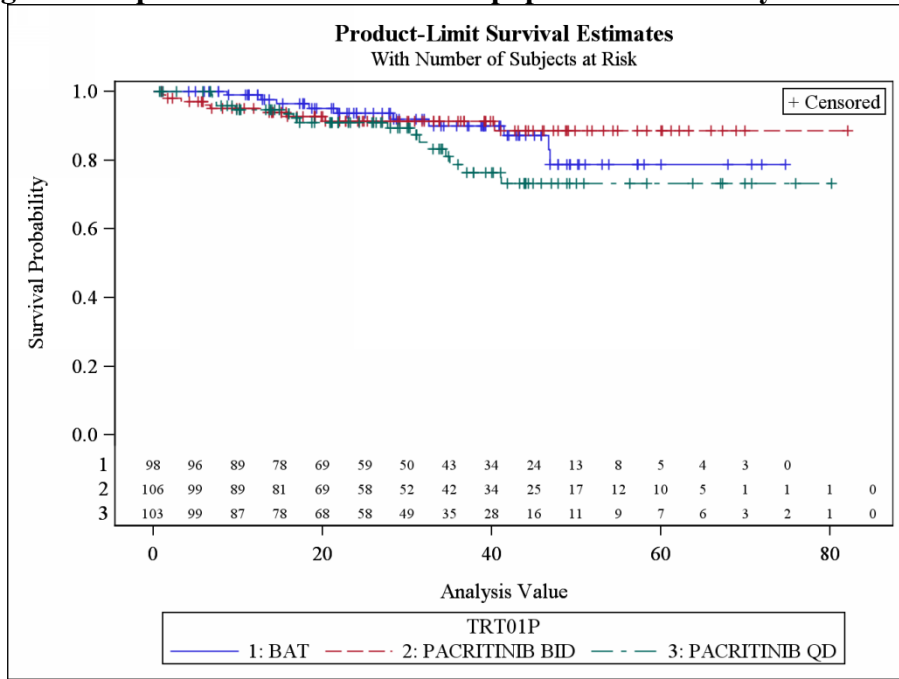
Figure 6 Kaplan-Meier Plot with Patients Censored at Crossover for Study PERSIST-2
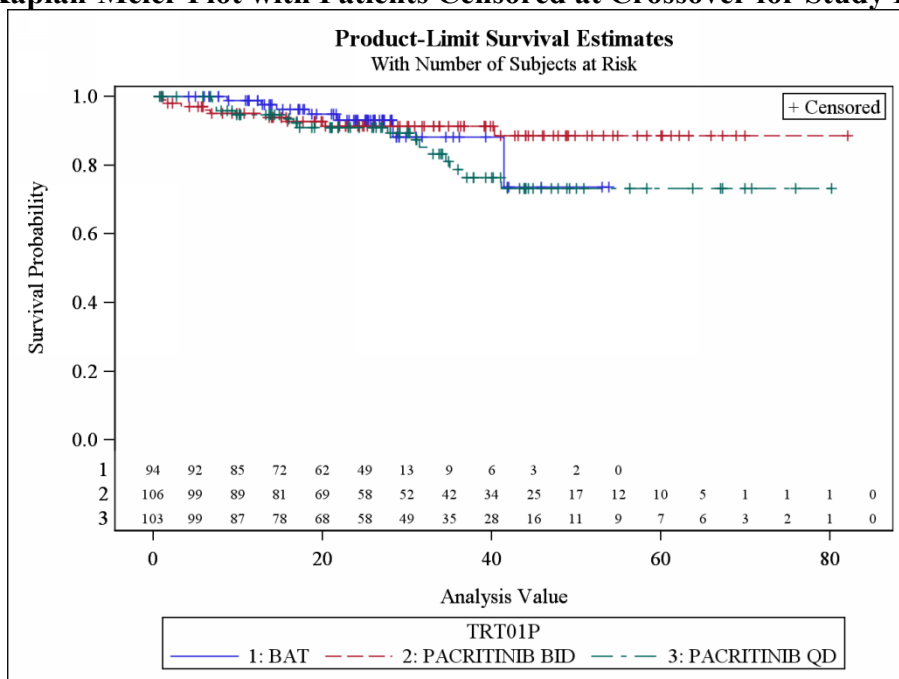
IDMC for Study PERSIST-1 and Study PERSIST-2

The IDMC meeting minutes showed that the IDMC meeting in February 2015 had an open session for PERSIST 1 and PERSIST 2, a closed session for PERSIST-1, and a separate closed session for PERSIST-2.

The following recommendations were included in the meeting minutes under the open session for PERSIST-1 and PERSIST-2:

> **Final recommendation to the sponsor**
>
> During the closed session, it was decided that the recommendation made to the sponsor will be:
>
> PERSIST-1 to be terminated and PERSIST-2 to have enrolment held subject to further recommendation.
> As the Trial Team will be unblinded for PERSIST-1 within 1-2 weeks and, at that point, will be able to analyze the safety and efficacy data for PERSIST-1 and be in a position to apply this information to the evaluation of PERSIST-2.
>
> Post-meeting notes: CTI requested a follow-up call with the IDMC to further discuss the rationale for the final recommendation. CTI will also meet with the IDMC to present PERSIST-1 Topline results prior to the next regularly scheduled IDMC meeting.

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The following recommendations were listed in the meeting minutes under the closed session for PERSIST-1.

Recommendation PERSIST-1

During the closed session, it was decided that the recommendation made to the sponsor will be to terminate the study due to the higher toxicity and higher incidence of deaths in PAC and the observed efficacy under the target of 30% of responders foreseen in the protocol (efficacy analyses performed on 299 patients out of the 327 in the ITT population).

The applicant continued the study citing internal or external experts' opinions, even after receiving recommendations of terminating study PERSIST-1 from the IDMC.

The IDMC was disbanded and a new IDMC was formed, but the Sponsor did not inform the Agency about that. The second IDMC had the first meeting on November 12, 2015 to discuss results regarding PERSIST-2 and did not comment on PERSIST-1.

Issues Identified

Based on current review of data, a few issues are identified:

- A risk increase in mortality is observed in both PERSIST-1 and PERSIST-2 studies:

  - For Study PERSIST-1, the hazard ratio of overall survival within the ITT population is 1.21 with data cut-off date of January 2015 and 1.29 with data cut-off date of October 2015. The analyses results indicate the patient randomized to the Pacritinib group has an increased risk of death compared with the patients randomized to the BAT group. The sensitivity analyses of overall survival with data censored at cross-over with either data cut-off date showed consistent results.

  - For Study PERSIST-2, the hazard ratio of overall survival is 1.75 within the ITT population (Pacritinib QD vs. BAT), and 1.36 with data censored at cross-over (Pacritinib QD vs. BAT). These analysis results were consistent with those from Study PERSIST-1 and showed that the patient randomized to the Pacritinib group has an increased risk of death compared with the patients randomized to the BAT group.

- FDA has concerns about the conduct of the trials involving IDMC review. The document of the interactions between the IDMC, additional experts and the sponsor (including correspondences, meeting minutes, data/analyses sources, etc.) do not appear to be complete for FDA to perform a thorough review of the trial conduct.

Application Status

Based on results from PERSIST-1 and PERSIST-2, the clinical team recommended a full clinical hold for both trials (refer to the clinical review). The sponsor withdrew the NDA on February 10, 2016.

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XIN GAO

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YUAN L SHEN

03/14/2016

RAJESHWARI SRIDHARA

03/14/2016

CLINICAL REVIEW

Application Type	NME NDA
Application Number	208712
Priority or Standard	Priority
Submit Date	December 30, 2015
Received Date	December 30, 2015
PDUFA Goal Date	August 30, 2016
Division / Office	DHP/OHOP
Reviewer Name	Vishal Bhatnagar, M.D.
Review Completion Date	February 23, 2016
Established Name	Pacritinib
Trade Name	(b) (4)
Therapeutic Class	FLT3/JAK2 inhibitor
Applicant	CTI Biopharma
Formulation	Capsules: (b) (4)
Proposed Dosing	(b) (4)
Proposed Indication	Intermediate or high-risk myelofibrosis, including primary myelofibrosis, post PV myelofibrosis, and post-ET myelofibrosis, with thrombocytopenia (platelet count <50,000 μL)
Intended Population	Adults

Executive summary:

Intermediate and high risk myelofibrosis is a serious, life-threatening condition. CTI Biopharma submitted an NDA for pacritinib, a JAK2/FLT3 inhibitor, based on the results of the PERSIST-1 trial. In this phase 3, randomized trial, pacritinib was compared to best available therapy (BAT) with a primary endpoint of spleen volume reduction (SVR) in subjects with intermediate or high risk myelofibrosis. Subjects randomized to the BAT arm were allowed to crossover to pacritinib at week 24 without disease progression or earlier if a subject experienced disease progression. The proportion of all subjects in the ITT population achieving a ≥ 35% SVR from baseline to week 24 was 19% vs 5% for pacritinib and BAT respectively (p = 0.0003).

Review of topline safety results are notable for increased mortality (26% vs 6%) in the pacritinib arm compared to the BAT arm. Time-to-event analyses for overall survival (OS) showed excess mortality in the pacritinib arm: OS HR was 1.29 (95% CI 0.81, 2.13) on ITT analysis. In addition, there were higher rates of serious bleeding events (7% vs 1%) and heart failure (7% vs 2%) in the pacritinib arm. Similar results are apparent in subjects on pacritinib after crossing over from BAT (mortality rate 19%, serious bleeding 15%, cardiac failure 5%).

Review of the PERSIST-2 overall survival results also show a detriment in survival for the pacritinib arm (12% vs 7%). The OS HR was 1.29 (95% CI 0.63, 2.81). There are similar serious and fatal adverse events, specifically intracranial bleeding, cardiac failure, and cardiac arrest in PERSIST-2.

The independent data monitoring committee (IDMC) recommended termination of PERSIST-1 based on the overall survival results, but the Sponsor continued the trial, citing a consultant statistical review.

Based on results from PERSIST-1 and PERSIST-2, the clinical team recommended a full clinical hold for both trials. The sponsor withdrew the NDA on February 10, 2016.

Introduction:

Myelofibrosis is a myeloproliferative neoplasm (MPN) characterized by stem cell-derived clonal myeloproliferation, abnormal cytokine expression, bone marrow fibrosis, anemia, splenomegaly, extramedullary hematopoiesis, constitutional symptoms, cachexia, leukemic progression, and shortened survival. Mutations in JAK2 have been associated with myeloproliferative neoplasms, including polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). Myelofibrosis may present as either a primary MPN or following an antecedent diagnosis of PV or ET (post-polycythemia vera [PPV] or post-essential thrombocythemia [PET]). Regardless of the original diagnosis, primary MF (PMF), PPV-MF, and PET-MF have a common disease course, characterized by elevated numbers of CD34+ stem cells in the marrow in the early phase of the disease, followed by marrow fibrosis with decreasing numbers of CD34+ cells in the marrow and a corresponding increase in splenic and liver engorgement by CD34+ cells in the later phases. In addition to the clonal proliferation of a multipotent hematopoietic progenitor cell, an event common to all chronic MPNs, these disorders are characterized by colonization of extramedullary sites such as the spleen or liver.

Currently, allogeneic hematopoietic stem cell transplantation and the JAK2 inhibitor ruxolitinib are the only therapies with the potential to prolong overall survival, although only stem cell transplantation is thought to be potentially curative.

Pacritinib is a Janus kinase 2/FMS-like receptor tyrosine kinase 3 (JAK2/FLT3) inhibitor. Pacritinib led to reductions in spleen size in subjects with MF, even those with thrombocytopenia in two phase I/II trials, SB1518-2007-001 and SB1518-2008-003. Currently, two phase 3 trials are underway: PERSIST-1 and PERSIST-2. The sponsor is seeking an indication for pacritinib in patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis, with thrombocytopenia (platelet counts <50,000/μL) based on the results of PERSIST-1.

The PERSIST-1 study was a multicenter, randomized, controlled, phase III trial. It compared the efficacy and safety of pacritinib with that of BAT in subjects with PMF, PPV-MF, or PET-MF. A total of 327 eligible subjects were randomized in a 2:1 allocation to pacritinib 400 mg orally, once daily or best available therapy. BAT included hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, symptom directed treatment or no treatment. Splenic irradiation and ruxolitinib were not permitted for subjects in the BAT arm.

The primary objective of this PERSIST-1 study was to compare the efficacy of pacritinib with that of BAT in subjects with PMF, PPV-MF, or PET-MF; the efficacy measure for this analysis was the proportion of subjects achieving a $\geq$ 35% reduction in spleen volume from baseline to week 24, as measured by magnetic resonance imaging or computed tomography scan. The key secondary objective of the study was the proportion of subjects with $\geq$ 50% reduction in total symptom score (TSS) from baseline to week 24 on the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF TSS 2.0).

By the data cutoff of January 17, 2015, 220 subjects were enrolled in the pacritinib arm and 106 in the BAT arm. On preliminary review of the study population data, baseline characteristics appear to be balanced between treatment arms. Of the subjects on BAT, 60/106 (56%) were on hydroxyurea and 40/106 (37%) were being observed without treatment for myelofibrosis, while the remaining six subjects were on one of the other above-mentioned treatments.

PERSIST-2 is a randomized, controlled, phase 3 study in PMF, PPV-MF, or PET-MF; the co-primary endpoints are (1) proportion of patients achieving a > 35% reduction in spleen volume from baseline to Week 24, as measured by MRI or CT scan and (2) proportion of patients achieving a > 50% reduction in TSS from baseline to Week 24 on the MPN-SAF TSS 2.0. A special protocol assessment (SPA) was granted in October 2013 for PERSIST-2. In PERSIST-2, "best available therapy" includes ruxolitinib, whereas in PERSIST-1 this was not allowed. Patients will be randomized 1:1:1 to pacritinib 400 mg daily, pacritinib 200 mg BID, and BAT.

In both of these trials, subjects in the BAT arm were able to crossover to pacritinib if they met all of the following:

- Subject had to complete at least 24 weeks on BAT, or had progression of disease prior to week 24; progression was declared based only on an increase in splenic volume of ≥ 25% from baseline, on centrally read MRI or CT scan
- Subject had not undergone splenic irradiation or splenectomy
- Subject did not meet criteria for leukemic transformation

In PERSIST-1, 82/106 subjects had crossed over from BAT to pacritinib at the time of data cutoff. Of the 82 subjects who crossed over to pacritinib, 15 had splenic or leukemic progression prior to crossover; the remainder (N=67) had no evidence of splenic or leukemic progression prior to crossover. Those who crossed over from BAT to Pacritinib had similar exposures to both drugs, as shown in Table 1.

Table 1: Duration of treatment by arm

Duration of Treatment (weeks)	Pacritinib (N=220)	BAT (N=106)	BAT→Pac (N=82)
Median	36	26	22
Minimum, maximum	0, 97	3, 84	0, 64

Figure 1: Dose exposure plot
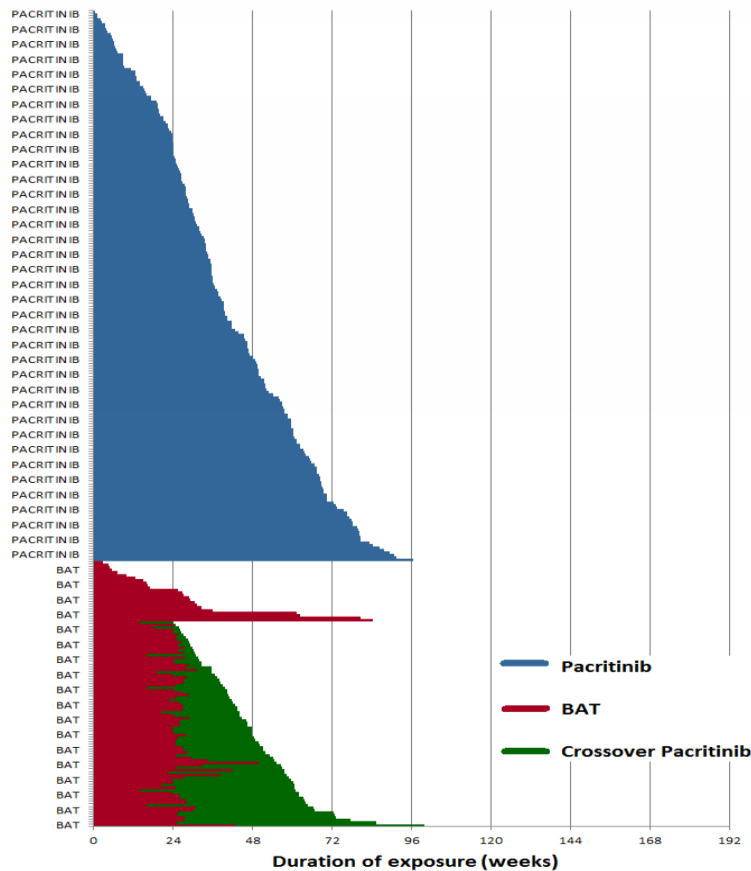
Data sources

PERSIST-1 data was submitted to NDA 208712 on December 30, 2015. The data cutoff date for the submitted safety and efficacy datasets was January 17, 2015. The sponsor submitted updated PERSIST-1 overall survival data with a cutoff of October 30, 2015. For PERSIST-2, safety tables and listings were submitted after agency request, with a cutoff of October 19, 2015. PERSIST-2 overall survival data was also submitted, with a data cutoff of January 26, 2016.

Efficacy results

Topline results of the efficacy results were in favor of pacritinib, although the primary endpoint did not meet the target response specified in the statistical analysis plan. Power and sample size calculations were based on an assumption that 30% of pacritinib and 3% of BAT treated subjects would achieve a ≥ 35% SVR from baseline for an effect size of 27%. The proportion of all subjects in the ITT population achieving a ≥ 35% SVR from baseline to week 24 was 19% vs 5% for pacritinib and BAT respectively (p = 0.0003), thus the actual effect size was 14%, half of predicted.

Statistically significant differences between treatment groups in favor of pacritinib were also observed for each subgroup of subjects by baseline platelet count (< 50,000/mcL, < 100,000 /mcL, and ≥ 100,000/mcL). Analysis of the secondary endpoint is complicated by the use of multiple symptom scores. In PERSIST-1, 179 (55%) subjects were administered MPN-SAF TSS version 1.0 and 148 (45%) were given MPN-SAF TSS version 2.0. According the sponsor, there was no statistically significant effect on the secondary endpoint (proportion of ITT subjects achieving a ≥ 50% reduction in TSS from baseline to week 24 as measured by the MPN-SAF TSS 2.0). Nineteen percent of pacritinib subjects versus 10% of BAT subjects achieved the secondary endpoint (p=0.24).

Safety results for PERSIST-1

In PERSIST-1, the sponsor's data interpretation is based on the original (initial) randomization arm. Specifically, adverse events experienced by subjects who crossed over from BAT to pacritinib were not included in the main safety analysis performed by the sponsor. As discussed above, a large proportion of subjects who were on BAT crossed over to pacritinib, and were exposed to pacritinib for a significant period of time. Topline safety results are presented in Table 2, with adverse events from the crossover arm included.

Table 2: Overall Summary of Adverse Events (Safety Population)

Type of AE	Pacritinib N=220 n (%)	BAT N=106 n (%)	BAT→Pac N=82 n (%)
Subjects who experienced ≥ 1 TEAE	197 (89)	81 (76)	69 (84)
Subjects experiencing Grade 3 or higher TEAE	138 (63)	44 (42)	40 (42)
Serious TEAEs	94 (43)	27 (26)	31 (38)
TEAEs with outcome of death	14 (6)	3 (3)	8 (10)

<u>Deaths</u>

Per the Agency's request, the sponsor submitted updated overall survival data with a cutoff of October 30, 2015. As of this data cutoff, 81 randomized subjects died. A listing of deaths is provided in Appendix A. Table 3 summarizes the deaths in PERSIST-1.

Table 3: Deaths that Occurred During PERSIST-1

	Pacritinib N=220 n (%)	BAT N=106 n (%)	BAT→Pac N=90 n (%)
Total Deaths	58 (26)	6 (6)	17 (19)

The proportion of subjects who died is higher in the crossover population and pacritinib arm compared to the BAT arm. Below are Kaplan-Meier curves for overall survival by randomized arm, without censoring for crossover (Figure 2) and with censoring for crossover (Figure 3).

Figure 2: Kaplan-Meier Curve - Overall Survival (ITT Analysis), Cutoff October 2015
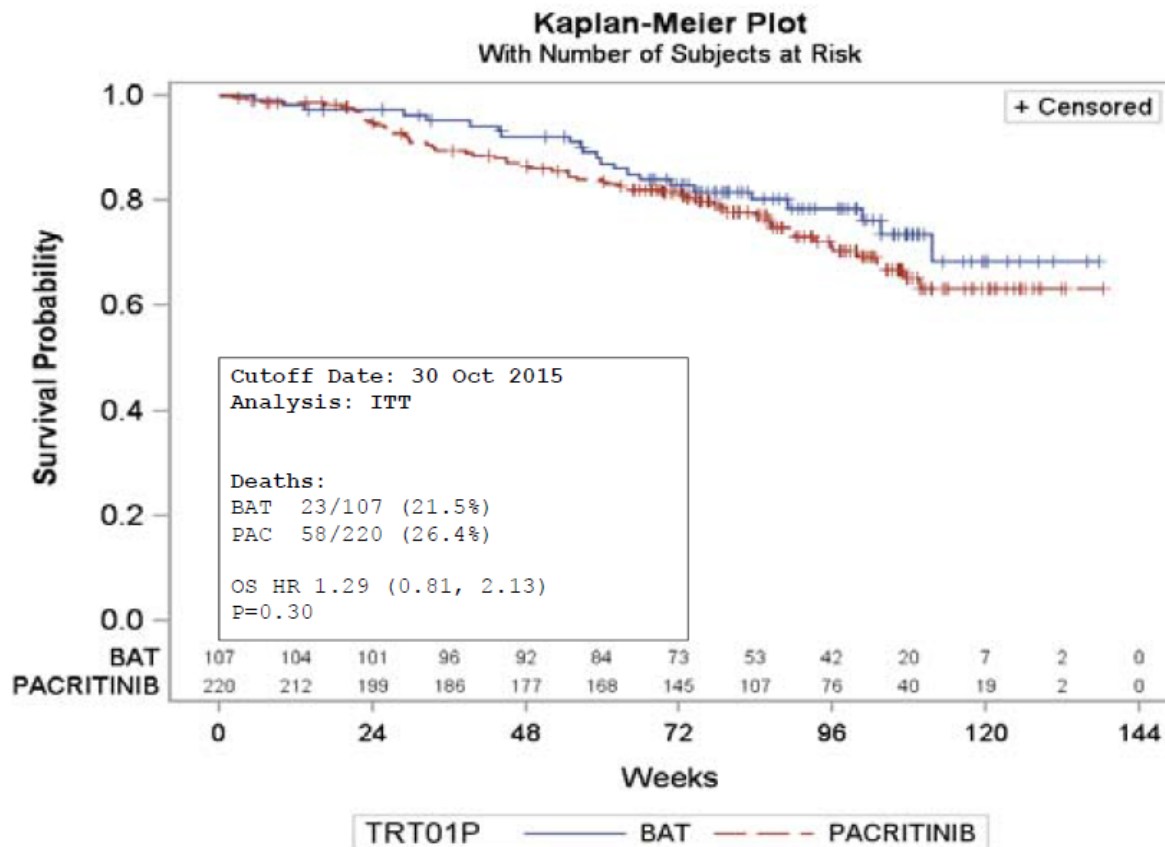
Figure 3: Kaplan-Meier Curve - Overall Survival Censoring for Crossover, Cutoff October 2015

Kaplan-Meier Plot
With Number of Subjects at Risk

Cutoff Date: 30 Oct 2015
Analysis: Censor BAT arm on crossover

Deaths:
BAT   6/107   (5.6%)
PAC   58/220 (26.4%)

OS HR 1.66 (0.75, 4.40)
P=0.25

BAT	107	104	92	17	12	10	9	7	7	3	1	0
PACRITINIB	220	212	199	186	177	168	145	107	76	40	19	2	0

Weeks: 0, 24, 48, 72, 96, 120, 144

TRT01P ——— BAT — — — PACRITINIB
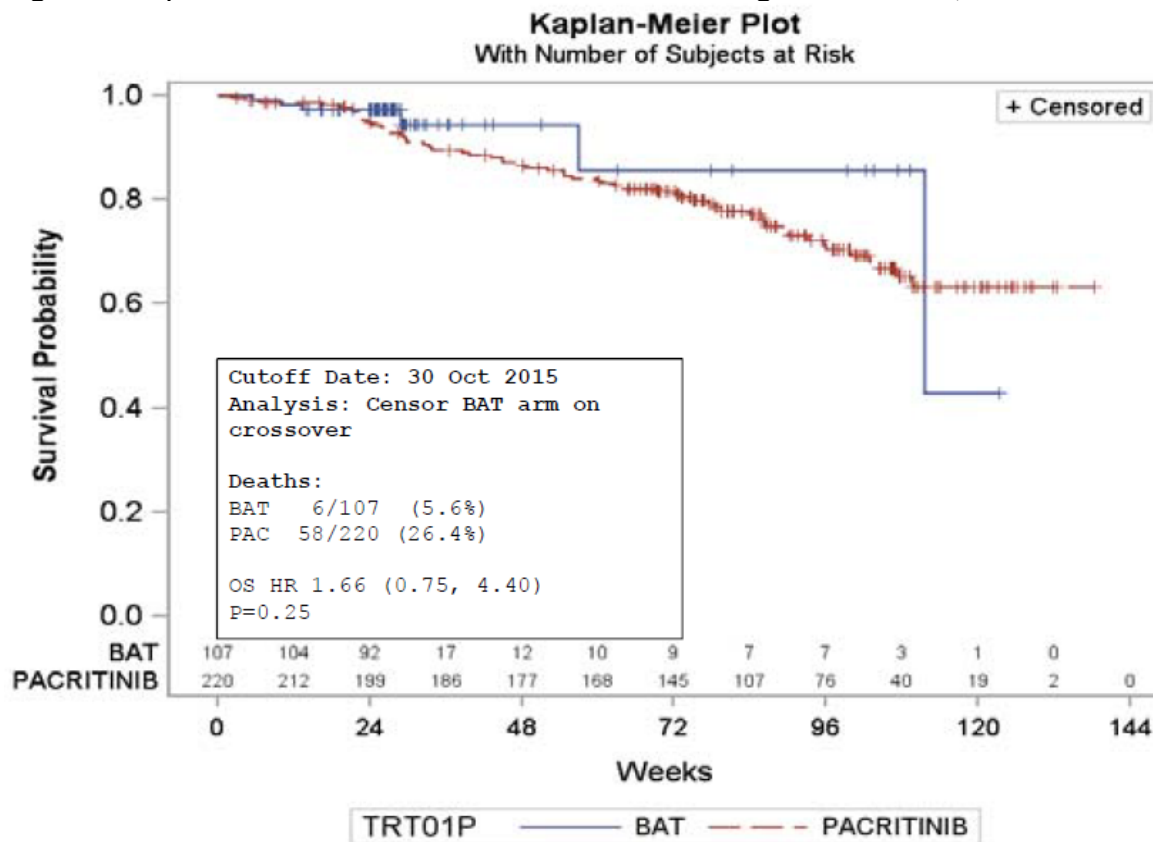
Heart failure

The PERSIST-1 protocol excluded subjects with any of the following:
Clinically symptomatic and uncontrolled cardiovascular disease
History of any of the following, within six months prior to randomization:

1. myocardial infarction
2. severe/unstable angina
3. symptomatic congestive heart failure
4. New York Heart Association Class II, III, or IV congestive heart failure

With the data cutoff date of January 17, 2015, the rate of any grade heart failure was higher in the pacritinib arm (16/220, 7%) and the crossover arm (4/82, 5%) versus the BAT arm (2/106, 2%).

Table 4: Listing of Subjects with Heart Failure

Patient	Arm	AE	Grade	Treatment Day
(b) (6)	BAT	Cardiac Failure	5	39
	BAT	Cardiac failure	3	94
	PAC	Cardiac failure	3	41
	PAC	Cardiac failure	3	55

Patient (b) (6)	Arm	AE	Grade	Treatment Day
	PAC	Cardiac failure	1	57
	PAC	Cardiac failure	3	65
	PAC	Cardiac failure congestive	4	68
	PAC	Pulmonary edema	3	76
	PAC	Cardiac failure congestive	3	76
	PAC	Left ventricular	2	79
	PAC	Cardiac failure	3	92
	PAC	Cardiac failure	3	126
	PAC	Cardiac failure congestive	3	145
	PAC	Cardiac failure	3	207
	PAC	Pulmonary edema	3	244
	PAC	Cardiac failure	2	250
	PAC	Ejection fraction decreased	3	327
	PAC	Cardiac failure	2	429
	BAT→Pac	Cardiac failure	2	69*
	BAT→Pac	Cardiac failure congestive	2	195*
	BAT→Pac	Cardiac failure	4	211*
	BAT→Pac	Cardiac failure congestive	3	287*

*Day 1 = first day of crossover pacritinib treatment

QT prolongation and cardiac arrhythmias

The rates of grade 2 and 3 QT prolongation are higher in pacritinib treated patients than BAT. Table 5 lists the rate of grade 2 and 3 QT prolongation in PERSIST-1.

Table 5: QT Prolongation by Arm

	Pacritinib N=220 n (%)	BAT N=106 n (%)	BAT→Pac N=82 n (%)
Grade 2	9 (4)	2 (2)	4 (5)
Grade 3	4 (2)	0	0

Additionally, there were two sudden deaths and one Grade 4 ventricular tachycardia reported in the pacritinib arm.

Bleeding events

There was a similar rate of bleeding AEs between arms, as described in Table 6 below. The most common bleeding AEs in all arms were epistaxis, contusion and hematoma. Although the proportion of bleeding events across arms was similar, the bleeding events in the pacritinib and crossover arms were higher in severity. In the pacritinib arm there was a higher proportion of bleeding SAEs (7%) and fatal AEs (2%) compared to BAT. In the crossover arm, 15% (12/82) of

subjects experienced bleeding SAEs. Five subjects in the pacritinib arm, four subjects in the crossover arm, and one subject in the BAT arm had intracranial bleeding TEAEs.

Table 6: Summary of Bleeding Events by Arm

	Pacritinib N=220 n (%)	BAT N=106 n (%)	BAT→Pac N=82 n (%)
Bleeding AEs	54 (25)	20 (19)	19 (23)
Bleeding SAEs	15 (7)	1(1)	12 (15)
Grade 5 bleeding events	2 (1)	0	2 (2)

Safety results for PERSIST-2

The clinical team requested overall survival data for PERSIST-2. Review of the PERSIST-2 overall survival results (data cutoff of January 26, 2016) also show a detriment in survival for the pacritinib arm (12% vs 7%). The OS HR was 1.29 (95% CI 0.63, 2.81).

Figure 4: Kaplan-Meier Curve – PERSIST-2 Overall Survival (ITT Analysis)
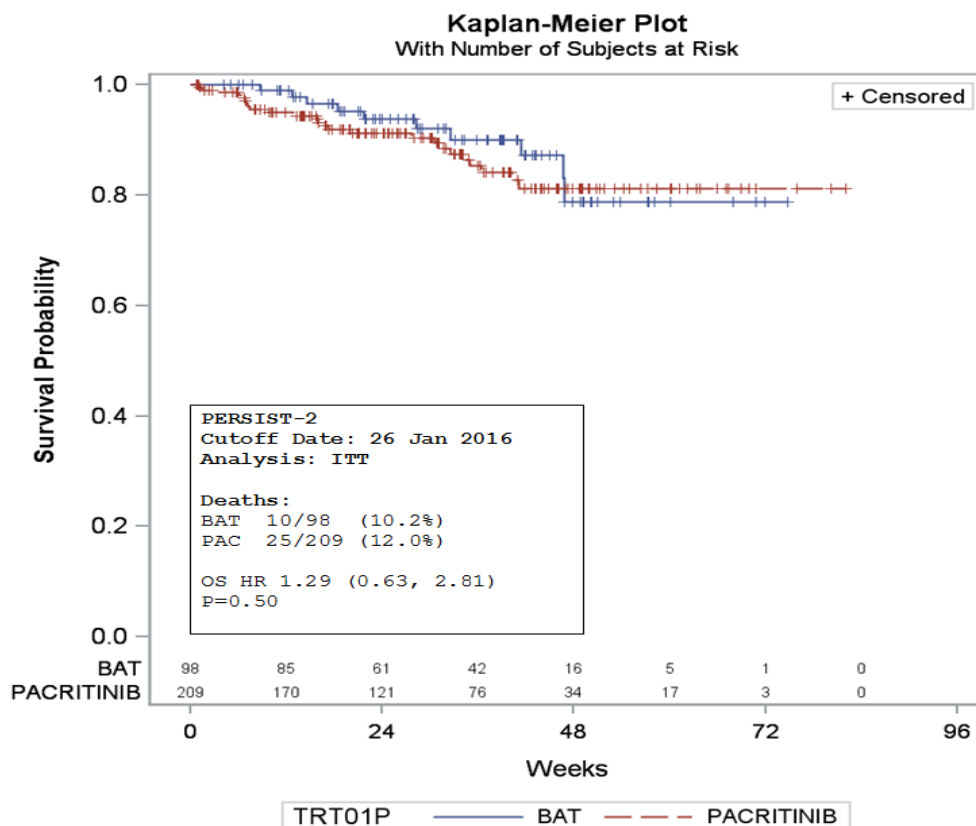
The sponsor has submitted safety tables with a data cutoff of October 19, 2015. Topline safety results are presented in Table 7, with adverse events from the crossover arm included.

Table 7: Summary of AEs in PERSIST-2

Type of AE	Pacritinib N=138 n (%)	BAT N=67 n (%)	BAT→Pac N=18 n (%)
Subjects who experienced ≥ 1 TEAE	120 (87)	48 (72)	8 (44)
Subjects experiencing Grade 3 or 4 TEAE	71 (51)	27 (40)	4 (22)
Serious TEAEs	45 (33)	15 (22)	3 (17)

Of the 18 deaths in PERSIST-2 that listings/tables/narratives are available: 12 were in the pacritinib arm, 5 in the BAT arm, and one in the crossover arm. Table 8 is a listing of fatal TEAEs, not including disease progression. There are three cerebral hemorrhages and two cardiac deaths in patients exposed to pacritinib.

Table 8: Listing of patients with Fatal TEAEs in PERSIST-2

Patient	Arm	Cause of death	Study day
(b) (6)	PAC	Cerebral hemorrhage	8
	PAC	Cerebral hemorrhage	9
	PAC	Pulmonary embolism	50
	PAC	Cardiac arrest	51
	PAC	Cardiac failure	121
	PAC	Pulmonary Edema	245
	BAT-> PAC	Cerebral hemorrhage	28*
	BAT	Septic shock	89
	BAT	Splenic infarct	100
	BAT	Sudden neurological degradation	198
	BAT	Failure to thrive	282

*Day of crossover = day 1

IDMC findings

On February 6, 2015, the IDMC recommended termination of PERSIST-1 based on the number of treatment emergent deaths, proportion of grade 3/4 TEAEs and SAEs in the setting of a lower than expected proportion of subjects achieving ≥ 35% SVR. Refer to table 1 for a listing of all IDMC meetings including the February 6, 2015 meeting. Of note, the CRO (b) (4) was involved in PERSIST-1 and the VP of Medical Affairs was present at the February 6 IDMC meeting. Based on the IDMC's recommendation, the Sponsor requested an independent review by (b) (4) a CTI employee not affiliated with the PERSIST-1 or PERSIST-2 study team. On March 5, 2015, subsequent to database lock, the Sponsor hired an independent expert ((b) (4)) and statisticians ((b) (4)) to review topline results and the IDMC recommendations, who disagreed with the IDMC. On May 27, 2015, the original IDMC re-iterated their recommendation to terminate PERSIST-1 to the study steering committee.

The Sponsor met with the Agency on June 2, 2015 for a pre-NDA type B meeting, but the IDMC recommendation was not disclosed at that time. On June 25, 2015, the IDMC made its final recommendation to terminate PERSIST-1 and to disallow crossover in PERSIST-2. CTI Biopharma informed the Agency on June 29, 2015 regarding the IDMC recommendations. Refer to table 2 for subsequent Agency interactions with the Sponsor regarding the IDMC. In regards to continuation of PERSIST-1, the Sponsor cited reviews performed by hired independent statisticians and did not follow the IDMC recommendation. The IDMC was disbanded and a new IDMC was formed, but the Sponsor did not inform the FDA regarding the dissolution and reformation of the IDMC. The second IDMC met on November 12, 2015 to discuss results regarding PERSIST-2 and did not comment on PERSIST-1.

Although the Agency has open and closed minutes of the formal IDMC meetings, we are relying on the Sponsor's account of interactions for the March 5, 2015, May 27, 2015 and June 25, 2015 meetings.

Table 9: Agency Interactions with CTI Biopharma

Date	Interaction
June 2, 2015	Pre-NDA Agency meeting. No mention of IDMC recommendation.
June 29, 2015	CTI requests a teleconference regarding IDMC recommendation.
July 15, 2015	CTI changes to Type B meeting request to answer one question "Based on internal pharmacovigilance review and in consultation with the Study Steering committee members, CTI Biopharma is proceeding with the PAC325 and PAC326 studies per protocol. Does the FDA agree that this is acceptable?"
July 31, 2015	CTI amends question to "Based on internal pharmacovigilance review and in consultation with the Study Steering committee members, CTI Biopharma is proceeding with the PAC325 and PAC326 studies per protocol. Does the FDA agree that not terminating and continuing PAC325 and 326 could provide valuable data for the evaluation of the safety and efficacy of pacritinib?"
August 18, 2015	Meeting package submitted to FDA, including IDMC charter, the independent statistics review of the IDMC findings, and CVs for the independent statistical review team.
September 17, 2015	FDA Written Response: "We have not analyzed the data. The Agency understands the challenging situation of interpreting non-significant results and forming meaningful conclusions. The Agency recommends you address any safety issues, especially one of potential increased mortality. The Agency wants you to be aware of two points: The earlier a safety signal is addressed in development the better. The Agency has multiple avenues to address unresolved safety concerns including recommending another trial prior to approval, a REMS, or PMR to name a few.

A potential way to address this safety signal would be to eliminate cross-over on PERSIST-2. This may provide more informative data and leave less residual doubt." |

Table 10: Summary of IDMC meetings

IDMC Meeting #	Date	PERSIST-1 enrollment PAC	BAT	Recommendation
1	September 16, 2013	38	19	**Continue, without modification**
2	January 6, 2014	78	38	**Continue, without modification**
3	March 6, 2014	120	59	**Continue, without modification**
4	May 23, 2014	160	77	Concerns regarding number of PAC grade 3/4 TEAEs, PAC TEAEs leading to withdrawal. **Continue with careful examination of safety results at next meeting**
5	July 31, 2014	194	93	No significant differences in safety signals except GI AEs and thrombocytopenia. **Continue, without modification**
6	October 30, 2014	219	106	Higher incidence of TEAE, TEAE leading to withdrawal, Grade 3 or 4 TEAE and SAE in PAC arm noted. Treatment emergent deaths: PAC 13 vs BAT 3 vs Crossover 2. **Continue, without modification**
7	February 6, 2015	220	106	**During the closed IDMC meeting, it was decided that the recommendation made to the sponsor will be to terminate the study due to the higher toxicity and higher incidence of deaths in PAC and the observed efficacy under the target of 30% of responders foreseen in the protocol (efficacy analyses performed on 299 patients out of the 327 in the ITT population).** **In the open session minutes, the IDMC recommended the following: PERSIST-1 to be terminated and PERSIST-2 to have enrolment held subject to further recommendation. As the Trial Team will be unblinded for PERSIST-1 within 1-2 weeks and, at that point, will be able to analyze the safety and efficacy data for PERSIST-1 and be in a position to apply this information to the evaluation of PERSIST-2.**
8 (Second IDMC)	November 12, 2015	Fully Enrolled		**Continue, without modification**

Regulatory Action

DHP placed IND 078406 on partial clinical hold on February 4, 2016 based on updated PERSIST-1 overall survival data received on February 3, 2016. DHP placed IND 078406 on full clinical hold on February 8, 2016 based on PERSIST-2 overall survival data received on February 8, 2016.

The Sponsor withdrew the NDA on February 10, 2016. The Sponsor does not plan on fulfilling any information requests submitted to the NDA, including a submission of the 120 day safety update. The Agency provided the following recommendation in the withdrawal acknowledgement letter:

"We have identified serious safety signals for (a) detrimental effect on overall survival based on PERSIST-1 and PERSIST-2 trial results, and (b) fatal and life-threatening safety issues of hemorrhage including intracranial hemorrhage, cardiac failure, and arrhythmias including sudden death. On February 8, 2016, we placed all clinical trial protocols under IND 078406 on full clinical hold and refer you to the full clinical hold letter for the conditions and recommendations of the full clinical hold regulatory action.

You will need to conduct new adequate and well-controlled randomized clinical trials of pacritinib for your proposed indication. The pacritinib dose should be adequately justified prior to the initiation of the randomized controlled trials (RCTs). Even with the conduct of new RCTs, you will need to adequately explain the adverse findings from PERSIST-1 and PERSIST-2 in order to support an overall favorable benefit-risk assessment for pacritinib for your proposed indication."

Appendix A: Listing of Deaths in PERSIST-1 with data cutoff date of January 17, 2015

Patient	Arm	Cause of death	Study day*	Days since treatment discontinuation**
(b) (6)	PAC	Cardio-respiratory arrest	18	2
	PAC	Hypoxia	34	6
	BAT	Cardiac failure	39	9
	PAC	Renal failure acute	48	3
	BAT	Sepsis	70	1
	BAT	Disease progression	93	6
	PAC	Disease progression	118	10
	PAC	Disease progression	136	38
	PAC	Multi-organ failure	147	12
	PAC	Renal failure acute	152	14
	PAC	Disease progression	161	39
	PAC	Traumatic intracranial hemorrhage	161	6
	PAC	Pneumonia	161	11
	PAC	Disease progression	167	2
	PAC	Unknown	172	122
	PAC	Disease progression	182	34
	PAC	Post-surgery complications	187	49
	PAC	Pneumonia	187	17
	PAC	Acute leukemia	203	195
	PAC	Shock	206	4
	BAT	Neutropenic sepsis	207	169
	PAC	Cardio-respiratory arrest	209	69
	PAC	Disease progression	209	35
	PAC	Hemorrhage	230	19
	Crossover	Hemorrhage intracranial	231	2
	PAC	Disease progression	234	195
	PAC	Disease progression	238	102
	PAC	Multi-organ failure	272	19
	Crossover	Multi-organ failure	275	45
	PAC	Disease progression	279	25
	PAC	Unknown	297	233
	Crossover	Acute leukemia	309	38
	PAC	Septic shock	314	227
	PAC	Disease progression	316	139
	PAC	Disease progression	332	60
	PAC	Disease progression	342	182
	Crossover	Sudden death	384	21
	PAC	Respiratory failure	384	160
	PAC	Cardiac failure	391	49
	Crossover	Disseminated intravascular coagulation	398	5

Patient	Arm	Cause of death	Study day*	Days since treatment discontinuation**
(b) (6)	Crossover	Disease progression	414	19
	PAC	Acute leukemia	420	205
	Crossover	Pneumonia	432	2
	PAC	Disease progression	439	268
	Crossover	Complication after stem cell transplantation	449	166
	Crossover	Complication after stem cell transplantation	461	48
	Crossover	Splenic rupture	520	9
	PAC	Disease progression	589	171
	Crossover	Status epilepticus	704	5

*Day 1 = day of randomization
** Day 1= day of discontinuation

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/s/

VISHAL BHATNAGAR
02/24/2016

ROMEO A DE CLARO
02/24/2016