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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enpaxiq

International non-proprietary name: pacritinib

Procedure No. EMEA/H/C/004193/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine transaminase (SGPT)
AML	acute myeloid leukemia
ALP	alkaline phosphatase
AST	aspartate transaminase (SGOT)
$AUC_{0\text{-}inf}$	Area under the curve 0 to infinity
BAT	Best available therapy
BCS	Biopharmaceutics Classification System
Bid	twice daily
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CT	Computed tomography
CV	coefficient of variation
ET	essential thrombocythemia
FDA	Food and Drug Administration
FLT3	fms-related tyrosine kinase 3
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
Hct	hematocrit
Hgb	hemoglobin
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
JAK2	Janus kinase 2
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities

µl	microliter
mg	milligram
MRI	magnetic resonance imaging
MPN	myeloproliferative neoplasms
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
NDA	New Drug Application
nM	nanomolar
PAC	pacritinib
PAC325	Phase 3 randomized, controlled study (PERSIST-1)
PD	pharmacodynamic
PERSIST-1	A randomized controlled phase 3 Study of pacritinib
PET-MF	post-essential thrombocythemia myelofibrosis
PGIA	Patient Global Impression Assessment
PK	pharmacokinetic
PMF	primary myelofibrosis
PPV-MF	post-polycythemia vera myelofibrosis
PV	Polycythemia vera
qd	once daily
Qid	four times daily
RBC	red blood cell (count)
RD	Recommended dose
SAE	serious adverse event
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (aspartate transaminase; AST)
SGPT	serum glutamic pyruvic transaminase (alanine transaminase; ALT)
SmPC	Summary of Product Characteristics
SOC	System organ class
Tid	three times daily
t_{max}	Time to maximum concentration
TSS	Total Symptom Score
US	United States
WBC	white blood cell

1. Recommendation

Based on the CHMP review of the data on quality, safety, efficacy and risk management plan, the CHMP considers that the application for Enpaxiq in the treatment of splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF), post-polycythaemia vera myelofibrosis (PPV-MF), and post-essential thrombocythaemia myelofibrosis (PET-MF), is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality

- Redefinition of proposed starting materials.

Non-clinical

- Pharmacological selectivity of pacritinib

Clinical

- Insufficient evidence of safety and efficacy in the myelofibrosis population

New active substance status

Based on the review of the data the CHMP considers that the active substance pacritinib contained in the medicinal product Enpaxiq could be qualified as a new active substance in itself provided that satisfactory responses are given to the concerns as detailed in the List of Questions.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication for Enpaxiq is in *the treatment of splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF), post-polycythaemia vera myelofibrosis (PPV-MF), and post-essential thrombocythaemia myelofibrosis (PET-MF)*.

2.1.2. Epidemiology

Myelofibrosis is a myeloproliferative disorder that is characterized by a clonal stem cell proliferation. Myelofibrosis can present as an apparently de novo disorder termed primary myelofibrosis (PMF), or evolve from other myeloproliferative disorders and can be termed secondary myelofibrosis, post-polycythaemia vera myelofibrosis (PPV-MF) or post-essential thrombocythaemia myelofibrosis (PET-MF). Synonyms to denote PMF include agnogenic myeloid metaplasia, chronic idiopathic myelofibrosis (CIMF), idiopathic myelofibrosis, myelofibrosis, and myelofibrosis with myeloid metaplasia (MMM).

The 10-year risk of developing myelofibrosis is < 4% in essential thrombocythaemia and 10% in polycythaemia vera. The median age at diagnosis is approximately 65 years, with equal incidence in

men and women. The incidence of PMF has been shown to increase with age and is estimated at 0.4 to 1.4 cases per 100,000 individuals per year.

2.1.3. Biologic features

The clonal stem cell proliferation is associated with production of elevated levels of several inflammatory and pro-angiogenic cytokines and a peripheral blood smear showing a leukoerythroblastic pattern with varying degrees of circulating progenitor cells. Resulting bone marrow stromal reaction includes varying degrees of collagen fibrosis, osteosclerosis and angiogenesis. The altered bone marrow milieu results in release of haematopoietic stem cells into the blood and extramedullary haematopoiesis, particularly hepatomegaly and splenomegaly.

2.1.4. Clinical presentation

Myelofibrosis results in laboratory and physical exam abnormalities including progressive anaemia, leucopoenia or leucocytosis, thrombocytopenia or thrombocythaemia, ineffective haematopoiesis and haematopoietic failure, massive splenomegaly and portal hypertension, and progression to leukaemia.

Clinically, patients suffer from the consequences of massive splenomegaly including abdominal pain or discomfort and pain under the left costal margin, risk of vascular events (including thrombosis and haemorrhage), severe constitutional symptoms (fevers, night sweats, weight loss), a hypermetabolic state, cachexia and premature death.

Causes of death for patients with MF include leukaemic transformation, infections, bleeding, thrombosis, heart failure, liver failure, solid tumours, respiratory failure, and portal hypertension.

2.1.5. Management

The only potentially curative therapy for MF remains allogenic stem cell transplantation (allo-SCT). However, this option is usually possible only in younger patients; is dependant in the availability of a donor; and associated with significant risks and mortality.

Drug treatment is available with the approved drug Jakavi (ruxolitinib), also a JAK inhibitor (JAK 1/2). The proposed indication is similar to the approved indication for the JAK 1/2 inhibitor- ruxolitinib (Jakavi). Ruxolitinib was authorised as Jakavi in the EU (August 2012) and as Jakafi by the US FDA in 2011, for the treatment of myelofibrosis. The EU approved indication for Jakavi is: *Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.*

Unmet medical need: Studies with Jakavi excluded patients with platelets <50000. Further, the product information (Jakavi SmPC) states that treatment with Jakavi should be discontinued when platelets fall below 50000/mm^3 and that there is limited information in patients with platelet counts in between 50000 and 100000/mm^3. Therefore it can be considered that there is a need for treatment in the patients with low platelet counts.

The claim made by the applicant is that pacritinib fulfils this unmet need and can be prescribed in patients without restriction in patients with platelet counts <100000/uL. A rationale for pacritinib having no effect on the platelet counts unlike other JAK2 inhibitor is not discussed.

2.2. About the product

Pacritinib (SB1518) is a novel Janus kinase 2 and fms-like receptor tyrosine kinase 3 (JAK2/FLT3) inhibitor.

As an inhibitor of JAK2, pacritinib has potential application in the treatment of myeloproliferative neoplasms (MPNs), including primary and secondary myelofibrosis, polycythemia vera (PV), and essential thrombocythemia (ET). The intended target indication for pacritinib is treatment for splenomegaly or symptoms in adult patients with Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PPV) Myelofibrosis and Post-Essential Thrombocythemia (PET) Myelofibrosis.

2.3. The development programme/compliance with CHMP guidance/scientific advice

This product has received formal CHMP scientific advice and advice from several national agencies in relation to the proposed indication.

2.4. General comments on compliance with GMP, GLP, GCP

The pivotal study PERSIST-1 included patient populations with low platelet counts with instructions to administer study medication without any dose modification. A scientific rationale to justify this is not provided and raises concerns about the risks placed on the patients with low platelet counts in the study. The study report itself lists 9 subjects (2.8% of study population) with major protocol deviations listed as “substantive GCP violations that impact safety and/or efficacy”.

2.5. Type of application and other comments on the submitted dossier

This application concerns a centralised procedure in accordance with Regulation 726/2004 and Article 3(2)(b).

The application is submitted in accordance with Article 8(3) of directive 2001/83/EC, as amended, for a new active substance, pacritinib citrate. The applicant has confirmed that the active substance pacritinib (present as a citrate salt), is not authorised in the EU, and furthermore it is not a salt, complex, or isomer or mixture of isomers, or a derivative of an authorised substance in accordance with Directive 2001/83/EC, as amended.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to API and the finished product are generally of sufficient quality in view of the present European regulatory requirements. A Major Objection has however been raised in relation to the proposed starting materials, which must be redefined.

The CHMP has been assured that acceptable standards of GMP are in place for this product type at the sites responsible for the manufacture, assembly, quality control and batch release of the finished product.

The finished products are formulated as hard capsules, which are manufactured by conventional techniques using well-known excipients.

3.1.2. Active Substance

3.1.3. General Information

The active substance pacritinib is isolated as the citrate salt. It is a ring-closed heterocycle very slightly soluble in water. The active substance includes a double –bond and has thus the potential for cis/trans isomerism. It is not hygroscopic and no polymorphs are reported under relevant conditions.

Manufacture, characterisation and process controls

The synthesis is described in three chemical transformation steps and one salt formation, however the proposed GMP-starting materials and cannot be accepted and must be redefined further back. A material classified as reagent should be designated as a GMP-starting material as well. The control strategy is seen as well-defined with an elaborate discussion on carry-over and acceptable specifications for the isolated intermediates. The specifications for the proposed GMP-starting materials and the carry-over discussions can be accepted with minor modifications.

The active substance and impurities have been characterised, however additional points for concern have been raised that must be addressed. No relevant double–bond isomerisation has been seen in development batches and the citrate salt has not been associated with polymorphism.

The synthesis includes a number of primary alkyl halides as starting materials, intermediates and impurities. The applicant has a detailed and well-presented discussion on control of substances, which largely can be accepted with some modifications. A discussion on control of potentially genotoxic impurities is included. Some issues have been identified in connection with this part that should be further discussed.

Specification

The drug substance specification, analytical methods and validations can be accepted with minor modifications. The batch analyses, reference standards and container closure system are adequately described. However, structural characterisation data of the related substances of the drug substance specification is missing and should be included.

Stability

Stability studies over 4 years at 25 °C long-term conditions and 6 months at 40 °C accelerated conditions are included. Stress studies and photostability in line with ICH Q1B are reported. The applicant proposed a re-test period of five years with the storage condition 20–25 °C. The proposed re-test period of five years can be accepted; however the proposed storage condition should be amended.

3.1.4. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished products are hard capsules, containing 100mg of the drug substance pacritinib, as pacritinib citrate.

The pharmaceutical development of the finished product has been described, the choice of excipients is justified and their functions explained. Concerns have been raised relating to the pacritinib salts used in formulations.

Manufacture of the product and process controls

Satisfactory batch formulae have been provided and the description of the manufacturing process, the controls in place and the process validation data provided are also satisfactory.

Product specification

The finished product specifications generally cover appropriate parameters for this dosage form and are generally acceptable; however, amendments have been requested to both the release and shelf-life specifications.

Analytical test procedures and method validations have been provided and are generally satisfactory; however minor issues need to be resolved. The batch analysis data provided is generally satisfactory and within the limits outlined.

The reference standards documentation provided is satisfactory.

Additional information has been requested regarding the container closure system and confirmation of the tests performed on this upon receipt.

Stability of the product

The conditions, under which the stability studies have been conducted, are in accordance with ICH stability guidance. Based on the stability data presented, a shelf-life of 4 years could be agreed; however the proposed storage conditions should be amended.

Adventitious agents

N/A

GMO

N/A

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

A number of concerns have been raised, that must be resolved before marketing authorisation can be granted.

3.2. Non clinical aspects

3.2.1. Pharmacology

The Applicant reports IC50 values of 6.0 nM and 14.8 nM JAK2 and FLT3 kinase activities, respectively, as well as JAK2V617F mutant kinase activity (IC50 = 9.4 nM). The IC50 values reported for cellular proliferation in human leukaemia and lymphoma cell lines (selected for their dependence on the target kinases) ranged from 30 nM to 240 nM.

Two in vitro studies assessing the inhibition of protein kinases are cited in the non-clinical over-view (Study RPT20131230-CTI-JWS-KP and RPT20140923-CTI-NC-KP-RV02). Only the final study report for RPT20140923-CTI-NC-KP-RV02 has been provided. Submission of the final study report of study RPT20131230-CTI-JWS-KP was requested**.**

The anti-tumour activity of pacritinib was showen in tumour models driven by FLT3 mutation or JAK2 mutation or over-expression. In nude mice bearing MV 4-11, an FLT3-dependent AML, pacritinib showed a dose-dependent inhibition of tumour growth, with complete regression at 92.8 mg/kg bid free base, po). In nude mice bearing JAK-2 dependent BaF3 cells, at 150 mg/kg bid free base, po, pacritinib treatment of mice inoculated with BaF3-JAK2 cells improved end-points such as leukocytosis, splenomegaly, and hepatomegaly.

To screen for potential interaction with secondary targets, pacritinib was examined against a panel of 56 pharmacologically common receptors, transporters, channel proteins and enzymes. In addition to the modest selectivity of pacritinib against a range of different kinases, a single concentration of 10 µM pacritinib showed potent inhibition of acetylcholine esterase (60%), MAO-A (64%), insulin receptor (97%) and 5-HT4 (~ 100%).

Subsequent studies for determination of IC50 values suggest that pacritinib may interact with a number of targets at clinical relevant concentration. These targets include the insulin receptor (IC50 = 0.5 µM), L-type calcium channel (IC50 = 2.8 µM) and the sodium channel site 2 (IC50 = 1.4 µM). The L-type calcium channel is located in e.g. cardiac nodal tissue (sinoatrial and atrioventricular nodes) and the sodium channel site 2 is a neurotoxin binding site that mediates enhanced activation and elimination of channel inactivation.

The exposure margins compared to the clinical dose (400 mg, unbound Cmax = 270 nM) were low (~ 5-fold). This is not considered sufficient given the potential adverse effects linked to these ion channels. The Applicant should discuss in-depth the clinical consequences of potential off-target activity by pacritinib, given the high systemic exposure in patients (total C_{max} =~ 22.5 µM at 6.67 mg/kg dose).The potential therapeutic efficacy of pacritinib in inflammatory diseases was evaluated in a mouse model of collagen-induced rheumatoid arthritis. The results indicate no utility of pacritinib for treatment of inflammatory arthritis.

In the dog cardiovascular studies, the unbound plasma concentration of pacritinib was low (Cmax = 10-50 nM) due to tolerability issues. This is approximately 5 to 20-fold below the unbound plasma concentration in patients (at 6.67 mg/kg dose). Even at this low compound exposure, two dogs displayed first and second degree of atrioventricular block (AV) block, respectively, after repeated dosing with pacritinib. The Applicant was asked to further discuss the cause of these adverse effects in the dog as well as their possible implications for human safety.

CNS dose-related toxicity was evaluated as part of clinical observations performed on repeat-dose toxicology studies. CNS-related behavioural observations, such as tremors (dogs and mice), hunched posture, decreased activity/muscle tone (rats) and decreased activity, salivation, jerky head movement, aggressive behaviour (dogs) were noted in animals at what appears to be high doses. In addition behavioural effects were noted in the pre- and post-natal developmental toxicity study in CD-1 mice effects on PEAK startle response, general swimming ability, in increase in time to escape and number of errors during the learning (but not memory) were noted. The Applicant attributes these findings to the frank toxicity seen in these studies. Given these findings, a dedicated modified Irwin's would have been appropriate; however given the stage of development of this compound and the clinical data (findings not seen clinically) no further comment will be made.

The Applicant provides no discussion of potential renal effects in the non-clinical over-view or the pharmacology summary. Given that a clinical renal impairment study has been conducted and renal function was monitored in clinical trials, there are sufficient clinical data to assess renal risk; therefore no further comment will be made non-clinically. No dosage adjustment is recommended in patients with renal impairment in the product literature.

3.2.2. Pharmacokinetics

Oral bioavailability varied across species ranging from 10% in rats, 24 to 39% in mice, and 24% in dogs. Pacritinib was generally rapidly absorbed after a single oral dose, with Tmax ranging from 0.5 to 4 hours in the plasma of mice, rats, and dogs, which is comparable to humans. The low and variable result for oral bioavailability across species suggests that pacritinib undergoes hepatic first-pass metabolism, which is supported by results from metabolism and excretion studies. Plasma half-life was between 1 and 6 hours after an oral or iv dose in mice, rats, and dogs. Plasma clearance following an iv dose of pacritinib in the mouse (8.0 L/h/kg), rat (1.6 L/h/kg), and dog (1.6 L/h/kg) was above the estimated human hepatic blood flow of 1.2 L/h/kg, suggesting that pacritinib is being cleared through mechanisms other than the liver. The Vdz in the mouse (14.2 L/kg), rat (7.9 L/kg), and dog (8.5 L/kg) after an iv dose exceeded the estimated total body water (0.6 L/kg) and demonstrates high distribution and binding of pacritinib to extravascular tissues.

Repeated-dose TK evaluations of pacritinib, and in some cases, the M1 metabolite, were conducted as part of general toxicology studies in mice, rats, and dogs, the 6 month carcinogenicity study in transgenic mice, and in embryo/foetal development (EFD) studies conducted in the mouse and rabbit. The doses tested in the TK studies were generally higher than the intended clinical dose (400 mg/kg qd, or 6.67 mg/kg in a 60 kg person). In general, results of these studies showed that systemic exposure (AUC and Cmax) to pacritinib increased with increase in pacritinib dose, accumulation of pacritinib occurred after repeat dosing, and no notable sex differences were observed, except in the rat. In studies in which the M1 metabolite was evaluated, exposure to the M1 metabolite increased with increase in pacritinib dose, and accumulation of the M1 metabolite was observed with repeat dosing.

The pharmacological characterisation, including activity data and pharmacokinetics, of the two major metabolites of pacritinib, namely M1 and M2, was not reported. The Applicant was asked to justify the absence of such data or to submit the relevant study reports. Furthermore, the Applicant should discuss whether M1 and M2 are expected to contribute to the overall efficacy and safety profile of pacritinib**.**

The effects of repeat dosing on accumulation (AUC) in non-pregnant vs. pregnant animals were inconsistent within and across species.

Overall, these results suggest that prolonged exposure to pacritinib could be associated with accumulation in normal and pregnant animals. The applicant has not provided an explanation for the accumulation. The applicant should provide an explanation for the finding of increasing systemic exposure (AUC and Cmax) and accumulation following repeated dosing and consider the toxicological consequences and the clinical relevance **.** In the single PK and repeat dose TK studies in mice, rats, and dogs conducted at much higher dose levels than used in the clinic, the plasma T1/2 for pacritinib could not be determined for most dose groups because the time allowed for terminal elimination phase was not adequate due to sustained concentrations.

In all species in which the TK of the M1 metabolite was evaluated (mouse, rat, rabbit), systemic exposure to pacritinib was greater than systemic exposure to the M1 metabolite. Relative to pacritinib,

exposure to the M1 metabolite ranged from 9% to 48% and from 9% to 62% in the 28-day and 13-week rat toxicity studies, respectively; and ranged from 13% to 47% in the rabbit EFD study.

Pacritinib was extensive distributed following a single oral dose of [14C]-pacritinib in mice. Concentrations of radioactivity in the contents of the alimentary canal and bile suggest that pacritinib is eliminated in faeces via biliary clearance in mice. The excretion results following oral dosing in BDC dogs provides further support for this mechanism. Binding to extravascular tissues also was demonstrated as exposure (AUC) to pacritinib in brain and lung tissue was about 1.78 times and 19 times higher, respectively, than in plasma after a single 46.4 mg/kg free base oral dose in mice. This may be due to the longer half-life of pacritinib in the tissues relative to plasma. At this dose level, lower than those typically associated with accumulation in the pacritinib toxicology studies, pacritinib was cleared from plasma and tissues by 24 hours post-dose.

Two studies assessed pacritinib distribution following oral administration in the mouse. The first was a limited tissue distribution study using a HPLC/MS-MS method, while the second was a QWBA study.

The data for CNS penetration appears contradictory between the two studies. The first study showed that exposure to pacritinib in the brain was around 2-fold that of plasma indicating there was considerable distribution of pacritinib into the CNS whilst by contrast the QWBA study suggested there was minimal distribution of the radioactivity to CNS. The observed discrepancy in distribution to CNS across the two nonclinical studies may be related to different bioanalytical methodologies and time points used.

Plasma protein binding of pacritinib was evaluated in non-GLP studies using equilibrium dialysis and relative plasma protein binding methods. Equilibrium dialysis results showed that pacritinib is highly bound to plasma protein (> 97%) in the mouse, rat, rabbit, dog, and human. Relative plasma protein binding (RPPB) evaluations detected a concentration-dependent decrease in RPPB ratios with increasing concentrations of pacritinib in human vs. mouse and dog plasma, and at 1 µg/mL, pacritinib binding to human plasma was 5-fold higher than that in the mouse.

In vitro, pacritinib was metabolized mainly by CYP3A4 in liver microsomes under conditions that mimic physiological conditions. Pacritinib did not inhibit of any of the CYP enzymes examined at concentrations up to 25 µM (equivalent to 11.8 µg/mL); the IC50 was > 5 µM (equivalent to 2.36 µg/mL) for CYP2C9, 2C19, CYP2D6 and CYP3A4 and > 25 µM (equivalent to 11.8 µg/mL) for CYP1A2. Pacritinib did not induce CYP1A2 and CYP3A4 at concentrations up to 10 µM (equivalent to 4.73 µg/mL) but rather caused a decline in CYP1A2 and CYP3A4/5 activity. Treatment-related morphological changes observed in cultured human hepatocytes treated with pacritinib were suggestive of cytotoxicity and were associated with a decline in CYP3A4/5 enzyme activity.

In vivo, the metabolic pathways of pacritinib seen in all species included oxidation, *N*-dealkylation, *O*-dealkylation, hydrolysis, and glucuronidation. A major metabolic pathway in all species included oxidation of pacritinib to the M1 metabolite; this is consistent with what has been observed in the human. Oxidation of pacritinib to 3a, 3b, 3c, or 3d metabolites was also a major pathway in nonclinical species but not in humans. In mice, rats, and rabbits, dehydrogenation was also seen, and in dogs, glutathione conjugation and sulfation pathways were observed. There were no unique metabolites identified in humans compared to nonclinical species. The metabolites identified in mice, rats, rabbits and dogs in vivo were similar to those observed in humans. The M1 metabolite was a predominant metabolite in the mouse, rat and rabbit, a finding consistent with nonclinical and clinical exposure data. However, the M2 metabolite, identified as a predominant metabolite in humans, with exposure roughly 10% that of pacritinib, was not a predominant metabolite in any of the nonclinical species.

Pacritinib is completely eliminated in mice following a single oral 100 mg/kg [14C]-pacritinib free base dose, with 92.76% of the total radioactivity recovered within 168 hours postdose. [14C]-Pacritinib was widely distributed, with the highest radioactivity observed in the contents of the alimentary canal and bile. The urinary bladder contents had much lower concentration of radioactivity, suggesting that biliary excretion was the major route of elimination. Similarly, in the dog, after dosing with 100 mg/kg [14C]-pacritinib free base, total radio-analytical recovery was achieved within 72 hours postdose, with the greatest fraction recovered within 8 hours post-dose. The majority (approximately 64%) of the administered dose was eliminated in the bile with minimal excretion in urine. These results indicate that the orally administered dose was readily absorbed through the gastrointestinal tract, then rapidly eliminated.

3.2.3. Toxicology

Pacritinib is a novel, selective Janus Kinase 2 (JAK2) inhibitor as well as an inhibitor of fms-like tyrosine kinase 3 (FLT3). Hence an anticipated effect is an impact on haematopoietic and lymphopoietic cell numbers and function, and on bone marrow and lymphoid organs.

Mice and dogs were selected as the most relevant nonclinical species for toxicological evaluations based on the similarity of their pacritinib metabolic profile to the human profile. The oral bioavailability of pacritinib in animal species was highest in mouse and dog. Rats and rabbits were used as needed for carcinogenicity and reproductive studies.

Single dose

The general findings in the single-dose tolerability studies of pacritinib in mice determined by the two genotoxicity studies were similar. The MTDs were 928.5 mg/kg free base in RPT164 and

1066.9 mg/kg free base in RPT178. In a 7- day range-finding study of pacritinib in the rat, pacritinib was well tolerated at doses up to 400 mg/kg bid pacritinib free base. In the dog, a single capsule with 30 mg/kg pacritinib free base was poorly tolerated due to adverse GI effects.

Repeated dose

Repeated-dose oral toxicity studies were conducted in the mouse, rat, dog, and rabbit. In the mouse, studies were for durations up to 26 weeks. In the rat, studies were conducted for 7- day, 28- day, and 13- week durations, in order to select doses for the 2-year rat carcinogenicity study. In the dog, pacritinib was administered by capsule in studies ranging from 7 days to 39 weeks in duration. Additionally, a 7-day repeated-dose study in non-pregnant rabbits was performed to determine appropriate doses for the dose range-finding rabbit embryo/fetal toxicity study. The dosing regimen in the pivotal studies evaluated the total daily dose administered twice daily as a divided dose. The M1 metabolite, identified in human clinical studies at < 10% of the parent exposure, was also evaluated in selected studies.

Adverse treatment-related effects were generally consistent across species and included reduced weight, reduced food consumption, gastrointestinal disturbances, and lymphoid depletion (reduced lymphocytes and histopathology findings in the thymus and spleen). Treatment-related effects were generally reversible following a recovery period or a reduction in the dose level. The one exception to this was the thymic atrophy observed after the 14 day recovery period in the 30 day study in the

mouse. In addition in the rat 28 day and 13 week studies, tubular degeneration in the testes and oligo/aspermia in the epididymides was reported.

Mice

Unscheduled deaths were reported following administration of pacritinib. The main toxicity findings reported at high dose levels in mice, which were generally reversible when dose levels were reduced or following a recovery phase (in the case of the 30 day study), included ruffled fur, unkempt appearance, hunching/hunched walking, dehydration, as well as decreased body weight and food consumption. Haematological changes included reductions in white blood cells, increases in neutrophils, increases in platelets, decreases in lymphocytes, and reductions in red cell mass (red blood cells, haemoglobin, and/or haematocrit). Slight decreases in spleen weights, histopathological changes in lymphoid tissues (consisting of splenic atrophy, thymic atrophy, alteration of lymphoid cellularity in the spleen and an increase in lymphoid cellularity in the medullary region of the thymus), and tubular vacuolation in kidneys were observed. With the exception of thymic atrophy, all treatment-related effects observed in the 30 day study were either not observed or were less prominent following a 14 day recovery period. It is possible that 14 days was not sufficient to observe complete thymic recovery. Relative liver weights were reduced in the 26 week study. In the 30 day study in early decedents histopathological findings included tubular vacuolation of the kidneys, as well as marked venostasis in the lungs, frequently combined with focal hemorrhage of various degrees, suggesting circulatory failure as the cause of death. In addition, ileum goblet cell hyperplasia was observed in the 26-week study.

Rat

In the rat repeated-dose studies, findings seen at the higher doses with longer durations included

abnormal faeces, firm abdominal structures, reductions in weight and food consumption, decreased white blood cells, increased neutrophils, increased platelets, decreased reticulocytes, decreased albumin and globulin, reduced spleen and thymic weights, lymphoid depletion in the spleen and thymus, and decreased haematopoiesis of the bone marrow. Intestinal mucosal hyperplasia was observed at doses $\geq$ 50 mg/kg, corresponding to a systemic exposure far below clinical therapeutic exposure. The reversibility of this finding was not evaluated. Relative liver and kidney weights were reduced in treated animals.In addition in the rat 28 day and 13-week studies, tubular degeneration in the testes and oligo/aspermia in the epididymides was reported. This finding appears not to have been reported in the other species.

Dog

Treatment related deaths occurred following treatment with pacritinib, the cause of which was not explained. Pivotal repeated-dose toxicity studies were performed for 30 days (with a 14-day recovery phase) and for 39 weeks in the dog. In the 30 day study, the top dose was reduced after the first week due to severe emesis and diarrhoea at the initial top dose. All treatment-related related effects observed in the 30 day study were reversible following a 14 day recovery period. In the 39-week study, the highest dose was 17.8 mg/kg bid free base on days 1 to 7, but due to severe emesis, abnormal faeces/diarrhoea, abnormal behaviour, mortality, and lymphadenopathy, the dose was reduced to 14.2 mg/kg bid free base for the remainder of the study. Dose-related observations at higher dose levels and/or longer dosing durations included emesis and diarrhoea. Severe symptoms of lymphadenopathy were observed in high dose animals. Liver weights were increased after 30 days treatment (correlating

with hepatocellular hypertrophy) but decreased after 39 weeks treatment (accompanied by reduced total protein and serum albumin levels and increased ALT, AST and SDH). Haematological effects included reductions in white blood cells, particularly neutrophils. Microscopic findings included lymphoid depletion in the Peyer's patches and spleen; hyperplasia of the thymic medulla; and increased incidence/severity of tubular vacuolation in the kidneys were also observed.Pulmonary thrombus formation was noted in 2/4 males at the top dose.

The Applicant was requested to discuss the mechanisms and clinical relevance of the morbidity and the associated mortality observed in pre-terminal dogs (30d+14d and 39w studies; e.g. tremors, ataxia, and inflammation), mice (30d+14d and 26w BALB/c mice; e.g. tremors, ataxia) and pregnant rabbits (non-pivotal and pivotal rabbit EFD studies).

The Applicant was asked to discuss possible mechanisms as well as the clinical relevance of the observed blood circulatory effects in mice and dogs (i.e. haemorrhage, venostasis, and thrombus), and to consider updating module SII in the RMP accordingly**.**

The Applicant was requested to discuss the clinical relevance of the intestinal ileum goblet cell hyperplasia found in 26w exposed mice and the mucosal hyperplasia detected in 28d and 13w exposed rats.

The Applicant was requested to discuss the clinical relevance of the liver weight reduction and hepatic biomarker changes observed in mice, rats and dogs. An update of the SII module of the RMP should be considered.

The Applicant was asked to discuss possible mechanisms as well as the clinical relevance of renal toxic effects in mice, rats and dogs (renal weight reduction, histopathological and/or biomarker changes).

The genotoxic potential of pacritinib was evaluated in three *in vitro* studies and two in vivo studies. The in vitro studies included two bacterial reverse mutation (Ames) assays (one non-GLP and one-GLP) and a GLP-compliant in vitro chromosomal aberration study in human peripheral blood lymphocytes. The in vivo studies conducted were bone marrow micronucleus assays in BALB/c or ICR mice. The data from one chromosomal aberrations assay (Study number: RPT164) showed what was called equivocal results, however the final study report was poorly written and a second statistical model was applied when the first showed a significant positive result. However a well-run and reported second chromosomal aberrations assay was conducted in which a negative result was seen. Over-all the standard genotoxicity panel showed no mutagenic or clastogenic activity for pacritinib by in vitro and in vivo testing.

Pacritinib was not carcinogenic in the 26-week transgenic (CByB6F1-Tg rasH2) mouse study. The rasH2 model is considered to be an acceptable alternative to a conventional mouse model. A conventional 2-year study in rats has not yet been completed but has been started and is ongoing. The final results of this study should be submitted as soon as available**.** Considering that pacritinib is not genotoxic and not carcinogenic in the rasH2 mouse model, and since there did not appear to be any pre-neoplastic lesions reported in the repeated dose toxicity studies, and considering the therapeutic indication, it is acceptable that should a MA be granted, the results of the 2-year study could be submitted as a post -authorization measure.

Reproductive and developmental toxicity

Segment I

There were no signs of adverse effects on male or female fertility in mice, giving a male fertility NOAEL of 71.2 mg/kg day in BALB/c mice and male and female fertility NOAEL of 250 mg/kg in CD-1 mice. In

repeat-dose toxicity studies, Sprague Dawley rats manifested testes degeneration and oligospermia after 28d (NOAEL 150 mg/kg day) and 13w (NOAEL 150 mg/kg day) exposure. The Applicant has not provided any relevant text about male reproductive organ toxicity in the SmPC 4.6 and 5.3 and is requested to do so, and to consider revising the SII module in the RMP.

Segment II (EFD)

In segment II studies in mice pacritinib caused increased post-implantation loss with a NOAEL of 150 mg/kg day (dose-range finding study RPT112505) and 100 mg/kg (pivotal study RPT112506; not statistically significant increase). Reduced foetal body weight and increased number of cleft palate malformations were observed in the pivotal EFD study in mice, at doses that generated reduced maternal body-weight gain, a body weight reduction of 7-8% plus reduced food-intake. In rabbits, reduced foetal body weight, skeletal anomalies (non-ossified sternebrae nos. 5 and/or 6), and small foetal spleens were observed at maternally toxic doses (maternal body-weight reduction of 5-6% with reduced food intake; NOAEL 30 mg/kg day.

Based on the findings in mice and rabbits, pacritinib is considered embryotoxic and teratogenic. The Applicant's proposed explanation for these effects – i.e. observed developmental effects were consistent with and likely secondary to, maternal toxicity – is questionable, given the relatively mild maternal effects at the corresponding dose-levels.

The exposure in terms of AUC at the foetal NOAEL (100 mg/kg) in the mouse EFD study is far below clinical therapeutic exposure, resulting in a margin of 0.03-0.04 depending on whether Gd6 or Gd15 values are used for the calculation. Thus, there is a concern for the use of pacritinib in pregnancy and in women of child-bearing potential. A contraindication in pregnancy is therefore proposed. It is recognized that contraindication in pregnancy may not be justified in life-threatening conditions; however, in the present indication for pacritinib the treatment is symptomatic and cannot be considered to belong to this category. It is also noted that the previously approved JAK-inhibitor, Jakavi, which has a similar indication, is contraindicated in pregnancy and breast-feeding

Segment III

In the segment III peri-/postnatal study in CD-1 mice there was a clear increase in pre-weaning deaths. While the Applicant stated that the low-dose morbidity effects are due to "weaning-stress" there are no additional arguments provided as to how this differs from treatment-related postnatal toxicity. A general increase in pre-weaning litter morbidity was observed both among detected dead and missing/cannibalized pups starting at the lowest dose. The NOAEL is therefore < 30 mg/kg day. It is unclear to what extent the increased mortality in the offspring is due to prenatal exposure effects manifesting postnatally and/or due to lactation-mediated direct exposure. In view of these uncertainties, including the lack of animal data regarding transfer to milk, a contraindication in breast-feeding would be appropriate.

Postnatal mouse litter losses were seen at doses lower than those generating reduced prenatal mouse foetal weights (250 mg/kg day; NOAEL 100 mg/kg day) and nominal maternal toxicity (corresponding to 5-8% body weight reduction and reduced food intake). There was furthermore a delayed male balano-preputial separation at the high dose (250 mg/kg day) and reduced male offspring body weight at attainment at the middle-dose (≥100 mg/kg day). Similarly, there was high-dose generated body weight reduction at attainment of vaginal patency in female offspring (no female delay in sexual maturation observed).

As sexual maturation is dependent on body weight and the F1 offspring had lower pre-weaning body-weights at the low to high dose and lower body weights post-weaning at the high-dose, it remains unclear if the effects on male sexual maturation were direct or indirect (i.e. body weight mediated).

Additionally, there was a dose-dependent reduction of startle response mean PEAK values at PND20 (statistically significant at the high-dose) and an increase in male ambulatory motor activity at the high-dose on PND21 but not at PND61. Furthermore, increased maze-escaping time was needed and learning errors committed in memory/learning tests on PND22 by both male and female offspring at the high-dose.

No studies in juvenile animals have been conducted. Myelofibrosis is rare in children. On 20 June 2014, the Paediatric Committee of the European Medicines Agency agreed to a product-specific waiver for all subsets of the paediatric population for pacritinib to include treatment of post-polycythemia vera myelofibrosis and treatment of post-essential thrombocythemia myelofibrosis.

Stand-alone local tolerance studies following oral administration of pacritinib have not been conducted; however, the effects of pacritinib on the gastrointestinal tract soon after administration were evaluated as part of the toxicity studies. Dose- and treatment duration related effects occurred at high dose levels in all test species. In the dog, effects included discoloured/soft/watery/mucoid faeces but without adverse histopathological observations. In the mouse, dilatation of the intestines and stomach were observed at gross necropsy but with no histopathological effects. In the rat, firm internal abdominal structures and abnormal faeces were recorded and gross pathology findings included increased intestinal thickness, pale gastrointestinal coloration, and mucosal hyperplasia of the intestines.

In a phototoxicity study in mice no skin reactions indicative of phototoxicity were observed following oral administration of pacritinib at 106.7 mg/kg bid for 4 consecutive days and subsequent exposure to an ultraviolet radiation dose equivalent to 0.5 minimal erythema dose.

Concerning impurities, the purity (% area) of test article batches ranged from 97.12 to 99.7%. At the concentrations present, none of the impurities are anticipated to impact the interpretation of the toxicity studies.

In terms of the dose expressed by surface area, the dog is the most sensitive nonclinical model, providing a safety margin of 1.14. The systemic exposure in the nonclinical species was lower than that in humans at similar dose levels. This was attributed largely due to the prolonged elimination half-life of pacritinib in humans. However, it would not have been possible to increase dose levels used in the pivotal studies, as these were the highest that were tolerable over the duration of the dosing phase.

3.2.4. Ecotoxicity / environmental risk assessment

Based on the data currently submitted, the pacritinib *PECsurfacewater* value is below the action limit of 0.01 µg/L and is not a PBT substance as LogDow does not exceed 4.5. Considering the above data, pacritinib is not expected to pose a risk to the environment.

However, currently it is not possible to make a definitive conclusion on the ERA, pending the submission of a study (OECD 117). The applicant should perform the following study: Partition Coefficient – HPLC method (OECD 117). The final results of the study should be submitted and the ERA updated accordingly.

3.2.5. Discussion on non-clinical aspects

Pacritinib is a potent ATP competitive inhibitor of wild type and mutant JAK2 (IC50 = 6 to 9.4 nM) and FLT3 (IC50 = 4.8 to 14.8 nM) but displays also moderate selectivity to a range of additional off-target kinases (e.g. JAK3, CLK1, CLK4, HIPK4, IRAK1, ROS1, TNK and TRKC with an IC50 < 20 nM). Pharmacological characterisation of the two major metabolites M1 and M2 was, not provided.

Additional secondary pharmacodynamics studies found that pacritinib inhibits a number of pharmacologically common receptors, transporters, ion channel proteins at clinically relevant concentrations. It also binds to the hERG potassium channel at relatively low concentrations (IC50 = 3.51 µM).

The Applicant argued that the high plasma protein binding prevents systemic concentrations of pacritinib reaching levels at which hERG inhibition (and other possible off-targets) may occur. Non-clinical pharmacokinetic mouse data indicates on the other hand that the exposure in tissues is higher/the terminal half-life is longer than in blood (2-fold in nervous tissue, 19-fold in lungs), indicating that effective tissue concentration can be reached over time. The PK of pacritinib were evaluated in mice, rats, rabbits, and dogs. Results from single dose absorption studies with pacritinib showed that oral bioavailability varied across species and was highest in the mouse (39%) and dog (24%) and lowest in the rat (10%). Pacritinib was rapidly absorbed after a single oral dose, with Tmax ranging from 0.5 to 4 hours in plasma from mice, rats, and dogs. Plasma half-life ranged between 1 and 6 hours after administration of a single oral or iv dose of pacritinib in mice, rats, and dogs. Results from the repeat-dose TK studies following oral administration of pacritinib were generally similar, and demonstrated increased systemic exposure (AUC and Cmax) with increase in pacritinib dose, and accumulation with repeat dosing. The M1 metabolite, a major metabolite in human and non-human species was characterized in select repeat dose toxicity studies, and found to increase in a dose-dependent manner in mouse, rat and rabbit. Plasma protein binding was high in the mouse, rat, rabbit, dog, and human; the percent bound was >97% in all the species.

The standard genotoxicity studies showed no mutagenic or clastogenic activity for pacritinib.

Pacritinib had no effect on mouse male or female fertility but generated male reproductive organ toxicity in rats. Pacritinib is considered teratogenic, possibly but not necessarily mediated via maternal toxicity. The fact that there was an increase in mouse postnatal mortality across doses (maternally mediated perinatal exposure) indicates that pacritinib either weakens (non-malformed) offspring prenatally so that they die postnatally and/or that it is transferred via lactation to the pups and causes direct toxicity. There are also signs that pacritinib, which is known to cross the mouse blood-brain barrier and has a longer terminal half-life in nervous tissue (2-fold compared to plasma), adversely affects cognitive developments in pre-weaning mice. Considering that pacritinib also binds to numerous nervous system relevant off-targets at effective concentrations covered by the total concentration in blood (e.g. Adenosine A2A, Serotonin 5-HT4, Dopamine D1, Dopamine D2S), pacritinib may have the potential to be an developmental neurotoxicant. Common findings in repeat dose studies in the test animal species were those anticipated based on the pharmacological effects of JAK inhibition. Adverse treatment-related effects were generally consistent across species and included reduced weight, reduced food consumption, gastrointestinal disturbances, and lymphoid depletion (reduced lymphocytes and histopathology findings in the thymus and spleen). Treatment-related effects, when observed, were generally reversible following a recovery period or a reduction in the dose level. There are however several findings the mechanisms of, and the clinical relevance of, have not been adequately addressed. These are detailed in the LoQ.

Pacritinib was not carcinogenic in the 26-week transgenic mouse study.

Overall, similar toxicities were observed in the mouse, rat, rabbit and dog, with the hematopoietic and GI systems as the major target organs. Treatment- related effects were generally reversible.

3.2.6. Discussion on non-clinical aspects

There is one major objection to an approval of Enpaxiq from a non-clinical perspective – which is related to the off-target activity of pacritinib. In addition, a number of other concerns have been formulated.

3.3. Clinical aspects

• *Tabular overview of clinical studies*

Table 01: Summary of Clinical Studies relevant to Efficacy

Study ID	Number of Study Centers (Locations)	Study Start Enrollment Status, Date Total Enrollment/ Enrollment goal	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective	# Subjects by Arm Entered/ Completed	Duration	Gender M/F Median age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
SB1518-2007-001	3 (US)	02 Aug 2008 to 15 Sep 2011 29 planned 33 enrolled	Phase 2, open label, single arm	PAC: 400 mg QD, oral	Efficacy, safety, QoL	PAC: 33/13	Minimum of two 28-day cycles	PAC: 22/11 67 (47-83)	CIMF (incl PMF, PET-MF, and PPV-MF) requiring therapy	Proportion of subjects with ≥ 35% SVR from baseline to week 24
SB1518-2008-003	6 (US, Australia)	18 Jun 2008 to 10 Oct 2011 planned 35 enrolled	Phase 2, open label, single arm	PAC: 400 mg QD, oral	Efficacy, safety, QoL	PAC: 35/17	≥ 60 weeks	PAC: 26/9 69 (44-85)	CIMF (incl PMF, PET-MF, PPV-MF) requiring therapy	Proportion of subjects with ≥ 35% SVR from baseline to week 24
PERSIST-1 (PAC325)	67 (US, Europe, Russia, Australia, NZ)	08 Jan 2013 to 17 Jan 2015 327 planned 327 enrolled	Phase 3, randomized, active-controlled efficacy and safety	PAC: 400 mg QD, oral BAT: physician-selected treatment	Compare efficacy of PAC with BAT in subjects with PMF, PPV-MF, or PET-MF	PAC: 220/167a BAT: 107/75a	Until disease progression, unacceptable toxicity, or subject no longer derived benefit from treatment	PAC: 125/95; 67 (23-87) BAT: 60/47; 65 (37-84)	Intermediate-1 or -2 or high risk PMF, PPV-MF, or PET-MF	Proportion of subjects with ≥ 35% SVR from baseline to week 24

Abbreviations: BAT, best available therapy; CIMF, chronic idiopathic myelofibrosis; NZ, New Zealand; PAC, pacritinib; PMF, primary myelofibrosis; PPV-MF, post polycythemia vera myelofibrosis; PET-MF, post essential thrombocythemia myelofibrosis; QD, once-daily; QoL, quality of life; SVR, spleen volume reduction; US, United States

[a] Completed 24 weeks of study treatment

3.3.1. Pharmacokinetics

Pacritinib has been studied in 4 completed clinical trials to date, including two phase 1/2 clinical studies in patients with advanced myeloid malignancies and chronic idiopathic myelofibrosis (SB1518-2007-001 & SB1518-2008-003), a study in patients with advanced lymphoid malignancies (SB1518-2007-002), and a Phase 3 pivotal trial in MF patients (PAC325; PERSIST 1). In addition, 9 clinical pharmacology and biopharmaceutics studies have been completed characterizing human ADME mass balance, drug interaction potential, food-effect, relative bioavailability, single dose PK, cardiac safety, and PK in renal and hepatic impairment.

An in vitro program was undertaken to assess the plasma protein binding for pacritinib, the QT prolongation potential, in vitro permeability, and the potential for metabolic and transporter interactions between pacritinib and other potentially co-administered drugs. The in vitro metabolism investigation focused on interactions of pacritinib with a number of CYP450 isoforms. In addition, the potential for interaction between pacritinib and common hepatic and renal transporters was assessed.

Pacritinib has low solubility at physiological pH, values reported are 0.13 and 0.07 mg/ml at pH 6.8 and 7.5, respectively, but higher at acidic pH. In vitro permeability is high but the percentage absorbed cannot be absolutely determined in vivo as there is no intravenous data. The results from the ADME study suggest recovery is predominantly as metabolites suggesting high absorption however the role of

metabolism in the gut is not clear and this cannot be absolutely determined as greater than 90%. Therefore it should be considered as BCS class 3/4.

The pacritinib capsule shows 58.6% bioavailability relative to a solution. There is a slight increase in exposure when administered with food, however the dose used (200 mg) was less than that proposed (400 mg). As non-linearity in PK was seen the proposed effect on the higher clinical dose requires clarification.

Protein binding is similar at 1 and 10 µg/ml: 98.9% and shows slight saturation at concentrations above 10 µg/ml. There are no data in plasma from hepatic or renal impaired subjects. V/F suggests some tissue distribution, however F is not known. Pacritinib is not a substrate for Pgp, BCRP or MRP2. There is no data to indicate whether pacritinib is a substrate of OAT1B1 and 1B3.

The elimination half-life in healthy volunteers is 34 hours. In the ADME study 400 mg was dosed as capsules with the radiolabel in suspension. Total recovery was 6% in urine and 87.3% in faeces making a total of 93.3%. However it is not clear how homogenous the solution was as the suspension may have a different rate of absorption than the capsules.

The major primary metabolites are oxidative metabolites. One major pathway was O-dealkylation on the phenol oxygen and resulted in metabolite M2, which was followed by glucuronidation to form metabolite M7. Another major pathway was oxidation on the pyrrolidine moiety which led to the metabolite M1. Metabolite M1 was hydrolyzed to metabolite M5, which was further oxidized to M9 and metabolite M6 was also derived from M1 by oxidation on the butane moiety. O-dealkylation on both benzylbutenyl ether oxygen and dehydrogenation on the pyrrolidine moiety of M1 formed metabolite M14 and M14a, which were further oxidized to metabolites M12 and M13. N-oxidation and N-dealkylation on the pyrrole nitrogen resulted in metabolites M3 and M8, respectively. In vitro studies are stated to show that CYP3A4 is the major P450 involved. However these studies are not performed to the standards currently expected. The enzymes involved in the elimination are therefore not considered to be fully elucidated. This makes the consideration of possible interaction studies, interpretation of current studies and considerations of polymorphisms in elimination pathways difficult.

The major circulating component in plasma is pacritinib (72% of the radioactivity). M1 and M2 are the main metabolites with M2 being just over 10% of total radioactivity and having lower pharmacological activity. However the plasma protein binding of M2 has not been determined.

The radioactive half-life is 55h, slightly longer than that of pacritinib, however this is could be due to better definition of the elimination phase. Most of the metabolites quantified had disappeared by the last time point measured 120h. However the position for M3 is not clear.

In the study performed in fed patients there is some non-linearity with a 2.5 fold increase in exposure for a 4 fold increase in dose (100- 400 mg). This is also apparent in the POPPK analysis. The mechanism is not known. There is a some modest accumulation but (<2 fold) following multiple dosing in patients; it is not clear if this is consistent with the elimination half-life. The results of a single dose proportionality study indicate that inter-individual % coefficient of variation (%CV) for Cmax and AUC ranged from 28.3 - 45.0%, indicating relatively high variability among subjects, while the intra-individual %CV for Cmax and AUC were low, ranging from 13.4 - 15.3. From the population model, inter-individual variability on clearance was 51.2%.

The population PK analysis for pacritinib evaluated data obtained from 13 clinical studies (SB1518-002, SB1518-004, SB1518-006, SB1518-001, SB1518-003, PAC101, PAC102, PAC103, PAC104, PAC105, PAC106, PAC107, and PAC325 (PERSIST-1)). In total, PK data from 354 subjects were included in this population PK analysis. For the typical 78-mg MF patient receiving 400 mg daily, oral clearance (CL/F)

was 2.35 L/hr, oral central volume Vc/F was 79.7 L, distribution clearance Q/F was 0.169 L/hr, peripheral volume Vp/F was 29.1 L, and the alpha and beta elimination half-lives were 21.6 and 129.8 hr respectively.

Healthy volunteers had a 37% greater exposure than myelofibrosis patients. The reason for this difference is not discussed. MF patients with low platelet counts had numerically greater AUC and Cmin values. In patients with extremely low platelet counts (>=50 & <100 × 10^9/L), median AUC was 205 µg×hr/mL, which was 27% greater than patients with normal platelet counts. This is also not explained.

Small increases in exposure in patients with renal impairment of up to 26% on AUC, are seen, but results are not presented also in terms of free drug concentrations. Pacritinib is not removed by dialysis. Unexpectedly there is a decrease in exposure in patients with hepatic disease, of up to 48% on AUC. This could be due to a higher free fraction and, again protein binding data is required in these patients.

Gender does not appear to impact on the PK of pacritinib, race also is not a significant covariate however there is insufficient data in Asian subjects. Further clarification is required on the effect of weight on the pharmacokinetics. Age is also suggested not to affect the pharmacokinetics, however a further analysis with the age groups recommended by the EMA is required.

Pacritinib is stated to not inhibit CYP 1A2, 2C9, 2C19, 2D6 or 3A4 at concentrations up to 5 µM, however the raw data is not presented in the report and the concentrations studies are not sufficient to rule out in vivo interactions. There are no data on inhibition of CYP 2C8 or 2B6 or on different CYP 3A4 substrates.

Pacritinib is stated to not induce CYP 3A4 or 1A2, however these data are also not to the standards currently expected and concentrations tested are not sufficient to rule out clinical studies.

The studies to investigate pacritinib as an inhibitor of transporters show that the IC50 for Pgp and BCRP are approx. 5 µM, again lower than calculated plasma and gut concentrations. IC50 for inhibition of OATP1B1 is 9.4 µM, which is similar to 50 fold plasma Cmax and higher than the hepatic inlet concentration (6.4 µM). There are no data to determine the drug as an inhibitor of OAT1, OAT3, OCT1 or OCT2.

Clarithromycin, a potent CYP 3A4 inhibitor, increases the AUC of pacritinib by 1.8 fold and the AUC of the metabolite M1 by 1.2 fold. It appears that a dose adjustment may be required in these individuals. Rifampin, a potent CYP 3A4 inducer, caused a 87% decrease in the AUC of pacritinib and 73% decrease in the AUC of M1. CYP 3A4 inducers are contra-indicated with pacritinib.

Other clinical interaction studies may be required dependent on the results of the in vitro studies on metabolism and transporters and on CYP450 and transporter inhibition, and induction of P450. Effect of drugs that modify gastric pH may be expected to alter the absorption of pacritinib e.g. PPIs.

The IC50 for binding to hERG is 3.5 µM, approx. 17 fold above the plasma Cmax. The dose used in the QT study is a single dose of 400 mg. Results suggest less than a 10 msec change for the upper bound of the 90% confidence interval however the model does not capture the variability of the data and some individuals were higher. In addition the exposure is lower than that which will be seen at steady state.

3.3.2. Pharmacodynamics

Pacritinib is a potent, selective inhibitor of wild-type JAK2 and FLT3 kinase activities, as well as JAK2V617F mutant kinase activity.

In vitro data showed that exposure to pacritinib in relevant cell reduction resulted in reduction in phospho-JAK2 and downstream transcription factors, including phospho-signal transducer and activator of transcription-3 (STAT3) and phospho-signal transducer and activator of transcription-5 (STAT5). However, in vivo data collected in the PAC101 study showed only 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.

The modest inhibition of STAT3 was attributed to low potency on JAK1. However the study utilised only a single dose therefore the concentrations tested are below those expected at steady state.

The population PD relationships have been explored utilising a number of models. The exposure efficacy analysis for spleen volume and total symptom score at week 24 shows no clear relationship; however, conclusions are limited by the analysis being based on data in quartiles. There is an apparent relationship for spleen volume at end of treatment with a sigmoidal Emax showing the best fit.

An exposure response relationship was seen for anaemia. Again it is considered that this could be improved by considering exposure as a continuous function and of Cmax values. In addition, projections are based on the typical individual without the variability in PK included. It is suggested that 400 mg is the maximal dose but this requires clarification. There was no clear exposure-response relationship for other adverse events including diarrhoea, nausea/vomiting, thrombocytopenia, or gastrointestinal disorders.

3.3.3. Conclusions on clinical pharmacology

The pharmacokinetics in healthy volunteers, patients and other sub-populations are reasonably well described, although there are a several points that require clarification.

The understanding around drug interactions is deficient with a lack of understanding of the clearance and a lack of *in vitro* data to support the potential of pacritinib to interact with other drugs.

Although *in vitro* data showed that exposure to pacritinib in relevant cell reduction assays resulted in reduction in phospho-JAK2 and downstream transcription factors, including phospho-signal transducer and activator of transcription-3 (STAT3) and phospho-signal transducer and activator of transcription-5 (STAT5); in vivo data collected in the PAC101 study showed only a modest pSTAT3 inhibition effect observed with administration of the 400 mg capsule or 80 mg oral solution formulation of pacritinib.

Further analysis is required around exposure response modelling for efficacy and safety.

3.3.4. Clinical efficacy

The proposed indication for Enpaxiq is in *the treatment of splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF), post-polycythaemia vera myelofibrosis (PPV-MF), and post-essential thrombocythaemia myelofibrosis (PET-MF)*.

The proposed indication is similar to the approved indication for the JAK 1/2 inhibitor- ruxolitinib (Jakavi). The claim made by the applicant is that pacritinib offers a benefit over Jakavi, as it can be prescribed in patients without restriction in patients with platelet counts <100000/uL.

Dose-response studies and main clinical studies

The efficacy of pacritinib in the proposed indication is based on the results of a Phase 3 randomized, controlled study (PERSIST-1 [PAC325]) that compared the safety and efficacy of pacritinib with “best available therapy” (BAT).

Supportive data are provided from two, single-arm, open-label studies of pacritinib (SB1518-2007-001 and SB1518-2008-003). Studies SB1518-2007-001 and SB1518-2008-003 were Phase 1/2 studies.

DOSE FINDING STUDIES:

Both the studies SB1518-2007-001 and SB1518-2008-003, listed above, included a phase 1 part that evaluated the safety and tolerability of pacritinib and, the maximum tolerated dose.

Study SB1518-2007-001- Phase 1

This was a phase 1/2 study to determine the MTD and the dose-limiting toxicities (DLT) of pacritinib when given as a single agent PO QD in subjects with advanced myeloid malignancies. Efficacy, PK profile, and PD activity of pacritinib were also to be assessed. The **primary objective** of phase 1 part of the study was to establish the maximum tolerated dose (MTD) of pacritinib as a single agent when administered orally (PO) once daily (QD) in subjects with advanced myeloid malignancies.

Secondary objectives included assessment of, safety and tolerability of pacritinib when administered once a day orally in subjects with advanced myeloid malignancies; pharmacokinetic (PK) profile and pharmacodynamic (PD) activity of pacritinib.

The phase 1 study used an open-label, dose-escalation design. The pacritinib starting dose for phase 1 of 100 mg PO QD was identified based on the highest non-severely toxic dose (HNSTD) in the dog, the most sensitive species, which was determined to be 20 mg/kg twice daily (BID). Based on the recommended calculation of 1/6th the HNSTD normalized to body surface area (BSA), the initial safe starting dose of pacritinib for phase 1 investigation was estimated to be 100 mg/day (i.e., 20 mg/kg/day × 20 kg/m2 conversion factor × 1/6 × 1.62 m2 BSA).

Cohorts of three to six subjects were enrolled at each pacritinib dose level, starting at a pacritinib dose of 100 mg QD. Each subject participated in only one cohort. Subjects at each dose level were treated and observed through the end of Cycle 1 before treatment of subjects at the next higher dose level of pacritinib could begin. Pacritinib was held on days 25 to 28 during Cycle 1 for PK sampling.

Following identification of the MTD and RD in phase 1, the phase 2 study evaluated the efficacy and safety profile of single-agent pacritinib at the RD in subjects with CIMF (including PET-/PPV-MF). The RD for phase 2 was identified based on exposure, safety, PD, and clinical benefit data from phase 1.

A total of 45 subjects were planned for the phase 1 and 43 were enrolled and analysed for DLT. Subjects recruited were those with histologically confirmed myeloid malignancy who failed standard therapies or were not candidates for palliative therapies.

Results:

Overall, 11.6% of subjects experienced a DLT in Cycle 1, with the largest proportion experiencing diarrhoea (7.0%).

The majority (83.7%) of the 43 subjects in the safety population of phase 1 reported at least one treatment-related TEAE. The **most frequently reported treatment-related TEAEs** overall were diarrhoea (65.1%), nausea (34.9%), vomiting (23.3%), and thrombocytopenia (11.6%). Across dose cohorts, larger proportions of subjects reported treatment-related TEAEs in cohorts with doses ≥ 400 mg. All subjects in the 400 mg, 500 mg, and 600 mg QD dose cohorts reported treatment-related TEAEs. The frequency of treatment-related TEAEs in subjects in the 100 mg, 150 mg, 200 mg, and 300

mg QD cohorts ranged from 50.0 to 83.3%. The incidence of the most common treatment-related TEAEs of diarrhoea and nausea was also highest in subjects in the ≥ 400 mg cohorts.

Table 2: Dose Limiting Toxicity During cycle 1 (DLT Evaluable Population)

System Organ Class\ Preferred Term	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)	All Patients (N=43)
Patients with any Dose Limiting Toxicity	0	1 (16.7%)	0	1 (16.7%)	0	1 (14.3%)	2 (33.3%)	5 (11.6%)
Eye disorders	0	0	0	0	0	0	1 (16.7%)	1 (2.3%)
Vision blurred	0	0	0	0	0	0	1 (16.7%)	1 (2.3%)
Gastrointestinal disorders	0	0	0	1 (16.7%)	0	1 (14.3%)	2 (33.3%)	4 (9.3%)
Diarrhoea	0	0	0	1 (16.7%)	0	1 (14.3%)	1 (16.7%)	3 (7.0%)
Nausea	0	0	0	0	0	0	1 (16.7%)	1 (2.3%)
Vomiting	0	0	0	0	0	0	1 (16.7%)	1 (2.3%)
General disorders and administration site conditions	0	0	0	0	0	0	1 (16.7%)	1 (2.3%)
Gait disturbance	0	0	0	0	0	0	1 (16.7%)	1 (2.3%)
Performance status decreased	0	0	0	0	0	0	1 (16.7%)	1 (2.3%)
Investigations	0	1 (16.7%)	0	0	0	0	0	1 (2.3%)
Electrocardiogram QT prolonged	0	1 (16.7%)	0	0	0	0	0	1 (2.3%)
Nervous system disorders	0	0	0	0	0	0	1 (16.7%)	1 (2.3%)
Dizziness	0	0	0	0	0	0	1 (16.7%)	1 (2.3%)

On the basis of the above data the 400 mg dose was chosen as the recommended dose to be studied in the phase 2 part of the study SB1518-2007-001.

Thirty-seven subjects (86.0%) demonstrated a best response of clinical benefit, defined as CR + PR + CImp + SD, with 13 subjects (30.2%) reporting a CImp, 24 subjects (55.8%) reporting SD, and one subject (2.3%) having progressive disease, according to the IWG-criteria for MF with myeloid metaplasia or AML as appropriate for each subject.

At least one TEAE was reported in each of the 43 subjects during phase 1 of the study. Overall, the most frequently occurring TEAEs were diarrhoea (72.1%), nausea (44.2%), vomiting (37.2%), and fatigue (30.2%). Larger proportions of subjects in cohorts with doses ≥ 400 mg compared to < 400 mg reported diarrhoea and nausea.

The majority (81.4%) of subjects experienced worst grade 3/4 TEAEs, while only 18.6% of subjects experienced worst grade 1/2 TEAEs. Anaemia and thrombocytopenia were the most frequently occurring grade 3/4 TEAEs.

Fourteen (32.6%) subjects who participated in the phase 1 study died: seven during the study due to TEAEs unrelated to pacritinib, four due to disease progression after the 30-day follow-up period, and three to unknown causes after the 30-day follow-up period. There were 44.2% of subjects who reported a treatment-emergent SAE. Overall, the most frequently occurring treatment-emergent SAEs were pneumonia, anaemia, pleural effusion, and subdural hematoma. The frequency of treatment related SAEs was 9.3% of subjects. Treatment-related SAEs included pleural effusion, tumour lysis syndrome, congestive cardiac failure, and diarrhoea; all of which resolved with supportive care.

Adverse events leading to study drug discontinuation occurred in 18.6% of subjects; three subjects due to grade 3 TEAEs, 2 subjects due to grade 4 TEAEs, and three subjects due to grade 5 TEAEs.

One subject each discontinued study drug due to treatment-related TEAEs including events of prolonged QTc, fatigue, and increased transaminases. All treatment-related TEAEs leading to discontinuation resolved, except for the grade 3 fatigue, which was ongoing at the end of study.

Study SB1518-2008-003- Phase 1

This was a phase 1/2 study of oral pacritinib (SB1518) in subjects with chronic idiopathic myelofibrosis (CIMF). The phase 1 part of the study was an open-label, multicentre, dose escalation study to determine the MTD and DLTs of pacritinib when administered orally once daily as a single agent in subjects with CIMF (including PET-/PPV-MF) regardless of their JAK2 mutational status.

Subjects were enrolled sequentially to one of five dose cohorts (100 mg, 200 mg, 400 mg, 500 mg, and 600 mg) and received pacritinib once daily for 28-consecutive days (one cycle) for up to one year, or longer in the absence of disease progression and unacceptable toxicity. A single subject served as a sentinel in cohort 1 (100 mg). Subsequent subjects were enrolled after the sentinel subject was treated for two weeks and showed no significant toxicities, as determined by the Investigator and Sponsor's medical monitor. For each dose level after the first (200 mg, 400 mg, 500 mg, and 600 mg) subjects were treated and observed through the end of the first cycle before the next dose level was initiated. Pacritinib capsules were administered orally once daily according to the assigned dose level without regard to food intake.

The primary objective for phase 1 was to determine the MTD and the DLTs of pacritinib, in order to determine the RD for phase 2. PK and PD parameters were to be assessed throughout the study. An exploratory efficacy endpoint was clinical response, as assessed by the International Working Group (IWG) criteria for Myelofibrosis Research and Treatment (IWG-MRT), from baseline to EOT. Analysis of adverse events (AEs) was based on TEAEs which were defined as AEs that occurred after the first dose of pacritinib and within 30 (+7) days after the last study treatment date.

Results

Three (15%) subjects experienced a cycle 1 DLT: 2/4 (50%) subjects in the 600 mg dose cohort (grade 3 nausea and fatigue in one subject and grade 3 intermittent diarrhoea in the other) and 1/6 (16.7%) subjects in the 500 mg cohort (peripheral vascular disease). Although only 1/6 subjects experienced a cycle 1 DLT in the 500 mg dose cohort, 5/6 (83.3%) subjects in this cohort required dose interruptions and three (60%) subjects required dose reductions due to AEs. In addition, 4/6 (66.7%) subjects in the 500 mg cohort experienced SAEs. Therefore, the 400 mg dose of pacritinib was identified as the RD to proceed into phase 2 of the study.

All subjects achieved clinical benefit as best response during the study, as defined by IWG-MRT criteria. A best response of stable disease was achieved in 85.0% (17/20) of subjects and a best response of CImp was achieved in 15.0% (3/20) of subjects.

All 20 subjects in the Safety Population study experienced at least one TEAE that was judged to be treatment related. The most common TEAEs related to pacritinib treatment were the GI events of diarrhoea (90.0%), nausea (45.0%), and vomiting (35.0%), and increased ALT (25.0%).

Treatment related hematologic events occurred infrequently (5%). Half of the subjects experienced treatment related grade 3/4 TEAEs.

Death occurred in three (15%) subjects overall, including one subject in the 100 mg cohort and two subjects in the 600 mg cohort. None of the TEAEs with an outcome of death (lower lobe pneumonia, AML, and acute renal failure) were assessed as treatment related.

SAEs were reported in eight (40.0%) subjects; however, the SAE was assessed as treatment related in two (10%) subjects. Approximately one-third (35%) of the subjects were withdrawn from the study due to a TEAE.

Conclusions of dose finding studies:

The starting doses for the phase 1 parts of the studies were chosen on the basis of animal data collected in the most sensitive species, dogs. The phase 1 parts of both the above studies determined diarrhoea, nausea and fatigue as the dose limiting toxicity. Both studies suggest 500 mg to be the MTD for pacritinib. However, on the basis of the observed incidence of AEs, SAEs, and dose interruptions the next lower dose of 400 mg was the dose chosen as the recommended dose for the phase 2 parts of both studies. This is considered acceptable.

The most frequently reported treatment-related TEAEs included thrombocytopenia (11.6%) in addition to the diarrhoea, nausea and vomiting, with larger proportions of subjects reporting treatment-related TEAEs in cohorts with doses ≥ 400 mg. The majority (81.4%) of subjects experienced worst grade 3/4 TEAEs, while only 18.6% of subjects experienced worst grade 1/2 TEAEs. Anaemia and thrombocytopenia were the most frequently occurring grade 3/4 TEAEs. The incidence of haematological toxicity noted in the phase 1 studies, including thrombocytopenia, raises concerns and doubts about the applicant's claim that pacritinib can be safely used in thrombocytopenic patients with platelet counts <50,000/mm^3 and without dose reduction in patients with platelet counts <200,000/mm^3. This is also concerning as bleeding events (subdural hematoma) is listed among the commonest treatment emergent serious adverse events.

MAIN CLINICAL STUDY

Study PAC325- PERSIST 1

This was a randomized controlled phase 3 study that compared oral pacritinib against best available therapy (BAT) in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. The study period included in the presented data was from 8th January 2013 (first subject enrolled) to 17th January 2015 (last subject completed 24 week visit—data cut off).

Subjects chosen for the study (as per the main inclusion criteria) were aged at least 18 years old who had Intermediate -1 or -2 or High Risk PMF, PPV-MF, or PET-MF, with palpable splenomegaly ≥ 5 cm below the left costal margin in mid-clavicular line; had a total symptom score ≥ 13 on the MPN-SAF TSS 2.0; an Eastern Cooperative Oncology Group performance status of 0 to 3; a peripheral blast count <10%; an absolute neutrophil count 500/µL; had any level of baseline platelet and haemoglobin, including dependence on platelet or red blood cell transfusions; had no prior treatment with a JAK2 inhibitor; had adequate liver and renal function, were at least 6 months from prior splenic irradiation, were at least 12 months from prior ^{32}P therapy.

Test Product, Dose and Mode of Administration: Pacritinib capsules were administered orally at 400 mg per day. Subjects were to self-administer four 100 mg capsules per day orally, once a day (400 mg daily), at the same time of day, with or without food.

The initial study period was 24 weeks but subjects were allowed to stay on study drug until disease progression or the occurrence of unacceptable toxicity or until the subject no longer derived benefit from treatment. Subjects are to be followed for 3 years for survival and transformation to AML.

Reference Therapy, Dose and Mode of Administration: Best available therapy included any physician-selected treatment for PMF, PPV-MF, or PET-MF with the exclusion of JAK inhibitors, and could have included any treatment received before study entry. Best available therapies also could have included no treatment (watch and wait) or symptom directed treatment without MF-specific treatment.

The **primary objective** was to compare the efficacy of pacritinib with that of best available therapy (BAT) in subjects with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPVMF), or post-essential thrombocythemia myelofibrosis (PET-MF) for the proportion of subjects achieving a ≥35% reduction in spleen volume from baseline to week 24, as measured by magnetic resonance imaging (MRI) or computed tomography (CT).

The **key secondary objective** was to compare pacritinib with that of best available therapy for the proportion of subjects with ≥ 50% reduction in total symptom score from baseline to week 24 on the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF TSS 2.0).

Other secondary objectives were to compare pacritinib to BAT with respect to:

• Proportion of subjects with baseline platelet count <100,000/μL achieving ≥ 35% reduction in spleen volume from baseline to week 24 as measured by MRI or CT scan

• Proportion of subjects with baseline platelet count <100,000/μL achieving ≥ 50% reduction in TSS from baseline to week 24

• Proportion of subjects with baseline platelet count <50,000/μL achieving ≥ 35% reduction in spleen volume from baseline to week 24 as measured by MRI or CT scan

• Proportion of subjects with baseline platelet count <50,000/μL achieving ≥ 50% reduction in TSS from baseline to week 24

The **exploratory objectives** of the study included Overall survival (OS), Progression-free survival (PFS), Leukaemia-free survival (LFS); Time to achievement of ≥ 35% reduction in spleen volume from baseline by MRI or CT scan; Duration of maintenance of ≥ 35% reduction in spleen volume from baseline; Best response in spleen volume by MRI or CT scan; Duration of treatment; Achievement of red blood cell (RBC) transfusion independence; Achievement of reduced RBC transfusion dependence; Clinical improvement in haemoglobin level; Frequency of RBC transfusions; Achievement of platelet transfusion independence; Clinical improvement in platelet count; Frequency of platelet transfusions; Change in *JAK2V617F* allele burden; Quality of life, as measured by the EQ-5D-5L and EORTC QLQ-C30 version 3.0

The **PK and pharmacodynamic (PD) objectives** of the study were to assess exposure and exposure-response relationships pertaining to the safety and efficacy of pacritinib.

Sample size- The PERSIST-1 study was powered for both the primary and secondary endpoints. A difference in response rates of 27% was expected for the primary and 40% for the secondary endpoint. This calculation took into account that only about 150 subjects would have received the MPN-SAF TSS 2.0 after the amendment was introduced.

Randomisation- Eligible subjects were randomized in a 2:1 ratio to either pacritinib (400 mg daily) or BAT using a central interactive web response system or interactive voice response system. Randomization was performed by geographic region (North America, Europe, Russia, and Oceania) and stratified by the risk category (Intermediate-1 or -2 vs High Risk) and by platelet count (< 50,000/μL vs 50,000 to < 100,000/μL vs ≥ 100,000/μL). Permuted blocks within strata were used to restrict treatment allocation.

Blinding- Investigators, site personnel, subjects and clinical monitors were unblinded throughout the duration of the study. The CTI Pharmacovigilance department was unblinded to SAE data originating from the study. The sponsor and independent radiographic assessors were blinded during the study. The sponsor remained blinded until the database lock for primary analysis. Independent radiographic assessors remained blinded throughout the entire study.

The primary endpoint of the study was measured by MRI or CT scan, assessed by an independent radiology facility and analysed using the Intent-to-treat (ITT) population. Subjects with a missing week 24 spleen volume, including those who met the criteria for disease progression and crossover to treatment with pacritinib or who dropped out of the study before week 24 were considered to have not achieved the ≥ 35% reduction.

For the analysis of TSS the results obtained from the two versions of the questionnaire are presented separately.

The type I error is adequately controlled by testing endpoints following a hierarchy.

Results

A total of 327 subjects were randomly assigned to the pacritinib 400 mg arm (220 subjects [67.3%]) or the BAT arm (107 subjects [32.7%]) and all are included in the ITT population. One subject in the BAT arm (subject 49001-0112) was randomized, but withdrew from the study (reason unknown) before a scheduled BAT treatment could begin.

Overall, 74% (242/327) of all randomized subjects completed 24 weeks of study treatment (167/220 [75.9%] in the pacritinib arm and 75/107 [70.1%] in the BAT arm).

- **Participant flow**

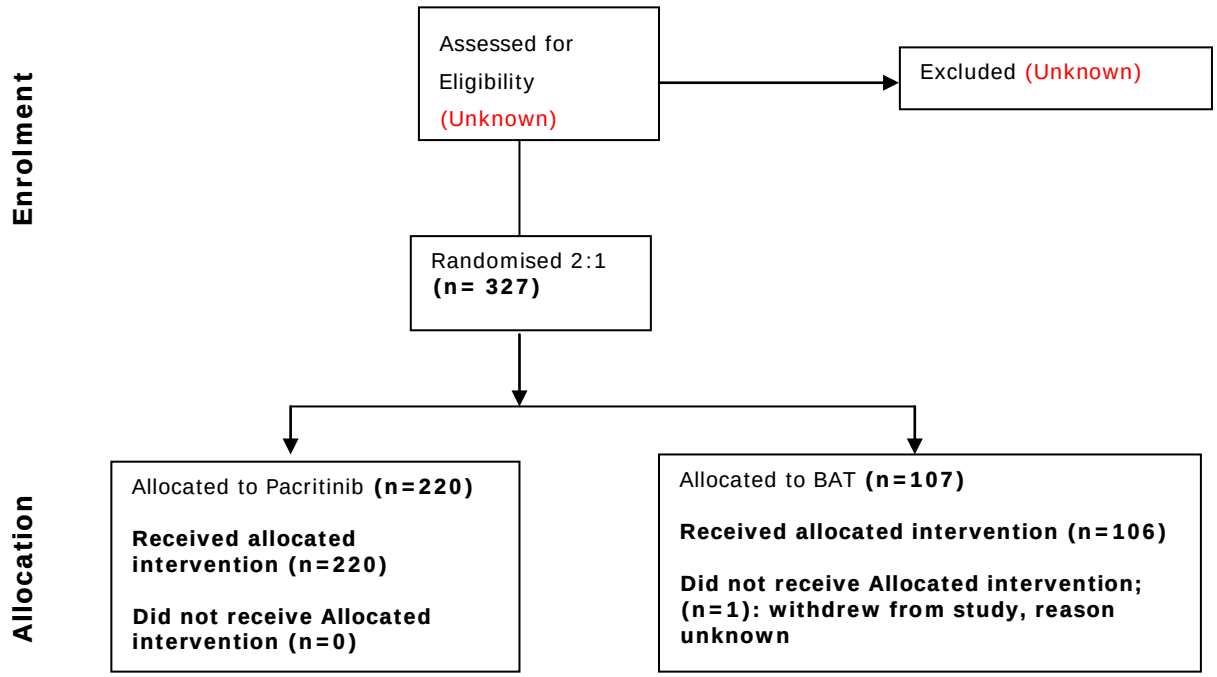


Table 3: Disposition (ITT Population)

	Pacritinib N = 220 n (%)	BAT N = 107 n (%)	Total N = 327 n (%)
Randomized subjects	220 (100.0)	107 (100.0)	327 (100.0)
Completed 24 weeks of study treatment	167 (75.9)	75 (70.1)	242 (74.0)
Subjects who discontinued initial study treatment on or prior to week 24	53 (24.1)	32 (29.9)	85 (26.0)
Subjects who discontinued initial study treatment on or prior to data cut-off	96 (43.6)	98 (91.6)	194 (59.3)
Death	3 (1.4)	1 (0.9)	4 (1.2)
Adverse event[a]	32 (14.5)	3 (2.8)	35 (10.7)
Progressive disease	10 (4.5)	12 (11.2)	22 (6.7)
Non-compliance with study drug	0	1 (0.9)	1 (0.3)
Investigator's decision	16 (7.3)	78 (72.9)	94 (28.7)
Withdrawal by subject[b]	28 (12.7)	3 (2.8)	31 (9.5)
Other	7 (3.2)	0	7 (2.1)
Subjects who crossed over from BAT to pacritinib	NA	85 (79.4)	NA
Subjects who discontinued pacritinib after crossover[c]	NA	25 (29.4)	NA
Death	NA	1 (1.2)	NA
Adverse event	NA	10 (11.8)	NA
Progressive disease	NA	2 (2.4)	NA
Investigator's decision	NA	7 (8.2)	NA
Withdrawal by subject[b]	NA	5 (5.9)	NA
Subjects who discontinued the study	49 (22.3)	22 (20.6)	71 (21.7)
Death	34 (15.5)	15 (14.0)	49 (15.0)
Investigator's decision	2 (0.9)	3 (2.8)	5 (1.5)
Withdrawal by subject[b]	11 (5.0)	3 (2.8)	14 (4.3)
Other	2 (0.9)	1 (0.9)	3 (0.9)

AE, adverse event; BAT, best available therapy; ITT, intent-to-treat; NA, not applicable.

Table 14.1.2.1
Patient Disposition up to Week 24
ITT Population

	Pacritinib N=220 [n (%)]	BAT N=107 [n (%)]	Total N=327 [n (%)]
Randomized Patients (ITT Population)	220 (100.0)	107 (100.0)	327 (100.0)
Patients Who Received Any Dose of Study Treatment (Safety Population)	220 (100.0)	106 (99.1)	326 (99.7)
Patients Who Discontinued Initial Study Treatment Prior to Week 24	53 (24.1)	32 (29.9)	85 (26.0)
Death	1 (0.5)	1 (0.9)	2 (0.6)
Adverse Event	20 (9.1)	2 (1.9)	22 (6.7)
Progressive Disease	3 (1.4)	9 (8.4)	12 (3.7)
Physician Decision	7 (3.2)	18 (16.8)	25 (7.6)
Withdrawal by Subject[1]	18 (8.2)	2 (1.9)	20 (6.1)
Other	4 (1.8)	0	4 (1.2)

The main reasons for premature treatment discontinuation in the pacritinib arm were AEs (14.5%) and withdrawal by subject (12.7%) which included subject decision and subject's withdrawal of consent from study.

In the BAT arm, the main reasons for premature treatment discontinuation were investigator's decision (72.9%) and progressive disease (11.2%). Investigator's decisions to discontinue BAT included decision to cross-over to pacritinib after week 24, and included decision in cases in which it was in the subject's best interest to be withdrawn from study procedures.

Table 4: Summary of Demographic and Baseline Characteristics (ITT Population)

	Pacritinib N = 220 n (%)	BAT N = 107 n (%)	p-value	Total N = 327 n (%)
Age (years)				
Mean (SD)	65.5 (10.9)	64.8 (9.1)	0.507	65.3 (10.3)
Median (IQR)	67.0 (60.0, 73.0)	65.0 (59.0, 72.0)		66.0 (60.0, 73.0)
Minimum, maximum	23, 87	37, 84		23, 87
< 65 years	85 (38.6)	52 (48.6)	0.095	137 (41.9)
≥ 65 years	135 (61.4)	55 (51.4)		190 (58.1)
Gender			0.906	
Female	95 (43.2)	47 (43.9)		142 (43.4)
Male	125 (56.8)	60 (56.1)		185 (56.6)
Race			0.766	
Asian	2 (0.9)	1 (0.9)		3 (0.9)
Black or African American	2 (0.9)	0		2 (0.6)
Not Reported	23 (10.5)	8 (7.5)		31 (9.5)
Other	2 (0.9)	0		2 (0.6)
White	191 (86.8)	98 (91.6)		289 (88.4)
Ethnicity			0.767	
Hispanic or Latino	5 (2.3)	2 (1.9)		7 (2.1)
Not Hispanic or Latino	160 (72.7)	82 (76.6)		242 (74.0)
Not reported	52 (23.6)	23 (21.5)		75 (22.9)
Unknown	3 (1.4)	0		3 (0.9)
Height (cm)				
n	217	103		320
Mean (SD)	169.1 (10.01)	168.6 (8.93)	0.699	168.9 (9.66)
Median (IQR)	169.0 (162.0, 176.0)	168.0 (161.0, 176.0)		168.8 (161.8, 176.0)
Minimum, maximum	138, 196	152, 189		138, 196
Weight (kg)				
n	220	106		326
Mean (SD)	70.6 (13.58)	71.0 (13.79)	0.788	70.7 (13.63)
Median (IQR)	70.8 (60.9, 79.0)	70.4 (61.4, 78.9)		70.5 (61.0, 79.0)
Minimum, maximum	41, 110	38, 115		38, 115
BMI (kg/m^2)				
n	217	103		320
Mean (SD)	24.6 (3.70)	24.8 (3.82)	0.579	24.7 (3.73)
Median (IQR)	24.3 (21.9, 26.4)	24.5 (22.3, 26.9)		24.4 (22.1, 26.7)
Minimum, maximum	16, 37	15, 35		15, 37
ECOG PS			0.643	
0	66 (30.0)	30 (28.0)		96 (29.4)
1	126 (57.3)	66 (61.7)		192 (58.7)
2	26 (11.8)	9 (8.4)		35 (10.7)
3	2 (0.9)	2 (1.9)		4 (1.2)
Geographic region			0.970	
Europe	137 (62.3)	66 (61.7)		203 (62.1)
North America	3 (1.4)	2 (1.9)		5 (1.5)
Oceania	45 (20.5)	21 (19.6)		66 (20.2)
Russia	35 (15.9)	18 (16.8)		53 (16.2)

BAT, best available therapy; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; ITT, intent-to-treat.

A summary of baseline disease characteristics, including spleen length, JAK2V617F mutational status, and platelet count for the ITT population is provided in table 5. There is a statistically significant difference in the percentage of JAK2V617F positivity between the 2 arms with a higher percentage in the BAT arm. Though this being a randomised study, the difference must be due to chance and the p-value is therefore of little use, it still highlights a large difference between the treatment arms. This needs further discussion regarding the effect of this difference on the study outcomes.

Table 5: Baseline Disease Characteristics (ITT Population)

	Pacritinib N = 220 n (%)	BAT N = 107 n (%)	p-value	Total N = 327 n (%)
Current MF diagnosis			0.150	
Primary MF	144 (65.5)	59 (55.1)		203 (62.1)
PPV-MF	48 (21.8)	33 (30.8)		81 (24.8)
PET-MF	27 (12.3)	15 (14.0)		42 (12.8)
Missing	1 (0.5)	0		1 (0.3)
Spleen Volume (cm^3)[a]				
n	218	107		NA
Mean (SD)	2223.3 (1189.9)	2367.0 (1164.4)		NA
Median (IQR)	2005.6 (1396.6, 2889.0)	2152.7 (1545.2, 3136.0)		NA
Minimum, maximum	472.1, 7947.9	436.1, 5403.6		NA
Spleen length by physical exam (cm)				
n	219	106		325
Mean (SD)	12.3 (5.9)	12.8 (6.0)	0.566	12.5 (5.9)
Median (IQR)	12.0 (8.0, 16.0)	12.0 (8.0, 17.0)		12.0 (8.0, 17.0)
Minimum, maximum	4.0, 33.0	4.0, 30.0		4.0, 33.0
Bone marrow biopsy completed	219 (99.5)	107 (100.0)	1.000	326 (99.7)
Cellularity			0.957	
Absent	4 (1.8)	1 (0.9)		5 (1.5)
Hypocellular (< 20%)	38 (17.4)	17 (15.9)		55 (16.9)
Normocellular (20%-40%)	25 (11.4)	10 (9.3)		35 (10.7)
Hypercellular (41%-100%)	138 (63.0)	73 (68.2)		211 (64.7)
Not done	9 (4.1)	3 (2.8)		12 (3.7)
Other	5 (2.3)	2 (1.9)		7 (2.1)
Missing	0	1 (0.9)		1 (0.3)
Reticulin and collagen fibrosis staging			0.018	
MF0	3 (1.4)	5 (4.7)		8 (2.5)
MF1	29 (13.2)	13 (12.1)		42 (12.9)
MF2	76 (34.7)	49 (45.8)		125 (38.3)
MF3	104 (47.5)	34 (31.8)		138 (42.3)
Missing	7 (3.2)	6 (5.6)		13 (4.0)
Myeloblast				
n	192	99		291
Mean (SD)	2.2 (2.5)	2.0 (2.7)	0.556	2.1 (2.6)
Median (IQR)	1.0 (0.0, 4.0)	1.0 (0.0, 3.0)		1.0 (0.0, 4.0)
Minimum, maximum	0.0, 15.0	0.0, 17.0		0.0, 17.0
JAK2V617F positive	154 (70.0)	92 (86.0)	0.001	246 (75.2)
Platelet count group			0.984	
< 50,000/uL	35 (15.9)	16 (15.0)		51 (15.6)
≥ 50,000 - < 100,000/uL	37 (16.8)	18 (16.8)		55 (16.8)
≥ 100,000/uL	148 (67.3)	73 (68.2)		221 (67.6)
Time since current MF diagnosis (years)				
n	219	107		326
Mean (SD)	2.9 (4.2)	3.6 (4.9)	0.194	3.2 (4.5)
Median (IQR)	1.0 (0.3, 4.0)	1.8 (0.3, 5.3)		1.1 (0.3, 4.6)
Minimum, maximum	0.0, 28.1	0.0, 29.8		0.0, 29.8
Non-bone marrow diagnostic criteria at initial MF diagnosis				
Prior PV per WHO criteria	49 (22.3)	33 (30.8)		82 (25.1)
Prior ET per WHO criteria	30 (13.6)	15 (14.0)		45 (13.8)
Leukoerythroblastosis	106 (48.2)	54 (50.5)		160 (48.9)
Observed increased serum LDH	166 (75.5)	80 (74.8)		246 (75.2)
Anaemia	145 (65.9)	70 (65.4)		215 (65.7)
Palpable splenomegaly	215 (97.7)	105 (98.1)		320 (97.9)
Weight loss >10% over last 6 months	59 (26.8)	25 (23.4)		84 (25.7)
Night sweats	126 (57.3)	53 (49.5)		179 (54.7)

	Pacritinib N = 220 n (%)	BAT N = 107 n (%)	p-value	Total N = 327 n (%)
Unexplained fever above 37.5°C	12 (5.5)	11 (10.3)		23 (7.0)
Randomized DIPSS risk category[b]			0.744	
Intermediate-1 or Intermediate-2	185 (84.1)	92 (86.0)		277 (84.7)
High (score = 5-6)	35 (15.9)	15 (14.0)		50 (15.3)
Current DIPSS prognostic score[c]			1.000	
Intermediate-1 or Intermediate-2	187 (85.0)	92 (86.0)		279 (85.3)
Intermediate-1 (score = 1-2)	124 (56.4)	49 (45.8)		173 (52.9)
Intermediate-2 (score = 3-4)	63 (28.6)	43 (40.2)		106 (32.4)
High (score = 5-6)	32 (14.5)	15 (14.0)		47 (14.4)
Missing	1 (0.5)	0		1 (0.3)
Transfusion history (within 90 days prior to informed consent)				
RBC (units/30 days)				
Subjects who received at least one unit	61	26		87
Mean (SD)	2.8 (2.3)	2.2 (1.5)	0.199	2.6 (2.1)
Median (IQR)	2.0 (1.0, 3.7)	2.0 (1.0, 3.0)		2.0 (1.0, 3.3)
Minimum, maximum	0.3, 11.0	0.7, 6.7		0.3, 11.0
Platelets (times/30 days)				
Subjects who received at least one transfusion	10	6		16
Mean (SD)	1.2 (1.4)	1.6 (1.3)	0.601	1.4 (1.3)
Median (IQR)	0.7 (0.3, 1.3)	1.5 (0.3, 2.7)		0.7 (0.3, 2.3)
Minimum, maximum	0.3, 4.3	0.3, 3.3		0.3, 4.3
RBC transfusion dependence[d]			0.928	
Dependent	35 (15.9)	15 (14.0)		50 (15.3)
Independent	156 (70.9)	75 (70.1)		231 (70.6)
Indeterminate	29 (13.2)	14 (13.1)		43 (13.1)
Missing	0	3 (8)		3 (0.9)
Platelet transfusion dependence[e]			0.687	
Dependent	4 (1.8)	3 (.8)		7 (2.1)
Independent	216 (98.2)	104 (97.2)		320 (97.9)

BAT, best available therapy; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocytopenia; IQR, interquartile range; ITT, intent-to-treat; LDH, lactate dehydrogenase; MF, myelofibrosis; NA, not applicable; PET, post-essential thrombocytopenia; PPV, post-essential polycythemia vera; PV, polycythemia vera; RBC, red blood cell; SD, standard deviation; WHO, World Health Organization.

[a] P-value was not calculated for baseline spleen volume.

[b] Determined by investigator, and reflects data entered into interactive web response system for stratification.

[c] Reflects data entered into electronic data capture.

[d] Defined as per Gale et al (36).

[e] Dependence defined as any episode of platelet transfusion within the past month.

Primary Efficacy Endpoint:

For the ITT population, there was a significant (p = 0.0003) difference between treatment arms for the overall **proportion of subjects achieving a ≥ 35% SVR from baseline to week 24**, with a greater proportion of subjects in the pacritinib arm achieving a ≥ 35% SVR than in the BAT arm (pacritinib, 42/220 [19.1%]; BAT 5/107 [4.7%]).

Additionally, there were significant differences between treatment arms for subgroups of subjects by baseline platelet count, with a greater proportion of subjects in the pacritinib arm achieving a ≥ 35% SVR in each subgroup than in the BAT arm (p = 0.0451, p = 0.0086, and p = 0.0105 for the < 50,000/μL, < 100,000/μL, and ≥ 100,000/μL subgroups, respectively)

Table 6: Proportion of Subjects Achieving a ≥ 35% Spleen Volume Reduction from Baseline to Week 24 (ITT Population)

Analysis Group	Pacritinib N = 220 n (%) [95% CI][a]	BAT N = 107 n (%) [95% CI][a]	Difference (PAC – BAT) % [95% CI][b]	p-value[c]
Overall	42 (19.1) [14.1, 24.9]	5 (4.7) [1.5, 10.6]	14.4 [7.1, 20.6]	0.0003
Platelet count subgroup[d]				
< 50,000/μL	8/35 (22.9) [10.4, 40.1]	0/16 [0.0, 20.6]	22.9 [1.4, 36.2]	0.0451
< 100,000/μL	12/72 (16.7) [8.9,27.3]	0/34 [0.0, 10.3]	16.7 [4.6, 25.0]	0.0086
≥ 100,000/μL	30/148 (20.3) [14.1, 27.7]	5/73 (6.8) [2.3, 15.3]	13.4 [3.7, 21.6]	0.0105

BAT, best available therapy; CI, confidence interval; ITT, intent-to-treat; PAC, pacritinib.

[a] 95% CIs based on Clopper-Pearson method.

[b] 95% CIs based on Agresti-Caffo method.

[c] p-value from Fisher Exact test.

[d] The step-down procedure used to ensure an overall Type 1 error rate of 5%(see Section 9.6.2) specified that formal analyses of the primary endpoint (proportion of subjects achieving ≥ 35% SVR) would only be performed for subgroups of subjects if the secondary endpoint (proportion of subjects achieving ≥ 50% reduction in TSS) was statistically significant between treatment arms. Since there was no statistical significance between treatment arms for the secondary endpoint, the significance levels cited for these subgroups are only nominal.

Key Secondary Efficacy Endpoint:

The secondary endpoint in the study was the proportion of subjects with a ≥ 50% reduction from baseline to week 24 in the subject reported outcome instrument, MPN-SAF TSS 2.0. The first version of this instrument (MPN-SAF TSS) was administered to the first 179 subjects enrolled in the study, who continued to use this version throughout their participation in the study. However, after discussion with FDA, agreement was reached on modified questions to be included in the instrument. The new version (termed MPN-SAF TSS 2.0) was administered to all subsequently enrolled subjects throughout their participation in the study.

A total of 148 subjects (100 pacritinib, 48 BAT) were administered the MPN-SAF TSS 2.0 and comprise the ITT population for this endpoint.

Overall, 19/100 (19.0%) subjects in the pacritinib arm and 5/48 (10.4%) subjects in the BAT arm had a ≥ 50% reduction from baseline to week 24 in TSS 2.0, which was not statistically different (p = 0.2368).

Table 7: Proportion of Subjects with ≥ 50% Reduction in Total Symptom Score per MPN-SAF TSS 2.0 from Baseline to Week 24 (ITT TSS 2.0 Population)

Analysis Group	Pacritinib N = 100 n/N (%) [95% CI][a]	BAT N = 48 n/N (%) [95% CI][a]	Difference (PAC – BAT) % [95% CI][b]	p-value[c]
Overall	19 (19.0) [11.8, 28.1]	5 (10.4) [3.5, 22.7]	8.6 [-4.2, 19.5]	0.2368
Platelet count subgroup				
< 50,000/μL	3/11 (27.3) [6.0, 61.0]	0/5 [0.0, 52.2]	27.3 [-19.6, 52.6]	0.5089
< 100,000/μL	7/28 (25.0) [10.7, 44.9]	1/13 (7.7) [0.2, 36.0]	17.3 [-10.0, 36.7]	0.3983
≥ 100,000/μL	12/72 (16.7) [8.9, 27.3]	4/35 (11.4) [3.2, 26.7]	5.2 [-10.0, 18.1]	0.5730

BAT, best available therapy; CI, confidence interval; ITT, intent-to-treat; MPN-SAF TSS 2.0, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score, v2.0; PAC, pacritinib.

[a] 95% CIs based on Clopper-Pearson method.

[b] 95% CIs based on Agresti-Caffo method.

[c] p-value from Fisher Exact test.

- **Ancillary analyses and exploratory analyses**

Stratified and Sub-group Analysis- Proportion of Subjects Achieving a ≥ 35% SVR from Baseline to Week 24:

For the stratified analyses of the ITT population using the randomized strata, there were significant differences between treatment arms for the proportion of subjects with a ≥ 35% SVR from baseline to week 24 after adjusting for geographical region (p = 0.0006), DIPSS risk category (Intermediate 1 or 2 vs High Risk, p = 0.0005), and baseline platelet count (< 50,000/μL; ≥ 50,000 to < 100,000/ μL; ≥ 100,000/ μL; p = 0.0005).

For all subgroups analysed (by DIPSS risk category, baseline platelet count, gender age, geographic region [except North America], *JAK2V617F* status at baseline, baseline MF diagnosis, and reticulin and collagen fibrosis staging), a greater proportion of subjects in the pacritinib arm than in the BAT arm had a ≥ 35% SVR from baseline to week 24. As these were exploratory analyses, p-values were not determined.

Table 8: Proportion of Subjects with a ≥ 35% SVR from Baseline to Week 24 by Subject Subgroup (ITT Population)

Analysis Group	Pacritinib N = 220 n/N (%) [95% CI][a]	BAT N = 107 n/N (%) [95% CI][a]	Difference (PAC – BAT) % [95% CI][b]
Overall	42 (19.1) [14.1, 24.9]	5 (4.7) [1.5, 10.6]	14.4 [7.1, 20.6]
DIPSS risk category[c]			
Intermediate-1	25/124 (20.2) [13.5, 28.3]	1/49 (2.0) [0.1, 10.9]	18.1 [7.9, 25.6]
Intermediate-2	12/63 (19.0) [10.2, 30.9]	4/43 (9.3) [2.6, 22.1]	9.7 [-4.5, 22.3]
High	5/32 (15.6) [5.3, 32.8]	0/15 [0.0, 21.8]	15.6 [-5.2, 28.8]
Baseline platelet count			
< 50,000/μL	8/35 (22.9) [10.4, 40.1]	0/16 [0.0, 20.6]	22.9 [1.4, 36.2]
≥ 50,000 to < 100,000/μL	4/37 (10.8) [3.0, 25.4]	0/18 [0.0, 18.5]	10.8 [-6.4, 22.0]
≥ 100,000	30/148 (20.3) [14.1, 27.7]	5/73 (6.8) [2.3, 15.3]	13.4 [3.7, 21.6]
Gender			
Male	22/125 (17.6) [11.4, 25.4]	3/60 (5.0) [1.0, 13.9]	12.6 [2.6, 20.7]
Female	20/95 (21.1) [13.4, 30.6]	2/47 (4.3) [0.5, 14.5]	16.8 [4.9, 26.1]
Age			
< 65 years	18/85 (21.2) [13.1, 31.4]	0/52 [0.0, 6.8]	21.2 [10.6, 29.4]
≥ 65 years	24/135 (17.8) [11.7, 25.3]	5/55 (9.1) [3.0, 20.0]	8.7 [-2.5, 18.0]
Region			
North America	0/3 [0.0, 70.8]	1/2 (50.0) [1.3, 98.7]	-50.0 [-90.3, 30.3]
Europe	26/137 (19.0) [12.8, 26.6]	3/66 (4.5) [0.9, 12.7]	14.4 [4.9, 22.2]
Russia	8/35 (22.9) [10.4, 40.1]	0/18 [0.0, 18.5]	22.9 [2.5, 36.1]
Oceania	8/45 (17.8) [8.0, 32.1]	1/21 (4.8) [0.1, 23.8]	13.0 [-5.6, 26.6]
JAK2V617F mutation status at baseline			
Present	28/154 (18.2) [12.4, 25.2]	4/92 (4.3) [1.2, 10.8]	13.8 [5.7, 20.9]
Absent	14/61 (23.0) [13.2, 35.5]	0/13 [0.0, 24.7]	23.0 [0.7, 33.6]
Baseline MF diagnosis			
Primary MF	28/144 (19.4) [13.3, 26.9]	2/59 (3.4) [0.4, 11.7]	16.1 [6.5, 23.4]
Secondary MF	14/75 (18.7) [10.6, 29.3]	3/48 (6.3) [1.3, 17.2]	12.4 [-0.1, 23.1]
Reticulin and collagen fibrosis staging			
MF Grade 0-1 (low)	7/32 (21.9) [9.3, 40.0]	1/18 (5.6) [0.1, 27.3]	16.3 [-5.9, 32.9]
MF Grade > 1 (high)	33/180 (18.3) [13.0, 24.8]	3/83 (3.6) [0.8, 10.2]	14.7 [6.7, 21.2]

BAT, best available therapy; CI, confidence interval; DIPSS, Dynamic International Prognostic Scoring System; ITT, intent-to-treat; MF, myelofibrosis; PAC, pacritinib; SVR, spleen volume reduction .

[a] 95% CIs based on the Clopper-Pearson method.

[b] 95% CIs based on the Agresti-Caffo method.

[c] The denominator for the DIPSS risk group is 219.

Proportion of Subjects Achieving ≥ 35% Reduction in Spleen Volume by Visit:

For the ITT population, the proportion of all subjects with a ≥ 35% SVR was significantly greater in the pacritinib arm than in the BAT arm at all time-points through week 60. Decreasing numbers of responding ITT subjects reached the post-week 24 time point due to the date of their randomization relative to the date of data cut-off (date of last subject completing week 24). The proportion of all subjects with a ≥ 35% SVR was also significantly greater in the pacritinib arm than in the BAT arm for best overall response and for best response up to weeks 24, 36, 48, and 60 ($p < 0.0001$ for all).

Table 9: Proportion of Subjects with ≥35% SVR from Baseline by Visit (ITT Population)

Visit	Pacritinib N = 220 n (%) [95% CI][a]	BAT N = 107 n (%) [95% CI][a]	p-value[b]
Best overall response	59 (26.8) [21.2, 33.2]	7 (6.5) [2.7, 13.0]	< 0.0001
Week 12	32 (14.5) [10.2, 19.9]	1 (0.9) [0.0, 5.1]	< 0.0001
Week 24	42 (19.1) [14.1, 24.9]	5 (4.7) [1.5, 10.6]	0.0003
Best response through week 24	52 (23.6) [18.2, 29.8]	5 (4.7) [1.5, 10.6]	< 0.0001
Week 36	33 (15.0) [10.6, 20.4]	2 (1.9) [0.2, 6.6]	0.0001
Best response through week 36	57 (25.9) [20.3, 32.2]	6 (5.6) [2.1, 11.8]	< 0.0001
Week 48	17 (7.7) [4.6, 12.1]	2 (1.9) [0.2, 6.6]	0.0418
Best response through week 48	57 (25.9) [20.3, 32.2]	7 (6.5) [2.7, 13.0]	< 0.0001
Week 60	14 (6.4) [3.5, 10.4]	1 (0.9) [0.0, 5.1]	0.0258
Best response through week 60	58 (26.4) [20.7, 32.7]	7 (6.5) [2.7, 13.0]	< 0.0001

BAT, best available therapy; CI, confidence interval; ITT, intent-to-treat; SVR, spleen volume reduction.

[a] 95% CIs based on the Clopper-Pearson method.

[b] p-value from Fisher Exact test.

Duration of Spleen Volume Response:

The duration of response was determined for the ITT responders population (i.e., subjects who achieved ≥ 35% SVR from baseline at any time; n = 59 pacritinib; n = 7 BAT). The duration of response was calculated by two methods:

1) the time from a ≥ 35% SVR from baseline to a < 35% reduction from baseline and ≥ 25% increase from nadir and

2) the time from a ≥ 35% SVR from baseline to < 10% reduction from baseline.

Based on Kaplan-Meier analyses, for those subjects achieving the ≥ 35% SVR from baseline at any time, there were no significant differences between treatment arms for the duration of response using the increase from nadir to define loss of response.

The median (95% CI) duration of response based on increase from nadir was not reached (not applicable, [NA]) in the pacritinib arm (CI: 48.3, NA) and 37.0 (CI: NA, NA) weeks in BAT arm. The median (95% CI) duration of response based on <10% reduction from baseline was also not reached (48.3, NA) in the pacritinib arm and 49.0 (NA, NA) in the BAT arm.

Table 10: Duration of Spleen Volume Reduction

Statistics	Pacritinib (N=59)	BAT (N=7)
Number of Events (<35% reduction and >=25% increase from nadir)	12 (20.3%)	1 (14.3%)
Median Duration Based on Nadir in Weeks (95% C.I.)	NA (48.3, NA)	37.0 (NA, NA)
Probability (95% CI)/# at risk		
Week 12	96% (84%, 99%) / 44	100% (100%, 100%) / 3
Week 24	91% (79%, 97%) / 30	100% (100%, 100%) / 2
Week 36	76% (58%, 87%) / 17	100% (100%, 100%) / 1
Week 48	71% (52%, 84%) / 10	0% (NA, NA) / 0
Week 60	57% (33%, 75%) / 4	0% (NA, NA) / 0
Week 72	NA (NA, NA) / 0	0% (NA, NA) / 0
Week 84	NA (NA, NA) / 0	0% (NA, NA) / 0
Week 96	NA (NA, NA) / 0	0% (NA, NA) / 0
Week 108	NA (NA, NA) / 0	0% (NA, NA) / 0
Log-rank Test P-value		0.566
Hazard Ratio (95% C.I.)		0.55 (0.07, 4.33)

Overall Survival, Progression-Free Survival, and Leukaemia-Free Survival

Median times have not been reached in one or both treatment arms for these endpoints.

The results suggest a detrimental effect, for treatment with pacritinib, on overall survival and leukaemia free survival. Some of these times to event analyses are confounded by the censoring at crossover from BAT to Pacritinib. The experimental arm looks worse than the control when this is done, most likely because by censoring at cross-over these subjects can no longer have an event for the control arm, however in the experimental arm all events are counted. For the OS analysis with no censoring at cross-over the trend is also for worse survival on Pacritinib than BAT. Furthermore the rank-preserving structural failure time (RPSFT) analysis planned in the SAP has not been presented.

For the PFS analysis there are no subjects censored due to crossover but for the LFS analysis there are many. It is not clear if this is because cross-over occurred at progression, but the CSR suggests it occurred at week 24. The applicant should explain the reason for the discrepancy between the two analyses. The LFS analysis should also be presented without censoring at crossover.

Kaplan-Meier plots of OS, PFS, and LFS are presented in the figures below.

Table 11: Overall Survival, Progression-free Survival, and Leukaemia-free Survival (ITT Population)

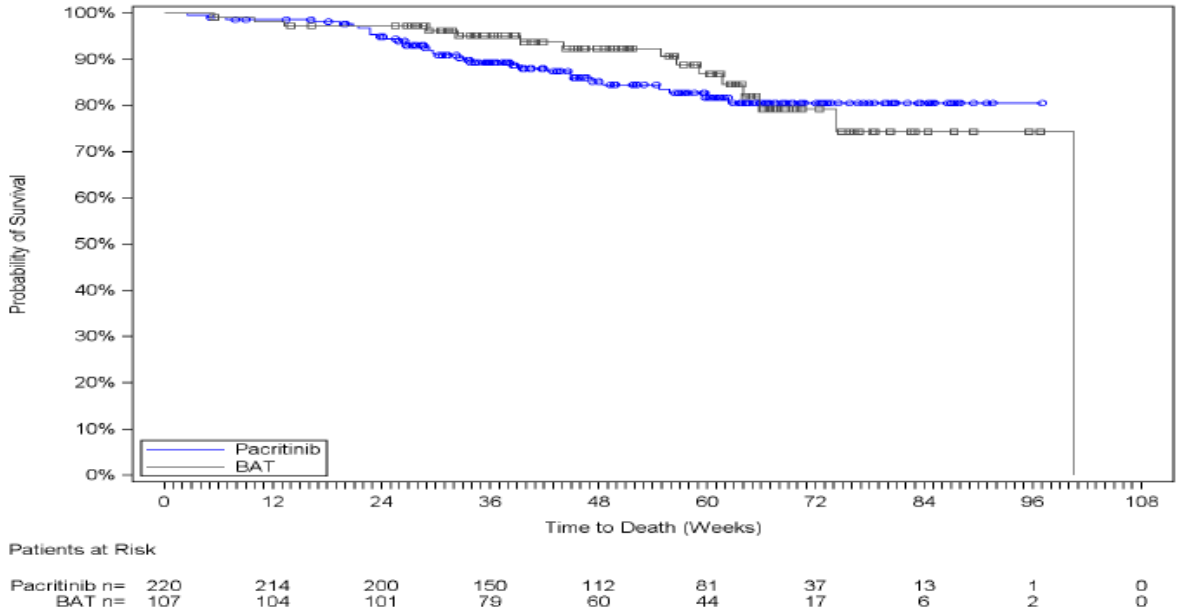
Statistics	Pacritinib N = 220	BAT N = 107	p-value[a]	Hazard Ratio (95% CI)
Overall survival[b]				
Number (%) events [death]	33 (15.0)	15 (14.0%)		
Median (95% CI): weeks	NA (NA, NA)	101 (NA, NA)	0.553	1.21 (0.65, 2.26)
Overall survival, censoring subjects at crossover				
Number (%) events [death]	33 (15.0)	4 (3.7)		
Median (95% CI): weeks	NA (NA, NA)	NA (NA, NA)	0.163	2.10 (0.72, 6.07)
Progression-free survival				
Number (%) events [progression/death]	44 (20.0)	29 (27.1)		
Median (95% CI)	NA (NA, NA)	68.3 (62.9, NA)	0.347	0.80 (0.50, 1.28)
Leukemia-free survival				
Number (%) events [leukemic transformation/death]	35 (15.9)	6 (5.6)		
Median (95% CI): weeks	NA (NA, NA)	NA (NA, NA)	0.219	1.74 (0.71, 4.23)

BAT, best available therapy; CI, confidence interval; ITT, intent-to-treat; NA, not applicable.

[a] p-value from Log-rank test.

[b] The total of 48 deaths does not take into account subject 39001-0303, who died several days after the data cutoff date but was included in the database and is included in the Listing of Deaths, Listing 14.2.3.

Figure CE01: Kaplan-Meier Curve of Overall Survival (ITT Population)



BAT, best available therapy; ITT, intent-to-treat.

Note: Two subjects remained in the BAT treatment arm until week 96, after which both subjects died.

Figure CE02: Kaplan-Meier Curve of Progression-free Survival (ITT Population)

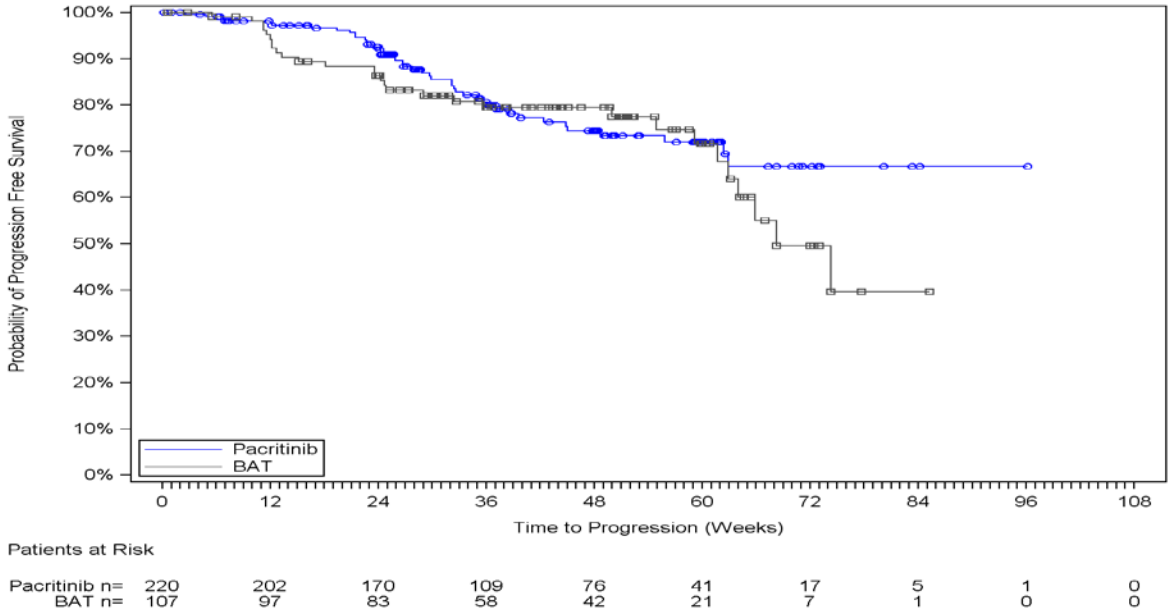
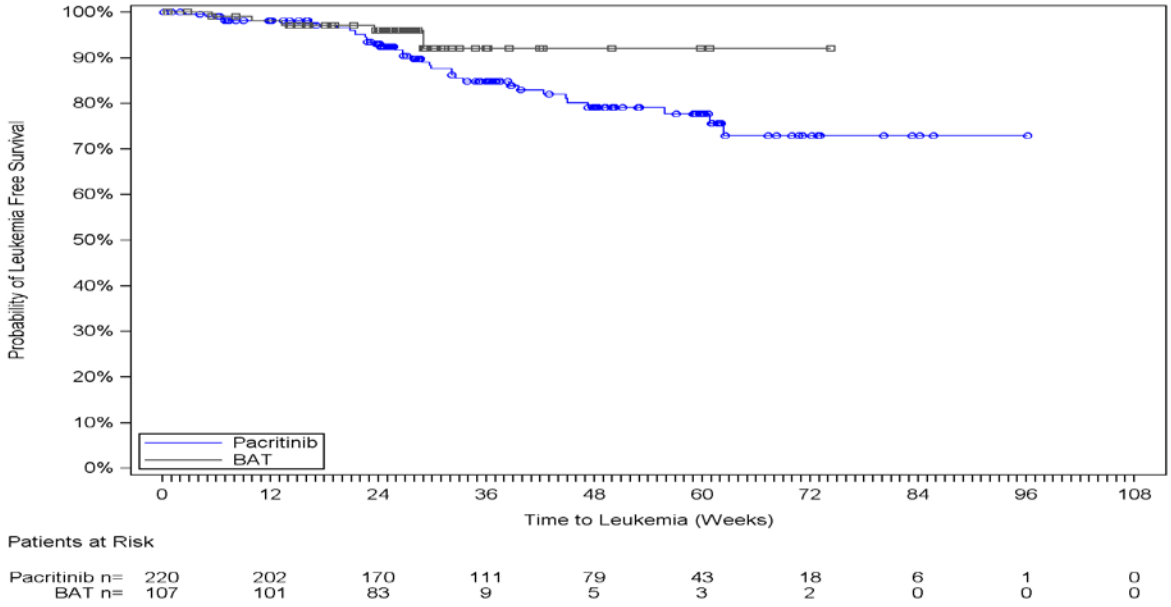


Figure CE03: Kaplan-Meier Curve of Leukaemia-free Survival (ITT Population)



Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12: Summary of efficacy for trial PAC325/ PERSIST-1

Title: PERSIST-1 A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis			
Study identifier	PAC325		
Design	A multicentre, randomized, controlled, phase 3 study comparing the efficacy and safety of pacritinib with that of best available therapy (BAT) in subjects with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF).		
	Duration of main phase:	8^{TH} January 2013 to 17^{th} January 2017	
	Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	not applicable	
Hypothesis	Superiority		
Treatments groups ***(2:1 randomisation)***	**Test Treatment**	**Pacritinib** capsules were administered orally at **400 mg per day**. The **initial study period was 24 weeks** but subjects were allowed to stay on study drug until disease progression or the occurrence of unacceptable toxicity or until the subject no longer derived benefit from treatment. Subjects are to be followed for 3 years for survival and transformation to AML. **220 patients** randomised	
	Reference treatment	**Best available therapy (BAT)** included any physician-selected treatment for PMF, PPV-MF, or PET-MF **with the exclusion of JAK inhibitors**, **and could have included any treatment received before study entry**. **107 patients** randomised	
Endpoints and definitions	**Primary endpoint**	Proportion of subjects achieving ≥35% reduction in spleen volume from baseline to week 24 as measured by MRI or CT	
	Secondary endpoint	Proportion of subjects with ≥50% reduction in TSS from baseline to week 24 as measured by the MPN-SAF TSS 2.0	

	Exploratory Endpoints	Sixteen exploratory endpoints	1. verall survival (OS) 2. rogression-free survival (PFS) 3. eukaemia-free survival (LFS) 4. ime to achievement of ≥ 35% reduction in spleen volume from baseline by MRI or 1. T scan 5. uration of maintenance of ≥ 35% reduction in spleen volume from baseline 6. est response in spleen volume by MRI or CT scan 7. uration of treatment 8. chievement of red blood cell (RBC) transfusion independence 9. chievement of reduced RBC transfusion dependence 10. linical improvement in haemoglobin level 11. requency of RBC transfusions 12. chievement of platelet transfusion independence 13. linical improvement in platelet count 14. requency of platelet transfusions 15. hange in JAK2V617F allele burden 2. 6. Quality of life, as measured by the EQ-5D-5L and EORTC QLQ-C30 version 3.0
Database lock	26th February 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	**Treatment group**	**Pacritinib**	**BAT**
	Number of subjects	220	107
	Primary endpoint (≥35% SVR from baseline to week 24) **N (%)**	42 (19.1%)	5 (4.7%)
	95% CI *(Clopper-Pearson method)*	[14.1; 24.9]	[1.5; 10.6]

	Number of subjects	100	48
	Secondary endpoint (≥50% reduction in TSS 2.0 from baseline to week 24) **N (%)**	19 (19)	5 (10.4)
	95% CI	[11.8, 28.1]	[3.5, 22.7]

Effect estimate per comparison	**Primary endpoint**	**Pacritinib vs BAT**	**Difference**
		Percentage-%	14.4
		95% CI *(Agresti-Caffo method)*	[7.1; 20.6]
		P-value	0.0003
	Secondary endpoint	**Pacritinib vs BAT**	**Difference**
		Percentage-%	8.6
		95% CI (Agresti-Caffo method)	[-4.2, 19.5]
		P-value	0.2368

Clinical studies in special populations

N/A

Analysis performed across trials (pooled analyses AND meta-analysis)

N/A

Supportive studies

The results of the phase 2 parts of the uncontrolled phase 1/2 studies, **SB1518-2007-01 and SB1518-2008-003**, are summarised here as supportive data.

Of the 68 subjects enrolled in the Phase 2 studies, 39 subjects (57.4%) had primary MF and 29 subjects (42.6%) had baseline platelet counts < 100,000/μL, and 11 subjects (16.2%) had baseline platelet counts < 50,000/μL. The Phase 2 studies included subjects at least 18 years of age with CIMF and a spleen at least 5 cm below the costal margin.

Of the 68 subjects enrolled in the Phase 2 studies, 66 subjects (97.1%) received study drug. Thirty subjects (44.1%) completed the study. The most common reason for terminating the study was the Sponsor's decision to terminate the study (20 [29.4%] subjects).

Table 13: Disposition of Subjects in Phase 2 Studies (All Enrolled Population)

Number (%) Subjects	Overall N = 68
Received at least one dose of study drug: n (%)	66 (97.1)
Discontinued study drug: n (%)	66 (97.1)
Reason for study drug discontinuation: n (%)	
Adverse event/serious adverse event	11 (16.7)
Death	2 (3.0)
Disease progression	11 (16.7)
Lack of response	14 (21.2)
Protocol deviation	1 (1.5)
Sponsor's decision	20 (30.3)
Subject withdrew consent	7 (10.6)
Terminated study: n (%)	68 (100.0)
Reason for study termination	
Completed study	30 (44.1)
Death	7 (10.3)
Sponsor's decision to terminate study	20 (29.4)
Subject withdrew consent	11 (16.2)
Time on Study (months): n	68
Mean (SD)	10.7 (6.96)
Minimum, maximum	0.1, 20.1

SD, standard deviation.

For the 66 subjects who received study drug, the mean duration of treatment was 316. The relative dose intensity was 87.1%.

Efficacy Results

Proportion of Subjects with ≥ 35% Reduction in Spleen Volume

Among all subjects enrolled in the Phase 2 studies, 18 subjects (26.5%) achieved ≥35% SVR from baseline at some time during the study, with 9 of these subjects (13.2%) achieving ≥35% SVR at week 24.

Table 14: Proportion of Subjects in Phase 2 Studies who Achieved ≥ 35% SVR from Baseline by Visit (All Enrolled Population)

Visit	Overall N = 68 n (%) [95% CI][a]
Best overall response	18 (26.5) [16.5, 38.6]
Week 12	13 (19.1) [10.6, 30.5]
Week 24	9 (13.2) [6.2, 23.6]
Best response through week 24	13 (19.1) [10.6, 30.5]
Week 36	12 (17.6) [9.5, 28.8]
Best response through week 36	17 (25.0) [15.3, 37.0]
Week 48	9 (13.2) [6.2, 23.6]
Best response through week 48	18 (26.5) [16.5, 38.6]
Week 60	9 (13.2) [6.2, 23.6]
Best response through week 60	18 (26.5) [16.5, 38.6]
Week 72	3 (4.4) [0.9, 12.4]
Best response through week 72	18 (26.5) [16.5, 38.6]

CI, confidence interval; NA, not applicable; SVR, spleen volume reduction.
[a] 95% CIs based on the Clopper-Pearson method

Proportion of Subjects with ≥ 50% Reduction in MFSAF TSS

Overall, 30 subjects (44.1%) had ≥ 50% reduction in MFSAF TSS at some time during the study, with 27 subjects (39.7%) achieving ≥ 50% reduction in MFSAF TSS by week 24.

Table 15: Proportion of Subjects in Phase 2 Studies who Achieved ≥ 50% Reduction in MFSAF TSS from Baseline by Visit (All Enrolled Subjects)

Visit	Overall N = 68 n (%) [95% CI][a]
Best overall response	30 (44.1) [32.1, 56.7]
Week 4	10 (14.7) [7.3, 25.4]
Week 12	13 (19.1) [10.6, 30.5]
Best response through week 12	21 (30.9) [20.2, 43.3]
Week 24	16 (23.5) [14.1, 35.4]
Best response through week 24	27 (39.7) [28.0, 52.3]
Week 36	10 (14.7) [7.3, 25.4]
Best response through week 36	30 (44.1) [32.1, 56.7]
Week 48	8 (11.8) [5.2, 21.9]
Best response through week 48	30 (44.1) [32.1, 56.7]
Week 60	5 (7.4) [2.4, 16.3]
Best response through week 60	30 (44.1) [32.1, 56.7]

CI, confidence interval; MFSAF TSS, myelofibrosis symptom assessment form total symptom score.
[a] 95% CIs based on the Clopper-Pearson method

3.3.5. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy data for pacritinib is derived mainly from the pivotal study PAC325- PERSIST 1 trial. Supportive data generated from phase 2 parts of the phase 1/2 studies SB1518-2007-001 and SB1518-2008-03 are also provided.

The dose of pacritinib to be studied in the pivotal trial in patients with myelofibrosis was derived from the phase I dose response parts of the studies SB1518-2007-001 and SB1518-2008-03. The dose of 400 mg was chosen as the recommended dose for the phase 2 studies and subsequently used in the phase 3 pivotal PERSIST-1 study.

The phase 2 studies' results show activity of pacritinib in the proposed patient population with 13.2% of patients achieving a >35% reduction in spleen volume at week 24.

The pivotal study was a randomised open labelled study comparing pacritinib against best available therapy. The study was initiated after the approval of another JAK inhibitor- Jakavi, but the BAT arm excluded treatment with Jakavi. Further, the BAT arm could have included treatments previously received and therefore may have been treatments which had already failed. Therefore, for several reasons as stated the BAT arm treatments may have been sub-optimal. This is possibly highlighted again by the high numbers of investigator decided withdrawal of patients from the BAT arm of the study, without disease progression or adverse effects. The claim being made is that pacritinib fulfils an unmet medical need in patients with low platelet counts where the use of Jakavi is not recommended.

JAK2 mediates cytokine signalling for red blood cells and platelets production and its inhibition causes anaemia and low platelets. Lowering of platelets and red blood cells is expected side effect due to inhibition of normal JAK2 by JAK2 inhibitors. Therefore, the inclusion of patients with low platelets, irrespective of the platelet count and without any dose modification, is considered a concern from a

safety. There is no scientific explanation or rationale as to why pacritinib should have no effect on the platelets counts, when the phase 1/2 studies showed thrombocytopenia as one of the commonest adverse events.

The selection of the primary endpoint of a >35% reduction in spleen volume is considered acceptable. However the time-point of 24 weeks is lesser than that of 48 weeks required in the EU for the previously approved product Jakavi.

The reduction in total symptom score is also an acceptable endpoint which was studied. However the assessment was not available for all patients on the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF TSS 2.0).

It is worth noting that the investigators and subjects were unblinded to treatment and this could have affected certain behaviour such as treatment withdrawal or the TSS scoring of the secondary efficacy endpoint.

The proportion of subjects discontinuing treatment before week 24 is slightly higher on BAT than the pacritinib arm of the PERSIST-1 study. Given that this is an open label study and that withdrawals are counted as failures, it is important to understand the reasons for withdrawal. 17% of subjects discontinued the BAT arm before week 24 due to investigator's decision without progressive disease or adverse events. This could have had a considerable impact on the results.

There is a statistically significant difference in the percentage of JAK2V617F positivity between the 2 arms with a higher percentage in the BAT arm. Though this being a randomised study, the difference must be due to chance and the p-value is therefore of little use, it still highlights a large difference between the treatment arms and the relevance of this difference needs further evaluation and discussion.

Efficacy data and additional analyses

The efficacy results of the PERSIST-1 study show a statistically significant effect in spleen volume reduction at 24 weeks favouring the pacritinib arm. There is a 14.4% difference in the proportion of patients who achieved a ≥35% reduction in spleen volume from baseline to week 24, favouring the pacritinib arm. However, this result may have been affected by the 17% of patients withdrawn from the BAT arm before 24 weeks due to reasons other than progression of disease or adverse events. Further clarification has been sought regarding this. Further, the proportion of pacritinib treated patients achieving the primary endpoint at 24 weeks in the PERSIST-1, which is 19.1% of pacritinib treated patients (ITT population), is lower than that achieved in the COMFORT-1 pivotal study for Jakavi (41.9% of ruxolitinib treated patients achieving ≥35% reduction from baseline in spleen volume at Week 24).

The results of the primary endpoint are not supported by the secondary endpoint results. There was no statistically significant difference between pacritinib and BAT with regards to the secondary endpoint- ≥50% reduction in total symptom score from baseline to week 24 on the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF TSS 2.0).

The percentage of patients with a ≥35% SVR from baseline at 48 weeks is 7.7% in the pacritinib arm. This again appears inferior to the 28.5% achieved by Jakavi in the pivotal COMFORT-II trial. This brings to question the durability of response to pacritinib.

More concerning is the fact that there appears to be a detrimental effect on overall survival and leukaemia free survival with increased number of events in the pacritinib arm. This is a major concern.

3.3.6. Conclusions on clinical efficacy

Overall there are several issues that need to be addressed in relation to the efficacy data presented. The Applicant has provided insufficient evidence of the efficacy of pacritinib in patients with myelofibrosis.

3.3.7. Clinical safety

An integrated safety analysis has been presented by subject population whereby data from healthy subjects and non-cancer subjects (hepatic and renal impairment study subjects) were analysed separately from cancer study subjects. The former group is referred to as the healthy volunteer/non-cancer study subjects. Cancer subjects from uncontrolled clinical studies were classified based on whether they had MF or a non-MF cancer (lymphoid cancers).

A separate integrated analysis was performed on MF subjects only, with MF subjects from uncontrolled studies being classified based on their pacritinib dose level (100 – 300 mg QD, 400 mg QD, and 500-600 mg QD). Data from pacritinib-treated MF subjects from the controlled, phase 3, PERSIST-1 study are presented along with integrated data from all MF subjects (from both uncontrolled and controlled studies) who were treated at the target pacritinib dose (400 mg QD) and all MF subjects treated with any dose of pacritinib.

Patient exposure

A total of 699 subjects have received pacritinib in 14 clinical studies (including 82 subjects in PERSIST-1 who crossed over to pacritinib from BAT before the cut-off date). Three of these studies were conducted in myelofibrosis patients. The number of subjects exposed to pacritinib by clinical study category is summarized in Table CS-01. All subjects were dosed orally once daily.

Table CS-01. Number of Subjects and Subjects Exposed to Study Drug (All Studies)

Study Type	Number of Studies	Pacritinib Dosage	Number of Subjects Treated with Pacritinib (Safety Population)
Clinical pharmacology/pharmacokinetics	9	80-400 mg QD	206
Uncontrolled clinical studies in cancer subjects			
MF subjects only	2	100-600 mg QD	122
Advanced lymphoid malignancies only	2	100-600 mg QD	69
Controlled study in MF, PERSIST-1	1		
Subjects assigned to pacritinib arm		400 mg QD	220
Subjects on BAT who crossed-over to pacritinib[a]		400 mg QD	82
Total across all studies	14	100-600 mg QD	699

BAT, best available therapy; MF, myelofibrosis; QD, once daily

[a] In PERSIST-1, 85 subjects crossed over to pacritinib; 3 subjects crossed over to pacritinib after data cut-off (2015 JAN 17) and exposure data are not available for these 3 subjects in the locked database, hence they are not included.

Pacritinib was dosed at between 80 mg to 600 mg QD by oral administration in all completed studies.

Exposure in Healthy Volunteer/Non-cancer Studies: A total of 206 subjects make up the safety database for healthy volunteers and subjects from non-cancer studies (hepatic and renal impairment studies): 154 healthy volunteers and 52 renal or hepatic impaired subjects were treated with at least one dose of pacritinib. A maximum of three doses was administered to each subject with doses ranging

from 80 mg to 400 mg. Approximately 51.9% of subjects from healthy volunteer/non-cancer studies received one dose of pacritinib, 36.4% received two doses and 11.7% received three doses.

Exposure in Myelofibrosis Subjects: The mean duration of time that MF subjects in the uncontrolled studies received the doses of 100-300 mg pacritinib was longer (15.9 months, standard deviation [SD] = 11.8 months) than subjects who received either 400 mg or 500-600 mg pacritinib (11.2 [SD = 7.8] and 11.9 [SD= 9.7] months, respectively). The median duration of treatment among the 3 groups of pacritinib treated MF subjects were 10.6, 11.0, and 10.2 months for 100-300 mg, 400 mg, and 500-600 mg pacritinib, respectively.

In the controlled study, PERSIST-1, the mean duration of study drug exposure for subjects in the pacritinib treatment arm was 9.4 months (SD = 5.3 months), with a median of 8.4 months, compared to a mean duration of 5.5 months (SD = 3.6) and median of 5.0 months for subjects in the BAT treatment arm who subsequently crossed over to pacritinib by the time of data cut-off.

Overall, for MF subjects (from controlled and uncontrolled studies) treated at 400 mg pacritinib (N = 375), the mean duration of treatment was 8.9 months (SD = 5.9).

Approximately, 62.7 % (235/375) of these subjects treated with 400 mg pacritinib remained on treatment for ≥ 6 months, 28.0% (105/375) remained on treatment for ≥ 12 months and 9.6% (36/375) were still on treatment at 18 months.

At the time of database cut-off, the mean duration of treatment exposure for all MF subjects on any dose of pacritinib (N = 424), was 9.5 months (SD = 6.9). This includes subjects from the two uncontrolled clinical studies that were terminated early by the sponsor (SB1518-2007-001 and SB1518-2008-003). Approximately, 63.2 % (268/424) of these MF subjects treated with any dose of pacritinib remained on treatment for ≥ 6 months, 30.2% (128/424) remained on treatment for ≥ 12 months, and 13.0% (55/424) were still receiving pacritinib treatment at 18 months.

Table CS-02: Summary of Exposure (Safety Population, All Subjects Treated with Pacritinib)

	Uncontrolled Subject Studies				**Controlled PERSIST-1 Study**			
	MF Subjects							
	100-300 mg PAC QD N=27	**400 mg PAC QD N=73**	**500-600 mg PAC QD N=22**	**Non-MF Cancer Subjects N = 69**	**MF Subjects on 400 mg PAC N = 220**	**BAT Subjects on PAC after x-over[a] N=82**	**Overall MF Subjects on 400 mg PAC (incl. BAT x-over) N = 375**	**All MF Subjects on Pacritinib (incl. BAT x-over) N = 424**
Duration of Txt (mos)[b]								
Mean (SD)	15.9 (11.8)	11.2 (7.8)	11.9 (9.7)	3.7 (3.9)	9.4 (5.3)	5.5 (3.6)	8.9 (5.9)	9.5 (6.9)
Median (IQR)	10.6 (5.7, 25.4)	11.0 (3.7, 18.7)	10.2 (2.7, 21.3)	2.7 (1.0, 5.5)	8.4 (5.6, 13.7)	5.0 (2.6, 8.3)	8.2 (4.5, 13.2)	8.3 (4.5, 13.9)
Min, Max	0.7, 39.8	0.1, 31.5	1.2, 29.3	0.0, 20.7	0.1, 22.2	0.1, 14.9	0.1, 31.5	0.1, 39.8
Months Exposed n (%)								
≥ 1 Day	27 (100.0)	73 (100.0)	22 (100.0)	69 (100.0)	220 (100.0)	82 (100.0)	375 (100.0)	424 (100.0)
≥ 2 Months	25 (92.6)	62 (84.9)	17 (77.3)	37 (53.6)	203 (92.3)	67 (81.7)	332 (88.2)	374 (88.2)
≥ 6 Months	20 (74.1)	46 (63.0)	13 (59.1)	12 (17.4)	156 (70.9)	33 (40.2)	235 (62.7)	268 (63.2)

Table CS-02: Summary of Exposure (Safety Population, All Subjects Treated with Pacritinib)

	Uncontrolled Subject Studies				Controlled PERSIST-1 Study			
	MF Subjects							
	100-300 mg PAC QD N=27	400 mg PAC QD N=73	500-600 mg PAC QD N=22	Non-MF Cancer Subjects N = 69	MF Subjects on 400 mg PAC N = 220	BAT Subjects on PAC after x-over[a] N=82	Overall MF Subjects on 400 mg PAC (incl. BAT x-over) N = 375	All MF Subjects on Pacritinib (incl. BAT x-over) N = 424
≥ 12 Months	13 (48.1)	33 (45.2)	10 (45.5)	3 (4.3)	69 (31.4)	3 (3.7)	105 (28.0)	128 (30.2)
≥ 18 Months	11 (40.7)	20 (27.4)	8 (36.4)	1 (1.4)	16 (7.3)	0	36 (9.6)	55 (13.0)
≥ 24 Months	7 (25.9)	3 (4.1)	3 (13.6)	0	0	0	3 (0.8)	13 (3.1)
≥ 30 Months	5 (18.5)	1 (1.4)	0	0	0	0	1 (0.3)	6 (1.4)
≥ 36 Months	2 (7.4)	0	0	0	0	0	0	2 (0.5)
≥ 42 Months	0	0	0	0	0	0	0	0
Actual Dose Intensityc (mg/day)								
Mean (SD)	219.3 (79.2)	357.0 (64.9)	446.1 (86.2)	361.6 (120.1)	383.6 (39.6)	338.6 (60.4)	368.6 (53.6)	363.1 (70.7)
Median (IQR)	208.3 (150.0, 289.5)	388.3 (322.8, 400.0)	442.8 (376.4, 498.0)	392.7 (296.0, 400.0)	400.0 (393.4, 400.0)	353.8 (311.1, 391.7)	400.0 (356.7, 400.0)	398.8 (332.7, 400.0)
Min, Max	94.7, 386.9	87.5, 400.0	302.5, 600.0	92.0, 600.0	193.7, 400.0	166.1, 400.0	87.5, 400.0	87.5, 600.0

BAT, best available therapy; IQR, interquartile range; mos, months; MF, myelofibrosis; PAC, pacritinib; QD, once per day; txt, treatment; x-over, crossover.

[b] 85 subjects crossed over to PAC; 3 of these subjects crossed over to PAC after data cut-off (2015 JAN 17) the safety data after crossover were excluded from the summary

Duration = (date of last dose-date of first dose) + 1)/30.3475

Actual dose intensity (mg/day) = cumulative dose (mg)/duration of treatment (days)

Source: Refer to 5.3.5.3 ISS, Table 2.1.1 and Table 2.1.3

Extent of Exposure in Other Cancer Studies: 69 subjects with non-MF cancers were treated with pacritinib in phase 1/2 studies. The mean duration of treatment for these subjects was 3.7 months (SD = 3.9) compared to 9.5 months (SD = 6.9) for all MF subjects treated with pacritinib.

Adverse events

A summary of TEAEs by SOC and preferred term (by ≥ 10% incidence in preferred term) noted in the studies in myelofibrosis and non-MF cancer (lymphoid cancers) is provided in Table CS-03.

In the uncontrolled studies, nearly every subject experienced at least one TEAE.

Dose-related increases in TEAEs by SOC were apparent for the SOCs of gastrointestinal disorders and general disorders and administration site conditions. For gastrointestinal disorders, this dose-related increase can be attributed to TEAEs from the preferred terms of diarrhoea, nausea and vomiting. For all MF subjects treated with any dose of pacritinib, the TEAEs with the highest incidence rates were attributed to the SOCs of gastrointestinal disorders (79% [270/342]) blood and lymphatic disorders (44% [151/342]).

Table CS-03. Summary of Most Common Treatment-Emergent Adverse Events (≥10% Incidence in Any Subject Group) by System Organ Class, Preferred Term and Subject Population in Safety Population, Cancer Subject Studies

	Uncontrolled Studies		Controlled Study (PAC325)		
	MF Subjects (N=122) [n (%)]	Non-MF Cancer Subjects (N=69) [n (%)]	MF Subjects on Pacritinib (N=220) [n (%)]	MF Subjects on BAT (N=106) [n (%)]	All MF Subjects on Pacritinib (N=342) [n (%)]
Number of Subjects with >=1 TEAE	121 (99.2)	66 (95.7)	197 (89.5)	81 (76.4)	318 (93.0)
Blood and lymphatic system disorders	57 (46.7)	29 (42.0)	94 (40.9)	36 (34.0)	151 (44.2)
Anaemia	32 (26.2)	13 (18.8)	60 (27.3)	22 (20.8)	92 (26.9)
Thrombocytopenia	19 (15.6)	16 (23.2)	47 (21.4)	15 (14.2)	66 (19.3)
Neutropenia	4 (3.3)	10 (14.5)	9 (4.1)	2 (1.9)	13 (3.8)
Gastrointestinal disorders	114 (93.4)	53 (76.8)	156 (70.9)	42 (39.6)	270 (78.9)
Diarrhoea	98 (80.3)	41 (59.4)	129 (58.6)	14 (13.2)	227 (66.4)
Nausea	62 (50.8)	29 (42.0)	65 (29.5)	7 (6.6)	127 (37.1)
Vomiting	43 (35.2)	13 (18.8)	43 (19.5)	6 (5.7)	86 (25.1)
Abdominal pain	28 (23.0)	12 (17.4)	26 (11.8)	11 (10.4)	54 (15.8)
Constipation	24 (19.7)	22 (31.9)	20 (9.1)	7 (6.6)	44 (12.9)
Abdominal distension	17 (13.9)	3 (4.3)	7 (3.2)	2 (1.9)	24 (7.0)
General disorders and administration site conditions	89 (73.0)	39 (56.5)	79 (35.9)	41 (38.7)	168 (49.1)
Fatigue	53 (43.4)	19 (27.5)	27 (12.3)	10 (9.4)	80 (23.4)
Oedema peripheral	29 (23.8)	9 (13.0)	22 (10.0)	16 (15.1)	51 (14.9)
Pyrexia	18 (14.8)	15 (21.7)	18 (8.2)	11 (10.4)	36 (10.5)
Asthenia	16 (13.1)	4 (5.8)	13 (5.9)	7 (6.6)	29 (8.5)
Chills	7 (5.7)	8 (11.6)	4 (1.8)	1 (0.9)	11 (3.2)
Infections and infestations	62 (50.8)	25 (36.2)	68 (30.9)	32 (30.2)	130 (38.0)
Upper respiratory tract infection	13 (10.7)	6 (8.7)	14 (6.4)	7 (6.6)	27 (7.9)
Pneumonia	11 (9.0)	7 (10.1)	14 (6.4)	1 (0.9)	25 (7.3)
Investigations	56 (45.9)	13 (18.8)	41 (18.6)	11 (10.4)	97 (28.4)
Cardiac murmur	14 (11.5)	0	2 (0.9)	1 (0.9)	16 (4.7)

Table CS-03. Summary of Most Common Treatment-Emergent Adverse Events (≥10% Incidence in Any Subject Group) by System Organ Class, Preferred Term and Subject Population in Safety Population, Cancer Subject Studies

	Uncontrolled Studies		Controlled Study (PAC325)		
	MF Subjects (N=122) [n (%)]	Non-MF Cancer Subjects (N=69) [n (%)]	MF Subjects on Pacritinib (N=220) [n (%)]	MF Subjects on BAT (N=106) [n (%)]	All MF Subjects on Pacritinib (N=342) [n (%)]
Metabolism and nutrition disorders	65 (53.3)	22 (31.9)	43 (19.5)	17 (16.0)	108 (31.6)
Decreased appetite	21 (17.2)	12 (17.4)	14 (6.4)	3 (2.8)	35 (10.2)
Hyperuricaemia	13 (10.7)	3 (4.3)	7 (3.2)	1 (0.9)	20 (5.8)
Musculoskeletal and connective tissue disorders	69 (56.6)	16 (23.2)	49 (22.3)	27 (25.5)	118 (34.5)
Pain in extremity	18 (14.8)	1 (1.4)	11 (5.0)	9 (8.5)	29 (8.5)
Back pain	15 (12.3)	3 (4.3)	9 (4.1)	5 (4.7)	24 (7.0)
Bone pain	16 (13.1)	1 (1.4)	6 (2.7)	3 (2.8)	22 (6.4)
Nervous system disorders	49 (40.2)	20 (29.0)	48 (21.8)	20 (18.9)	97 (28.4)
Headache	14 (11.5)	8 (11.6)	12 (5.5)	2 (1.9)	26 (7.6)
Dizziness	17 (13.9)	7 (10.1)	5 (2.3)	3 (2.8)	22 (6.4)
Psychiatric disorders	33 (27.0)	11 (15.9)	16 (7.3)	6 (5.7)	49 (14.3)
Insomnia	20 (16.4)	3 (4.3)	9 (4.1)	3 (2.8)	29 (8.5)
Respiratory, thoracic and mediastinal disorders	57 (46.7)	32 (46.4)	60 (27.3)	32 (30.2)	117 (34.2)
Dyspnoea	19 (15.6)	9 (13.0)	13 (5.9)	10 (9.4)	32 (9.4)
Epistaxis	15 (12.3)	0	15 (6.8)	10 (9.4)	30 (8.8)
Cough	14 (11.5)	11 (15.9)	12 (5.5)	8 (7.5)	26 (7.6)
Skin and subcutaneous tissue disorders	75 (61.5)	18 (26.1)	48 (21.8)	21 (19.8)	123 (36.0)
Pruritus	24 (19.7)	3 (4.3)	12 (5.5)	4 (3.8)	36 (10.5)
Rash	14 (11.5)	4 (5.8)	10 (4.5)	6 (5.7)	24 (7.0)
Night sweats	16 (13.1)	2 (2.9)	2 (0.9)	2 (1.9)	18 (5.3)

A summary of TEAEs that occurred with a frequency over 5% in any subject group is presented (in descending order) by preferred term in CS-04, for all MF subjects. All 122 MF subjects from the uncontrolled studies with pacritinib have been combined. Diarrhoea, nausea, anaemia and vomiting

were the most common TEAEs observed across all studies in MF subjects. Many TEAEs occurred with similar frequencies between the uncontrolled and controlled studies, such as anaemia (26.2% and 27.3% in uncontrolled and controlled studies, respectively) and thrombocytopenia (15.6% and 21.4% in uncontrolled and controlled studies, respectively). However, some larger differences in frequency of TEAEs were noted, such as diarrhoea (80.3% and 58.6% in uncontrolled and controlled studies, respectively), nausea (50.8% and 29.5% in uncontrolled and controlled studies, respectively), fatigue (43.4% and 12.3% in uncontrolled and controlled studies, respectively) and peripheral oedema (23.8% and 10.0% in uncontrolled and controlled studies, respectively).

Table CS-04: Summary of Treatment-Emergent Adverse Events (≥ 5% Incidence in any Subject Group) in Myelofibrosis Subjects by Preferred Term (Safety Population)

	Uncontrolled Studies	Controlled PERSIST-1	All MF Subjects on PAC[a]
Preferred Term	100-600 mg PAC N=122 n (%)	MF Subjects on PAC N = 220 n (%)	N = 342 n (%)
Number of Subjects with ≥1 TEAE	121 (99.2)	197 (89.5)	318 (93.0)
Diarrhoea	98 (80.3)	129 (58.6)	227 (66.4)
Nausea	62 (50.8)	65 (29.5)	127 (37.1)
Anaemia	32 (26.2)	60 (27.3)	92 (26.9)
Vomiting	43 (35.2)	43 (19.5)	86 (25.1)
Fatigue	53 (43.4)	27 (12.3)	80 (23.4)
Thrombocytopenia	19 (15.6)	47 (21.4)	66 (19.3)
Abdominal pain	28 (23.0)	26 (11.8)	54 (15.8)
Oedema peripheral	29 (23.8)	22 (10.0)	51 (14.9)
Constipation	24 (19.7)	20 (9.1)	44 (12.9)
Pyrexia	18 (14.8)	18 (8.2)	36 (10.5)
Decreased appetite	21 (17.2)	14 (6.4)	35 (10.2)
Pruritus	24 (19.7)	12 (5.5)	36 (10.5)
Dyspnoea	19 (15.6)	13 (5.9)	32 (9.4)
Epistaxis	15 (12.3)	15 (6.8)	30 (8.8)
Asthenia	16 (13.1)	13 (5.9)	29 (8.5)
Insomnia	20 (16.4)	9 (4.1)	29 (8.5)
Pain in extremity	18 (14.8)	11 (5.0)	29 (8.5)
Upper respiratory tract infection	13 (10.7)	14 (6.4)	27 (7.9)
Cough	14 (11.5)	12 (5.5)	26 (7.6)
Headache	14 (11.5)	12 (5.5)	26 (7.6)
Pneumonia	11 (9.0)	14 (6.4)	25 (7.3)
Abdominal distension	17 (13.9)	7 (3.2)	24 (7.0)
Back pain	15 (12.3)	9 (4.1)	24 (7.0)
Rash	14 (11.5)	10 (4.5)	24 (7.0)
Bone pain	16 (13.1)	6 (2.7)	22 (6.4)
Dizziness	17 (13.9)	5 (2.3)	22 (6.4)
Hyperuricaemia	13 (10.7)	7 (3.2)	20 (5.8)
Arthralgia	10 (8.2)	9 (4.1)	19 (5.6)
Urinary tract infection	11 (9.0)	8 (3.6)	19 (5.6)

Table CS-04: Summary of Treatment-Emergent Adverse Events (≥ 5% Incidence in any Subject Group) in Myelofibrosis Subjects by Preferred Term (Safety Population)

Preferred Term	Uncontrolled Studies 100-600 mg PAC N=122 n (%)	Controlled PERSIST-1 MF Subjects on PAC N = 220 n (%)	All MF Subjects on PAC[a] N = 342 n (%)
Night sweats	16 (13.1)	2 (0.9)	18 (5.3)
Weight decreased	12 (9.8)	5 (2.3)	17 (5.0)
Cardiac murmur	14 (11.5)	2 (0.9)	16 (4.7)
Contusion	5 (4.1)	11 (5.0)	16 (4.7)
Muscle spasms	8 (6.6)	9 (4.1)	17 (5.0)
Abdominal pain upper	8 (6.6)	6 (2.7)	14 (4.1)
Dehydration	11 (9.0)	3 (1.4)	14 (4.1)
Dysgeusia	9 (7.4)	5 (2.3)	14 (4.1)
Dyspnoea exertional	9 (7.4)	5 (2.3)	14 (4.1)
Flatulence	11 (9.0)	4 (1.8)	15 (4.4)
Hyperkalaemia	9 (7.4)	5 (2.3)	14 (4.1)
Alanine aminotransferase increased	8 (6.6)	5 (2.3)	13 (3.8)
Electrocardiogram QT prolonged	1 (0.8)	12 (5.5)	13 (3.8)
Chills	7 (5.7)	4 (1.8)	11 (3.2)
Pleural effusion	7 (5.7)	5 (2.3)	12 (3.5)
Aspartate aminotransferase increased	7 (5.7)	3 (1.4)	10 (2.9)
Chest pain	8 (6.6)	2 (0.9)	10 (2.9)
Hypokalaemia	9 (7.4)	1 (0.5)	10 (2.9)
Cellulitis	7 (5.7)	2 (0.9)	9 (2.6)
Ecchymosis	7 (5.7)	1 (0.5)	8 (2.3)
Hyponatraemia	7 (5.7)	1 (0.5)	8 (2.3)
Stomatitis	7 (5.7)	1 (0.5)	8 (2.3)
Depression	7 (5.7)	0	7 (2.0)
Hypomagnesaemia	7 (5.7)	0	7 (2.0)

AE, adverse event; BAT, best available therapy; MF, myelofibrosis; PAC, pacritinib; TEAE, treatment-emergent adverse event

[c] 'All MF subjects on PAC' does not include any BAT subjects who crossed over to pacritinib.

Note: Subjects may have more than one AE per system organ class and preferred term. At each level (system organ class and preferred term), a subject is counted only once if he/she experienced one or more AE at that level. TEAEs are listed in this table if the preferred term was ≥ 5% in frequency in any subject group.

Myelofibrosis subjects from uncontrolled studies experienced grade 3/4 TEAEs at a frequency of 76.2% (93/122 subjects).

Subjects on the PERSIST-1 study had a frequency of grade 3/4 TEAEs at 61.4% (135/220 subjects) and all MF subjects treated at any dose of pacritinib experienced grade 3/4 TEAEs at a frequency of 66.7% (228/342 subjects).

The most **common grade 3/4 TEAEs** in all myelofibrosis patients (N = 342) were anaemia (21.1% [72/342]), thrombocytopenia (14.3% [49/324]), diarrhoea (8.5% [29/342]), and pneumonia (4.4% [15/342]).

Gender- Modest differences were seen in frequency between genders for a few TEAEs such as abdominal pain (18.4% for males and 11.8% for females) and pneumonia (10.2% for males and 2.9% for females). Apart from this no other gender-based differences were noted for the frequency of TEAEs in myelofibrosis subjects treated with any dose of pacritinib.

A comparison of the incidence of adverse events in the PERSIST is presented in the table CS-05 below. This provides a comparison of adverse events between the pacritinib and BAT treatment arms of the study.

Table CS-05: Incidence of Treatment-emergent Adverse Events by MedDRA System Organ Class (Safety Population)

MedDRA System Organ Class	Pacritinib N = 220 n (%)	BAT N = 106 n (%)
Subjects with ≥ 1 TEAE	197 (89.5)	81 (76.4)
Gastrointestinal disorders	156 (70.9)	42 (39.6)
Blood and lymphatic system disorders	94 (42.7)	36 (34.0)
General disorders and administration site conditions	79 (35.9)	41 (38.7)
Infections and infestations	68 (30.9)	32 (30.2)
Respiratory, thoracic, and mediastinal disorders	60 (27.3)	32 (30.2)
Musculoskeletal and connective tissue disorders	49 (22.3)	27 (25.5)
Nervous system disorders	48 (21.8)	20 (18.9)
Skin and subcutaneous tissue disorders	48 (21.8)	21 (19.8)
Metabolism and nutrition disorders	43 (19.5)	17 (16.0)
Investigations	41 (18.6)	11 (10.4)
Injury, poisoning, and procedural complications	33 (15.0)	12 (11.3)
Vascular disorders	29 (13.2)	15 (14.2)
Cardiac disorders	22 (10.0)	6 (5.7)
Renal and urinary disorders	17 (7.7)	6 (5.7)
Psychiatric disorders	16 (7.3)	6 (5.7)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	16 (7.3)	2 (1.9)
Eye disorders	9 (4.1)	6 (5.7)
Reproductive system and breast disorders	8 (3.6)	2 (1.9)
Ear and labyrinth disorders	5 (2.3)	1 (0.9)
Hepatobiliary disorders	5 (2.3)	4 (3.8)
Immune system disorders	2 (0.9)	0
Endocrine disorders	2 (0.9)	1 (0.9)
Congenital, familial, and genetic disorders	1 (0.5)	1 (0.9)
Surgical and medical procedures	1 (0.5)	0

BAT, best available therapy; MedDRA, medical dictionary for regulatory activities; TEAE, treatment emergent adverse event.

Serious adverse events and deaths

Serious Adverse Events

Healthy Volunteer/Non-cancer Studies**:** None of the 154 healthy subjects or 52 subjects with renal/hepatic impairment (non-cancer subjects) enrolled in the nine healthy volunteer/non-cancer subject studies experienced a treatment-emergent SAE.

Serious Adverse Events in Myelofibrosis Studies:

The following discussion of SAEs includes the 82 PERSIST-1 BAT subjects who crossed over from BAT to pacritinib at some point during the study.

Treatment-emergent SAEs were reported in 173/424 (40.8%) subjects with MF exposed to any dose of pacritinib; of the 375 MF subjects who received pacritinib 400 mg QD, 154 (41.1%) experienced at least one treatment-emergent SAE.

The most commonly reported treatment-emergent SAEs (at least two subjects in all MF subjects combined or all non-MF cancer subjects) are summarized for the integrated safety population by SOC and preferred term in table CS-06. In the MF studies, anaemia (5.7%) was the most commonly reported SAE in subjects treated with pacritinib, followed by pneumonia (3.1%), pyrexia (2.4%), cardiac failure (1.9%), cardiac failure congestive (1.7%), diarrhoea (1.7%), and subdural hematoma (1.7%).

Table CS-06: Treatment-Emergent Serious Adverse Events Reported in at Least Two MF or non-MF Cancer Subjects Overall (Safety Population, Cancer Studies)

System Organ Class Preferred Term	Uncontrolled Studies		Controlled PERSIST-1	Overall MF Subjects on 400 mg PAC[a] N = 375 n (%)	All MF Subjects on PAC[a] N = 424 n (%)
	MF Subjects N = 122 n (%)	Non-MF Cancer Subjects N = 69 n (%)	MF Subjects on PAC N = 220 n (%)		
Number of Subjects with ≥ 1 Treatment-Emergent SAE	48 (39.3)	17 (24.6)	92 (41.8)	154 (41.1)	173 (40.8)
Blood and lymphatic system disorders	9 (7.4)	0	22 (10.0)	32 (8.5)	36 (8.5)
Anaemia	5 (4.1)	0	15 (6.8)	22 (5.9)	24 (5.7)
Thrombocytopenia	1 (0.8)	0	3 (1.4)	4 (1.1)	4 (0.9)
Febrile neutropenia	1 (0.8)	0	2 (0.9)	3 (0.8)	3 (0.7)
Neutropenia	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.5)
Splenic infarction	2 (1.6)	0	0	1 (0.3)	2 (0.5)
Cardiac disorders	10 (8.2)	3 (4.3)	15 (6.8)	29 (7.7)	30 (7.1)
Cardiac failure	0	0	7 (3.2)	8 (2.1)	8 (1.9)
Cardiac failure congestive	4 (3.3)	1 (1.4)	3 (1.4)	8 (2.1)	8 (1.9)
Atrial fibrillation	2 (1.6)	0	3 (1.4)	6 (1.6)	6 (1.4)
Myocardial infarction	2 (1.6)	0	0	3 (0.8)	3 (0.7)
Gastrointestinal disorders	7 (5.7)	3 (4.3)	13 (5.9)	24 (6.4)	27 (6.4)
Diarrhoea	2 (1.6)	0	4 (1.8)	6 (1.6)	7 (1.7)
Abdominal pain	2 (1.6)	2 (2.9)	3 (1.4)	4 (1.1)	5 (1.2)
Gastrointestinal haemorrhage	3 (2.5)	0	1 (0.5)	3 (0.8)	4 (0.9)
Diverticular perforation	0	0	2 (0.9)	2 (0.5)	2 (0.5)
Vomiting	0	0	2 (0.9)	2 (0.5)	2 (0.5)
General disorders and administration site conditions	6 (4.9)	3 (4.3)	13 (5.9)	21 (5.6)	23 (5.4)
Pyrexia	2 (1.6)	1 (1.4)	7 (3.2)	9 (2.4)	10 (2.4)
Disease progression	0	0	3 (1.4)	4 (1.1)	4 (0.9)
General physical health deterioration	0	0	2 (0.9)	3 (0.8)	3 (0.7)
Chest pain	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Multi-organ failure	0	1 (1.4)	2 (0.9)	2 (0.5)	2 (0.5)
Oedema peripheral	1 (0.8)	0	1 (0.5)	3 (0.8)	3 (0.7)
Hepatobiliary disorders	1 (0.8)	1 (1.4)	2 (0.9)	5 (1.3)	5 (1.2)
Cholangitis	0	0	0	2 (0.5)	2 (0.5)
Infections and infestations	21 (17.2)	7 (10.1)	23 (10.5)	41 (10.9)	51 (12.0)
Pneumonia	5 (4.1)	3 (4.3)	7 (3.2)	10 (2.7)	13 (3.1)
Sepsis	2 (1.6)	2 (2.9)	1 (0.5)	5 (1.3)	6 (1.4)
Cellulitis	2 (1.6)	0	1 (0.5)	3 (0.8)	4 (0.9)
Lobar pneumonia	2 (1.6)	0	2 (0.9)	3 (0.8)	4 (0.9)
Bronchitis	1 (0.8)	0	1 (0.5)	2 (0.5)	2 (0.5)
Septic shock	2 (1.6)	0	0	1 (0.3)	2 (0.5)
Urinary tract infection	1 (0.8)	0	1 (0.5)	2 (0.5)	2 (0.5)

Table CS-06: Treatment-Emergent Serious Adverse Events Reported in at Least Two MF or non-MF Cancer Subjects Overall (Safety Population, Cancer Studies)

System Organ Class Preferred Term	Uncontrolled Studies		Controlled PERSIST-1	Overall MF Subjects on 400 mg PAC[a] N = 375 n (%)	All MF Subjects on PAC[a] N = 424 n (%)
	MF Subjects N = 122 n (%)	Non-MF Cancer Subjects N = 69 n (%)	MF Subjects on PAC N = 220 n (%)		
Injury, poisoning and procedural complications	6 (4.9)	1 (1.4)	11 (5.0)	21 (5.6)	23 (5.4)
Subdural haematoma	3 (2.5)	1 (1.4)	2 (0.9)	6 (1.6)	7 (1.7)
Fall	0	0	1 (0.5)	2 (0.5)	2 (0.5)
Post procedural haemorrhage	0	0	2 (0.9)	2 (0.5)	2 (0.5)
Metabolism and nutrition disorders	6 (4.9)	1 (1.4)	4 (1.8)	10 (2.7)	11 (2.6)
Dehydration	3 (2.5)	0	1 (0.5)	3 (0.8)	4 (0.9)
Hyponatraemia	1 (0.8)	0	1 (0.5)	3 (0.8)	3 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (4.1)	1 (1.4)	13 (5.9)	17 (4.5)	20 (4.7)
Basal cell carcinoma	0	0	4 (1.8)	4 (1.1)	4 (0.9)
Squamous cell carcinoma	0	0	4 (1.8)	4 (1.1)	4 (0.9)
Acute myeloid leukaemia	2 (1.6)	1 (1.4)	0	0	2 (0.5)
Squamous cell carcinoma of skin	0	0	2 (0.9)	2 (0.5)	2 (0.5)
Nervous system disorders	4 (3.3)	3 (4.3)	4 (1.8)	7 (1.9)	10 (2.4)
Cerebrovascular accident	1 (0.8)	2 (2.9)	1 (0.5)	1 (0.3)	2 (0.5)
Haemorrhage intracranial	1 (0.8)	0	0	1 (0.3)	2 (0.5)
Syncope	1 (0.8)	0	1 (0.5)	1 (0.3)	2 (0.5)
Renal and urinary disorders	2 (1.6)	1 (1.4)	7 (3.2)	7 (1.9)	9 (2.1)
Renal failure acute	1 (0.8)	1 (1.4)	2 (0.9)	2 (0.5)	3 (0.7)
Respiratory, thoracic and mediastinal disorders	6 (4.9)	4 (5.8)	15 (6.8)	23 (6.1)	25 (5.9)
Epistaxis	1 (0.8)	0	4 (1.8)	5 (1.3)	5 (1.2)
Pleural effusion	2 (1.6)	1 (1.4)	2 (0.9)	3 (0.8)	5 (1.2)
Dyspnoea	0	0	2 (0.9)	3 (0.8)	3 (0.7)
Pulmonary hypertension	2 (1.6)	0	0	2 (0.5)	2 (0.5)
Pulmonary embolism	1 (0.8)	2 (2.9)	0	1 (0.3)	1 (0.2)
Pulmonary oedema	0	0	2 (0.9)	2 (0.5)	2 (0.5)
Vascular disorders	3 (2.5)	0	7 (3.2)	12 (3.2)	13 (3.1)
Haematoma	0	0	2 (0.9)	3 (0.8)	3 (0.7)
Haemorrhage	1 (0.8)	0	1 (0.5)	3 (0.8)	3 (0.7)
Hypertensive crisis	0	0	2 (0.9)	2 (0.5)	2 (0.5)

AE, adverse event; BAT, best available therapy; MF, myelofibrosis; PAC, pacritinib; SAE, serious adverse event

[d] Both 'Overall MF subjects on 400 mg PAC', and 'All MF subjects on PAC' include the 82 BAT subjects who crossed over to pacritinib.

Note: Subjects may have more than one AE per system organ class and preferred term. At each level (system organ class and preferred term), a subject is counted only once if he/she experienced one or more AE at that level.

Source: Refer to 5.3.5.3 ISS, Table 4.3.1.1 and Table 4.3.1.3

A comparison of the serious adverse events between the 2 arms of the PERSIST 1 trial is summarised in the table below.

Table CS-07: Serious Adverse Events Occurring in at Least 1% of Subjects in Either Treatment Group (Safety Population)

System Organ Class Preferred Term	Pacritinib N = 220 n (%)	BAT N = 106 n (%)
Subjects with ≥ 1 treatment-emergent SAE	94 (42.7)	27 (25.5)
Blood and lymphatic system disorders	22 (10.0)	6 (5.7)
Anaemia	15 (6.8)	5 (4.7)
Thrombocytopenia	3 (1.4)	0
Cardiac disorders	15 (6.8)	2 (1.9)
Cardiac failure	7 (3.2)	1 (0.9)
Cardiac Failure Congestive	3 (1.4)	0
Atrial fibrillation	3 (1.4)	0
Gastrointestinal disorders	13 (5.9)	2 (1.9)
Diarrhoea	4 (1.8)	1 (0.9)
Abdominal pain	3 (1.4)	0
General disorders and administration site conditions	13 (5.9)	5 (4.7)
Pyrexia	7 (3.2)	1 (0.9)
Disease progression	3 (1.4)	1 (0.9)
Infections and infestations	23 (10.5)	6 (5.7)
Pneumonia	7 (3.2)	1 (0.9)
Sepsis	1 (0.5)	2 (1.9)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	13 (5.9)	2 (1.9)
Squamous cell carcinoma	4 (1.8)	1 (0.9)
Basal cell carcinoma	4 (1.8)	0
Respiratory, thoracic and mediastinal disorders	15 (6.8)	7 (6.6)
Dyspnoea	2 (0.9)	2 (1.9)
Epistaxis	4 (1.8)	0

BAT, best available therapy; SAE, serious adverse event.

Deaths

Healthy Volunteer/Non-cancer Studies: There were no deaths reported in the 154 healthy subjects or 52 subjects with renal/hepatic impairment (non-cancer subjects) enrolled in the nine healthy volunteer/non-cancer subject studies.

Treatment-Emergent Serious Adverse Events Leading to Death in Subjects Across Phase 1/2 and 3 Studies (Safety Population):

A summary of TEAEs treatment leading to death in PERSIST-1 subjects, including 82 BAT subjects who crossed over to pacritinib (safety population) is provided in table CS-08. Overall, deaths were attributed to TEAEs in 33/424 (7.8%) MF subjects treated with pacritinib. Deaths were attributed to TEAEs related to study medication in 2/424 (0.5%) subjects. The rates of fatal TEAEs overall and related to pacritinib were similar in MF subjects in the uncontrolled studies (9% and 0.8%, respectively).

Table CS-08: Summary of TEAE's Leading to Death in Subjects, Including BAT Subjects Who Crossed Over to Pacritinib (Safety Population)

	Uncontrolled Studies		Controlled Study (PAC325)			
	MF Subjects (N=122) [n (%)]	Non-MF Cancer Subjects (N=69) [n (%)]	MF Subjects on Pacritinib (N=220) [n (%)]	MF Subjects on BAT (N=106) [n (%)]	BAT Subjects on Pacritinib after Crossover [1] (N=82) [n (%)]	All MF Subjects on Pacritinib (N=424) [n (%)]
Number of Subjects with ≥ 1 TEAE leading to death	11 (9.0)	6 (8.7)	14 (6.4)	3 (2.8)	8 (9.8)	33 (7.8)
Number of Subjects with ≥ 1 related TEAE leading to death	1 (0.8)	0	1 (0.5)	0	--	2 (0.5)

BAT = best available therapy; MF = myelofibrosis; PAC = pacritinib
Notes: [1] 3 subjects crossed over to Pacritinib after data cut-off (2015-01-17), the safety data after crossover were excluded from the summary

Table CS-09 below summarizes fatal TEAEs by MedDRA SOC and preferred term and by pacritinib dose groups in MF subjects. The percentage of MF subjects with at least one fatal TEAE was higher in the 500 mg to 600 mg dose groups (18.2%) compared with the 100 mg to 300 mg (7.4%) and combined 400 mg (7.2%) dose groups. Thirty-three (7.8%) of the 424 MF subjects combined who received any dose of pacritinib and 27 (7.2%) of the 375 subjects combined who received the 400 mg dose experienced at least one TEAE with an outcome of death.

Table 1CS-09: Deaths By Dose Group (Safety Population, MF Subjects)

	Uncontrolled MF Studies			Controlled PERSIST-1		
System Organ Class Preferred Term	100 - 300 mg PAC N = 27 n (%)	400 mg PAC N = 73 n (%)	500 - 600 mg PAC N = 22 n (%)	400 mg PAC N = 220 n (%)	Overall MF Subjects on 400 mg PAC[a] N = 375 n (%)	All MF Subjects on PAC[a] N = 424 n (%)
Number of Subjects with ≥1 TEAE Leading to Death	2 (7.4)	5 (6.8)	4 (18.2)	14 (6.4)	27 (7.2)	33 (7.8)
Blood and lymphatic system disorders	0	0	0	0	1 (0.3)	1 (0.2)
Disseminated intravascular coagulation	0	0	0	0	1 (0.3)	1 (0.2)
Cardiac disorders	0	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Cardio-respiratory arrest	0	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Cardiac failure	0	0	0	0	0	0

Table 1CS-09: Deaths By Dose Group (Safety Population, MF Subjects)

System Organ Class Preferred Term	Uncontrolled MF Studies			Controlled PERSIST-1	Overall MF Subjects on 400 mg PAC[a]	All MF Subjects on PAC[a]
	100 - 300 mg PAC N = 27 n (%)	400 mg PAC N = 73 n (%)	500 - 600 mg PAC N = 22 n (%)	400 mg PAC N = 220 n (%)	N = 375 n (%)	N = 424 n (%)
General disorders and administration site conditions	0	0	1 (4.5)	5 (2.3)	7 (1.9)	8 (1.9)
Disease progression	0	0	0	3 (1.4)	4 (1.1)	4 (0.9)
Multi-organ failure	0	0	0	2 (0.9)	2 (0.5)	2 (0.5)
Sudden death	0	0	0	0	1 (0.3)	1 (0.2)
Asthenia	0	0	1 (4.5)	0	0	1 (0.2)
Infections and infestations	0	2 (2.7)	2 (9.1)	2 (0.9)	5 (1.3)	7 (1.7)
Pneumonia	0	0	0	2 (0.9)	3 (0.8)	3 (0.7)
Bacterial sepsis	0	1 (1.4)	0	0	1 (0.3)	1 (0.2)
Sepsis	0	1 (1.4)	0	0	1 (0.3)	1 (0.2)
Lobar pneumonia	0	0	1 (4.5)	0	0	1 (0.2)
Septic shock	0	0	1 (4.5)	0	0	1 (0.2)
Injury, poisoning and procedural complications	0	1 (1.4)	0	1 (0.5)	3 (0.8)	3 (0.7)
Splenic rupture	0	0	0	0	1 (0.3)	1 (0.2)
Subdural haematoma	0	1 (1.4)	0	0	1 (0.3)	1 (0.2)
Traumatic intracranial haemorrhage	0	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.7)	1 (1.4)	0	0	2 (0.5)	3 (0.7)
Acute leukaemia	0	0	0	0	1 (0.3)	1 (0.2)
Myelofibrosis	0	1 (1.4)	0	0	1 (0.3)	1 (0.2)
Acute myeloid leukaemia	1 (3.7)	0	0	0	0	1 (0.2)
Nervous system disorders	1 (3.7)	0	0	0	2 (0.5)	3 (0.7)
Haemorrhage intracranial	1 (3.7)	0	0	0	1 (0.3)	2 (0.5)
Status epilepticus	0	0	0	0	1 (0.3)	1 (0.2)

Table 1CS-09: Deaths By Dose Group (Safety Population, MF Subjects)

System Organ Class Preferred Term	Uncontrolled MF Studies			Controlled PERSIST-1	Overall MF Subjects on 400 mg PAC[a] N = 375 n (%)	All MF Subjects on PAC[a] N = 424 n (%)
	100 - 300 mg PAC N = 27 n (%)	400 mg PAC N = 73 n (%)	500 - 600 mg PAC N = 22 n (%)	400 mg PAC N = 220 n (%)		
Renal and urinary disorders	0	0	1 (4.5)	2 (0.9)	2 (0.5)	3 (0.7)
Renal failure acute	0	0	1 (4.5)	2 (0.9)	2 (0.5)	3 (0.7)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Hypoxia	0	0	0	1 (0.5)	1 (0.3)	1 (0.2)
Vascular disorders	0	1 (1.4)	0	2 (0.9)	3 (0.8)	3 (0.7)
Haemorrhage	0	1 (1.4)	0	1 (0.5)	2 (0.5)	2 (0.5)
Shock	0	0	0	1 (0.5)	1 (0.3)	1 (0.2)

AE, adverse event; BAT, best available therapy; MF, myelofibrosis; PAC, pacritinib; TEAE, treatment-emergent adverse event

[e] Both 'Overall MF subjects on 400 mg PAC', and 'All MF subjects on PAC' include the 82 BAT subjects who crossed over to pacritinib.

Note: Subjects may have more than one AE per system organ class and preferred term. At each level (system organ class and preferred term), a subject is counted only once if he/she experienced one or more AE at that level.

Deaths in the PERSIST-1 study:

The number of deaths in each arm of the study is summarized in the table below.

Table CS-10: Deaths (Safety Population)

Death	Pacritinib N = 220 n (%)	BAT N = 106 n (%)
All	34 (15.5)	15 (14.2)[a]
≤ 24 weeks	11 (5.0)	5 (4.7)
> 24 weeks	23 (10.5)	3 (2.8)

BAT, best available therapy.

[a] Seven of the 15 BAT subjects died following crossover to the PAC treatment arm.

Deaths attributed to an adverse event during the initial study phase (within 30 days after last dose of initial study medication or prior to crossover for BAT subjects who had crossover) are summarized by subject in the table below.

Table CS-11: Deaths Attributed to a Treatment-emergent Adverse Event During the Initial Study Phase

Subject	Age (yr)	Sex	Tx Duration (Days)	Days off Tx Prior to Death	Day of Death	AE Leading to Death	Relationship to Txt
Pacritinib arm							
64001-0200	81	F	17	2	18	Cardio-respiratory arrest	Unrelated
32002-0001	67	M	29	6	34	Hypoxia due to palliative sedation	Unrelated
61006-0210	78	M	46	3	48	Renal failure acute	Unrelated
61004-0027	84	F	107	10	116	Disease progression	Unrelated
31004-0134	64	M	135	12	146	Multi-organ failure	Unrelated
36001-0030	59	M	137	14	150	Renal failure acute	Unrelated
44007-0141	74	F	154	6	159	Traumatic intracranial haemorrhage	Unlikely
61003-0183	73	M	149	11	159	Pneumonia	Possible
36008-0239	61	M	164	2	165	Disease progression	Unrelated
31002-0076	71	M	253	25	277	Disease progression	Unlikely
36006-0215	68	M	171	17	187	Pneumonia	Unrelated
36007-0255	70	F	202	4	205	Shock	Unrelated
39001-0303	74	M	210	19	228	Haemorrhage	Unlikely
33005-0057	67	F	252	19	270	Multi-organ failure	Unlikely
BAT arm							
36005-0198	81	F	31	9	39	Cardiac failure	Unrelated
31003-0075	61	M	70	1	70	Small intestinal obstruction	Unrelated
61004-0161	75	F	88	6	93	Disease progression	Unrelated

AE, adverse event; BAT, best available therapy; F, female; M, male; Txt, treatment; yr, year.
Note: Deaths that occurred within 30 days after last dose of initial study medication or prior to crossover for BAT subjects who had crossover.

Deaths in Other Cancer Studies: The applicant states that deaths from any cause in the non-MF cancer studies are summarized ; however the ISS has not been provided.

The applicant states that death occurred in 13/69 (18.8%) non-MF cancer subjects who received pacritinib. Death was attributed to AEs in 8/69 (11.6%) subjects, to progressive disease in 4/69 (5.8%) subjects, and to unknown cause in 1/69 (1.4%) subject.

On-study deaths were reported in 4/69 (5.8%) non-MF cancer subjects. On-study deaths were attributed to AEs and to progressive disease in 2/69 (2.9%) subjects each. The fatal on-study TEAEs were cardio-respiratory arrest and acute renal failure. The incidence of on-study deaths was similar in the non-MF cancer studies (5.8%) and the MF studies (5.9%).

Nine of the 13 deaths in non-MF cancer subjects occurred more than 30 days after the last dose of study treatment. These deaths were attributed to AEs in 6/69 (8.7%) subjects, to progressive disease in 2/69 (2.9%) subjects, and unknown in 1/69 (1.4%) subject.

Laboratory findings

Mean changes from baseline for haematology parameters at week 24 and at final visit are summarized for MF subjects who received pacritinib in the table below.

Table CS-12: Summary of Haematology Values and from Baseline at Week 24 and Final Visit (Safety Population, All Cancer Subjects)

Parameter Visit Statistics	Uncontrolled Studies		Controlled PERSIST-1	Overall MF Subject on 400 mg PAC[a] N = 293	All MF Subjects on PAC[a] N = 342
	MF Subjects N = 122	Non-MF Cancer Subjects N = 69	MF Subjects on PAC N = 220		
Haemoglobin (g/L)					
Baseline					
n	122	68	220	293	342
Mean (SD)	99.8 (22.6)	121.8 (20.9)	107.8 (23.1)	106.0 (23.4)	105.0 (23.2)
Median (IQR)	95.5 (84.0, 113.0)	122.0 (105.0, 137.5)	105.5 (91.0, 121.5)	104.0 (89.0, 120.0)	102.0 (89.0, 120.0)
Min, Max	37, 181	82, 163	40, 173	37, 181	37, 181
Week 24					
Change from Baseline					
n	81	18	161	212	242
Mean (SD)	1.4 (18.7)	-9.2 (9.9)	-1.9 (15.1)	-1.3 (16.4)	-0.8 (16.5)
Median (IQR)	1.0 (-9.0, 12.0)	-8.0 (-13.0, -1.0)	-2.0 (-11.0, 6.0)	-1.5 (-11.0, 7.0)	-1.0 (-11.0, 8.0)
Min, Max	-44, 63	-30, 8	-51, 58	-51, 63	-51, 63

Table CS-12: Summary of Haematology Values and from Baseline at Week 24 and Final Visit (Safety Population, All Cancer Subjects)

Parameter Visit Statistics	Uncontrolled Studies		Controlled PERSIST-1	Overall MF Subject on 400 mg PAC[a]	All MF Subjects on PAC[a]
	MF Subjects N = 122	Non-MF Cancer Subjects N = 69	MF Subjects on PAC N = 220	N = 293	N = 342
Final Visit					
Change from Baseline					
n	121	67	218	290	339
Mean (SD)	-0.1 (17.3)	-7.1 (14.1)	-2.6 (16.0)	-1.5 (16.5)	-1.7 (16.5)
Median (IQR)	-2.0 (-11.0, 9.0)	-4.0 (-14.0, 1.0)	-1.5 (-12.0, 6.0)	-1.0 (-12.0, 7.0)	-2.0 (-12.0, 7.0)
Min, Max	-46, 49	-52, 26	-62, 63	-62, 63	-62, 63
Platelets ($\times 10^9$/L)					
Baseline					
n	122	68	213	286	335
Mean (SD)	213.6 (216.2)	178.6 (78.5)	236.9 (222.4)	223.9 (210.5)	228.4 (220.2)
Median (IQR)	138.0 (58.0, 277.0)	177.0 (136.0, 225.5)	166.0 (77.0, 343.0)	163.0 (69.0, 315.0)	161.0 (66.0, 318.0)
Min, Max	11, 1084	6, 420	8, 1066	8, 1066	8, 1084
Week 24					
Change from Baseline					
n	81	18	141	192	222
Mean (SD)	-27.4 (79.2)	-14.2 (52.8)	-24.1 (117.0)	-25.0 (106.7)	-25.3 (104.6)
Median (IQR)	-13.0 (-62.0, 1.0)	-17.0 (-44.0, 5.0)	-17.0 (-76.0, 20.0)	-16.0 (-75.5, 15.5)	-15.0 (-75.0, 13.0)
Min, Max	-226, 263	-94, 140	-488, 668	-488, 668	-488, 668
Final Visit					
Change from Baseline					
n	121	67	209	281	330
Mean (SD)	-46.8 (152.2)	-16.3 (71.6)	-22.8 (119.9)	-26.3 (117.7)	-31.6 (132.9)
Median (IQR)	-17.0 (-78.0, 2.0)	-6.0 (-45.0, 13.0)	-15.0 (-75.0, 20.0)	-15.0 (-73.0, 18.0)	-16.5 (-76.0, 13.0)
Min, Max	-675, 386	-310, 217	-466, 668	-466, 668	-675, 668
Leukocytes ($\times 10^9$/L)					
Baseline					
n	122	68	220	293	342
Mean (SD)	18.7 (23.5)	8.9 (12.0)	17.6 (20.8)	17.5 (20.2)	18.0 (21.7)
Median (IQR)	12.2 (5.8, 21.9)	5.9 (4.6, 8.3)	9.9 (6.1, 21.1)	10.2 (6.1, 21.3)	10.4 (6.0, 21.4)
Min, Max	0.5, 157.1	2.1, 92.5	1.2, 169.6	1.1, 169.6	0.5, 169.6
Week 24					
Change from Baseline					
n	81	18	160	211	241
Mean (SD)	-3.6 (17.6)	0.017 (1.4)	-1.6 (17.9)	-1.7 (16.2)	-2.3 (17.8)
Median (IQR)	-0.7 (-4.3, 1.4)	-0.1 (-0.9, 1.1)	-1.8 (-4.3 , 0.7)	-1.6 (-4.3, 0.9)	-1.5 (-4.3, 0.9)
Min, Max	-142.1, 17.4	-3.0, 2.2	-65.4, 165.0	-65.4, 165.0	-142.1, 165.0
Final Visit					

Table CS-12: Summary of Haematology Values and from Baseline at Week 24 and Final Visit (Safety Population, All Cancer Subjects)

Parameter Visit Statistics	Uncontrolled Studies		Controlled PERSIST-1	Overall MF Subject on 400 mg PAC[a] N = 293	All MF Subjects on PAC[a] N = 342
	MF Subjects N = 122	Non-MF Cancer Subjects N = 69	MF Subjects on PAC N = 220		
Change from Baseline					
n	121	67	218	290	339
Mean (SD)	-1.5 (16.4)	4.7 (21.2)	-0.04 (20.0)	-0.3 (18.6)	-0.6 (18.8)
Median (IQR)	-0.3 (-4.6, 3.5)	0.1 (-1.0, 2.0)	-0.8 (-4.4, 2.0)	-0.8 (-4.4, 2.0)	-0.6 (-4.5, 2.8)
Min, Max	-95.8, 55.6	-10.2, 164.5	-70.0, 165.0	-76.7, 165.0	-95.8, 165.0
Neutrophils ($\times 10^9$/L)					
Baseline					
n	122	68	201	274	323
Mean (SD)	12.0 (14.3)	4.4 (3.5)	12.2 (13.1)	11.7 (12.4)	12.1 (13.5)
Median (IQR)	7.9 (3.8 5.1)	3.5 (2.4, 5.1)	7.2 (4.3, 15.0)	7.3 (4.0, 14.6)	7.5 (3.9, 15.1)
Min, Max	0.1, 111.6	0.0, 24.0	0.2, 84.8	0.2, 84.8	0.1, 111.6

Table CS-12: Summary of Haematology Values and from Baseline at Week 24 and Final Visit (Safety Population, All Cancer Subjects)

Parameter Visit Statistics	Uncontrolled Studies		Controlled PERSIST-1	Overall MF Subject on 400 mg PAC[a] N = 293	All MF Subjects on PAC[a] N = 342
	MF Subjects N = 122	Non-MF Cancer Subjects N = 69	MF Subjects on PAC N = 220		
Week 24					
Change from Baseline					
n	80	18	118	169	198
Mean (SD)	-3.0 (13.1)	0.3 (1.4)	-2.8 (9.9)	-2.4 (8.8)	-2.9 (11.3)
Median (IQR)	-0.9 (-3.4, 0.7)	0.3 (-0.9, 1.1)	-1.4 (-3.6, 0.4)	-1.3 (-3.9, 0.4)	-1.3 (-3.6, 0.4)
Min, Max	-107.5, 14.5	-2.1, 3.4	-48.5, 31.3	-48.5, 31.3	-107.5, 31.3
Final Visit					
Change from Baseline					
n	121	67	199	271	320
Mean (SD)	-1.0 (10.8)	0.7 (5.4)	-1.8 (10.9)	-1.5 (10.6)	-1.5 (10.9)
Median (IQR)	-0.7 (-3.6, 1.6)	0.1 (-0.9, 1.5)	-1.3 (-4.2, 0.7)	-1.3 (-4.2, 0.8)	-1.1 (-4.1, 0.9)
Min, Max	-64.3, 59.5	-20.5, 20.7	-48.5, 68.1	-48.5, 68.1	-64.3, 68.1
Lymphocytes ($\times 10^9$/L)					
Baseline					
n	122	68	201	274	323
Mean (SD)	1.5 (1.5)	2.8 (9.8)	1.9 (2.4)	1.7 (2.1)	1.7 (2.1)
Median (IQR)	1.1 (0.7, 1.7)	1.1 (0.8, 1.7)	1.3 (0.8, 2.1)	1.3 (0.8, 2.0)	1.2 (0.8, 2.0)
Min, Max	0.2, 10.6	0.2, 81.4	0.0, 26.8	0.0, 26.8	0.0, 26.8
Week 24					
Change from Baseline					
n	80	18	118	169	198
Mean (SD)	0.3 (1.7)	-0.1 (0.5)	0.3 (1.6)	0.3 (1.5)	0.3 (1.6)
Median (IQR)	0.2 (-0.2, 0.5)	0.0 (-0.2, 0.1)	0.1 (-0.4, 0.7)	0.2 (-0.3, 0.6)	0.2 (-0.3, 0.6)
Min, Max	-4.2, 10.4	-1.5, 0.7	-2.4, 11.1	-2.5, 11.1	-4.2, 11.1

Table CS-12: Summary of Haematology Values and from Baseline at Week 24 and Final Visit (Safety Population, All Cancer Subjects)

Parameter Visit Statistics	Uncontrolled Studies		Controlled PERSIST-1	Overall MF Subject on 400 mg PAC[a] N = 293	All MF Subjects on PAC[a] N = 342
	MF Subjects N = 122	Non-MF Cancer Subjects N = 69	MF Subjects on PAC N = 220		
Final Visit					
Change from Baseline					
n	121	67	199	271	320
Mean (SD)	0.4 (1.9)	2.0 (15.2)	0.2 (2.6)	0.2 (2.3)	0.3 (2.3)
Median (IQR)	0.2 (-0.3, 0.8)	-0.1 (-0.4, 0.3)	0.2 (-0.3, 0.7)	0.2 (-0.3, 0.7)	0.2 (-0.3, 0.7)
Min, Max	-5.1, 9.4	-6.4, 123.7	-24.2, 11.6	-24.2, 11.6	-24.2, 11.6
Monocytes ($\times 10^9$/L)					
Baseline					
n	122	68	201	274	323
Mean (SD)	1.1 (2.5)	0.8 (0.9)	0.6 (0.9)	0.7 (1.6)	0.8 (1.7)
Median (IQR)	0.4 (0.2, 0.8)	0.6 (0.4, 0.8)	0.3 (0.1, 0.6)	0.3 (0.1, 0.7)	0.3 (0.1, 0.7)
Min, Max	0.0, 20.6	0.1, 6.5	0.0, 5.1	0.0, 20.6	0.0, 20.6
Week 24					
Change from Baseline					
n	80	18	118	169	198
Mean (SD)	-0.0 (0.7)	-0.2 (0.4)	0.0 (1.7)	0.0 (1.5)	0.0 (1.4)
Median (IQR)	0.0 (-0.2, 0.2)	-0.1 (-0.3, 0.0)	0.0 (-0.2, 0.1)	0.0 (-0.2, 0.1)	0.0 (-0.2, 0.1)
Min, Max	-2.4, 3.5	-1.5, 0.3	-3.1, 16.7	-3.1, 16.7	-3.1, 16.7
Final Visit					
Change from Baseline					
n	121	67	199	271	320
Mean (SD)	0.0 (2.2)	0.5 (2.7)	0.0 (1.6)	0.0 (1.8)	0.0 (1.9)
Median (IQR)	0.0 (-0.2, 0.3)	0.0 (-0.2, 0.2)	0.0 (-0.2, 0.1)	0.0 (-0.2, 0.2)	0.0 (-0.2, 0.2)
Min, Max	-17.6, 7.1	-2.1, 19.7	-4.0, 16.2	-17.6, 16.2	-17.6, 16.2

Table CS-12: Summary of Haematology Values and from Baseline at Week 24 and Final Visit (Safety Population, All Cancer Subjects)

Parameter Visit Statistics	Uncontrolled Studies		Controlled PERSIST-1	Overall MF Subject on 400 mg PAC[a]	All MF Subjects on PAC[a]
	MF Subjects N = 122	Non-MF Cancer Subjects N = 69	MF Subjects on PAC N = 220	N = 293	N = 342
Eosinophils ($\times 10^9$/L)					
Baseline					
n	120	67	201	273	321
Mean (SD)	0.4 (0.7)	0.2 (0.1)	0.3 (0.8)	0.3 (0.8)	0.3 (0.8)
Median (IQR)	0.1 (0.0, 0.4)	0.1 (0.1, 0.2)	0.1 (0.0, 0.2)	0.1 (0.0, 0.3)	0.1 (0.0, 0.3)
Min, Max	0.0, 4.7	0.0, 0.6	0.0, 7.4	0.0, 7.4	0.0, 7.4
Week 24					
Change from Baseline					
n	78	18	118	168	196
Mean (SD)	-0.1 (0.8)	0.0 (0.1)	0.0 (0.5)	0.0 (0.5)	0.0 (0.6)
Median (IQR)	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)
Min, Max	-4.6, 3.0	-0.4, 0.2	-3.2, 1.6	-3.2, 3.0	-4.6, 3.0
Final Visit					
Change from Baseline					
n	119	66	199	270	318
Mean (SD)	0.15 (1.0)	0.0 (0.1)	0.2 (1.2)	0.2 (1.1)	0.2 (1.1)
Median (IQR)	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)	0.0 (-0.1, 0.1)
Min, Max	-2.9, 6.4	-0.4, 0.6	-3.2, 13.9	-3.2, 13.9	-3.2, 13.9

BAT, best available therapy; IQR, interquartile range; MF, myelofibrosis; PAC, pacritinib.

[f] Neither 'Overall MF subjects on 400 mg PAC', nor 'All MF subjects on PAC' include any BAT subjects.

Note: Baseline is the last non-missing observation before the first dose of study treatment.

Grade 3/4 Laboratory Abnormalities

Treatment-emergent grade 3/4 select laboratory abnormalities are summarized for cancer studies in the following table. 189/342 [55.3%] of the MF subjects overall experienced at least one treatment-emergent grade 3/4 laboratory abnormality. The most common treatment-emergent grade 3/4 laboratory abnormalities were anaemia (24.0% of MF subjects overall) and platelet count decreased (20.8% of MF subjects overall).

Table CS-13: Summary of Treatment Emergent Grade 3/4 Laboratory Abnormalities by Abnormality (Safety Population)

Preferred Term	Uncontrolled Studies		Controlled PERSIST-1	Overall MF Subjects on 400 mg PAC[a]	All MF Subjects on PAC[a]
	MF Subjects N=122 n (%)	Non-MF Cancer Subjects N=69 n (%)	MF Subjects on PAC N=220 n (%)	N=293 n (%)	N=342 n (%)
Subjects with ≥ 1 Treatment Emergent Grade 3/4 Abnormality	83 (68.0)	29 (42.0)	106 (48.2)	153 (52.2)	189 (55.3)
Anaemia	38 (31.1)	10 (14.5)	44 (20.0)	61 (20.8)	82 (24.0)
Platelet count decreased	35 (28.7)	6 (8.7)	36 (16.4)	57 (19.5)	71 (20.8)

Table CS-13: Summary of Treatment Emergent Grade 3/4 Laboratory Abnormalities by Abnormality (Safety Population)

Preferred Term	Uncontrolled Studies		Controlled PERSIST-1	Overall MF	
	MF Subjects N=122 n (%)	Non-MF Cancer Subjects N=69 n (%)	MF Subjects on PAC N=220 n (%)	Subjects on 400 mg PAC[a] N=293 n (%)	All MF Subjects on PAC[a] N=342 n (%)
Lymphocyte count decreased	29 (23.8)	16 (23.2)	24 (10.9)	40 (13.7)	53 (15.5)
Neutrophil count decreased	8 (6.6)	8 (11.6)	13 (5.9)	18 (6.1)	21 (6.1)
Hyponatremia	7 (5.7)	3 (4.3)	9 (4.1)	12 (4.1)	16 (4.7)
White blood cell decreased	7 (5.7)	5 (7.2)	9 (4.1)	13 (4.4)	16 (4.7)
Hyperkalaemia	3 (2.5)	0	10 (4.5)	11 (3.8)	13 (3.8)
Alanine aminotransferase increased	2 (1.6)	0	4 (1.8)	5 (1.7)	6 (1.8)
Hypokalaemia	3 (2.5)	1 (1.4)	1 (0.5)	4 (1.4)	4 (1.2)
Aspartate aminotransferase increased	3 (2.5)	0	0	2 (0.7)	3 (0.9)
Blood bilirubin increased	2 (1.6)	0	1 (0.5)	3 (1.0)	3 (0.9)
Hyperglycaemia	0	0	3 (1.4)	3 (1.0)	3 (0.9)
Hypophosphatemia	0	0	3 (1.4)	3 (1.0)	3 (0.9)
Alkaline phosphatase increased	1 (0.8)	0	0	0	1 (0.3)
Creatinine increased	0	0	1 (0.5)	1 (0.3)	1 (0.3)
Hypomagnesaemia	0	0	1 (0.5)	1 (0.3)	1 (0.)

Table CS-13: Summary of Treatment Emergent Grade 3/4 Laboratory Abnormalities by Abnormality (Safety Population)

Preferred Term	Uncontrolled Studies		Controlled PERSIST-1	Overall MF	
	MF Subjects N=122 n (%)	Non-MF Cancer Subjects N=69 n (%)	MF Subjects on PAC N=220 n (%)	Subjects on 400 mg PAC[a] N=293 n (%)	All MF Subjects on PAC[a] N=342 n (%)
Hypocalcaemia	0	0	1 (0.5)	1 (0.3)	1 (0.3)
Hypoglycaemia	0	0	1 (0.5)	1 (0.3)	1 (0.3)

BAT, best available therapy; MF, myelofibrosis; QD, once daily; PAC, pacritinib

[g] Neither 'Overall MF subjects on 400 mg PAC', nor 'All MF subjects on PAC' include any BAT subjects.

Notes: Treatment-emergent abnormality is defined as any abnormality worsened by ≥ 1 grade (or change to opposite direction) compared to baseline through 30 days after last dose of study drug or any abnormality with grade ≥ 1 in severity if baseline data were missing.

Subjects may have more than one abnormality per analyte abnormality. At each analyte abnormality, a subject is counted only once if he/she experienced one or more abnormalities.

Analyte toxicity parameters are graded with CTCAE, Version 4.03.

Safety in special populations

Gender, Age, and Race: There were differences in frequency can be found between gender for a few TEAEs such as abdominal pain (18.4% for males and 11.8% for females) and pneumonia (10.2% for males and 2.9% for females.

Adverse events were also analysed by age group (< 65 years, ≥ 65 years. There were increases reported in TEAE frequencies in the ≥ 65 age group for anaemia (21.0% and 30.9 % for < 65 and ≥ 65 years of age respectively), thrombocytopenia (17.4% and 20.6 % for < 65 and ≥ 65 years of age respectively), diarrhoea (61.6% and 69.1% for < 65 and ≥ 65 years of age respectively), vomiting (19.6% and 28.9 % for < 65 and ≥ 65 years of age respectively), and fatigue (19.6% and 26.0 % for < 65 and ≥ 65 years of age respectively), but no other differences in TEAEs between the age groups were apparent.

Adverse events were not analysed by race due to the majority of subjects being Caucasian.

Renal Insufficiency: The safety and pharmacokinetics of single dose pacritinib (400 mg) were evaluated in subjects with mild (estimated glomerular filtration rate [eGFR] 60-89 mL/min/1.73m2 [N=8]), moderate (eGFR 30-59 mL/min/1.73m2 [N=8]), or severe renal impairment (eGFR 15-29 mL/min/1.73m2 [N=8]) as compared to matched healthy subjects (eGFR ≥90 mL/min/1.73m2 [N=7]). Eight additional subjects with end stage renal disease requiring haemodialysis were also enrolled.

The mean maximum serum concentration (Cmax) and area under the plasma concentration time curve (AUC) for pacritinib were similar in subjects with mild, moderate and severe renal impairment compared to subjects with normal renal function. Pacritinib is not removed by dialysis.

By preferred term, all TEAEs were reported in at most 1 subject per renal impairment group, except for diarrhoea and ECG QT prolonged. Diarrhoea was reported in 2 (25.0%) subjects in the moderate renal impairment group, 2 (25.0%) subjects in the severe renal impairment group, and 4 (50.0%) subjects in the ESRD group (3 [37.5%] subjects during the dialysis period and 2 [25.0%] subjects during the inter dialysis period). Diarrhoea was not reported in subjects in the mild renal impairment group or in matched healthy subjects. Electrocardiogram QT prolonged was reported in 3 (37.5%) subjects with ESRD (2 [25.0%] subjects during the dialysis period and 1 [12.5%] subject during the inter dialysis period) and in none of the other renal impairment groups, nor in matched healthy subjects. All TEAEs

resolved without sequelae, except anaemia in 1 subject in the ESRD group, who had anaemia as concomitant disease during the study.

Hepatic Insufficiency: The safety and PK of single dose pacritinib (400 mg) were evaluated in subjects with mild [Child-Pugh A (N=8)], moderate [Child-Pugh B (N=8)], or severe hepatic impairment [Child-Pugh C (N=4)] as compared to matched healthy subjects (N=8). The mean Cmax and area under the plasma concentration time curve (AUC) for pacritinib did not increase but rather decreased with increasing degree of hepatic impairment. No statistically significant difference in PAC-M1 metabolite plasma exposure could be evidenced between hepatic impaired subjects and healthy subjects.

No deaths or other SAEs were reported during the study. All AEs were grade 1 or 2 in severity. No TEAEs were reported in subjects with mild hepatic impairment. Four (50.0%), 3 (75.0%), and 4 (50.0%) subjects with moderate and severe hepatic impairment, and matched healthy subjects, respectively, were reported to have at least one TEAE during the study.

Immunological events

Immunological effects of pacritinib have not been discussed.

Safety related to drug-drug interactions and other interactions

Discontinuation due to AES

Discontinuations/ dose reductions as a result of adverse events need to be discussed.

3.3.8. Discussion on clinical safety

Overall, 93% of myelofibrosis patients treated with any dose of pacritinib experienced >1 TEAE. The commonest adverse events reported in the myelofibrosis patients were nausea, diarrhoea, vomiting, anaemia, thrombocytopenia and fatigue. The applicant reports that there appears to be a dose related trend in the incidence of diarrhoea, nausea, dysgeusia and decreased appetite. Further, on comparison with the adverse events seen in the BAT arm, the treatment with pacritinib was associated with higher incidences of haematological, gastrointestinal, infections and cardiovascular adverse events in the PERSIST-1 study. The commonest haematological adverse events were anaemia and thrombocytopenia. The haematological parameters summarised shows a reduction in mean haemoglobin levels and mean platelet counts over time on treatment with pacritinib. This is concerning as the applicant's claim is that pacritinib may be administered without and dose modification in case of thrombocytopenia.

The applicant further claims that there was no dose related increase in anaemia and thrombocytopenia, with the incidence not worse in the highest dose group (500-600 mg) than in the 400 mg dose group (anaemia: 12.3% [9/73] for 400 mg and 0% for 500-600 mg; thrombocytopenia: 12.3% [9/73] for 400 mg group and 9.1% [2/22] for 500- 600 mg group). However there are only a limited number of patients treated at the higher dose and these would have discontinued treatment due to dose limiting toxicities. The occurrence of drug- related anaemia and thrombocytopenia is expected to occur after a certain period of exposure to the drug unlike the GI adverse events which could have a more rapid onset. With increasing dose, an increase in GI adverse events has been noted but no corresponding increase in haematological toxicity. A reason may be that higher doses of pacritinib are likely to have been discontinued due to dose limiting toxicities before the occurrence of

the haematological adverse events. The applicant should also discuss the incidence of haematological adverse events in the healthy subject population, correlating with the duration of pacritinib treatment.

Of even greater concern is the increased number of deaths noted in the pacritinib arm compared to the BAT arm. Reasons for deaths include intracranial bleeding and cardiac events (cardiac failure and cardiac arrest). The occurrence of deaths due to bleeding events and the occurrence of thrombocytopenia is considered significant. The applicant's view that these deaths are unrelated to pacritinib treatment is not agreed with at present. This is also taking into consideration the higher number of deaths occurring in the pacritinib arm of the study compared to the BAT arm.

Incidences of QTc prolongation has also been seen in the phase 1/2 and phase 3 studies, even though the thorough QT study concluded no effect of pacritinib on QT prolongation.

An increased incidence of deaths in the ongoing PERSIST-2 study has been raised as a concern by the FDA. On the 8th of February, the FDA have placed a full clinical hold on the PERSIST-2 trial being conducted for pacritinib, as they have identified fatal and life-threatening safety issues in pacritinib treated patients: these include heart failure, haemorrhage including intracranial haemorrhage, and arrhythmias including sudden death. The FDA also noted that the excess mortality in pacritinib treated patients compared to the control arm in the PERSIST-1 trial. The PERSIST-2 trial also shows a detrimental effect on survival consistent with results from PERSIST-1. The deaths in PERSIST-2 in pacritinib-treated patients include intracranial haemorrhage, cardiac arrest and cardiac failure.

Additional data from the PERSIST-2 study has been provided by applicant. The review of patient data shows an increased number of deaths in the pacritinib treated patients compared to the BAT arm. There were 20 deaths in the pacritinib arm compared to 11 in the BAT arm. Most of the deaths in the BAT arm were attributed to disease progression. The causes of death in the pacritinib arm included cardiovascular events (4/20), thrombocytopenia (1/20) and bleeding events (2/20). These findings are consistent with the findings of the PERSIST-1 study.

The occurrence of fatal/ life-threatening bleeding and cardiac events, and the increased incidence of thrombocytopenia as one of the common adverse events are of serious concern. The only dose modifications recommended is to withhold dose in case of severe diarrhoea and bleeding, with modification advised for thrombocytopenia. This advice appears unsupported and unsafe, is contrary to recommendations of use for other approved JAK-2 inhibitors, taking into consideration the observed adverse events and fatal events with pacritinib.

3.3.9. Conclusions on clinical safety

There are serious concerns regarding the increased number of deaths and life threatening events seen with pacritinib due to bleeding events and cardiac events. Dose recommendations made for pacritinib appear inadequate and unsupported. The risks observed outweigh any demonstrated benefits.

3.4. Risk management plan

Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table RMP-01: Summary of the Safety Concerns as proposed by the applicant.

Summary of safety concerns	
Important identified risks	Anaemia Thrombocytopenia Diarrhoea/Nausea/Vomiting Haemorrhage
Important potential risks	QTc prolongation Infections Fatigue/Asthenia Drug interactions Embryotoxicity/Teratogenicity Hypersensitivity reactions Rash Pruritus Drug withdrawal
Missing information	Use in patients with hepatic impairment Use in patients with renal impairment Use in the paediatric population Use in breast feeding women Off label use Safety in elderly Safety in non-Caucasians Safety in patients with severe cardiac impairment

- The Applicant should consider what additional warnings need to be included in the SmPC e.g. Section 4.4 for subjects with clinically symptomatic or uncontrolled cardiovascular disease.
- Information in all patients with cardiac impairment should be considered missing information and not only severe cardiac impairment.

Pharmacovigilance plan

Summary of planned additional PhV activities from RMP

No additional pharmacovigilance activities are proposed in the RMP by the MAA.

Additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures

According to the MAA there are no risk minimisation measures that require the use of additional PhV activity for Enpaxiq.

Overall conclusions on the PhV Plan

Routine pharmacovigilance activities (primarily relying on spontaneous reporting) are suggested by the MAA for all safety concerns considered as missing information and important identified and potential risks. No additional pharmacovigilance activities are proposed in the RMP by the MAA. However, it is not agreed that routine pharmacovigilance activities are the most appropriate mean to investigate all safety concerns suggested by the MAA:

Important identified risks

As proposed by the MAA, the PRAC Rapporteur agrees that routine pharmacovigilance activities are sufficient for the important identified risks (Anaemia, Thrombocytopenia, Diarrhoea/Nausea/Vomiting, Haemorrhage).

Important potential risks

A thorough QTc study has already been performed. If the risk of QTc prolongation should be investigated further, routine pharmacovigilance (spontaneous reports) is unlikely to provide useful information due to confounders such as concomitant medication and diseases.

Routine pharmacovigilance activities are not considered appropriate to investigate the proposed important risks Infections and Fatigue/Asthenia since these conditions have a high baseline incidence in the myelofibrosis patient population. Controlled studies are more likely to provide useful information.

The investigation of Drug interactions by routine pharmacovigilance activities is not considered appropriate. Instead, cross-over clinical pharmacological studies are usually conducted for clearly defined suspected interactions.

Routine pharmacovigilance activities are considered sufficient for Embryotoxicity/Teratogenicity, Drug withdrawal and Hypersensitivity reactions.

The MAA has not provided a baseline incidence for Rash and Pruritus, this piece of information is usually needed in order to choose an appropriate study design. The MAA is requested to justify that routine pharmacovigilance activities are appropriate for the investigation of these proposed important potential risks.

Missing information

Use in patients with hepatic impairment and use in patients with renal impairment: These populations have already been studied in dedicated studies. Routine pharmacovigilance activities are considered sufficient.

A waiver has been granted in the paediatric population and dedicated studies are therefore not required.

Routine pharmacovigilance activities are appropriate for investigations of off-label use and use in breast feeding women.

Routine pharmacovigilance activities are suggested by the MAA to investigate the safety in elderly and safety in non-Caucasians. However, spontaneous reports and literature monitoring are not likely to shed light on these issues. Therefore, if appropriate, a dedicated controlled study should be considered.

The safety in patients with cardiac impairment has been suggested as missing information. A high baseline incidence of cardiac impairment is expected due to the age of the patient group (median age at diagnosis ranges from 54 to 62 years). A dedicated controlled study is therefore suggested to further investigate this piece of missing information.

It should be noted that the PRAC Rapporteur has questioned the relevance of several of the suggested important risks and missing information.

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is not sufficient to identify and characterise the risks of the product and the applicant should, if appropriate, propose studies designed to provide meaningful information.

Further modifications to the PhV plan may be necessary depending on the Applicants responses.

Risk minimisation measures

Table RMP-02: Summary of Risk Minimisation Measure

Safety Concern	**Routine Risk Minimisation Activities**	**Additional Risk Minimisation Activities**
Anaemia	Discussed in the following sections of the proposed SmPC: • **Section 4.8 - Undesirable effects** Prescription only medicine.	None proposed
Thrombocytopenia	Discussed in the following sections of the proposed SmPC: • **Section 4.2 - Posology and method of administration** • **Section 4.4 - Special warnings and precautions for use** • **Section 4.8 - Undesirable effects** Prescription only medicine.	None proposed
Diarrhoea/Nausea/Vomiting	Discussed in the following sections of the proposed SmPC: • **Section 4.2 - Posology and method of administration** • **Section 4.4 - Special warnings and precautions for use** • **Section 4.8 - Undesirable effects** Prescription only medicine.	None proposed

Table RMP-02: Summary of Risk Minimisation Measure

Safety Concern	Routine Risk Minimisation Activities	Additional Risk Minimisation Activities
Haemorrhage	• Discussed in the following sections of the proposed SmPC: • **Section 4.2 - Posology and method of administration** • **Section 4.8 - Undesirable effects** Prescription only medicine.	None proposed
QTc prolongation	• Discussed in the following sections of the proposed SmPC: • **Section 4.8 - Undesirable effects** Prescription only medicine.	None proposed
Infections	Discussed in the following sections of the proposed SmPC: • Section 4.8 - Undesirable effects Prescription only medicine.	None proposed
Fatigue/Asthenia	Discussed in the following sections of the proposed SmPC: • Section 4.7 - Effects on ability to drive and use machines • Section 4.8 - Undesirable effects Prescription only medicine.	None proposed
Drug interactions	Discussed in the following sections of the proposed SmPC: • Section 4.2 - Posology and method of administration • Section 4.4 - Special warnings and precautions for use • Section 4.5 - Interaction with other medicinal products and other forms of interaction Prescription only medicine.	None proposed
Embryotoxicity/Teratogenicity	Discussed in the following sections of the proposed SmPC: • Section 4.6 - Fertility, pregnancy and lactation • Section 5.3 - Preclinical safety data Prescription only medicine.	None proposed

Table RMP-02: Summary of Risk Minimisation Measure

Safety Concern	Routine Risk Minimisation Activities	Additional Risk Minimisation Activities
Hypersensitivity reactions	Discussed in the following sections of the proposed SmPC: • Section 4.3 - Contraindications • Section 4.8 - Undesirable effects Prescription only medicine.	None proposed
Rash	Discussed in the following sections of the proposed SmPC: • Section 4.8 - Undesirable effects Prescription only medicine.	None proposed
Pruritus	Discussed in the following sections of the proposed SmPC: • Section 4.8 - Undesirable effects Prescription only medicine.	None proposed
Drug withdrawal	Prescription only medicine.	None proposed
Use in patients with hepatic impairment	Discussed in the following sections of the proposed SmPC: • Section 4.2 - Posology and method of administration • Section 5.2 - Pharmacokinetic properties Prescription only medicine.	None proposed
Use in patients with renal impairment	Discussed in the following sections of the proposed SmPC: • Section 4.2 - Posology and method of administration • Section 5.2 - Pharmacokinetic properties Prescription only medicine.	None proposed
Use in the paediatric population	• Discussed in the following sections of the proposed SmPC: • Section 4.2 - Posology and method of administration • Section 5.1 - Pharmacodynamic properties • Section 5.2 - Pharmacokinetic properties Prescription only medicine.	None proposed

Table RMP-02: Summary of Risk Minimisation Measure

Safety Concern	Routine Risk Minimisation Activities	Additional Risk Minimisation Activities
Use in breast feeding women	Discussed in the following sections of the proposed SmPC: • Section 4.6 - Fertility, pregnancy and lactation Prescription only medicine.	None proposed
Off label use	Discussed in the following sections of the proposed SmPC: • Section 4.1 - Therapeutic indications Prescription only medicine.	None proposed
Safety in elderly	Discussed in the following sections of the proposed SmPC: • Section 4.2 - Posology and method of administration Prescription only medicine.	None proposed
Safety in non-Caucasians	Prescription only medicine.	None proposed
Safety in patients with severe cardiac impairment	Discussed in the following sections of the proposed SmPC: • Section 4.8 – Undesirable effects Prescription only medicine.	None proposed

The proposals made above are appropriate and acceptable based on the information available at the DLP of 22 Jan 2016 for the RMP version 1.0. The results of the interim analysis of the Persist1 and Persist2 may change this conclusion. Should this happen the RMP needs to be further reviewed and revised.

o Additional risk minimisation measures

No additional risk minimisation measures are proposed.

o Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted is of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s). However, further risk minimisation activities might be needed depending on the responses from the Applicant to the LoQ.

Conclusion

The CHMP and PRAC considered that the risk management plan could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

3.5. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

4. Orphan medicinal products

Pacritinib has been granted orphan designation in myelofibrosis on 25/08/2010 (Decision number EMA/OD/058/10).

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The proposed indication for Enpaxiq is in *the treatment of splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF), post-polycythaemia vera myelofibrosis (PPV-MF), and post-essential thrombocythaemia myelofibrosis (PET-MF)*.

Myelofibrosis is a myeloproliferative disorder that is characterized by a clonal stem cell proliferation. Myelofibrosis can present as an apparently de novo disorder termed primary myelofibrosis (PMF), or evolve from other myeloproliferative disorders and can be termed secondary myelofibrosis, post-polycythaemia vera myelofibrosis (PPV-MF) or post-essential thrombocythaemia myelofibrosis (PET-MF). Synonyms to denote PMF include agnogenic myeloid metaplasia, chronic idiopathic myelofibrosis (CIMF), idiopathic myelofibrosis, myelofibrosis, and myelofibrosis with myeloid metaplasia (MMM).

The 10-year risk of developing myelofibrosis is < 4% in essential thrombocythaemia and 10% in polycythaemia vera. The median age at diagnosis is approximately 65 years, with equal incidence in men and women. The incidence of PMF has been shown to increase with age and is estimated at 0.4 to 1.4 cases per 100,000 individuals per year.

The clonal stem cell proliferation is associated with production of elevated levels of several inflammatory and pro-angiogenic cytokines and a peripheral blood smear showing a leukoerythroblastic pattern with varying degrees of circulating progenitor cells. Resulting bone marrow stromal reaction includes varying degrees of collagen fibrosis, osteosclerosis and angiogenesis. The altered bone marrow milieu results in release of hematopoietic stem cells into the blood and extramedullary haematopoiesis, particularly hepatomegaly and splenomegaly.

Myelofibrosis results in laboratory and physical exam abnormalities including progressive anaemia, leucopoenia or leucocytosis, thrombocytopenia or thrombocythemia, ineffective haematopoiesis and haematopoietic failure, massive splenomegaly and portal hypertension, and progression to leukaemia.

Clinically, patients suffer from the consequences of massive splenomegaly including abdominal pain or discomfort and pain under the left costal margin, risk of vascular events (including thrombosis and

haemorrhage), severe constitutional symptoms (fevers, night sweats, weight loss), a hypermetabolic state, cachexia and premature death.

Causes of death for patients with MF include leukemic transformation, infections, bleeding, thrombosis, heart failure, liver failure, solid tumours, respiratory failure, and portal hypertension.

5.1.2. Available therapies and unmet medical need

The only potentially curative therapy for MF remains allogenic stem cell transplantation (allo-SCT). However, this option is usually possible only in younger patients; is dependant in the availability of a donor; and associated with significant risks and mortality.

Drug treatment is available with the approved drug Jakavi (ruxolitinib), also a JAK inhibitor (JAK 1/2). The proposed indication is similar to the approved indication for the JAK 1/2 inhibitor- ruxolitinib (Jakavi). Ruxolitinib was authorised as Jakavi in the EU (August 2012) and as Jakafi by the US FDA in 2011, for the treatment of myelofibrosis. The EU approved indication for Jakavi is: *Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.*

Unmet medical need:

Studies with Jakavi excluded patients with platelets <50000/cumm. Further, the product information (Jakavi SmPC) states that treatment with Jakavi should be discontinued when platelets fall below 50000/mm^3 and that there is limited information in patients with platelet counts in between 50000 and 100000/mm^3. Therefore it can be considered that there is a need for treatment in the patients with low platelet counts.

The claim made by the applicant is that pacritinib fulfils this unmet need and can be prescribed in patients without restriction in patients with platelet counts <100000/uL. A rationale for pacritinib having no effect on the platelet counts unlike other JAK2 inhibitor is not discussed.

5.1.3. Main clinical studies

The efficacy data for pacritinib is derived from the pivotal study PAC325- PERSIST 1 trial, which was a randomised open labelled study comparing pacritinib against best available therapy.

The BAT arm excluded treatment with Jakavi and could have included treatments previously received, and therefore may have been treatments which had already failed.

The primary efficacy endpoint of the study was the proportion of subjects achieving ≥ 35% reduction in spleen volume from baseline to week 24 as measured by MRI or CT.

The secondary efficacy endpoint of the study was the proportion of subjects with ≥ 50% reduction in TSS from baseline to week 24 as measured by the MPN-SAF TSS 2.0.

Both the above endpoints are accepted endpoints in myelofibrosis and study was powered for both the primary and secondary endpoints.

5.2. Favourable effects

For the ITT population, there was a significant (p = 0.0003) difference between treatment arms for the overall proportion of subjects achieving a ≥ 35% SVR from baseline to week 24, with a greater

proportion of subjects in the pacritinib arm achieving a ≥ 35% SVR than in the BAT arm (pacritinib, 42/220 [19.1%]; BAT 5/107 [4.7%]).

Additionally, there were significant differences between treatment arms for subgroups of subjects by baseline platelet count, with a greater proportion of subjects in the pacritinib arm achieving a ≥ 35% SVR in each subgroup than in the BAT arm ($p = 0.0451$, $p = 0.0086$, and $p = 0.0105$ for the < 50,000/μL, < 100,000/μL, and ≥ 100,000/μL subgroups, respectively)

A total of 148 subjects (100 pacritinib, 48 BAT) were administered the MPN-SAF TSS 2.0 and comprise the ITT population for this secondary endpoint. Overall, 19/100 (19.0%) subjects in the pacritinib arm and 5/48 (10.4%) subjects in the BAT arm had a ≥ 50% reduction from baseline to week 24 in TSS 2.0, which was not statistically different ($p = 0.2368$).

5.3. Uncertainties and limitations about favourable effects

The BAT arm could have included treatments previously received and therefore may have been treatments which had already failed. Therefore, the BAT arm treatments may have been sub-optimal. This is possibly highlighted again by the high numbers of investigator decided withdrawal of patients from the BAT arm of the study, without disease progression or adverse effects.

There is a lack of a scientific explanation or rationale as to why pacritinib should have no effect on the platelets counts, when the phase 1/2 studies showed thrombocytopenia as one of the commonest adverse events.

There is a 14.4% difference in the proportion of patients who achieved a ≥35% reduction in spleen volume from baseline to week 24, favouring the pacritinib arm. However, this result may have been affected by the 17% of patients withdrawn from the BAT arm before 24 weeks due to reasons other than progression of disease or adverse events. Further clarification has been sought regarding this. Further, the proportion of patients achieving the primary endpoint is lower than that seen at 24 weeks in the pivotal study for Jakavi- 41.9% of ruxolitinib treated patients achieving ≥ 35% reduction from baseline in spleen volume at Week 24 in the COMFORT-I study.

The results of the primary endpoint are not supported by a statistically significant result for the main secondary endpoint.

More concerning is the fact that there appears to be a detrimental effect on overall survival and leukaemia free survival with increased number of events in the pacritinib arm.

5.4. Unfavourable effects

Overall, 93% of myelofibrosis patients treated with any dose of pacritinib experienced >1 TEAE. The commonest adverse events reported in the myelofibrosis patients were nausea, diarrhoea, vomiting, anaemia, thrombocytopenia and fatigue.

Further, on comparison with the adverse events seen in the BAT arm, the treatment with pacritinib was associated with higher incidences of haematological, gastrointestinal, infections and cardiovascular adverse events in the PERSIST-1 study. The commonest haematological adverse events were anaemia and thrombocytopenia.

Of even greater concern is the increased number of deaths noted in the pacritinib arm compared to the BAT arm. Reasons for deaths include intracranial bleeding and cardiac events (cardiac failure and cardiac arrest). The increased incidence of deaths has been noted in the ongoing PERSIST-2 study as well.

On the 8th of February, the FDA have placed a full clinical hold on the PERSIST-2 trial being conducted for pacritinib, as they have identified fatal and life-threatening safety issues in pacritinib treated patients: these include heart failure, haemorrhage including intracranial haemorrhage, and arrhythmias including sudden death. The FDA also noted that the excess mortality in pacritinib treated patients compared to the control arm in the PERSIST-1 trial. The PERSIST-2 trial also shows a detrimental effect on survival consistent with results from PERSIST-1. The deaths in PERSIST-2 in pacritinib-treated patients include intracranial haemorrhage, cardiac arrest and cardiac failure.

Incidence of QTc prolongation has also been seen in the phase 1/2 and phase 3 studies, even though the thorough QT study concluded no effect of pacritinib on QT prolongation.

5.5. Uncertainties and limitations about unfavourable effects

The incidence of the common adverse events raises concerns about the applicant's claim that pacritinib may be administered without and dose modification in case of thrombocytopenia.

The applicant further claims that there was no dose related increase in anaemia and thrombocytopenia, with the incidence not worse in the highest dose group (500-600 mg) than in the 400 mg dose group (anaemia: 12.3% [9/73] for 400 mg and 0% for 500-600 mg; thrombocytopenia: 12.3% [9/73] for 400 mg group and 9.1% [2/22] for 500- 600 mg group). However there are only a limited number of patients treated at the higher dose and these would have discontinued treatment due to dose limiting toxicities. The occurrence of drug- related anaemia and thrombocytopenia is expected to occur after a certain period of exposure to the drug unlike the GI adverse events which could have a more rapid onset. With increasing dose, an increase in GI adverse events has been noted but no corresponding increase in haematological toxicity. A reason may be that higher doses of pacritinib are likely to have been discontinued due to dose limiting toxicities before the occurrence of the haematological adverse events.

The only dose modifications recommended is to withhold dose in case of severe diarrhoea and bleeding, with modification advised for thrombocytopenia. This advice appears unsupported and unsafe, is contrary to recommendations of use for other approved JAK-2 inhibitors, taking into consideration the observed adverse events and fatal events with pacritinib.

5.6. Effects Table

Table B/R 01. Effects Table for Enpaxiq in myelofibrosis (data cut-off: 17 Jan 2015).

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Spleen Volume Reduction	Proportion of subjects achieving ≥ 35% reduction in spleen volume from baseline to week 24 as measured by MRI or CT	n/N (%) [95% CI]	42/220 (19.1) [14.1, 24.9]	5/107 (4.7) [1.5, 10.6]	14.4% difference, favouring the pacritinib arm may have been affected by the 17% of patients withdrawn from the BAT arm before 24 weeks due to reasons other than progression of disease or adverse events.	
Unfavourable Effects						
Thrombocytopenia						
Bleeding events including intracranial bleeds-fatal and life threatening						
Cardiac events						
QTc prolongation						

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

The primary and secondary endpoints studied in the PERSIST-1 study are relevant.

5.7.2. Balance of benefits and risks

Pacritinib shows an effect on spleen volume reduction. However, the proportion of patients achieving >/=35% reduction in spleen volume at 24 weeks is much lower than those achieved on treatment with approved drug Jakavi.

A treatment effect is also seen in thrombocytopenic patients. However, the incidence of thrombocytopenia, life threatening and fatal bleeding events is concerning and the safe use in thrombocytopenic patients cannot be recommended.

The occurrence of fatal/ life-threatening bleeding and cardiac events, and the increased incidence of thrombocytopenia as one of the common adverse events are of serious concern.

A detrimental effect of pacritinib treatment on overall survival and leukaemia free survival is suggested.

The results of the ongoing PERSIST-2 study also shows an increased number of deaths, fatal and life threatening adverse events including cardiac events and bleeding events consistent with the results of the PERSIST-1 study.

5.7.3. Additional considerations on the benefit-risk balance

A more effective treatment exists in the form of another JAK 2 inhibitor, Jakavi.

Safety issues highlighted do not allow a recommendation for the use of pacritinib in thrombocytopenic patients, where an unmet medical need could be argued.

5.8. Conclusions

The overall B/R of Enpaxiq is negative.