Phase 1/2 study of pacritinib, a next generation JAK2/FLT3 inhibitor, in myelofibrosis or other myeloid malignancies

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Abstract

Background: Pacritinib (SB1518) is a highly selective kinase inhibitor with specificity for JAK2, FLT3, IRAK1, and CSF1R. This multicenter phase 1/2 study evaluated the maximum tolerated dose (MTD), safety, and clinical activity of pacritinib in patients with myelofibrosis (MF) and other advanced myeloid malignancies.

Methods: In the phase 1 dose-escalation part of the study, 43 adults with advanced myeloid malignancies received pacritinib 100 to 600 mg once daily (QD). In the phase 2 part of the study, 31 adults with refractory or intermediate- or high-risk newly diagnosed MF and any degree of cytopenia received pacritinib 400 mg QD. The primary endpoint is a ≥35% reduction in spleen volume at week 24 as determined by magnetic resonance imaging.

Results: Five patients (11.6%) experienced a dose-limiting toxicity during cycle 1 of phase 1. The clinical benefit rate was 86.0% (13 patients achieving clinical improvement and 24 patients having stable disease). The MTD was established at 500 mg QD, and the recommended phase 2 dose was 400 mg QD. In phase 2, the primary endpoint was achieved by 23.5% of evaluable patients (4/17), with 47.4% (9/19) achieving a ≥50% spleen length reduction at week 24 as measured by physical examination. At week 24, 38.9% of evaluable patients (7/18) achieved a ≥50% decrease in MF Quality of Life and Symptom Assessment total score. Gastrointestinal toxicities were the most common adverse events and were predominantly grade 1/2 in severity. Grade 3/4 anemia was reported in 5/31 patients and grade 3/4 thrombocytopenia was reported in 3/31 patients. The most frequent AEs considered to be treatment related were diarrhea (28/31), nausea (15/31), vomiting (9/31), and fatigue (4/31). Grade 3 treatment-related AEs were reported in seven patients (22.6%), four of whom had diarrhea. No grade 4/5 treatment-related AEs were reported. No leukopenia, neutropenia, or lymphopenia were reported.

Conclusions: Pacritinib was well tolerated and demonstrated clinical activity in MF. The study suggests that pacritinib has unique characteristics, namely a lack of substantial myelosuppression and manageable side effects, making it an attractive target for further evaluation in MF.

Trial registration: Retrospectively registered at www.clinicaltrials.gov (#NCT00719836) on July 20, 2008.

Keywords: FMS-like tyrosine kinase 3 inhibitors, Janus kinase 2 inhibitors, Myelofibrosis, Myeloid malignancies, Myelosuppression, Pacritinib, Pharmacokinetics, Quality of Life, Splenomegaly

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Background
Aberrant activation of the JAK/STAT pathway plays a central role in myeloproliferative neoplasms (MPNs), a group of heterogeneous diseases including polycythemia vera (PV), essential thrombocytosis (ET), and chronic idiopathic myelofibrosis (MF) [1, 2]. The discovery of a dominant gain-of-function mutation in the JAK2 gene (JAK2V617F) in most patients with PV, and 30–60% of patients with ET or MF allowed identification of JAK2 as a new therapeutic target for these disorders [3–6]. MPN patients negative for JAK2V617F may display mutations in the thrombopoietin receptor gene (MPL) [7] or the calreticulin gene (CALR) [8], which may also lead to dysregulated JAK/STAT-dependent processes. Greater understanding of the JAK/STAT pathway and its role in MPNs has led to the development of therapeutic JAK inhibitors. These agents are not mutation specific and are effective in MPN patients with and without the JAK2 mutation [9].

FMS-like tyrosine kinase 3 (FLT3) mutations involve internal tandem duplications of the juxtamembrane domain-coding sequence are found in 20–30% of patients with acute myeloid leukemia (AML), typically in de novo AML, and are associated with poor clinical outcomes [10–12]. Upregulation of FLT3 may also be involved in driving the abnormal production of peripheral platelets, characteristic of MF [13].

Pacritinib (SB1518) is a kinase inhibitor with specificity for JAK2, FLT3, IRAK1, and CFS1R [14–16]; it does not have specificity for JAK1 at pharmacologically-relevant levels [14]. Pacritinib demonstrated a favorable safety and pharmacological activity profile in preclinical hematologic malignancy models [17, 18]. The objectives of this multicenter phase 1/2 study were to determine the maximum tolerated dose (MTD), pharmacokinetics, safety, and clinical activity of pacritinib in patients with MF and other advanced myeloid malignancies.

Methods
This clinical study included a phase 1 dose escalation component to establish the MTD of pacritinib in patients with advanced myeloid malignancies, followed by an open-label, single-arm phase 2 component to assess the clinical activity (based on spleen response rate) and tolerability of pacritinib administered at the recommended dose in patients with MF.

Ethics, consent, and data analysis
The study was conducted at three centers in the USA between June 2008 and October 2011 in accordance with the Declaration of Helsinki, International Conference on Harmonization guidelines, and relevant laws and regulations. The protocol was approved by the institutional review boards at each study site. Written informed consent was obtained from all patients prior to participation. Data collection, data entry, and database lock were performed by S*BIO Pte Ltd (the original study sponsor) and data analysis was performed by CTI BioPharma Corp. (who acquired pacritinib in 2012). All authors had access to primary clinical trial data.

Patients
Patients were eligible for inclusion in phase 1 if they had a histologically confirmed myeloid malignancy and had failed standard therapies or were not candidates for palliative therapies. Eligible malignancies included AML; chronic myeloid leukemia (CML) in accelerated or blast phase; high-risk myelodysplastic syndrome (refractory anemia with 5–19% bone marrow blasts or chronic myelomonocytic leukemia with >5% bone marrow blasts); and advanced MF with ≥1 poor prognostic feature (hemoglobin <10 g/dL, platelets <100 × 10^9/L, white blood cells <4 or >30 × 10^9/L, or symptomatic splenomegaly ≥10 cm below the left costal margin). Patients were eligible for inclusion in phase 2 if they had MF (including post-ET [PET]-/post-PV [PPV]-MF) that had relapsed or was not well controlled with standard therapy and had splenomegaly ≥5 cm below the costal margin. Patients were also eligible if they had newly diagnosed MF classified as intermediate- or high-risk [19] and were not suitable for standard therapy. In both components of the study, patients were required to be aged ≥18 years with Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; adequate liver and renal function; corrected QTc interval ≤0.47 s (Bazett formula); a 2-week window from prior disease-directed therapy with recovery from prior toxicities to grade ≤1; and a 1-week window from prior hydroxyurea and CYP3A4 inducer/ inhibitor treatment. Patients with uncontrolled intercurrent illness, concurrent malignancy, HIV, or active hepatitis A, B, or C were excluded, as were those who were pregnant, lactating, or unwilling/unable to undergo a magnetic resonance imaging (MRI) scan (phase 2 only).

Study design and treatment
Phase 1 was a 3 + 3 dose-escalation study. Three to six patients were enrolled at each dose level, depending upon observed dose-limiting toxicities (DLTs) in the cohort. Each patient participated in only one cohort. Oral pacritinib was administered to the first cohort at 100 mg once daily (QD) for 25 consecutive days in a 28-day cycle in cycle 1, with 3 days of rest for pharmacokinetic (PK) sampling, followed by continuous 28-day dosing for the remaining cycles. Subsequent cohorts received escalating pacritinib dose levels of 150, 200, 300, 400, 500, and 600 mg QD. All patients at each dose level were observed through the end of the first cycle before the next dose level could begin treatment.
Each patient enrolled in phase 1 was allowed two dose escalations at the investigator's discretion and with the sponsor's approval. Those who had completed ≥3 treatment cycles without disease progression could escalate to the last dose level cleared as tolerable. Once the MTD was reached, patients treated at lower dose levels (including those who had undergone one previous dose escalation) were permitted to escalate to the recommended dose.

A DLT was defined as a grade 3/4 non-hematologic adverse event (AE), a clinically significant grade 4 hematologic AE that persisted >28 days in the absence of active hematologic malignancy with bone marrow involvement, or grade 4 febrile neutropenia/granulocytopenia during cycle 1 that was possibly, probably, or definitely related to the study drug. In addition, any other clinically significant events that resulted in study drug interruption and/or dose reduction could be considered a DLT. Grade 3 diarrhea or vomiting were only considered DLTs if they persisted for >7 days despite treatment. Fatigue was only considered a DLT if it was grade 4 and persisted for >2 weeks. In patients with grade 2 alanine aminotransferase/aspartate aminotransferase elevations at baseline, elevations were only considered DLTs if they exceeded three times the baseline level and were confirmed 1 week later. Recurrence of prior grade 3 hyperuricemia was not considered a DLT.

Phase 2 dose selection was based on exposure, safety, pharmacodynamic, and clinical benefit data from phase 1. In phase 2, patients received pacritinib 400 mg QD without interruption in a 28-day cycle.

Treatment was able to be withheld for up to 2 weeks for treatment-emergent AEs. After toxicity resolution, patients could resume treatment at the same or a reduced dose at the discretion of the investigator after discussion with the sponsor (Additional file 1: Table S1). Up to two dose reductions were allowed; however, re-escalation was not permitted.

Two forms of pacritinib were developed. The study was initiated with the hydrochloride (HCl) salt formulation, which was also used for non-clinical and early clinical development. A citrate salt formulation containing the same active moiety was later designed to improve the physical stability of the product. Six new patients were enrolled in phase 1 and received pacritinib citrate salt 200 mg QD. Patients enrolled in phase 1 were subsequently switched to the citrate salt and all patients enrolled in phase 2 received the citrate salt.

**Study procedures**

At screening/baseline, patients underwent a medical history, physical examination, vital sign assessment, ECOG PS assessment, electrocardiogram, and assessment of hematologic parameters and blood chemistry. Hematology/blood chemistry, physical examinations, and vital sign assessments were performed throughout treatment. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCIC-CTCAE), version 3.0, with relationship to treatment assigned by the investigator and were recorded from the first dose of pacritinib until 30 days after the last dose. Bone marrow biopsy and/or aspirate samples were drawn at baseline, on day 1 of cycle 4 and cycle 10, as clinically indicated, and at the termination visit. Disease response and progression were determined using the relevant International Working Group (IWG) criteria [20–23].

In phase 1, full PK sampling was performed on days 1 and 15 of cycle 1 and day 1 of cycle 2. Trough PK samples were drawn prior to dosing on days 8 and 22 of cycle 1 and at 24, 48, and 72 h after dosing on day 25 of cycle 1. A sample was collected before dosing on day 1 of cycles 4, 7, and 10. Pacritinib concentrations were determined using a validated liquid chromatography/tandem mass spectrometry method. An analysis of clinical exposures from the HCl and citrate salts of pacritinib was performed comparing Day 1 PK data from 12 patients who received the HCl salt formulation in the 200 mg cohorts of this study and two other pacritinib studies [NCT00741871 and NCT00745550] with six patients in the 200 mg cohort of this study who received the citrate salt formulation.

In phase 2, abdominal MRI to assess spleen and liver volume was performed on day 1 of cycles 1, 4, and 7 and then day 1 of every third cycle through cycle 25. Spleen size (length) was also assessed by manual palpation with each scheduled physical examination. The phase 2 study protocol was amended in September 2009 to include the MF Quality of Life and Symptoms Assessment Tool. The tool was derived from the MF Symptom Assessment Form [24] and rated disease-related symptoms (worst fatigue, early satiety, abdominal pain or discomfort, night sweats, itching, and bone pain) and overall quality of life on a scale of 0 (absent) to 10 (worst imaginable). The instrument was administered pre-dose on day 1 of cycles 1, 2, 4, 7, and 10 and then on day 1 of every third cycle through cycle 25.

**Statistical analysis**

The primary objective of phase 1 was to establish the MTD of pacritinib in patients with advanced myeloid malignancies, defined as the highest dose level at which no more than one out of six patients in the cohort experienced a DLT during cycle 1 (25 days) of therapy. The DLT-evaluable population included all patients who completed at least 18 of the 25 originally assigned doses in cycle 1, or those who did not complete the required number of assigned doses and had a DLT.
Secondary objectives in phase 1 of the study included safety and PK analysis. Clinical benefit rate was assessed as an exploratory endpoint, defined as the proportion of patients who experienced a complete response, partial response, clinical improvement, or stable disease (SD) during the study.

The primary endpoint of the phase 2 component was the proportion of the efficacy population who achieved a ≥35% reduction in spleen volume from baseline at week 24, as measured by MRI. Spleen response rate was also assessed in terms of a ≥35% reduction in spleen volume by MRI up to week 24 and end of treatment and as a ≥50% reduction in spleen length by physical examination up to week 24 and end of treatment. Duration of response was not analyzed due to limitations in the proportion of responders. An exploratory endpoint was the proportion of patients with a ≥50% reduction in MF Quality of Life and Symptoms Assessment Tool at week 24 compared with baseline.

The planned sample size of 29 patients for the phase 2 component provided 80% power to detect a spleen response rate of ≥30% versus the null hypothesis of a response rate of ≤10%, with α = 0.05 (two-sided). The efficacy-evaluable population included those patients with a baseline and corresponding follow-up value. The safety population included all enrolled patients who received ≥1 dose of pacritinib.

**Results**

**Phase 1**

**Patients**

In phase 1, 43 patients with advanced myeloid malignancies (MF: n = 36; AML: n = 7) were treated with pacritinib at doses ranging from 100 to 600 mg QD. Subject demographics and baseline characteristics are shown in Table 1.

The majority of patients had splenomegaly (n = 28; 65.1%). At baseline, grade 2 or higher anemia and thrombocytopenia were reported in 28 (65.1%) and 21 (48.8%) patients, respectively. Of the 43 patients, 18 (41.9%) completed the study and 25 (58.1%) discontinued the study, primarily because of disease progression (n = 9) and the sponsor’s decision to terminate the study for financial reasons (n = 7).

**DLTs and MTD**

All 43 patients enrolled in phase 1 were evaluable for DLT assessment. Overall, five patients (11.6%) experienced a DLT during cycle 1 (Table 2). Diarrhea that was considered to be a DLT was reported in one patient at each of the following dose levels: 300, 500, and 600 mg. One patient in the 150 mg cohort experienced grade 3 QTc prolongation (QTc of 460 ms at screening, 491 ms on cycle 1 day 1, 504 ms on cycle 1 day 15, and 519 ms on cycle 1 day 22 [last assessment available]). The patient had

| Pacritinib | 100 mg | 150 mg | 200 mg | 300 mg | 400 mg | 500 mg | 600 mg | All patients<sup>a</sup> |
|-----------|--------|--------|--------|--------|--------|--------|--------|-------------------------|
| n = 3     | 72.0   | 67.6   | 69.0   | 64.5   | 67.5   | 65.0   | 74.5   | 71.0                    |
| (59–78)   | (66–86)| (63–76)| (50–77)| (52–83)| (49–77)| (53–76)| (49–86)|                        |
| Male, n (%) | 2 (66.7) | 5 (83.3) | 7 (77.8) | 3 (50.0) | 2 (33.3) | 4 (57.1) | 4 (66.7) | 27 (62.8) |
| ECOG PS, n (%) | 0   | 2 (33.3) | 5 (55.6) | 4 (66.7%) | 3 (50.0) | 4 (57.1) | 0       | 18 (41.9)  |
| 1         | 2 (66.7) | 2 (33.3) | 4 (44.4) | 1 (16.7) | 2 (33.3) | 2 (28.6) | 5 (83.3) | 18 (41.9)  |
| 2         | 1 (33.3) | 2 (33.3) | 0       | 1 (16.7) | 1 (16.7) | 1 (14.3) | 1 (16.7) | 7 (16.3)   |
| Median disease duration, months (range) | 5.0 (4.1–6.7) | 25.8 (8.6–174.4) | 45.9 (2.3–410.2) | 37.4 (8.5–341.8) | 27.4 (5.1–132.2) | 36.9 (10.0–182.9) | 99.2 (13.7–196.9) | 36.9 (2.3–410.2) |
| Current malignancy type, n (%) | 0     | 3 (50.0) | 0       | 0       | 3 (50.0) | 0       | 1 (16.7) | 7 (16.3)   |
| AML       | 1/3 (33.3) | –       | –       | 2/3 (66.7) | –       | 1/1 (100) | 4/7 (57.1) |                        |
| JAK2 mutation<sup>b</sup>, n/N (%) | 3 (100.0) | 3 (50.0) | 9 (100.0) | 6 (100.0) | 3 (50.0) | 7 (100.0) | 5 (83.3) | 36 (83.7)  |
| Myelofibrosis | 2/3 (66.7) | 2/3 (66.7) | 8/9 (88.9) | 5/6 (83.3) | 3/3 (100) | 5/7 (71.4) | 4/5 (80.0) | 29/36 (80.6) |
| Median prior systemic therapies, n (range) | 1.0 (0–4) | 3.0 (2–4) | 1.0 (0–4) | 2.0 (1–4) | 2.0 (1–4) | 2.0 (0–4) | 3.0 (1–4) | 3.0 (0–4)  |
| Median time since last cancer treatment, months (range) | 2.4 (1.5–3.2) | 1.2 (0.1–6.3) | 2.0 (0.5–39.6) | 8.0 (0.5–37.1) | 1.5 (0.5–24) | 2.8 (0.7–27.1) | 63 (0.6–21.7) | 2.2 (0.1–39.6) |

<sup>a</sup>86% of patients were white

<sup>b</sup>All JAK2 mutations were V617F

AML acute myeloid leukemia, ECOG PS Eastern Cooperative Oncology Group Performance Status, MDS myelodysplastic syndrome
baseline atrial fibrillation, a history of inferior myocardial infarction and right bundle branch block, hypokalemia and was receiving amiodarone, solifenacin, and fluconazole. Pacritinib was discontinued and the QTc prolongation resolved. One patient in the pacritinib 600 mg cohort experienced six distinct grade 1 or 2 events that were individually assessed as not serious but were considered as DLTs when taken together (Table 2). Relevant prior history included prostate cancer, renal cell carcinoma-post partial nephrectomy, cataract surgery, celiac sprue, and vertigo. Pacritinib was interrupted and the dosage was reduced to 400 mg QD. Nausea and vomiting resolved with antiemetic therapy. Dizziness and the decrease in performance status resolved; however, blurred vision and gait disturbance were ongoing at the end of follow-up.

The MTD of pacritinib was determined to be 500 mg QD. Although only one of seven patients in the 500 mg QD cohort experienced a DLT, two discontinued treatment due to AEs, three required dose interruptions, three required dose reductions, and three experienced a serious AE (SAE). Therefore, pacritinib 400 mg QD was selected as the recommended phase 2 dose.

### Safety

Table 3 summarizes treatment-emergent AEs occurring in ≥10% of patients in phase 1. The most frequent AEs were gastrointestinal in nature and were mainly grades 1 or 2 in severity. There were no discernible trends observed across dose cohorts in the incidence of AEs; however, diarrhea and nausea were reported more frequently in patients receiving doses ≥400 vs <400 mg. Anemia and thrombocytopenia were the most frequent grade 3/4 AEs, occurring in seven (16.3%) and 6 (14.0%) patients, respectively. Eight patients discontinued pacritinib because of an AE, three of which were considered to be treatment related (grade 3 prolonged QTc [resolved], grade 3 fatigue [ongoing at the end of follow-up], and grade 3 increased transaminases [resolved]). Dose interruptions or reductions due to AEs occurred in 18 and 9 patients, respectively.

The most frequent AEs considered to be treatment related were diarrhea (65.1%), nausea (34.9%), vomiting (23.3%), and thrombocytopenia (11.6%). Across dose cohorts, larger proportions of patients reported treatment-related AEs in cohorts administered doses ≥400 mg. Grade 3 and 4 treatment-related AEs were reported in nine patients (20.9%) and two patients (4.7%), respectively. No grade 4 gastrointestinal AEs occurred.

SAEs occurred in 19 patients (44.2%) during phase 1 (Additional file 1: Table S2). Four patients (9.3%) experienced a total of five SAEs considered to be treatment related (pleural effusion [two patients; one each in the 100 and 200 mg QD cohorts], tumor lysis syndrome and congestive heart failure [one patient; 400 mg QD cohort], and diarrhea [one patient; 600 mg QD cohort]). All treatment-related SAEs resolved with supportive care. Fourteen patients (32.6%) in phase 1 died during study participation (10 with MF and four with AML). Seven deaths (involving four patients with MF and three with AML) were attributed to AEs (subdural hematoma, intracranial hemorrhage, septic shock, asthma, cardiorespiratory arrest, anemia, and AML; Additional file 1: Table S2). None of the AEs were considered to be related to treatment. After the 30-day post-treatment discontinuation follow-up, four patients

### Table 2: Dose-limiting toxicities in phase 1 (n = 43)

| Pacitinib dose cohort | Patients, n | DLTs in first cycle | Description | Outcome |
|-----------------------|-------------|---------------------|-------------|---------|
| 100 mg                 | 3           | 0                   |             |         |
| 150 mg                 | 6           | 1 (16.7)            | Grade 3 ECG QT prolong from days 18–47 | Resolved following pacitinib discontinuation. |
| 200 mg                 | 9*          | 0                   |             |         |
| 300 mg                 | 6           | 1 (16.7)            | Grade 3 diarrhea on days 3–4. | Resolved following interruption of pacitinib and treatment with antidiarrheal medication. Pacitinib was restarted. |
| 400 mg                 | 6           | 0                   |             |         |
| 500 mg                 | 7           | 1 (14.3)            | Grade 2 diarrhea on days 8–140. | Resolved following dose reduction to 400 mg and treatment with antidiarrheal medication. |
| 600 mg                 | 6           | 2 (33.3)            | Grade 3 diarrhea beginning on day 11. Grade 1 nausea; grade 1 vomiting; grade 2 dizziness, grade 2 gait disturbance, grade 2 performance status decreased, grade 2 vision blurred | Pacitinib was interrupted then reduced to 400 mg. Antidiarrheal medication was started. Diarrhea was ongoing at the end of treatment. |

*This cohort included three patients treated with the pacitinib HCl salt formulation and an additional six patients treated with the citrate salt formulation. The two salt forms have been shown to be pharmaceutically equivalent.

**DLT: dose-limiting toxicity, ECG: electrocardiogram**
died due to disease progression and three died due to unknown causes.

**Pharmacokinetics**

Pacritinib PK values are shown in Additional file 1: Tables S3 and S4. Median time to maximum concentration ($T_{\text{max}}$) values ranging from 4 to 8 h post dose and 2.5 to 5 h post dose were reported on days 1 and 15, respectively. On day 1, mean maximum concentration ($C_{\text{max}}$), trough concentration ($C_{\text{24}}$) and systemic exposure of pacritinib ($\text{AUC}_{0-24}$) generally increased in a dose-related manner; however, increases in exposure appeared to be less than dose-proportional, with systemic exposure appearing to plateau beyond the 400 mg dose level. On day 15, mean $C_{\text{max}}$, $C_{\text{24}}$ and $\text{AUC}_{0-24}$ did not appear to increase in a dose-related manner within the 100–300 mg dose range and, while exposure was higher at the 400 mg dose level relative to the 300 mg dose level, it appeared to plateau above the 400 mg dose level. The between-patient coefficient of variation for $C_{\text{max}}$ and $\text{AUC}_{0-24}$ ranged from 25 to 63% on day 1 and 20–54% on day 15, indicating relatively high variability across patients.

**Table 3** Treatment-emergent adverse events occurring in $\geq 10\%$ of patients in phase 1 ($n = 43$)

| Treatment-emergent AEs, n (%) | 100 mg | 150 mg | 200 mg | 300 mg | 400 mg | 500 mg | 600 mg | All patients |
|------------------------------|--------|--------|--------|--------|--------|--------|--------|-------------|
| $n = 3$                      | 100.0  | 100.0  | 100.0  | 100.0  | 100.0  | 100.0  | 100.0  | 100.0       |
| $n = 6$                      | 6.67   | 3.33   | 5.56   | 5.00   | 6.00   | 7.00   | 6.00   | 6.00        |
| $n = 9$                      | 1.67   | 2.22   | 1.67   | 2.33   | 3.00   | 3.00   | 2.00   | 1.67        |
| $n = 6$                      | 3.33   | 3.33   | 3.33   | 3.33   | 3.33   | 4.00   | 4.00   | 3.33        |
| $n = 7$                      | 1.67   | 1.11   | 1.67   | 2.33   | 2.33   | 2.33   | 2.00   | 1.67        |
| $n = 6$                      | 6.67   | 3.33   | 1.11   | 0.00   | 2.00   | 2.00   | 3.00   | 3.00        |
| Edema peripheral             | 6.67   | 3.33   | 1.11   | 0.00   | 2.00   | 2.00   | 3.00   | 1.00        |
| Pyrexia                      | 3.33   | 3.33   | 2.22   | 1.67   | 2.33   | 2.33   | 2.00   | 2.33        |
| Anemia                       | 0.00   | 1.67   | 1.11   | 1.67   | 2.33   | 2.33   | 2.00   | 1.67        |
| Constipation                 | 6.67   | 3.33   | 2.22   | 1.67   | 2.33   | 2.33   | 2.00   | 1.67        |
| Abdominal distension         | 0.00   | 2.22   | 1.67   | 3.00   | 1.43   | 1.43   | 1.00   | 2.33        |
| Dyspnea                      | 6.67   | 1.67   | 0.00   | 0.00   | 2.33   | 1.43   | 3.00   | 9.00        |
| Astenia                      | 6.67   | 3.33   | 1.11   | 0.00   | 1.43   | 2.33   | 6.00   | 6.70        |
| Decreased appetite           | 6.67   | 3.33   | 0.00   | 0.00   | 3.00   | 1.67   | 8.00   | 1.70        |
| Epistaxis                    | 6.67   | 1.67   | 1.11   | 2.33   | 1.67   | 1.00   | 1.67   | 7.00        |
| Thrombocytopenia             | 3.33   | 3.33   | 0.00   | 1.67   | 2.33   | 1.43   | 1.67   | 2.00        |
| Abdominal pain               | 3.33   | 1.67   | 1.11   | 1.67   | 2.33   | 1.43   | 0.00   | 6.00        |
| Back pain                    | 3.33   | 3.33   | 0.00   | 1.67   | 2.33   | 1.43   | 0.00   | 7.00        |
| Insomnia                     | 3.33   | 1.67   | 2.22   | 1.67   | 1.67   | 1.43   | 0.00   | 7.00        |
| Hyperuricemia                | 3.33   | 1.67   | 0.00   | 0.00   | 1.43   | 3.50   | 5.00   | 1.70        |
| Cardiac murmur               | 3.33   | 0.00   | 1.11   | 0.00   | 1.67   | 1.43   | 2.33   | 6.00        |
| Dizziness                    | 0.00   | 2.22   | 1.67   | 1.67   | 1.43   | 1.67   | 1.67   | 6.00        |
| Night sweats                 | 3.33   | 0.00   | 1.11   | 0.00   | 2.33   | 1.43   | 1.67   | 6.00        |
| Neutropenia                  | 3.33   | 2.33   | 0.00   | 1.67   | 1.67   | 0.00   | 2.00   | 4.70        |
| Chills                       | 0.00   | 3.00   | 0.00   | 1.67   | 1.43   | 1.67   | 5.00   | 1.67        |
| Cough                        | 3.33   | 1.67   | 1.11   | 1.67   | 1.67   | 0.00   | 5.00   | 1.67        |
| Dehydration                  | 0.00   | 1.67   | 0.00   | 2.33   | 1.43   | 1.67   | 5.00   | 1.67        |
| Hyperbilirubinemia           | 3.33   | 1.67   | 1.11   | 1.67   | 1.67   | 0.00   | 5.00   | 1.67        |
| Pain in extremity            | 100.0  | 0.00   | 1.67   | 0.00   | 1.67   | 0.00   | 5.00   | 1.67        |
| Petechiae                    | 6.67   | 3.33   | 0.00   | 0.00   | 1.43   | 0.00   | 5.00   | 1.67        |
| Skin lesion                  | 0.00   | 4.66   | 1.11   | 0.00   | 0.00   | 0.00   | 5.00   | 1.67        |
| Upper respiratory tract infection | 0.00   | 3.33   | 2.22   | 1.67   | 0.00   | 0.00   | 5.00   | 1.67        |

*Worst grade during treatment*
The mean PK profiles of pacritinib when dosed as citrate and HCl salts were similar (Additional file 1: Figure S1).

**Efficacy**

The clinical benefit rate was 94.4% (34/36) in patients with MF and 42.9% (3/7) in patients with AML, giving an overall clinical benefit rate of 86.0% (13 patients achieving clinical improvement and 24 patients having SD). One patient was reported to have progressive disease, and disease response was not reported for five patients. No clear dose–response correlation was observed.

**Phase 2 Patients**

Thirty-one patients were included in the safety population. Table 6 summarizes common treatment-emergent AEs occurring in ≥10% of patients. Gastrointestinal toxicities were reported by all patients. No leukopenia, neutropenia, or lymphopenia was reported during the study. Twenty-two patients (71.0%) reported at least one grade 3/4 AE, most frequently anemia (n = 5), diarrhea (5), fatigue (5), and bone pain (4). Grade 3 or 4 thrombocytopenia was reported in three patients. One patient with post-PV MF reported two AEs of pancytopenia, grade 3 and 4 in severity, that were considered unrelated to study drug and resolved. Three patients (9.7%) discontinued pacritinib because of an AE (grade 2 diarrhea, grade 3 diarrhea, and grade 2 anemia). Fourteen patients had dose interruptions and 14 patients had dose reductions because of AEs, most frequently related to diarrhea.

The most frequent AEs considered to be treatment related were diarrhea (n = 28; 90.3%), nausea (15; 48.4%), vomiting (9; 29.0%), and fatigue (4; 12.9%). Grade 3 treatment-related AEs were reported in seven patients (22.6%), four of which were diarrhea. No grade 4 treatment-related AEs were reported.

Change over time in hematologic parameters is shown in Additional file 1: Table S6. The percentage change in hemoglobin measurements at each study visit through week 60 relative to baseline remained between a median of −0.5% and +10.1% (range −31% to +146%). At week 24, 10/20 patients (50.0%) had hemoglobin levels <10 g/L and 1/20 patients (5.0%) had hemoglobin levels <8 g/L. During the study, 16 patients (51.6%) received RBC transfusions (median 1 units, range 2–73 units). Platelet counts changed modestly on treatment, with a baseline median platelet count of 126 × 10^9/L and ranging from a median of 89 to 155 × 10^9/L through week 60 on study. At week 24, 10/20 patients (50.0%) and 2/20 patients (10.0%) had platelet counts <100 × 10^9/L and <50 × 10^9/L, respectively. During the study, three patients (9.7%) received platelet transfusions (median 3 units, range 2–38 units). At week 24, 2/20 patients (10.0%) had leukocyte counts >25 × 10^9/L. The median discontinuation of pacritinib prior to week 24 (seven due to lack of response, one due to AEs, and one each due to disease progression, death, and withdrawal of consent) and three remained on pacritinib after week 24, but did not complete the week 24 MRI.

At week 24, 38.9% of evaluable patients (7/18) had achieved a ≥50% reduction in MF Quality of Life and Symptom Assessment total score relative to baseline (Table 5). Improvement was seen in each of the individual symptoms, as well as the overall quality of life score (Additional file 1: Table S5).

**Efficacy**

Spleen responses are summarized for the efficacy evaluable population (Table 5) and displayed as median percent change from baseline up to week 60 (Fig. 1). The primary endpoint (proportion of evaluable patients achieving ≥35% spleen volume reduction at week 24 by MRI) was 23.5% (4/17), with 47.4% (9/19) achieving a ≥50% spleen length reduction at week 24 by physical examination. When assessed up to the end of treatment, 30.4% of patients (7/23) achieved the objective spleen volume reduction and 38.7% (12/31) achieved the objective spleen length reduction. Of the 31 patients who received at least one dose of pacritinib, 14 were not evaluable for spleen response at week 24: 11 discontinued pacritinib prior to week 24 (seven due to lack of response, one due to AEs, and one each due to disease progression, death, and withdrawal of consent) and three remained on pacritinib after week 24, but did not complete the week 24 MRI.

The clinical benefit rate was 94.4% (34/36) in patients with MF and 42.9% (3/7) in patients with AML, giving an overall clinical benefit rate of 86.0% (13 patients achieving clinical improvement and 24 patients having SD). One patient was reported to have progressive disease, and disease response was not reported for five patients. No clear dose–response correlation was observed.

**Phase 2 Patients**

Thirty-one patients with MF were enrolled in phase 2, 31 of whom received at least one dose of pacritinib 400 mg QD. Patient demographics and baseline characteristics are shown in Table 4. All patients had splenomegaly with a median length below the left costal margin (as determined by physical examination) of 19 cm (range 7–29). At baseline, grade 2 or higher anemia and thrombocytopenia were reported in 20 (60.6%) and 11 (33.3%) patients, respectively. Six patients (19.4%) were red blood cell (RBC) transfusion dependent at baseline and ten patients (33.3%) had received RBC transfusions within the 180 days prior to study entry. No patients were considered platelet transfusion dependent at baseline, but one patient had received platelet transfusions within 180 days prior to study enrollment. Of the 33 patients enrolled, 13 (39.4%) completed the study and 20 patients (60.6%) discontinued the study prior to completion, primarily because of the sponsor’s decision to terminate the study (n = 12) and subject withdrawal of consent (n = 5). Of the 31 patients who received at least one dose of pacritinib, median duration of treatment was 11.5 months (range 1.0–20.1). Median actual dose intensity was 371 mg/day (range 208–400) and relative dose intensity was 92.9% (range 52.1–100.0%).

**Safety**

The clinical benefit rate was 94.4% (34/36) in patients with MF and 42.9% (3/7) in patients with AML, giving an overall clinical benefit rate of 86.0% (13 patients achieving clinical improvement and 24 patients having SD). One patient was reported to have progressive disease, and disease response was not reported for five patients. No clear dose–response correlation was observed.
neutrophil count was 6.98 \times 10^9/L at baseline and the median ranged from 3.83 to 6.00 \times 10^9/L through week 60 on study.

SAEs occurred in 13 patients (41.9%), two of which were considered to be related to pacritinib (grade 3 diarrhea and grade 3 dehydration; Additional file 1: Table S7). Nine patients (27.3%) who participated in the phase 2 study died during the study due to AEs. One patient died from disease progression after the 30-day follow-up and five died due to unknown causes after the 30-day follow-up. None of the deaths were considered related to pacritinib (Additional file 1: Table S7).

Discussion

This multicenter phase 1/2 study has provided proof-of-concept for selective JAK2/FLT-3 inhibition with pacritinib as a treatment strategy in MF. Patients treated with pacritinib demonstrated notable reductions in spleen volume and improvements in MF-related symptoms, consistent with findings of another phase 2 study of pacritinib in MF [25] and a phase 3 randomized controlled trial comparing pacritinib with best-available therapy (PERSIST-1) [26, 27]. While the pathogenesis of this disease is complex, it appears that JAK inhibition reduces the inflammatory and proliferative phenotype associated with JAK/STAT-signaling aberrancy [28]. Indeed, the improvements in constitutional symptoms seen with pacritinib in this study are indicative that suppression of JAK2 even in the absence of JAK1 blockade is sufficient for inhibition of the inflammatory cytokine pathway responsible for disease symptoms.

In the dose-escalation phase of the study, the MTD was determined to be 500 mg/day, but due to increased tolerability, the recommended daily dose of pacritinib to be taken forward into phase 2 clinical development was 400 mg. This

| Table 4 Baseline characteristics and demographics for patients enrolled in phase 2 \((n = 33)^a\) |
|-----------------------------------------------|
| Pacritinib 400 mg \( n = 33^b \) |
| **Median age, years (range)** | 67.0 (47–83) |
| **Male, \( n \) (\%)** | 22 (66.7) |
| **Median time from initial diagnosis, months (range)** | 31.8 (0.3–210.0) |
| **Median prior systemic therapies, \( n \) (range)** | 1 (0–4) |
| **Median time since last MF treatment, months (range)** | 1.68 (0.6–36.4) |
| **ECOG PS, \( n \) (\%)** |
| 0 | 6 (18.2) |
| 1 | 19 (57.6) |
| 2 | 8 (24.2) |
| **JAK2 mutation\(^d\), \( n \) (\%)** | 27 (81.8) |
| **Type of myelofibrosis, \( n \) (\%)** |
| Primary myelofibrosis | 17 (51.5) |
| Post-polycythemia vera myelofibrosis | 12 (36.4) |
| Post-essential thrombocythemia myelofibrosis | 4 (12.1) |
| **Current Lille Score, \( n \) (\%)** |
| High risk | 1 (3.0) |
| Intermediate risk | 7 (21.2) |
| Low risk | 2 (6.1) |
| Missing\(^e\) | 23 (69.7) |
| **Current DIPSS risk category, \( n \) (\%)** |
| High risk | 7 (21.2) |
| Intermediate-2 risk | 9 (27.3) |
| Intermediate-1 risk | 3 (9.1) |
| Indeterminate\(^f\) | 14 (42.4) |
| **Hemoglobin** |
| Median\(^g\), g/L (range) | 90.0 (37–144) |
| Grade 0–2, \( n \) (\%) | 27 (81.8) |
| Grade 3, \( n \) (\%) | 6 (18.2) |
| Baseline hemoglobin level, \( n \) (\%) |
| <10 g/L | 20 (60.6) |
| <8 g/L | 6 (18.2) |
| RBC-transfusion dependent\(^g\), \( n \) (\%) | 6 (19.4) |
| **Platelets** |
| Median\(^h\), \( \times 10^9 \)/L (range) | 126.0 (28–494) |
| Grade 0–2, \( n \) (\%) | 29 (87.9) |
| Grade 3, \( n \) (\%) | 4 (12.1) |
| Baseline platelet count, \( n \) (\%) |
| <100 \( \times 10^9 \)/L | 10 (42.4) |
| <50 \( \times 10^9 \)/L | 4 (12.1) |
| Platelet-transfusion dependent\(^g\), \( n \) (\%) | 0 |

\(^a^\)Two patients enrolled in the study did not receive the study drug: one patient withdrew consent before beginning treatment and the second patient was unable to undergo magnetic resonance imaging (one of the eligibility criteria)

\(^b^\)97% of patients were white

\(^c^\)In patients who had received prior treatment \((n = 25)\)

\(^d^\)All JAK2 mutations were V617F

\(^e^\)Case report forms were designed for direct entry of Lille score by sites; however, some versions of the forms were missing the field for entry of Lille score

\(^f^\)Unable to calculate DIPSS risk category due to missing baseline peripheral blood blasts

\(^g^\)In the safety population \((n = 31)\)

DIPSS Dynamic International Prognostic Scoring System, ECOG PS Eastern Cooperative Oncology Group Performance Status

neutrophil count was 6.98 \times 10^9/L at baseline and the median ranged from 3.83 to 6.00 \times 10^9/L through week 60 on study.

SAEs occurred in 13 patients (41.9%), two of which were considered to be related to pacritinib (grade 3 diarrhea and grade 3 dehydration; Additional file 1: Table S7). Nine patients (27.3%) who participated in the phase 2 study died during the study due to AEs. One patient died from disease progression after the 30-day follow-up and five died due to unknown causes after the 30-day follow-up. None of the deaths were considered related to pacritinib (Additional file 1: Table S7).
Table 5 Summary of best spleen response and symptom score change from baseline in phase 2 (efficacy evaluable population)a

| Endpoint                                      | Patients achieving endpoint, n/N (%) | 95% CI         |
|-----------------------------------------------|--------------------------------------|----------------|
|                                               | At week 24 visit                      | Up to week 24 visit | At end of treatment | Up to end of treatment |
| ≥35% spleen volume reduction by MRI           | 4/17 (23.5)                          | 5/23 (21.7)       | 4/23 (17.4)         | 7/23 (30.4)            | 6.8–49.9                  | 95% CI 5.0–38.8          |
| ≥50% spleen length reduction by physical exam | 9/19 (47.4)                          | 12/31 (38.7)      | 9/31 (29.0)         | 12/31 (38.7)           | 24.4–71.1                 | 95% CI 14.2–48.0         |
| ≥50% reduction in MF Quality of Life and Symptom Assessment total symptom score | 7/18 (38.9)                          | 12/29 (41.4)      | 4/29 (13.8)         | 12/29 (41.4)           |                             |                            |

aPatients included in the efficacy evaluable population are those who had both a non-missing baseline measurement and post-baseline measurement at or through the time point specified.

MRI: magnetic resonance imaging.

Fig. 1 Median percent change in (a) spleen volume and (b) spleen length from baseline in efficacy evaluable population of the phase 2 study.
is consistent with the PK profile of pacritinib, where exposure began to plateau at the 400 mg dose. Pacritinib had an acceptable tolerability profile in this study, with the most common AEs being gastrointestinal disorders, most of which were grade 1 or 2 in severity and resolved with treatment interruptions/dose reductions and supportive care. Gastrointestinal disorders (diarrhea) accounted for treatment discontinuations in only two patients. Of particular interest was the low rate of treatment-emergent anemia or thrombocytopenia during pacritinib treatment, despite no exclusion from participation based on baseline hemoglobin level or platelet count. This is consistent with results from the phase 3 PERSIST-1 study, which showed that pacritinib resulted in durable reductions in spleen volume and symptom burden, including in patients with baseline thrombocytopenia [29].

This study was terminated by the sponsor (S*BIO Pte Ltd, Singapore) for financial reasons in October 2011, meaning that only the data fields assessed as critical for evaluation of efficacy and safety were queried for missing, incorrect or discrepant data prior to database lock. This early termination required all patients who were still receiving pacritinib to stop, limiting our ability to fully assess the long-term effects of pacritinib exposure.

JAK kinase inhibitors have shown the potential to produce durable responses and improve survival in MF [30, 31]; however, minimizing toxicity and avoiding drug resistance are ongoing challenges. Indeed, options remain limited for patients with thrombocytopenia, who are not suitable for treatment with the only currently licensed JAK inhibitor, ruxolitinib. These results suggest that pacritinib has unique characteristics, namely a lack of substantial myelosuppression and manageable non-hematological side effects.

### Conclusions

In this study, pacritinib demonstrated clinical activity in patients with MF that had relapsed or that was poorly controlled with or not suitable for standard therapy. The lack of substantial myelosuppression and manageable side effects seen with pacritinib make it an attractive target for further development in MF.

### Additional files

**Table 6** Treatment-emergent adverse events occurring in ≥10% of patients in phase 2 (n = 31)

| Treatment-emergent AEs, n (%) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any grade |
|------------------------------|---------|---------|---------|---------|-----------|
| Diarrhea                     | 14 (45.2) | 9 (29.0) | 5 (16.1) | 0       | 28 (90.3) |
| Fatigue                      | 2 (6.5)  | 11 (35.5) | 4 (12.9) | 1 (3.2) | 18 (58.1) |
| Nausea                       | 9 (29.0) | 6 (19.4)  | 1 (3.2)  | 0       | 15 (51.6) |
| Edema peripheral             | 6 (19.4) | 5 (16.1)  | 1 (3.2)  | 0       | 12 (38.7) |
| Vomiting                     | 7 (22.6) | 3 (9.7)   | 1 (3.2)  | 0       | 11 (35.5) |
| Abdominal pain               | 3 (9.7)  | 3 (9.7)   | 3 (9.7)  | 0       | 9 (29.0)  |
| Insomnia                     | 7 (22.6) | 2 (6.5)   | 0        | 0       | 9 (29.0)  |
| Pruritus                     | 4 (12.9) | 4 (12.9)  | 1 (3.2)  | 0       | 9 (29.0)  |
| Pain in extremity            | 5 (16.1) | 2 (6.5)   | 0        | 1 (3.2) | 8 (25.8)  |
| Night sweats                 | 4 (12.9) | 3 (9.7)   | 0        | 0       | 7 (22.6)  |
| Anemia                       | 0        | 1 (3.2)   | 3 (9.7)  | 2 (6.5) | 6 (19.4)  |
| Bone pain                    | 1 (3.2)  | 1 (3.2)   | 4 (12.9) | 0       | 6 (19.4)  |
| Astenia                      | 4 (12.9) | 1 (3.2)   | 0        | 0       | 5 (16.1)  |
| Constipation                 | 5 (16.1) | 0        | 0        | 0       | 5 (16.1)  |
| Dyspnea                      | 4 (12.9) | 0        | 1 (3.2)  | 0       | 5 (16.1)  |
| Cardiac murmur               | 0        | 4 (12.9)  | 0        | 0       | 4 (12.9)  |
| Hyperuricemia                | 2 (6.5)  | 0        | 0        | 2 (6.5) | 4 (12.9)  |
| Pyrexia                      | 4 (12.9) | 0        | 0        | 0       | 4 (12.9)  |
| Rash                         | 2 (6.5)  | 1 (3.2)   | 1 (3.2)  | 0       | 4 (12.9)  |
| Upper respiratory tract infection | 3 (9.7) | 1 (3.2)   | 0        | 0       | 4 (12.9)  |
| Weight decreased             | 4 (12.9) | 0        | 0        | 0       | 4 (12.9)  |

**Additional file 1:** Table S1. Dose adjustment and toxicity management guidelines—non-hematologic toxicities. Table S2. Serious adverse events and deaths occurring in phase 1 component of the study (n = 43). Table S3. Day 1 pharmacokinetics of pacritinib in the phase 1 part of the study (n = 43). Table S4. Day 15 pharmacokinetics of pacritinib in the phase 1 part of the study (n = 43). Table S5. Percent change from baseline at week 24 for individual and total symptom scores from the Myelofibrosis Quality of Life and Symptom Assessment Tool—phase 2 (efficacy
evaluable population. Table S6 Median percent change from baseline in hematologic parameters over time in the phase 2 component of the study (n = 31). Table S7 Serious adverse events and deaths occurring in the phase 2 component of the study (n = 31). Figure S1 Mean concentration-time profiles of pacritinib when dosed as hydrochloride and citrate salts at a dose of 200 mg. (DOC 296 kb)

Abbreviations
AE: Adverse event; AML: Acute myeloid leukemia; C24: Trough concentration; Cmax: Maximum concentration; CML: Chronic myeloid leukemia; DLT: Dose-limiting toxicity; ECOG PS: Eastern Cooperative Oncology Group performance status; ET: Essential thrombocythemia; FLT3: FMS-like tyrosine kinase 3; HCl: Hydrochloride; IWG: International Working Group; MF: Myelofibrosis; MPN: Myeloproliferative neoplasm; MRI: Magnetic resonance imaging; MTD: Maximum tolerated dose; PET: Post-essential thrombocythemia; PK: Pharmacokinetic; PPV: Post-polycythemia vera; PV: Polycythemia vera; QD: Once daily; RBC: Red blood cell; SAE: Serious adverse event; SD: Stable disease

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Availability of data and materials
The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
SV designed the research; SV, OO, and HJD performed the research; SV, OO, JWS, TG, SA, and HJD critically assessed and revised the manuscript and approved the final manuscript. All authors read and approved the final version; and TG performed the statistical analysis. JWS, TG, SA, and HJD analyzed or interpreted the data; SV, OO, JWS, TG, SA, and HJD collected data.

Competing interests
SV received research support for the conduct of this study. OO has served on advisory boards for CTI BioPharma Corp, Baxalta Incorporated, Celgene, Incyte, Sunesis, and Spectrum. JWS, TG, and SA are employees of CTI BioPharma Corp. HJD has no conflicts of interest to report.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization guidelines, and relevant laws and regulations. The protocol was approved by the institutional review boards at each study site. Written informed consent was obtained from all patients prior to participation.

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