Thorough QT Analysis of a Single Dose of Pacritinib: Results of the PAC107 Study

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Conclusions

- **Pacritinib administered as a single 400 mg dose was not associated with QT prolongation** and did not have a meaningful effect on any other electrocardiogram (ECG) parameter
- This analysis is limited by administering a single dose of pacritinib, and serum pacritinib concentrations not reaching the steady-state expected with the approved 200 mg twice-daily (BID) dose
  - However, assay sensitivity was demonstrated by the single-dose moxifloxacin response, supporting the validity of these results

Introduction

- Pacritinib is a JAK2/IRAK1/ACVR1 inhibitor[1,2] approved for the treatment of patients with myelofibrosis who have severe thrombocytopenia[3]
- The prescribing information for pacritinib includes a warning for QT prolongation[3]
  - However, data on the effect of pacritinib on the QT interval are derived from clinical studies of patients with myelofibrosis, and thus these analyses are confounded by the use of concomitant QT interval-prolonging supportive medications
- The impact of pacritinib monotherapy on the QT interval has not been published previously

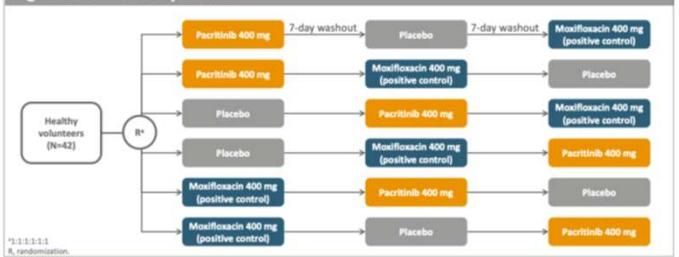
Aim

- To evaluate the impact of pacritinib monotherapy compared with placebo and a positive control (moxifloxacin) on QT interval in healthy subjects

Methods

- Healthy volunteers were treated in a randomized, controlled, single-center, 3-period crossover study with pacritinib 400 mg, moxifloxacin 400 mg (positive control), and placebo (negative control)
  - The study was blinded for pacritinib and placebo, and open-label for moxifloxacin
- Each treatment period involved monotherapeutic drug administration followed by a 7-day washout, with a 14-day follow-up after the final treatment period (**Figure 1**)
- Cardiodynamic ECGs were collected continuously from 1 hour pre-dose through 24 hours post-dose, then for 15 min every 12 hours on Days 2–7 of each treatment period
  - Blood samples were also collected pre-dose and up to 168 hours post-dose for pharmacokinetic (PK) analysis
- QT interval calculations were corrected by the Fridericia method (QTcF)

Figure 1. PAC107 Study Schema



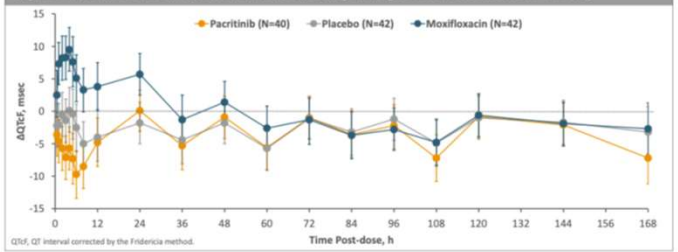
Results

- 42 healthy subjects were randomized, received study treatment, and included in the safety population (mean [standard deviation] age: 37 [8.6] years; 59.5% male; 69.0% White)
  - 41 completed the study and were included in the PK population (1 patient withdrew for personal reasons)
  - 40 were included in the QTc population (2 participants did not have QTc data available for all 3 periods); baseline ECG parameters were balanced across treatment groups

Pacritinib Monotherapy Does Not Prolong the QTcF Interval

- A statistically significant shortening of the QTcF interval after administration of pacritinib was observed, with the maximal shortening of 9.7 msec (90% confidence interval [CI]: -13.4, -6.1) occurring at the 6-hour timepoint, followed by recovery to baseline by the 12-hour timepoint (**Figure 2**)
- By contrast, a statistically significant prolongation of QTcF was demonstrated after moxifloxacin administration, with maximal mean lengthening of 9.5 msec (90% CI: 6.2, 12.9) at the 4-hour timepoint (**Figure 2**)
- The QTcF after placebo administration was similar to baseline

Figure 2. No increase in QTcF Interval Following a Single Dose of Pacritinib 400 mg



The PK Profile of Pacritinib was Consistent with Previous Studies

- The mean C_{max} of pacritinib was 3770 ng/mL, occurring at a median t_{max} of 6.0 hours (**Figure 3**)
- Pacritinib concentration declined in a monophasic manner, with a mean $t_{½}$ of 36.4 hours

Figure 3. Plasma Pacritinib Concentration Declined in a Monophasic Manner

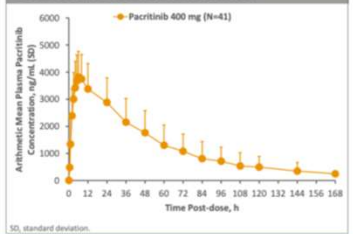
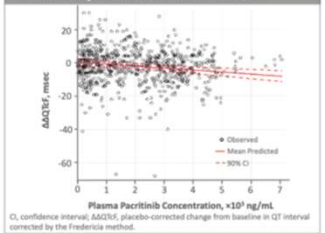


Figure 4. Pacritinib Plasma Concentration is Inversely Correlated with ΔΔQTcF



Pacritinib Plasma Concentration is Negatively Associated with QTcF Interval

- A small, but statistically significant, inverse relationship was found between plasma levels of pacritinib and the QTcF interval (**Figure 4**)
- The QT shortening effect at this level was not clinically relevant

The Safety Profile of Pacritinib was Consistent with Previous Studies

- Treatment-emergent adverse events (TEAEs) occurring were reported more frequently when individuals were administered pacritinib 400 mg versus placebo (**Table**)
  - The most commonly reported TEAEs following pacritinib administration were diarrhea (29.3%) and nausea (12.2%; **Table**)
- The majority of TEAEs reported among individuals administered pacritinib were Grade 1 and related to the gastrointestinal system
- No TEAEs greater than Grade 2, serious adverse events, adverse events leading to study withdrawal, or deaths were reported during the study

Table. Summary of TEAEs[a]

MedDRA PT	Pacritinib 400 mg (N=41)	Placebo (N=42)	Moxifloxacin (N=42)
Total all-cause TEAEs, n (%)	18 (43.9)	9 (21.4)	9 (21.4)
Diarrhea	12 (29.3)	1 (2.4)	–
Nausea	5 (12.2)	1 (2.4)	2 (4.8)
Constipation	2 (4.9)	–	–
Headache	1 (2.4)	2 (4.8)	2 (4.8)
Dysmenorrhea	1 (2.4)	–	2 (4.8)
Total treatment-related[b] TEAEs, n (%)	14 (34.1)	2 (4.8)	3 (7.1)
Diarrhea	11 (26.8)	1 (2.4)	–
Nausea	4 (9.8)	1 (2.4)	2 (4.8)

[a]Only TEAEs occurring in ≥2 subjects in any treatment group are reported here.
[b]Determined to be possibly, probably, or definitely related to study drug.
MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; TEAE, treatment-emergent adverse event.

References

1. Singer JW, et al. *J Exp Pharmacol*. 2016;8:11–19. **2.** Oh ST, et al. *Blood Adv*. 2023;7:5835–5842. **3.** VONJO® (pacritinib) Prescribing Information. Available at: https://www.ctibiopharma.com/VONJO_USPI.pdf. Accessed: July 2024.

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Disclosures

SB, PS, PK: Employees of Sobi Inc. and have received payment of unvested equity awards from CTI BioPharma Corp., a Sobi company, following its acquisition in June 2023 by Sobi US Holding, which is wholly owned by Sobi AB. **JD:** Employment and stock/other ownership with AbbVie. **SA-F and LW:** None.

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