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# A PHASE 1 OPEN LABEL STUDY TO DETERMINE THE PHARMACOKINETICS OF PACRITINIB IN PATIENTS WITH MILD TO SEVERE RENAL IMPAIRMENT AND END STAGE RENAL DISEASE (ESRD) COMPARED WITH HEALTHY SUBJECTS

**Suliman Al-Fayoumi[1], Sherri Amberg[1], Huafeng Zhou[1], Lindsey Millard[1], Jack W. Singer[1], Mary Campbell[1]**

[1]CTI BioPharma Corp., Seattle, WA

## INTRODUCTION

- Adequate characterization of the pharmacokinetics (PK) of drugs in patients with renal impairment is required by regulatory authorities to support appropriate dosage recommendations in labeling
- Pacritinib is an oral kinase inhibitor with specificity for JAK2, FLT3, CSF1R, and IRAK1[1-3] under investigation to treat MF
- In a phase 1 human ADME study, pacritinib was found to be excreted primarily as metabolites in feces, suggesting extensive biliary clearance and hepatic metabolism[4]
- M1 and M2, the two major identified metabolites of pacritinib, exhibit relatively low pharmacologic potency and are unlikely to significantly contribute to its activity[4]
  - $IC_{50s}$ for JAK2 of pacritinib, M1, and M2 are 0.012 μM, 0.023 μM, and 0.058 μM, respectively; M1 and M2 each constituted approximately 10% of plasma exposure relative to pacritinib
- This study aimed to assess the PK and safety profiles of pacritinib and M1 in patients with mild, moderate, severe renal impairment or ESRD vs healthy volunteers with normal renal function

## METHODS

### Key Inclusion/Exclusion Criteria

- Male and/or female subjects age 18-85 y
- Body mass index of 18.0-33.0 mg/kg$^2$
- Negative test for drugs of abuse (including alcohol)
- Negative test for hepatitis B, hepatitis C, and HIV infection
- Serum creatinine result and eGFR values consistent with the degree of renal impairment:
  - Healthy participants: eGFR ≥90 mL/min/1.73 m$^2$
  - Mild RI: eGFR 60-89 mL/min/1.73 m$^2$
  - Moderate RI: eGFR 30-59 mL/min/1.73 m$^2$
  - Severe RI: creatinine clearance from eGFR 15-29 mL/min/1.73 m$^2$
  - End stage renal disease (ESRD): patients must have been on a stable dialysis regimen for at least 6 months
- Acceptable clinical condition as determined by past medical history, physical examination, ECG, vital signs, laboratory tests, and urinalysis

### Study Design

- Healthy volunteers and those with mild, moderate, or severe RI were administered a single 400 mg dose of pacritinib capsules
- Patients with ESRD received 2 single 400 mg doses of pacritinib capsules during different treatment periods 14 days apart: Dialysis (pacritinib given 4 h prior to dialysis) and Inter-Dialysis (pacritinib given immediately following dialysis)
- Plasma and urine were sampled up to 168 h post-dose for healthy volunteers and patients with mild, moderate, or severe RI
- Plasma and dialysate were sampled up to 72 h post-dose for patients with ESRD
- Adverse events (AEs) were monitored for all participants

### Pharmacokinetic Assessments

- Plasma, dialysate, and urine concentrations of pacritinib and M1 were determined by a validated, sensitive, and specific HPLC/tandem MS assay as previously described[5]
  - Lower limit of quantitation was 20 ng/mL for pacritinib and 4 ng/mL for the M1 metabolite

### Safety Assessments

- Safety assessments included physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (blood chemistry, hematology), and AE monitoring
- Healthy volunteers and RI patients without ESRD additionally received clinical laboratory evaluations on urinalysis
- Treatment-related AEs were defined as at least possibly pacritinib-related according to the Investigator

### Statistical Methods

- The influence of RI on PK parameters was assessed using an analysis of variance (ANOVA) model appropriate for the parallel-group design
  - Natural log transformed maximum plasma concentration ($C_{max}$), area under the plasma concentration-time curve (AUC), and renal clearance ($CL_R$) were included for patients in all groups except patients with ESRD during the dialysis period
- PK parameter point estimates and the 90% confidence intervals (CIs) were estimated from the model, and CIs were converted to inference on the ratios of geometric least squares means (LSM) by exponential transformation

## RESULTS

### Table 1. Summary of Demographics

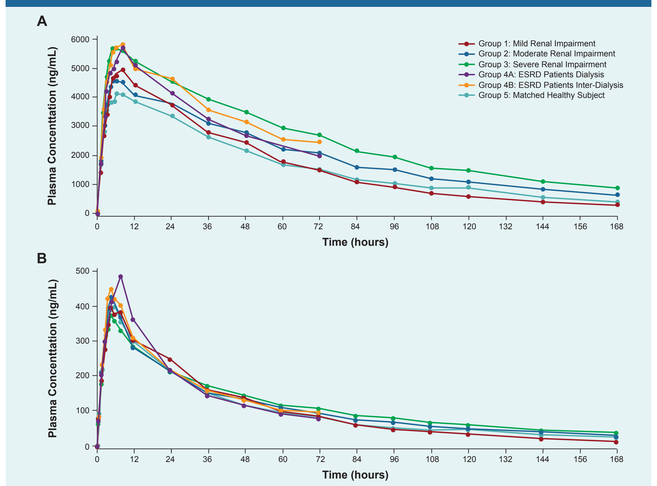
| Variable | Group 1: Mild RI n=8 | Group 2: Moderate RI n=8 | Group 3: Severe RI n=8 | Group 4: ESRD n=8 | Group 5: Healthy Subjects n=7 | Total Subjects N=39 |
|---|---|---|---|---|---|---|
| **Age, y** | | | | | | |
| Median (range) | 53.0 (36-66) | 60.0 (42-66) | 60.5 (36-74) | 59.5 (50-74) | 55.0 (43-66) | 58.0 (36-74) |
| **Height, cm** | | | | | | |
| Median (range) | 162.5 (152.0-167.0) | 167.5 (158.0-170.0) | 166.0 (161.0-187.0) | 164.3 (151.5-176.0) | 166.0 (158.0-172.0) | 165.0 (151.5-187.0) |
| **Weight, kg** | | | | | | |
| Median (range) | 78.25 (60.5-88.9) | 82.55 (70.0-91.1) | 81.15 (59.8-98.8) | 76.00 (51.5-92.0) | 73.00 (61.0-91.0) | 78.80 (51.5-98.8) |
| **BMI, kg/m$^2$** | | | | | | |
| Median (range) | 29.75 (23.1-32.2) | 30.15 (24.2-32.9) | 29.20 (20.9-31.4) | 27.00 (22.1-33.4) | 27.6 (22.1-31.5) | 29.1 (20.9-33.4) |
| **Gender, n (%)** | | | | | | |
| Female | 7 (87.5) | 5 (62.5) | 4 (50.0) | 3 (37.5) | 3 (42.9) | 22 (56.4) |
| Male | 1 (12.5) | 3 (37.5) | 4 (50.0) | 5 (62.5) | 4 (57.1) | 17 (43.6) |
| **Race, n (%)** | | | | | | |
| White | 8 (100) | 8 (100) | 8 (100) | 8 (100) | 7 (100) | 39 (100) |

BMI, body mass index; ESRD, end stage renal disease; RI, renal impairment.

### Pharmacokinetic Profile of Pacritinib and M1 Metabolite Over Time

- Time to maximum plasma concentration ($T_{max}$) for pacritinib was reached at 8, 6, and 5.5 h post-dose in patients with mild, moderate, and severe RI, respectively; $T_{max}$ was 7 and 8 h post-dose in ESRD and healthy participants, respectively (**Figure 1A**)
- $T_{max}$ for M1 metabolite was reached at 5 h post-dose in patients with mild, moderate, and severe RI, ESRD patients in the inter-dialysis period, and healthy volunteers; $T_{max}$ was reached at 8 h post-dose in ESRD patients in the dialysis period (**Figure 1B**)
- Elimination of pacritinib and M1 metabolite were comparable across all groups
- Urinary excretion of unchanged pacritinib was minimal (1.0-1.4% of dose over 72 h), and RI did not decrease urinary excretion (**Table 2**)

### Figure 1: Mean Plasma Concentrations of (A) Pacritinib and (B) M1 Metabolite Over Time




ESRD, end stage renal disease.

### Table 2. Urinary Excretion of Pacritinib

| Urinary Excretion (unit)[a] | Group 1: Mild RI n=8 | Group 2: Moderate RI n=8 | Group 3: Severe RI n=8 | Group 5: Healthy Subjects n=7 |
|---|---|---|---|---|
| $Ae_{0\text{-}72\ h}$ | 4.40 ± 2.75 | 4.77 ± 3.00 | 5.77 ± 2.04 | 3.96 ± 2.38 |
| Fe (% dose) | 1.10 ± 0.687 | 1.19 ± 0.750 | 1.44 ± 0.510 | 0.989 ± 0.596 |

[a]Values are arithmetic mean ± SD

$Ae_{0\text{-}t}$, amount of unchanged drug excreted in the urine up to t h post-dose; Fe, fraction unchanged drug excreted in urine as the cumulative urinary excretion expressed as % of dose; RI, renal impairment.

### Pharmacokinetic Parameters of Pacritinib and M1 Metabolite

- PK analysis of pacritinib revealed higher mean total exposure of pacritinib in patients with RI vs. healthy controls, which is unlikely to be of clinical relevance (**Tables 3** & **4**)
- PK analysis of M1 metabolite demonstrated no change in mean $C_{max}$ or AUC in patients with RI vs. healthy controls
- $C_{max}$ of M1 ranged from 0.391-0.505 μg/mL across all RI groups and $AUC_{0\text{-}t}$ ranged from 13.6-19.2 μg•h/mL
  - Mean $C_{max}$ and AUC of pacritinib and M1 were similar for patients with ESRD during dialysis and inter-dialysis periods
- Mean apparent total clearance (CL/F) for pacritinib was comparable across RI groups

### Table 3. Pharmacokinetic Parameters of Pacritinib

| PK Parameter | Group 1: Mild RI n=8 | Group 2: Moderate RI n=8 | Group 3: Severe RI n=8 | Group 4: ESRD n=8 | | Group 5: Healthy Subjects n=7 |
|---|---|---|---|---|---|---|
| | | | | Dialysis | Inter-Dialysis | |
| $C_{max}$, μg/mL | 5.00 ± 2.22 | 4.75 ± 0.896 | 5.83 ± 2.86 | 6.01 ± 2.45 | 5.97 ± 2.27 | 4.26 ± 0.596 |
| $T_{max}$ (range), h | 8.00 (4.00-12.00) | 6.00 (5.00-24.00) | 5.50 (3.00-8.00) | 6.96 (4.08-12.00) | 7.00 (5.00-8.00) | 8.00 (3.00-24.00) |
| $AUC_{0\text{-}t}$, μg•h/mL | 274 ± 106 | 334 ± 103 | 430 ± 287 | 243 ± 149 | 267 ± 136 | 268 ± 75.5 |
| $t_{1/2}$, h | 39.4 ± 9.11 | 58.0 ± 13.3 | 55.6 ± 17.2 | 44.0 ± 23.3 | 54.1 ± 37.6 | 44.7 ± 11.4 |
| CL/F, L/h | 1.57 ± 0.622 | 1.32 ± 0.622[a] | 1.41± 1.11[b] | 2.96 ± 1.15[c] | NC[d] | 1.58 ± 0.862 |
| $CL_R$, L/h | 0.0250 ± 0.0184 | 0.0206 ± 0.0110 | 0.0277 ± 0.0188 | NA | NA | 0.0210 ± 0.0188 |
| Vz/F, L | 86.1 ± 28.8 | 98.1 ± 49.2[a] | 90.9 ± 43.8[b] | 87.8 ± 6.20[c] | NC[d] | 99.3 ± 48.9 |

Values are the arithmetic mean ± SD, except median (range) for $T_{max}$

[a]n=6; [b]n=7; [c]n=3; [d]n=2. Individual subject data was excluded if the extrapolated part of $AUC_{0\text{-}\infty}$ exceeded 20% of the total $AUC_{0\text{-}\infty}$.

$AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time of dosing to last measurable concentration; CL/F, apparent total clearance; $CL_R$, renal clearance; $C_{max}$, maximum plasma concentration; NA, not applicable; NC, not calculated; $t_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration; Vz/F, apparent total volume of distribution.

### Table 4. Summary of Inferential Statistical Analysis of Pacritinib Main PK Parameters

| PK Parameter | Comparison | Ratio of Geometric LSMs (ANOVA) | | |
|---|---|---|---|---|
| | | Point Estimate | 90% CI | |
| $C_{max}$, μg/mL | Mild RI vs. Normal | 111.18 | 82.23 | 150.32 |
| | Moderate RI vs. Normal | 110.92 | 82.04 | 149.98 |
| | Severe RI vs. Normal | 124.32 | 91.95 | 168.09 |
| | ESRD vs. Normal | 132.96 | 98.34 | 179.77 |
| $AUC_{0\text{-}t}$, μg•h/mL | Mild RI vs. Normal | 100.94 | 65.08 | 156.57 |
| | Moderate RI vs. Normal | 124.50 | 80.26 | 193.10 |
| | Severe RI vs. Normal | 139.27 | 89.79 | 216.02 |
| | ESRD vs. Normal | 91.38 | 58.91 | 141.73 |
| $AUC_{0\text{-}72h}$, μg•h/mL | Mild RI vs. Normal | 106.71 | 71.97 | 158.23 |
| | Moderate RI vs. Normal | 117.36 | 79.15 | 174.20 |
| | Severe RI vs. Normal | 130.52 | 88.02 | 193.54 |
| | ESRD vs. Normal | 125.29 | 84.49 | 185.77 |
| $AUC_{0\text{-}\infty}$, μg•h/mL | Mild RI vs. Normal | 98.49 | 65.08 | 149.05 |
| | Moderate RI vs. Normal | 118.92 | 76.18 | 185.66 |
| | Severe RI vs. Normal | 123.81 | 80.71 | 189.94 |
| $CL_R$, L/h | Mild RI vs. Normal | 96.46 | 50.86 | 182.97 |
| | Moderate RI vs. Normal | 101.83 | 53.96 | 193.15 |
| | Severe RI vs. Normal | 124.90 | 65.85 | 236.90 |

ANOVA, analysis of variance; $AUC_{0\text{-}\infty}$, area under the plasma concentration-time curve from 0 h extrapolated to infinity; $AUC_{0\text{-}72h}$, area under the plasma concentration-time curve from 0 h to 72 h post-dose; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from 0 h to the last measurable concentration; CLR, renal clearance; $C_{max}$, maximum plasma concentration; LSM, least squares mean; PK, pharmacokinetic; RI, renal impairment.

### Safety

- All adverse events (AEs) reported were grade 1-2 in severity
- The most common AE by preferred term was diarrhea, followed by ECG QT interval prolongation (**Table 5**)
- Treatment-related AEs identified included leukopenia, neutropenia, diarrhea, flatulence, nausea, ECG QT interval prolongation, and bone pain

### Table 5. Summary of AEs (>1 Event) Observed in RI Groups

| SOC and preferred term, n (%) | Group 1: Mild RI n=8 | Group 2: Moderate RI n=8 | Group 3: Severe RI n=8 | Group 4: ESRD n=8 | | Group 5: Healthy Subjects n=7 |
|---|---|---|---|---|---|---|
| | | | | Dialysis | Inter-Dialysis | |
| **Any AE** | 1 (12.5) | 4 (50.0) | 4 (50.0) | 6 (75.0) | 3 (37.5) | 2 (28.6) |
| **Blood and lymphatic system** | 0 | 1 (12.5) | 0 | 2 (25.0) | 1 (12.5) | 0 |
| Anemia | 0 | 0 | 0 | 1 (12.5) | 1 (12.5) | 0 |
| Neutropenia | 0 | 1 (12.5) | 0 | 1 (12.5) | 0 | 0 |
| **Gastrointestinal** | 0 | 4 (50.0) | 3 (37.5) | 4 (50.0) | 2 (25.0) | 2 (28.6) |
| Diarrhea | 0 | 2 (25.0) | 2 (25.0) | 3 (37.5) | 2 (25.0) | 0 |
| Nausea | 0 | 1 (12.5) | 1 (12.5) | 0 | 0 | 0 |
| **Investigations** | 1 (12.5) | 0 | 0 | 2 (25.0) | 1 (12.5) | 0 |
| ECG QT prolonged | 0 | 0 | 0 | 2 (25.0) | 1 (12.5) | 0 |

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; ESRD, end stage renal disease; RI, renal impairment; SOC, system organ class.

### Electrocardiogram Findings

- An increase in QTcF was observed in ESRD patients:
  - Increase in QTcFof 30-60 ms above baseline was observed in 2 (25.0%) ESRD patients during the dialysis period, and 1 (12.5%) ESRD patient during the inter-dialysis period. The worst on-study QTcF for these subjects were 452, 453, and 459 ms. No changes in QTcF>60 ms were observed
  - These subjects all had electrolyte abnormalities during the study, mostly grade 1. Relevant cardiovascular concomitant diseases in 2 out of 3 of these subjects included hypertension in 2 subjects and ischemic heart disease in 1 subject
- In addition to the above mentioned AEs, 2 subjects had on-study QTcF>450 ms that were not reported as AEs
  - 1 ESRD patient with QTcF 454 ms and 1 severe RI patient with QTcF 453 ms
- The incidence of treatment-emergent ECG abnormalities, including heart rate, PR interval, QRS width, and QTcF interval, was low
  - Reported in at most 1 patient per renal group

## CONCLUSIONS

- PK parameters and renal excretion of pacritinib and M1 metabolite were not appreciably affected by RI
  - No appreciable change between groups in the PK profile over time or PK parameters of pacritinib or M1 metabolite
  - No appreciable urinary excretion of pacritinib
  - Minimal elimination of pacritinib and M1 metabolite during dialysis
- All AEs reported were grade 1-2 in severity
  - Diarrhea was the most common AE
  - ECG abnormalities were reported in 3 (37.5%) ESRD patients, including 2 (25.0%) during the dialysis period, and 1 (12.5%) during the inter-dialysis period
- The administration of single 400 mg doses of pacritinib to patients with RI was safe and well tolerated, and dosage adjustments for patients with RI are not warranted

### References

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### Disclosures

- **SAF**, **SA**, **HZ**, **LM**, **JWS**, and **MC**: Employment and equity ownership in CTI BioPharma Corp.

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