Abstract CT159

INVESTIGATION OF ABSORPTION, METABOLISM, EXCRETION, AND MASS BALANCE OF [^{14}C]-PACRITINIB IN HEALTHY SUBJECTS: A PHASE 1 STUDY

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INTRODUCTION

- Dysregulation in tyrosine kinase signaling has been implicated in development of hematologic malignancies including myelofibrosis and lymphomas[1-5]
- Pacritinib is an oral kinase inhibitor with specificity for JAK2, FLT3, CSF1R, and IRAK1[6-8]
- In mouse distribution studies of radiolabeled pacritinib, approximately 91% of administered dose was recovered in the feces, suggesting an important role for biliary elimination in clearance of pacritinib
- This phase 1 trial investigated clearance pathways, excretion, pharmacokinetics (PK), and recovery of pacritinib, its major metabolites, and total radioactivity in healthy volunteers

METHODS

Key Inclusion/Exclusion Criteria

- Male subjects age 18-55
- Body mass index of 19.0-29.0 mg/kg^2
- No clinical laboratory value outside of the normal reference range (unless deemed not clinically significant)
- Negative test for hepatitis B, hepatitis C, and HIV infection
- No use of prescription medicine within 21 days of study day 1 unless approved by sponsor
- No use of over-the-counter medications or non-prescription preparations known to induce drug metabolizing enzymes (including CYP450) within 7 days prior to study day 1
- No diarrhea, nausea, or vomiting within 7 days of study day 1
- ECG findings within normal limits (e.g., QTc interval ≤450 msec)
- No history of risk factors for torsade de pointes (e.g., heart failure, hypokalemia [serum potassium <3.0 mmol/L], family history of long QT syndrome)

Study Design

- Study volunteers were administered a single 400 mg dose of pacritinib (4 x 100 mg) capsules
- To enable detection and quantitation of dose-related material independent of possible biotransformation, subjects were simultaneously administered a single dose of [^{14}C]-pacritinib as a suspension (100 µCi radioactivity per <1 mg of pacritinib in 30 mL suspension)
- Blood, urine, and feces were sampled predose and up to 42 days postdose
  - Blood was sampled for PK predose, at 0.5, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 h postdose and every 24 h thereafter until day 10, or study discharge criteria were met (no later than day 14)
  - Urine was sampled predose, 0-6, 6-12, and 12-24 h postdose and every 24 h thereafter until study discharge criteria were met (no later than day 14)
  - Fecal sampling occurred predose (1 sample obtained between day −3 and day 1) and every 24 h starting at dosing until study discharge criteria were met (no later than day 14)
- Pacritinib and metabolites were identified using HPLC-MS/MS/radio flow-through detector (RFD), high resolution mass spectrometry, and authentic metabolite standards as described previously[9]

Pharmacokinetic Assessments

- PK parameters for [^{14}C]-pacritinib were derived by non-compartmental PK analysis of plasma concentration-time profiles
- PK parameters were calculated for each subject based on plasma and/or blood concentrations of pacritinib and total [^{14}C] radioactivity
- Amount excreted in urine (Ae_u), percent dose excreted, and renal clearance (CL_R) were calculated based on the urine radioactivity concentrations
- Amount excreted in feces (Ae_f), and percent dose excreted were calculated based on fecal radioactivity concentrations

Safety Assessments

- Treatment-emergent adverse events (AEs) and serious AEs (SAEs) were assessed continuously through the end of the study
- Absolute values and changes from baseline to each timepoint up to end of study were assessed for ECG parameters
- QTc was calculated by Bazett's (QTcB) and Fridericia's (QTcF) correction using QT and RR ECG parameters

RESULTS

Summary of Demographics

- A total of 6 healthy male subjects were enrolled and included in the study
- Median age was 24 y and all subjects were Caucasian (**Table 1**)
- Three subjects never smoked and 3 quit smoking for >3 mo prior to study
- Subjects consumed ≤2 units of alcohol per week and ≤2 units of caffeine per day

Table 1. Summary of Demographics

Variable	Total Subjects (N=6)
Age, y	
Mean (SD)	24.5 (2.95)
Median	24.0
Minimum	22
Maximum	30
Sex, n (%)	
Male	6 (100)
Race, n (%)	
Caucasian	6 (100)
Ethnicity, n (%)	
Not Hispanic or Latino	6 (100)

Pharmacokinetic Parameters of Pacritinib and Metabolites

- Peak radioactivity in plasma was reached approximately 2 h following administration (**Table 2**)
- Mean apparent volume of distribution and apparent clearance in plasma were 137 L and 1.73 L/h, respectively
- Elimination half-life for total radioactivity in plasma was 55.1 h
- Twelve pacritinib metabolites were identified: M1, M2, M3, M5, M6, M7, M8, M9, M12, M13, M14, and M14a
- Pacritinib was the predominant radioactive component (72%) recovered in plasma from 0.5-120 h with mean maximum concentration (C_{max}) of 4117.2 ng/mL
  - Mean C_{max} for M2, M1, M3, and M8 were 887.0, 854.5, 292.3, and 148.6 ng/mL, respectively
  - Mean metabolite exposure ratios for major metabolites, M1 and M2, in plasma relative to pacritinib were 0.0963 and 0.105, respectively

Table 2. Pharmacokinetic Parameters for Pacritinib and Major Metabolites

Variable	Pacritinib (N=6)	M1 (N=6)	M2 (N=6)
C_{max}, ng•Eq/mL, mean (%CV)	4120 (22)	874 (25)	887 (35)
T_{max}, h, median (range)	1.54 (1.50-4.00)	2.50 (1.00-4.00)	3.00 (2.00-6.02)
AUC_{0-t}, h•ng•Eq/mL, mean (%CV) M/P ratio	152,000 (26) NA	13,500 (36) 0.0963 (44)	14,400 (67) 0.105 (71)
$AUC_{0-\infty}$, h•ng•Eq/mL, mean (%CV)	169,000 (24)	17,400 (NA)[a]	35,600 (NA)[a]
λ_z, 1/h, mean (%CV)	0.0202 (16)	0.0421 (NA)[a]	0.0432 (NA)[a]
$t_{1/2}$, h, mean (%CV)	34.9 (15)	16.5 (NA)[a]	16.0 (NA)[a]
Vd/F, L, mean (%CV)	125 (23)	NA	NA
CL/F, L/h, mean (%CV)	2.47 (19)	NA	NA

[a]N=1.

AUC_{0-t}, area under the plasma concentration-time curve from time 0 to last measureable concentration; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero to infinity; CL/F, apparent total body clearance; C_{max}, maximum plasma concentration; CV, coefficient of variance; Eq, equivalent; λ_z, apparent terminal elimination rate constant; M/P, AUC_{0-t} (metabolite)/AUC_{0-t} (parent); NA, not applicable; $t_{1/2}$, apparent terminal elimination half-life; T_{max}, time to maximum plasma concentration; Vd/F, apparent total volume of distribution.

Recovery of Pacritinib and Metabolites in Urine and Feces

- Mean recovery of radioactivity in urine (0-48 h) was 3.22% of administered dose (**Table 3**)
  - M7, a glucuronidated metabolite, was the predominant radioactive component in urine (3.03% of administered dose)
  - Pacritinib recovered in urine accounted for 0.12% of administered dose
- From 0-240 h postdose, mean recovery of radioactivity in feces was 85.5% of administered dose (**Table 4**)
  - Pacritinib was detected by MS in fecal samples, but not by RFD
  - Metabolite M2 was the predominant radioactive fecal component, (24.1% of administered dose)
- Intact pacritinib was minimally excreted in urine and feces (**Tables 3,4**); most radioactivity was recovered as metabolites in the feces (**Figure 1**)

Table 3. Recovery of Pacritinib and Renal Metabolites in Urine

Parameter, mean (%CV)	Pacritinib (N=6)	M5 (N=6)	M7 (N=6)	Total (N=6)
Ae_u, mg•Eq	0.468 (245)	0.327 (245)	12.1 (17)	12.9 (16)
Ae_u, %	0.117 (245)	0.0817 (245)	3.03 (17)	3.22 (16)
CL_R, L/h	0.00539 (245)	NA	NA	NA

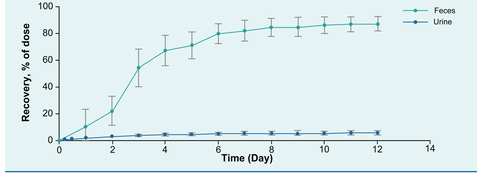
Ae_u, total amount excreted into urine over the collection intervals (0-48 h); Ae_u%, percent dose excreted into urine over the collection interval (0-48 h); CL_R, renal clearance; CV, coefficient of variance; Eq, equivalent; NA, not applicable.

Table 4. Recovery of Pacritinib and Metabolites in Feces

Analyte	Ae_f, mg•Eq, mean (%CV) (N=6)	Ae_f, %, mean (%CV) (N=6)
Pacritinib	Not detected	Not detected
M2	96.5 (40)	24.1 (40)
M5	54.3 (22)	13.5 (22)
M6	61.4 (28)	15.3 (28)
M8	36.8 (29)	9.19 (29)
M9	41.5 (21)	10.4 (21)
M10	3.01 (115)	0.750 (115)
M11	0.800 (167)	0.200 (167)
M12	16.8 (88)	4.18 (88)
M13	12.0 (108)	2.99 (108)
M14	16.1 (80)	4.03 (80)
M14a	1.12 (195)	0.278 (194)
M15	2.24 (160)	0.557 (160)
Total	343 (7)	85.5 (7)

Ae_f, total amount excreted into feces over the collection intervals (0-240 h); Ae_f%, percent dose excreted into feces over the collection interval (0-240 h); CV, coefficient of variance.

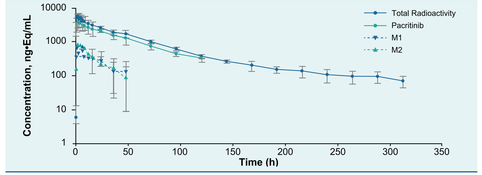
Figure 1. Cumulative Excretion in Urine and Feces Over Time



Elimination of Total Plasma Radioactivity, Pacritinib, and Major Metabolites Over Time

- Plots of mean total plasma radioactivity and concentrations of pacritinib and its major metabolites over time are shown in **Figure 2**
- Metabolites M3, M8, and P9 are not included in the plots as they were mostly below the limit of quantitation

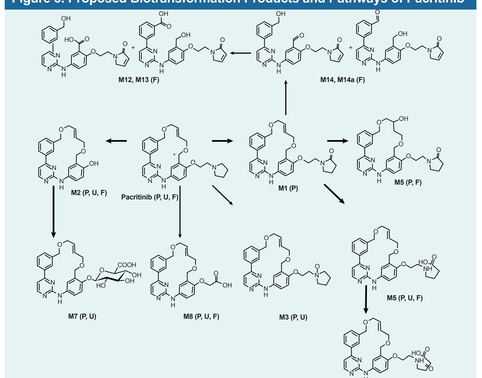
Figure 2. Elimination of Total Plasma Radioactivity, Pacritinib, and Major Metabolites Over Time



Biotransformation Products and Pathways of Pacritinib

- A total of 15 [^{14}C]-pacritinib metabolite peaks were detected in human plasma, urine, and feces
- Based on their mass spectral data, the proposed metabolic pathways include oxidation, *N*-dealkylation, *O*-dealkylation, hydrolysis, and dehydrogenation as shown in **Figure 3**
- The 2 major identified metabolites (M1 and M2) exhibit relatively low pharmacological potency and are unlikely to significantly contribute to the activity of pacritinib
  - The half-maximal inhibitory concentrations 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

Figure 3. Proposed Biotransformation Products and Pathways of Pacritinib[a]



[a]Bold arrows indicate major metabolic pathways.

F, Feces; P, plasma; U, urine.

Safety

- Five individuals (83.3%) reported 9 total AEs (**Table 5**)
- All AEs were grade 1 and were predominantly gastrointestinal AEs including diarrhea (5 events in 4 individuals) and nausea (1 event in 1 individual)
  - All AEs were reversible and resolved upon completion of the study
- There were no SAEs and no subjects discontinued due to AEs
- There were no clinically significant abnormalities in vital signs or by physical examination
- All subjects had normal ECG findings with the exception of one subject who had sinus arrhythmia (e.g. tachycardia) noted at baseline and several times after treatment, all deemed not clinically significant

Table 5. Adverse Events

Preferred term	Overall, n (%) (N=6)	Total Events, n	AE Grades, (%)
Number of subjects with ≥1 AE	5 (83.3)	9	1 (100)
Diarrhea	4 (66.7)	5	1 (100)
Nausea	1 (16.7)	1	1 (100)
Muscle spasms	1 (16.7)	1	1 (100)
Nasal congestion	1 (16.7)	1	1 (100)
Dry skin	1 (16.7)	1	1 (100)
Number of subjects with SAEs	0	0	0

AE, adverse event; SAE, serious adverse event

CONCLUSIONS

- Following oral administration, pacritinib was the predominant moiety recovered in plasma
  - Individual pacritinib metabolites constitute ≤10% of total radioactivity in plasma
- Pacritinib was extensively metabolized; the major metabolites (M1, oxidation; M2, dealkylation) have relatively low pharmacological potency and are unlikely to substantially contribute to the activity of pacritinib
- Intact pacritinib was minimally excreted in urine and feces
- Most radioactivity was recovered as metabolites in feces, suggesting extensive biliary clearance and hepatic metabolism of pacritinib; no dosage adjustments are anticipated to be required for patients with renal impairment

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Disclosures

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

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