Allogeneic hematopoietic stem cell transplants (HSCTs) may be a potentially curative treatment option for patients with hematologic malignancies. However, allogeneic HSCT may lead to serious and even fatal complications such as graft-versus-host disease (GVHD), where alloreactive T cells attack healthy tissue rather than tumor cells. Chronic GVHD occurs in 30% to 70% of patients and there is an urgent unmet clinical need for new therapies for chronic GVHD. Itacitinib (INCB039110) adipate is currently in a late-phase trial for the treatment of patients with chronic GVHD. It is a novel and potent inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases with preferential selectivity for JAK1 that is implicated in the pathophysiology of GVHD. Itacitinib is administered in the form of a sustained-release (SR) tablet. This formulation allows for once-daily dosing with a longer half-life and a reduced peak-to-trough ratio compared to the immediate-release formulation and can be administered without regard to food.

The absorption, distribution, metabolism, and excretion properties of itacitinib have been characterized in healthy volunteers following administration of $^{14}$C-itacitinib oral solution (~4.9 mg) with a 300-mg dose of itacitinib delivered as SR tablets and demonstrated that elimination of itacitinib occurs primarily by oxidative metabolism. In vitro data indicate that metabolism is mediated by cytochrome P450 (CYP) 3A (data on file, Incyte Corporation). The coadministration of the strong CYP3A inhibitor itraconazole with itacitinib showed an increase in the maximum plasma drug concentration ($C_{\text{max}}$) and area under the plasma concentration–time curve from time zero to infinity ($AUC_{(0-\infty)}$) of approximately 3-fold and 5-fold, respectively, whereas the coadministration of the strong

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CYP3A4 inducer rifampin showed a decrease in the
C_{\text{max}} and AUC_{0-\infty} of approximately 80\%.
The renal elimination of itacitinib is minimal, with approximately
8.4\% of the dose of SR itacitinib eliminated in the urine as
unchanged drug.\(^7\)

Even for drugs with minimal renal clearance, a pharma-
cokinetic study should be performed in individuals
with impaired renal function when the drug is likely
to be used in patients with renal impairment. Dosage
adjustments may be required\(^9\) in these patients because
renal failure can alter hepatic drug metabolism\(^10,11\)
and drug transporter systems.\(^12\) Renal impairment is
commonly seen in patients after HSCT\(^13,14\); therefore,
it is important to characterize the effect of renal im-
pairment on itacitinib pharmacokinetics to identify if
dosage adjustments may be required in patients with
renal impairment.

The objective of this clinical study was to evaluate
the effect of renal impairment on the plasma exposure
of itacitinib. Participants with end-stage renal disease
(ESRD) were included to determine how itacitinib
should be dosed for patients on dialysis. This study also
evaluated plasma protein binding of itacitinib in partic-
ipants with severe renal impairment and ESRD com-
pared with participants with normal renal function,
determined the renal clearance and dialysate clearance
of itacitinib, and determined the fraction of itacitinib
that is excreted in urine and dialysate.

Methods
The study was conducted in accordance with the Inter-
national Conference on Harmonization Good Clinical
Practice guidelines, applicable regulations, guidelines
governing clinical study conduct, and by the principles
in the Declaration of Helsinki. The study protocol
was approved by the institutional review boards of
the study sites (Orlando Clinical Research Center,
Orlando, Florida; Riverside Clinical Research Cen-
ter, Edgewater, Florida; and Orange County Research
Center, Tustin, California), and all participants gave
written informed consent before participation in the
study.

Study Design and Participants
This study was a single-dose, open-label, parallel-
group study of itacitinib in participants with severe
renal impairment or ESRD and participants with
normal renal function (controls) matched by demo-
graphic characteristics including age (±10 years), sex,
and body mass index (±20\%). Participants were as-
signed to renal function groups according to the
estimated glomerular filtration rate (eGFR) as cal-
culated by the Modification of Diet in Renal Dis-
ease equation, and use of hemodialysis. Participants
with normal renal function (eGFR ≥90 mL/min/
1.73 m\(^2\); n = 10), severe renal impairment (eGFR <30
mL/min/1.73 m\(^2\), not on dialysis; n = 8), and ESRD
(eGFR <30 mL/min/1.73 m\(^2\), on dialysis; n = 8) were
enrolled. The enrollment of participants with mild and
moderate renal impairment was optional based on the
results from the severe cohort.

In the normal renal function and severe renal im-
pairment groups (Figure 1A), all participants received
a single 300-mg dose (3 × 100 mg SR tablets) of
itacitinib after a medium-fat meal. In the ESRD group
(Figure 1B), participants received a single 300-mg dose
(3 × 100 mg SR tablets) after a medium-fat meal in
2 treatment periods: 4 hours before the start of a
hemodialysis session in the first treatment period and
1 hour after the end of a hemodialysis session in the
second treatment period. Participants were confined
to the study site 1 day before dosing and remained
at the site until study procedures were completed on
day 4. The medium-fat meal was defined as a meal
of around 500 calories, providing approximately 35%
calories from fat. The composition of the meal was
similar in all study participants.

Pharmacokinetic Sampling and Bioanalysis
The blood samples for the assay of itacitinib in the
plasma were collected into lavender-top dipotassium
ethylenediaminetetraacetic acid–containing collection
tubes before dosing (0 hours) and at 0.5, 1, 2, 3, 4,
6, 8, 12, 16, 24, 36, 48, and 72 hours after dosing.
Urine samples were collected in containers without
preservatives over the following intervals: −12 to 0,
0 to 8, 8 to 24, 24 to 48, and 48 to 72 hours after
dosing. In the ESRD group (period 1 only), dialysate
samples were collected during the hemodialysis ses-
sion at 4 (start of the hemodialysis session), 5, 6, 7,
and 8 (end of the hemodialysis session) hours after
dosing. The plasma samples were assayed by a vali-
dated liquid chromatography–tandem mass spectrom-
etry (LC-MS/MS) method with a linear range of 5
to 5000 nmol/L. Detailed methods on the itacitinib
plasma assay have been described elsewhere.\(^8\)
Three plasma analytical quality control (QC) samples
were included in each plasma analysis run: a low QC
sample (15 nmol/L), a middle QC sample (250 nmol/L)
and a high QC sample (4000 nmol/L). Interassay preci-
sion for this assay ranged from 1.7\% to 3.5\% (CV\%),
and interassay accuracy ranged from −3.3\% to 1.6\%.
The analysis of the urine samples used a validated
LC-MS/MS method with a linear range of 0.025 to
25 μmol/L. In this method, 25 μL of the urine sample
was placed in individual wells of a 96-well plate. An
aliquot of 500 μL of internal standard (dissolved in
50:50 methanol:water) was added, following which the
plate was capped, vortexed, and centrifuged. The plate
was then placed in the autosampler tray and injected into an LC-MS/MS system for analysis, using the same LC-MS/MS conditions as those described elsewhere.\(^8\)

Three urine analytical QC samples were included in each urine analysis run: low QC sample (0.075 \(\mu\)mol/L), middle QC sample (1 \(\mu\)mol/L), and high QC sample (20 \(\mu\)mol/L). Interassay precision of this assay ranged from 1.6% to 4.6% (CV%), and interassay accuracy ranged from −0.9% to −0.4%. For the dialysate, the samples were diluted 1:9 (dialysate:plasma, v:v) and analyzed using a similar validated plasma method, albeit with a lower linear range of 0.3 to 300 nmol/L. This matrix matching of the dialysate samples to plasma for analysis using this plasma method was partially validated before sample analysis. Three plasma analytical QC samples were included in the single dialysate sample analysis run: low QC sample (0.9 nmol/L), middle QC sample (20 nmol/L), and high QC sample (240 nmol/L). Interassay precision was not calculated since QC samples were analyzed in duplicate for the run. The interassay accuracy for this assay ranged from −0.8% to 0.5%.

Plasma protein binding was analyzed by a non–Good Laboratory Practices assay. Unbound fraction of itacitinib was determined by equilibrium dialysis using venous plasma samples collected 4 hours after dosing. Briefly, a semipermeable membrane with a molecule weight cutoff of 10 000 daltons separated the plasma-containing compartment and plasma-free compartment containing phosphate buffer. The system was allowed to equilibrate at 37°C for 2 hours, then samples were collected from each compartment for determination of itacitinib concentrations by LC-MS/MS. Samples from the plasma-containing compartment were normalized with an equal volume of phosphate buffer, and samples from the plasma-free compartment were normalized with an equal volume of plasma prior to analysis using the plasma method with the range of 5 to 5000 nmol/L. A partial validation of this 1:1 matrix-matching prior to sample analysis assured data integrity. Three plasma analytical QC samples were included in each protein binding sample analysis run: a low QC sample (15 nmol/L), a middle QC sample (250 nmol/L), and a high QC sample (4000 nmol/L).

Figure 1. Clinical study design for normal renal function and severe renal impairment groups (A) and end-stage renal disease groups (B). A, 3 × 100-mg itacitinib dose; CRU, clinical research unit; HD, hemodialysis; PK, pharmacokinetics.
Interassay precision for this analysis ranged from 0.9% to 4.0% (CV%), and interassay accuracy ranged from -0.5% to 3.3%. The resulting protein binding sample concentrations were used to calculate a fraction unbound for individual participants.

Pharmacokinetics and Statistical Analyses
Standard noncompartmental pharmacokinetic methods were used to analyze itacitinib plasma concentrations using Phoenix WinNonlin version 8.0 (Certara, Princeton, New Jersey). The $C_{\text{max}}$ and time to maximum plasma drug concentration ($t_{\text{max}}$) values were taken directly from the observed plasma concentration data. The terminal phase disposition rate constant ($\lambda$) was estimated using a log-linear regression of the concentration data in the terminal elimination phase, and the terminal elimination half-life was estimated as $\ln(2)/\lambda$. Total $AUC_{0-\infty}$ was calculated as $AUC_{0-t} + Ct/\lambda$, where $Ct$ was the last measurable concentration. Apparent clearance was calculated as dose/$AUC_{0-\infty}$ with the apparent volume of distribution during the assessment time.

Safety Assessments
Each adverse event (AE) was coded using the Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term (version 21.0). All AEs were listed and summarized using descriptive methodology. AEs for each renal function group were presented by association with the study drug and severity. The severity of AEs was described and graded using grades 1 to 4 from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Descriptive statistics were calculated for clinical laboratory test data, 12-lead electrocardiograms, and vital signs by renal function group at each assessment time.

Results
Participant Disposition
Twenty-six participants (16 men and 10 women) were enrolled and completed the clinical study. The demographic characteristics across all 3 renal function groups are shown in Table 1. In the healthy participants, demographic characteristics (ie, age, sex, and body mass index) were matched to both severe renal impairment and ESRD groups.

Pharmacokinetic Results
The mean itacitinib plasma concentrations versus time profiles by renal function group are presented in Figure 2. The $C_{\text{max}}$ and $AUC_{0-\infty}$ were 700 nmol/L and 3050 nmol·hr/L, respectively, with a median $t_{\text{max}}$ of 3 hours. When itacitinib was dosed after a hemodialysis session (treatment period 2), the geometric mean $C_{\text{max}}$ and $AUC_{0-\infty}$ were 580 nmol/L and 2890 nmol·hr/L, respectively, with a median $t_{\text{max}}$ of 4 hours. For participants with ESRD, the geometric mean $C_{\text{max}}$ and $AUC_{0-\infty}$ were 495 nmol/L and 2480 nmol·hr/L, respectively, with a median $t_{\text{max}}$ of 3 hours when itacitinib was dosed before the start of a hemodialysis session (treatment period 1). When itacitinib was dosed after a hemodialysis session (treatment period 2), the geometric mean $C_{\text{max}}$ and $AUC_{0-\infty}$ were 580 nmol/L and 2890 nmol·hr/L, respectively, with a median $t_{\text{max}}$ of 5 hours. When pharmacokinetics in the renal impairment groups were compared with the normal renal function group, the geometric mean ratio (90% confidence interval) was 1.65 (1.13-2.39), 0.71 (0.49-1.03), and 0.83 (0.57-1.20) for $C_{\text{max}}$ and 2.23 (1.56-3.18), 0.81 (0.57-1.16), and 0.95 (0.66-1.36) for $AUC_{0-\infty}$ for the severe renal impairment, ESRD treatment period 1, and ESRD treatment period 2 groups, respectively (Table 2 and Figure 3).

Plasma Protein Binding
The protein binding of itacitinib was independent of renal function and similar across all evaluated renal function groups with an average fraction unbound of 30.4%, 37.1%, and 39.6% in participants with normal renal function, severe renal impairment, and ESRD, respectively.
### Table 1. Study Demographic Information Across Renal Function Groups in the Clinical Study

| Demographic Characteristic | Normal Renal Function (n = 10) | Severe Renal Impairment (n = 8) | ESRD (n = 8) |
|----------------------------|--------------------------------|---------------------------------|-------------|
| Age, y, median (range)     | 62.5 (44.0-76.0)               | 73.0 (56.0-80.0)                | 55.0 (41.0-62.0) |
| Height, cm, median (range) | 173 (163-185)                  | 170 (156-188)                   | 174 (161-188) |
| Weight, kg, median (range) | 84.7 (72.7-106.5)              | 89.5 (66.1-99.7)                | 96.7 (75.0-124.7) |
| BMI, kg/m², median (range) | 29.60 (23.6-37.0)              | 29.55 (25.8-36.8)               | 30.45 (26.3-37.7) |
| Sex, n (%)                 |                                |                                 |             |
| Male                       | 6 (60.0)                       | 5 (62.5)                        | 5 (62.5)    |
| Female                     | 4 (40.0)                       | 3 (37.5)                        | 3 (37.5)    |
| Race, n (%)                |                                |                                 |             |
| White                      | 4 (40.0)                       | 7 (87.5)                        | 1 (12.5)    |
| African American           | 5 (50.0)                       | 1 (12.5)                        | 7 (87.5)    |
| Asian                      | 0                             | 0                               | 0           |
| Other                      | 1 (10.0)                       | 0                               | 0           |
| eGFR at check-in, mL/min/1.73 m², median (range) | 96.5 (88-125) | 28 (13-32) | 7.0 (5-7.0) |

BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

Classification of participants was based on values at screening. One subject in the severe group had an eGFR of 27 mL/min/1.73 m² at screening, which shifted to 32 mL/min/1.73 m² at check-in.

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### Renal Clearance and Dialysate Clearance of Itacitinib in Participants With Varying Degrees of Renal Function

In participants with normal renal function, the average renal clearance of itacitinib was 11.8 L/h, whereas itacitinib renal clearance was 3.03 L/h in the severe renal impairment group. The renal clearance was approximately 6% and 3% of total itacitinib clearance in the normal renal function and severe renal impairment groups, respectively. The fraction of the dose eliminated in the urine as itacitinib was 7.2% and 3.7% in the normal renal function and severe renal impairment groups, respectively. Itacitinib dialysate clearance was 2.01 L/h, which was approximately 1% of the total clearance of itacitinib in this group. The average fraction of the dose excreted in dialysate as itacitinib was 0.9%.

### Safety Results

The single 300-mg oral dose of itacitinib was well tolerated when administered to participants with normal renal function and participants with severe renal...
Table 2. Summary of Itacitinib Pharmacokinetic Parameters by Renal Function Group

| Group/Comparison            | Cmax, nmol/L | tmax, h | AUC0-∞, nmol*h/L | AUC0-½, nmol*h/L | Half-life, h | CL/F, L/h | Vz/F, L |
|-----------------------------|-------------|---------|-----------------|-----------------|-------------|-----------|---------|
| Normal renal function (n = 10) | 821 ± 588  | 3.0 (2.0-6.0) | 3290 ± 1630   | 3360 ± 1640   | 6.18 ± 6.88 | 194 ± 78.7 | 1400 ± 1150 |
| Severe renal impairment (n = 8) | 1250 ± 521 | 4.0 (3.0-8.0) | 7250 ± 2660  | 7350 ± 2690  | 7.96 ± 7.28 | 89.5 ± 54.1 | 812 ± 507 |
| ESRD period 1 (n = 8) | 522 ± 172 | 3.0 (3.0-6.0) | 2620 ± 1190 | 2670 ± 1210 | 5.27 ± 1.92 | 234 ± 86.7 | 1690 ± 800 |
| ESRD period 2 (n = 8) | 623 ± 253 | 5.0 (3.0,6.0) | 3020 ± 1260 | 3080 ± 1260 | 4.32 ± 1.43 | 199 ± 67.3 | 1280 ± 724 |

Geometric mean ratios and 90% CIs

| Comparison                  | PK Parameter | GMR |
|-----------------------------|--------------|-----|
| Severe renal impairment vs normal renal function | Cmax | 1.65 (1.13-2.39) |
| ESRD period 1 vs normal renal function | AUC0-∞ | 0.71 (0.49-1.03) |
| ESRD period 2 vs normal renal function | AUC0-∞ | 0.83 (0.57-1.20) |

AUC, area under the plasma concentration curve; CI, confidence interval; CL/F, apparent oral clearance; Cmax, maximum plasma drug concentration; ESRD, end-stage renal disease; SD, standard deviation; tmax, time to reach maximum plasma drug concentration; Vz/F, apparent volume of distribution during the terminal phase.

Pharmacokinetic parameters are shown as mean ± standard deviation; tmax is shown as median (range).

Discussion

This clinical study was performed to evaluate the impact of renal impairment and hemodialysis on the pharmacokinetics of a single oral dose of itacitinib. Patients with severe renal impairment showed an approximately 2-fold increase in itacitinib exposure compared with patients with normal renal function.

From a pilot study in patients with acute GVHD receiving itacitinib with corticosteroids, in patients comitantly taking potent CYP3A4 inhibitors (mainly posaconazole), there was an approximate 2-fold increase in exposure of itacitinib relative to the exposure in patients not taking a strong CYP3A4 inhibitor.16 Despite this increased exposure, itacitinib was well tolerated with the incidence and severity of AEs as expected in this population, and there was no exacerbation of corticosteroid relative AEs. This formed the basis of the therapeutic window supporting a 2-fold increase may not be clinically relevant. Consequently, this clinical study did not enroll patients with mild or moderate renal impairment. Additional dosage adjustment of itacitinib is not currently recommended for participants with severe renal impairment, although final dosage recommendations will be based on the totality of data from this study and late-phase patient studies in GVHD. Consequently, this clinical study did not enroll patients with mild and moderate renal impairment.

The fraction of the itacitinib dose eliminated as unchanged drug in the urine was 7.2% in the normal renal
function group and 3.7% in the severe renal impairment group. These results support previously generated data\(^7\) that renal clearance plays a minor role in the elimination of itacitinib. Although it is not clear why there was a 2-fold increase in plasma exposure of itacitinib in the severe renal impairment group compared with the normal renal function group, potential explanations include itacitinib pharmacokinetic variability and altered bioavailability or nonrenal clearance mechanisms\(^17,18\) in patients with renal failure. For the participants with ESRD, hemodialysis may have resulted in improvement of hepatic metabolic activity as shown by Nolin et al,\(^19\) resulting in plasma exposures that were more similar to that seen in the healthy matched participants. When comparing exposures in the severe renal impairment group vs the ESRD group, it should be noted that there are differences in racial composition in the 2 groups. Seven of 8 participants in the ESRD group were African American vs only 1 of 8 participants in the severe renal impairment group. This may affect the pharmacokinetics of itacitinib due to differences in metabolism across racial groups. For example, a greater proportion of African Americans express the intermediate or extensive metabolizer phenotype of CYP3A5 while whites predominantly express the poor CYP3A5 metabolizer phenotype.\(^20\) Therefore, there is a possibility that such difference may have contributed to the higher itacitinib exposures in the severe renal impairment group. The contribution of race to differences in pharmacokinetics will be determined in a population pharmacokinetics analysis. Finally, the protein-binding data showed that itacitinib protein binding was independent of renal function and was similar to prior in vitro plasma protein-binding data where the unbound fraction was approximately 35% (data on file, Incyte Corporation).

**Conclusions**

In summary, itacitinib was well tolerated across all participants with normal renal function and renal impairment and demonstrated a consistent safety profile. Although itacitinib exposure in the severe renal impairment group showed 1.6-fold increase in \(C_{\text{max}}\) and 2.2-fold increase in \(\text{AUC}_{0-\infty}\) relative to healthy matched participants with normal renal function, this increase in itacitinib exposure may not be clinically relevant. This is based on prior characterization of the risk-benefit profile in patients with acute GVHD who demonstrated a similar magnitude of increase in itacitinib exposure due to coadministration of a potent CYP3A inhibitor, mainly posaconazole. No dose adjustment is currently recommended for itacitinib in patients with severe renal impairment. However, final recommendations will be based on the totality of data from this study and the therapeutic window defined using exposure/response analyses from the late-phase studies in patients with GVHD. Given that there was little effect on \(C_{\text{max}}\) and \(\text{AUC}\) in the ESRD group compared with the normal renal function group, no dosage adjustment is recommended for itacitinib in patients with ESRD on hemodialysis and itacitinib can be administered without regard to time of dialysis.

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**Conflicts of Interest**

Incyte Corporation contributed to the study design, research, and interpretation of the data and the writing, review, and approval of the manuscript. N.S., A.M.B., N.E., G.Z., S.P., Z.X., B.Y., X.C., S.Y., and N.P. are current or former employees of Incyte Corporation and may hold Incyte corporation stock or stock options. T.M. is an employee and equity owner of Orlando Clinical Research Center and declares no other conflicts of interest.

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**Data Sharing**

Access to individual subject-level data is not available for this study.

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Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.