An Open-Label, Phase 1 Study to Assess the Effects of Hepatic Impairment on Pomalidomide Pharmacokinetics

Yan Li1, Xiaomin Wang3, Liangang Liu2, Chengyue Zhang1, Diana Gomez1, Josephine Reyes1, Maria Palmisano1, and Simon Zhou1

Abstract

Pomalidomide is an immunomodulatory drug and the dosage of 4 mg per day taken orally on days 1-21 of repeated 28-day cycles has been approved in the European Union and United States to treat patients with relapsed/refractory multiple myeloma. Because pomalidomide is extensively metabolized prior to excretion, a total of 32 subjects (8 healthy subjects in group 1; 8 subjects with severe hepatic impairment in group 2; 8 subjects with moderate hepatic impairment in group 3; and 8 subjects with mild hepatic impairment in group 4) were enrolled in a multicenter, open-label, single-dose study to assess the impact of hepatic impairment on pomalidomide exposure. Following administration of a single oral dose of 4-mg pomalidomide, the geometric mean ratios of pomalidomide total plasma exposures (AUC) were 171.5%, 157.5%, and 151.2% and the geometric mean ratios of pomalidomide plasma peak exposures (Cmax) were 75.8%, 94.8%, and 94.2% for subjects with severe, moderate, or mild hepatic impairment, respectively, versus healthy subjects. Pomalidomide administered as a single oral 4-mg dose was safe and well tolerated by healthy subjects and subjects with severe, moderate, or mild hepatic impairment. Based on the pharmacokinetic results from this study, the pomalidomide prescribing information approved by the US Food and Drug Administration recommends for patients with mild or moderate hepatic impairment (Child-Pugh classes A or B), a 3-mg starting daily dose (25% dose reduction) and for patients with severe hepatic impairment (Child-Pugh class C), a 2-mg starting daily dose (50% dose reduction).

Keywords
dose recommendation, hepatic impairment, pomalidomide, pharmacokinetics

Pomalidomide, an immunomodulatory drug analogue structurally similar to thalidomide,1,2 is an immunomodulatory agent with antineoplastic activity.3,4 In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells5-9 and showed immunomodulatory activity.10-12 Pomalidomide has been studied for treatment of various hematologic and non-neoplastic hematologic disorders,1,13-15 and the dosage of 4 mg per day taken orally on days 1-21 of repeated 28-day cycles is approved (in combination with dexamethasone) in the European Union and United States for the treatment of patients with multiple myeloma who have received ≥2 prior therapies, including lenalidomide and bortezomib (in the European Union; a proteasome inhibitor in the United States), and who have progressed on or within 60 days of completion of the last therapy or have disease progression on the last therapy.1,13,15 This combination (pomalidomide plus low-dose dexamethasone) increased progression-free survival and overall survival compared with high-dose dexamethasone.1,13 Thrombocytopenia, neutropenia, and anemia were the most common grade 3/4 adverse events.13

The pharmacokinetics (PK) of pomalidomide after a single oral dose of 4 mg in plasma was characterized by rapid absorption (median time to peak plasma drug concentration [tmax] 2.50-3.25 hours post dose) and rapid elimination (mean terminal half-
younger populations. As hepatic metabolism represents a relatively major clearance pathway for pomalidomide, hepatic impairment could potentially affect pomalidomide’s PK by decreasing hepatic clearance. Therefore, a total of 32 subjects (8 healthy subjects in group 1; 8 subjects with severe hepatic impairment in group 2; 8 subjects with moderate hepatic impairment in group 3; and 8 subjects with mild hepatic impairment in group 4) were enrolled in a multicenter, open-label, single-dose study to assess the effect of hepatic impairment on pomalidomide exposure (CC-4047-CP-009). The primary objective of this study was to evaluate the effect of various degrees of hepatic impairment on the PK of a single oral dose of pomalidomide in male subjects; the secondary objective of this study was to evaluate the effect of hepatic impairment on the safety of a single oral dose of pomalidomide in male subjects.

Methods
All subjects provided written informed consent prior to screening. This study was conducted and monitored in accordance with Celgene procedures and the study protocol. These procedures comply with the ethical principles of the International Conference on Harmonisation (ICH) harmonised tripartite guideline E6 (R1): Good Clinical Practice (GCP), as required by the major regulatory authorities. The conduct also complied with the Declaration of Helsinki, Title 21 of the US Code of Federal Regulations, Parts 50 and 56 concerning informed consent and institutional review board regulations, and applicable national, state, and local laws or regulations. This study was conducted in 2 clinical sites: DaVita Clinical Research (Minneapolis, Minnesota) and Division of Clinical Pharmacology, University of Miami (Miami, Florida) and was approved by the institutional review boards of Western Institutional Review Board (Puyallup, Washington) and University of Miami Human Subjects Research Office (Miami, Florida), respectively.

Study Design
This was a multicenter, open-label, single-dose study designed to assess the impact of severe (part 1, group 2) hepatic impairment on the PK of pomalidomide following oral administration of a single 4-mg dose of pomalidomide. Healthy subjects with normal hepatic function (part 1, group 1) were enrolled for PK comparison. Degrees of hepatic impairment were determined during screening by the subject’s score according to the Pugh modification of the Child Classification of Severity of Liver Disease. Because exposures in severely hepatically impaired subjects were substantially different from the healthy subjects, subjects with moderate and mild hepatic impairment (part 2, group 3 and group 4) were enrolled. Group 1 and
group 2 subjects were matched with respect to age (±10 years) and weight (±13.61 kg [±30 pounds]). Subjects in groups 3 and 4 were also similar to subjects in group 1 with respect to age and weight. Although light smokers (defined as smoking no more than 10 cigarettes, or consuming the equivalent in tobacco, per day) could participate in the study, smoking or the use of other tobacco products was not allowed for 7 days, from prior to baseline admission to the end of all study procedures.

The entire study consisted of a screening phase, one treatment period, and a follow-up telephone call. Parts 1 and 2 were conducted sequentially, with part 2 initiation dependent on the results from part 1. Within no more than 21 days (day –21) and no less than 2 days (day –2) prior to the start of the treatment, subjects underwent routine screening procedures, including complete physical examination (PE), 12-lead electrocardiogram (ECG), vital signs, clinical laboratory safety tests (chemistry, hematology, and urinalysis), serology screen, and food/alcohol screen. Eligible subjects returned to the study center on day –1 of period 1 for baseline assessments. During the study period, subjects were confined at the study center from day –1 through the morning of day 3. Subjects were discharged from the study center on day 3 upon completion of study procedures. Upon completion of part 1, PK and safety data were reviewed by the investigator and Celgene and a decision was made to initiate part 2.

Results from separate clinical data assessing the impact of food on pomalidomide PK showed there was no clinically relevant effect of food intake on pomalidomide exposure, demonstrated by food only decreasing area under the plasma concentration time curve from time 0 extrapolated to infinity (AUC) by 8% (data on file). Although food does not affect pomalidomide PK and pomalidomide can be taken without regard to food consumption, as indicated on the product label, food restriction was still applied to all enrolled subjects in group 1 with respect to age and weight. Although light smokers (defined as smoking no more than 10 cigarettes, or consuming the equivalent in tobacco, per day) could participate in the study, smoking or the use of other tobacco products was not allowed for 7 days, from prior to baseline admission to the end of all study procedures.

**Blood Collection for Pharmacokinetic Analysis**
Serial blood samples were collected pre dose and up to 48 hours post dose at the following time points: 0 (pre dose), 0.25, 1, 2, 2.5, 4, 6, 8, 12, 24, 30, 40, and 48 hours post dose) for determination of plasma pomalidomide concentrations.

**Safety Assessment**
Safety was monitored throughout the study. Safety evaluations included adverse event (AE) reporting, PEs, vital sign measurements, 12-lead ECGs, and clinical laboratory safety tests. All concomitant medications were assessed and recorded throughout the study, from the time the informed consent document was signed until study completion (follow-up safety telephone call). Adverse events and serious AEs (SAEs) were assessed and recorded from the time the subject signed the informed consent document until study completion (follow-up safety telephone call), and when made known to the investigator within 28 days after the last dose of pomalidomide (and SAEs that were suspected of being related to pomalidomide made known to the investigator at any time thereafter).

If repeated safety measurements were needed at discharge, subjects were instructed to return to the study center at appropriate times for further testing. Otherwise, the safety follow-up was conducted by telephone 7 days ± 1 day from the last dose.

**Bioanalytical Methodology**
To determine human plasma samples for pomalidomide concentrations, a validated liquid chromatography-tandem mass spectrometry assay was utilized. As an internal standard, plasma samples were spiked with stable 13C-labeled pomalidomide. Pomalidomide and 13C-labeled pomalidomide were extracted from plasma (stabilized with citric acid) using liquid-liquid extraction with methyl tertiary butyl ether. After transfer to a new tube, the solvent was evaporated and the samples were reconstituted and injected for liquid chromatography-tandem mass spectrometry analysis using a Phenomenex analytical column (Luna C18 (2), 50 × 2.0 mm, 5 μm, Torrance, California). Positive ions were measured in the multiple reaction monitoring mode using a SciexAPI-4000 tandem mass spectrometer (Sciex, Framingham, Massachusetts) equipped with a Turbo Ion Spray source. For the quality control samples, the accuracy range was 91.0–106.9%. The lower limit of quantification was 0.25 ng/mL.

**Pharmacokinetic Analyses**
Noncompartmental PK parameters such as maximum plasma drug concentration \(C_{max}\), \(t_{max}\), AUC_{0-4}, AUC, \(t_{1/2}\), CL/F, and percentage of AUC due to extrapolation
from the time for the last quantifiable concentration to infinity (AUC%extrap) were calculated from the plasma concentration-time data with Phoenix Win-Nonlin Professional Version 6.3 (Pharsight, a Certara company, St. Louis, Missouri). Actual sampling times were used in the calculations. Descriptive statistics (sample size, mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum) were provided for concentrations at each time point and for all PK parameters.

Statistical Analyses
No formal sample size calculation was performed. Up to 32 subjects (8 healthy subjects in group 1; 8 subjects in group 2; 6-8 subjects in group 3; and 6-8 subjects in group 4) were chosen as a suitable number to achieve the objective of this study, based on other similar studies from the literature. The goal was to have a sufficient number of evaluable plasma concentration time points to adequately characterize the PK of the study drug in each group.

For AUC₀⁻ᵗ, AUC, and Cₘₐₓ, an analysis of variance (ANOVA) model was performed to calculate the ratio of geometric means (GMR) and its 90% confidence interval between subjects with hepatic impairment and matched healthy subjects. The ANOVA model included group (severe, moderate, mild, and healthy) as fixed effect. The tₘₐₓ was analyzed by nonparametric method.

All safety assessments, including AEs, vital sign measurements, clinical laboratory information, concomitant medications, PEs, and ECG interpretations, were tabulated and summarized as appropriate. Adverse events were recorded and classified using the Medical Dictionary for Drug Regulatory Activities classification system (Celgene-approved version). Treatment emergent AEs (TEAEs) were summarized by frequency, severity, and relatedness to study drug. The frequency (number of TEAEs and number of subjects experiencing a TEAE) of TEAEs were tabulated by system organ class and preferred term. In the per-subject analyses, a subject having the same event more than once was counted only once. Laboratory and vital sign data were summarized descriptively (sample size, mean, standard deviation, minimum, median, and maximum). There was no statistical comparison of safety parameters between treatments.

Results
Demographic and Other Baseline Characteristics
A total of 32 subjects were enrolled and 32 subjects (100%) completed the study. Demographic data are presented in Table 1. Overall, demographic characteristics were similar across the groups. All subjects were male and the majority were white (87.5%) and Hispanic or Latino (62.5%). Two subjects in the mild hepatic impairment group and one subject in the moderate hepatic impairment group had medical history findings that were considered clinically significant. None of the medical history findings prevented the subjects from enrolling into the study.

Five subjects (two subjects in the mild hepatic impairment group, two subjects in the moderate hepatic impairment group, and one subject in the severe hepatic impairment group) had a positive drug screen result at screening and/or day –1. The positive results were due to prescribed medications, which were allowed per protocol. A total of 14 subjects (6 subjects in the mild hepatic impairment group, 5 subjects in the moderate hepatic impairment group, and 3 subjects in the severe hepatic impairment group) had a positive result for hepatitis B virus surface antigen or hepatitis C virus antibody, or both. The positive results were allowed per protocol. None of the PE findings at screening

Table 1. Demographic and Other Baseline Characteristics

| Demographics | 1 Healthy Subjects (n = 8) | 2 Severe Haptic Impairment (n = 8) | 3 Moderate Haptic Impairment (n = 8) | 4 Mild Haptic Impairment (n = 8) | Total (N = 32) |
|--------------|---------------------------|-----------------------------------|-------------------------------------|-------------------------------|----------------|
| Age (years)  | Mean (range)              | 55.8 (50–66)                      | 53.1 (42–62)                       | 59.3 (54–69)                  | 56.4 (51–68)   | 56.1 (42–69)   |
|              | Height (cm)               | 175.18 (167.0–182.3)              | 171.50 (152.0–182.0)               | 171.13 (160.0–181.0)          | 174.50 (165.0–187.0) | 173.08 (152.0–187.0) |
|              | Weight (kg)               | 86.28 (70.0–101.2)                | 90.48 (69.0–114.0)                 | 87.46 (71.5–100.3)            | 86.85 (71.7–103.0) | 87.77 (69.0–114.0) |
|              | Body mass index (kg/m²)   | 28.10 (24.3–31.9)                 | 30.79 (23.9–36.6)                  | 29.88 (24.9–35.2)             | 28.66 (23.1–34.4) | 29.36 (23.1–36.6) |
| Race, n (%)  | White                     | 7 (87.5)                          | 7 (87.5)                           | 8 (100)                       | 6 (75.0)        | 28 (87.5)       |
|              | Black or African American | 1 (12.5)                          | 1 (12.5)                           | 0                             | 2 (25.0)        | 4 (12.5)        |
| Ethnicity, n (%) | Hispanic or Latino  | 6 (75.0)                          | 6 (75.0)                           | 5 (62.5)                      | 3 (37.5)        | 20 (62.5)       |
|              | Not Hispanic or Latino    | 2 (25.0)                          | 2 (25.0)                           | 3 (37.5)                      | 5 (62.5)        | 12 (37.5)       |
precluded subjects from entering the study. All subjects received a follow-up telephone call.

**Plasma Pharmacokinetic Analyses of Pomalidomide**

Mean plasma concentration profiles of pomalidomide from group 1 (subjects with normal hepatic function), group 2 (subjects with severe hepatic impairment), group 3 (subjects with moderate hepatic impairment), and group 4 (subjects with mild hepatic impairment) are presented in Figure 1. Mean plasma concentration-time profiles of pomalidomide were well characterized over the 48-hour postdose sampling interval, both in healthy subjects and in subjects with mild, moderate, or severe hepatic impairment. The AUC%extrap from all subjects was lower than 20% (range 0.4%–12.8%), suggesting adequate PK sampling schedule for subjects with various degrees of hepatic impairment.

The summary of the PK parameters of pomalidomide from group 1, group 2, group 3, and group 4 are presented by group in Table 2. Following administration of a single oral dose of 4-mg pomalidomide, pomalidomide was absorbed, with Cmax of 60.7, 56.2, 58.0, and 49.1 μg/L and AUC of 497.8, 787.2, 810.0, and 908.3 μg·h/L from healthy subjects and subjects with mild, moderate, and severe hepatic impairment, respectively. In general, the PK parameters in the healthy group from this study were similar to those from the previous drug interaction study.22

For subjects with normal hepatic function, pomalidomide was rapidly absorbed, with a median tmax of 1.5 hours following administration of a single oral dose of pomalidomide. For subjects with impaired hepatic function, pomalidomide was absorbed with longer tmax (2.0 hours, 2.25 hours, and 2.5 hours for subjects with mild, moderate, and severe hepatic impairment, respectively).

The mean t1/2 was similar in subjects with impaired hepatic function (10.3, 10.1, and 12.7 hours for subjects with mild, moderate, and severe hepatic impairment, respectively) and greater than that in subjects with healthy hepatic function (6.2 hours).

**Effect of Hepatic Impairment on the PK of Pomalidomide**

For AUC0-t, AUC, and Cmax, ANOVA was performed to compare PK parameters of pomalidomide between the groups of subjects with hepatic impairment and the healthy subjects. The results are presented in Table 3 and Table 4.

Following administration of a single oral dose of 4-mg pomalidomide, the GMR (%) of pomalidomide AUC was 171.5%, 157.5%, and 151.2% for subjects with severe hepatic impairment versus healthy subjects, for subjects with moderate hepatic impairment versus healthy subjects, and for subjects with mild hepatic impairment versus healthy subjects, respectively.

### Table 2. Summary of Pomalidomide Plasma Pharmacokinetic Parameters, by Group

| Pomalidomide PK Parameters | Group 1 (Healthy Subjects) n = 8 | Group 2 (Severe Hepatic Impairment) n = 8 | Group 3 (Moderate Hepatic Impairment) n = 8 | Group 4 (Mild Hepatic Impairment) n = 8 |
|---------------------------|----------------------------------|----------------------------------------|------------------------------------------|--------------------------------------|
| AUC0-t (μg·h/L)           | 493.3 (122.4)                    | 821.9 (289.2)                          | 764.5 (239.6)                           | 728.4 (243.8)                        |
| AUC (μg·h/L)              | 497.8 (124.6)                    | 908.3 (358.9)                          | 810.0 (261.1)                           | 787.2 (317.5)                        |
| Cmax (μg/L)               | 60.7 (14.1)                      | 49.1 (18.5)                            | 58.0 (15.1)                             | 56.2 (7.3)                           |
| tmax (h)a                | 1.5 (1.0, 2.5)                   | 2.5 (1.0, 6.0)                         | 2.25 (1.0, 4.0)                         | 2.0 (2.0, 4.0)                       |
| t1/2 (h)                 | 6.2 (1.0)                        | 12.7 (3.9)                             | 10.1 (3.5)                              | 10.3 (4.9)                           |
| CL/F (L/h)               | 8.4 (1.9)                        | 5.4 (3.3)                              | 5.6 (2.6)                               | 5.8 (2.2)                            |

AUC0-t, area under the plasma concentration time curve from time 0 to last time with detectable levels; AUC, area under the plasma concentration-time curve from time 0 extrapolated to infinity; CL/F, apparent total plasma clearance when dosed orally; Cmax, maximum observed plasma concentration; PK, pharmacokinetic; tmax, time to maximum plasma concentration; t1/2, half-life in terminal phase.

Arithmetic mean (standard deviation) data are presented.

aMedian (min, max).
Table 3. Statistical Comparison of Pomalidomide Plasma Pharmacokinetic Parameters (AUC₀₋ₜ, AUC, and Cₘₐₓ)

| Pharmacokinetic Parameter (Unit) | Group                        | N  | Geometric Mean | Comparison     | Ratio (%) of Geometric Mean (Impaired vs Healthy) | 90%CI of Ratio of Geometric Mean |
|---------------------------------|------------------------------|----|----------------|----------------|---------------------------------------------------|----------------------------------|
| AUC₀₋ₜ (μg·h/L)                | Severe hepatic impairment    | 8  | 762.1          | Severe vs healthy | 158.4                                            | (116.6–215.0)                   |
|                                 | Moderate hepatic impairment  | 8  | 725.0          | Moderate vs healthy | 150.6                                            | (110.9–204.5)                   |
|                                 | Mild hepatic impairment      | 8  | 692.8          | Mild vs healthy   | 143.9                                            | (106.0–195.4)                   |
|                                 | Healthy                      | 8  | 481.3          |                 |                                                   |                                  |
| AUC (μg·h/L)                    | Severe hepatic impairment    | 8  | 832.8          | Severe vs healthy | 171.5                                            | (123.5–238.4)                   |
|                                 | Moderate hepatic impairment  | 8  | 764.4          | Moderate vs healthy | 157.5                                            | (113.3–218.8)                   |
|                                 | Mild hepatic impairment      | 8  | 733.9          | Mild vs healthy   | 151.2                                            | (108.8–210.1)                   |
|                                 | Healthy                      | 8  | 485.5          |                 |                                                   |                                  |
| Cₘₐₓ (μg/L)                     | Severe hepatic impairment    | 8  | 44.9           | Severe vs Healthy | 75.8                                             | (57.7–99.7)                     |
|                                 | Moderate hepatic impairment  | 8  | 56.2           | Moderate vs Healthy | 94.8                                             | (72.1–124.6)                    |
|                                 | Mild hepatic impairment      | 8  | 55.8           | Mild vs Healthy   | 94.2                                             | (71.6–123.8)                    |
|                                 | Healthy                      | 8  | 59.2           |                 |                                                   |                                  |

AUC₀₋ₜ, area under the plasma concentration time curve from time 0 to last time with detectable levels; AUC, area under the plasma concentration time curve from time 0 extrapolated to infinity; CI, confidence interval; Cₘₐₓ, maximum observed plasma concentration; PK, pharmacokinetic.

Table 4. Statistical Comparison of Pomalidomide Plasma Pharmacokinetic Parameters (tₘₐₓ)

| Pharmacokinetic Parameter (Unit) | Group                        | N  | Geometric Mean | Comparison   | Median Difference (Impaired–Healthy) | 90%CI of Median Difference |
|---------------------------------|------------------------------|----|----------------|--------------|--------------------------------------|---------------------------|
| tₘₐₓ (h)                        | Severe hepatic impairment    | 8  | 2.5            | Severe vs Healthy | 0.75                                                | (0.00–2.50)               |
|                                 | Moderate hepatic impairment  | 8  | 2.38           | Moderate vs Healthy | 1.0                                                 | (0.00–1.50)               |
|                                 | Mild hepatic impairment      | 8  | 2.25           | Mild vs Healthy   | 1.0                                                 | (0.00–1.50)               |
|                                 | Healthy                      | 8  | 1.5            |               |                                                     |                           |

PK, pharmacokinetic; tₘₐₓ, time to maximum plasma concentration.

Healthy subjects, and for subjects with mild hepatic impairment versus healthy subjects, respectively.

Following administration of a single oral dose of 4-mg pomalidomide, the GMR (%) of pomalidomide Cₘₐₓ was 75.8%, 94.8%, and 94.2% for subjects with severe hepatic impairment versus healthy subjects, for subjects with moderate hepatic impairment versus healthy subjects, and for subjects with mild hepatic impairment versus healthy subjects, respectively.

The difference in pomalidomide median tₘₐₓ was 0.75, 1.0, and 1.0 for subjects with severe hepatic impairment versus healthy subjects, for subjects with moderate hepatic impairment versus healthy subjects, and for subjects with mild hepatic impairment versus healthy subjects, respectively.

Safety
Overall, 6 of 32 (18.8%) subjects reported a total of 8 TEAES. The majority of TEAES were reported by subjects in the mild hepatic impairment group (4 subjects, 50.0%); 1 subject each in the severe and moderate hepatic impairment groups reported TEAES (12.5%). No TEAES were reported by the healthy subjects in this study. A total of 3 subjects (9.4%) reported at least
1 TEAE related to pomalidomide; 2 subjects (25.0%) in the mild hepatic impairment group and 1 subject (12.5%) in the severe hepatic impairment group. No deaths, SAEs, or TEAEs leading to discontinuation were reported.

All TEAEs were mild in severity except for 1 subject with the moderate TEAE of bronchitis. No severe TEAEs were reported during the study. Overall, 1 subject (9.4%) had TEAEs of diarrhea, nausea, headache, and flushing that were suspected of being related to pomalidomide.

No deaths or other SAEs were reported and no subjects were discontinued during this study.

Discussion
Assessing the effect of hepatic impairment on drug exposures is required for all investigational drugs if hepatic metabolism and/or excretion accounts for a substantial portion (>20% of the absorbed drug) of the elimination of a parent drug or active metabolite.20,21 In the human [14C]pomalidomide absorption, metabolism, and excretion study,16 even though 72.8% of total [14C]-radioactivity was recovered in urine, unchanged pomalidomide was detected as a minor radio-component in the urine, accounting for only 2.2% of the dose, while the 4 predominant metabolites (hydrolysis of glutarimide and glucuronide conjugates of hydroxylated pomalidomide) accounted for 52.8% of the dose excreted in the urine, suggesting extensive metabolism of pomalidomide prior to its excretion. In addition, a meta-analysis pooling data from patients with relapsed and refractory multiple myeloma with normal renal function, moderately impaired renal function, and severely impaired renal function showed there was no remarkable difference in pomalidomide exposure among different renal function groups, suggesting pomalidomide is cleared predominately via nonrenal routes, accounting for approximately 70% of pomalidomide total body clearance.18 Both studies suggest that the liver plays the predominant role in eliminating pomalidomide in vivo.

Impaired hepatic clearance could result in increased pomalidomide exposure and, in turn, potentially manifest as increased adverse reactions (thrombocytopenia, neutropenia, and anemia) in patients with impaired hepatic function. The target patient population for pomalidomide tends to be elderly and may have some degree of hepatic impairment; therefore, it is clinically relevant to assess the impact of hepatic impairment on pomalidomide exposure.

This was a multicenter, open-label, single-dose study designed to assess the effect of hepatic impairment on the PK of pomalidomide following oral administration of a single 4-mg dose of pomalidomide. The dose of 4 mg was chosen because it is the intended clinical starting dose for multiple myeloma patients. Subjects with normal or impaired hepatic function were enrolled for PK comparison.

Pomalidomide was teratogenic in preclinical species when administered during the period of organogenesis. To minimize risk of exposure of females of child-bearing potential to pomalidomide, only male subjects were enrolled in this study. However, previous pomalidomide population PK showed there was no clinically relevant impact of sex or other demographic factors (age, body weight, body surface area, and race) on pomalidomide PK, which supports the applicability of the data collected from male subjects in this study to female subjects.23 Healthy male subjects and male subjects with severe hepatic impairment were matched with respect to age (±10 years) and weight (±13.61 kg [±30 pounds]). To the extent possible, subjects in the moderate and mild hepatic impairment groups were similar to the healthy subjects with respect to age and weight.

Results from a separate clinical study assessing the impact of CYP1A2 induction by smoking on pomalidomide PK showed that pomalidomide PK was not remarkably affected in heavy smokers (approximately 25 cigarettes per day); in heavy smokers, AUC was 30% lower and Cmax was 14.4% higher than in nonsmokers (data on file). Therefore, light smokers (defined as smoking no more than 10 cigarettes, or consuming the equivalent in tobacco, per day) could participate in the study. However, smoking or the use of other tobacco products was not allowed from 7 days prior to baseline admission to the end of all study procedures. In fact, only 1 enrolled subject with mild hepatic impairment in this study was a light smoker. A sensitivity analysis was conducted and demonstrated that including or excluding the PK data from this subject did not alter the PK findings and conclusions.

This study showed that pomalidomide PK were adequately characterized in subjects with various degrees of hepatic impairment. Severe hepatic impairment decreased pomalidomide clearance and increased its exposure by approximately 70%; mild and moderate hepatic impairment had similar effects on pomalidomide clearance and increased its exposure by approximately 50% and approximately 60%, respectively. These findings suggest hepatic metabolism is reduced moderately (30%–50%) by hepatic impairment and is relatively sensitive to degree of hepatic impairment. In addition to slower metabolism and elimination, hepatic impairment appeared to cause slower and/or incomplete pomalidomide absorption, as reflected in the longer tmax and lower Cmax values. Taken together, hepatic impairment moderately reduced pomalidomide metabolism and elimination; these effects were countered by slower and/or reduced pomalidomide oral absorption, with the
net effect being a moderate increase (50%–70%) in pomalidomide exposure.

Regarding safety, pomalidomide administered as a single oral 4-mg dose was safe and well tolerated by healthy male subjects and male subjects with severe, moderate, or mild hepatic impairment. Overall, 6 of 32 subjects (18.8%) reported a total of 8 TEAEs. Three subjects (9.4%) reported at least one TEAE related to study drug; two subjects (25.0%) in the mild hepatic impairment group and one subject (12.5%) in the severe hepatic impairment group. No TEAEs were reported by the healthy subjects. All TEAEs were mild in severity except for 1 subject in the moderate hepatic impairment group with the moderate TEAE of bronchitis. Overall, 3 subjects (9.4%) had TEAEs of diarrhea, nausea, headache, and flushing that were suspected of being related to investigational product. All TEAEs resolved by the end of the study. There were no deaths and no subject discontinued due to a TEAE. Mean alanine aminotransferase, aspartate aminotransferase, bilirubin, and glucose values were elevated in subjects with hepatic impairment but were not considered clinically significant. No subject had a clinical laboratory, vital sign, or ECG result that was considered clinically significant or reported as a TEAE. There were no apparent group-related trends in clinical laboratory results, vital sign measurements, or 12-lead ECG results.

In conclusion, a single dose of 4-mg pomalidomide was safe and well tolerated by healthy male subjects and male subjects with severe, moderate, or mild hepatic impairment. Following administration of a single oral dose of 4-mg pomalidomide, the GMRs of pomalidomide AUC were 171.5%, 157.5%, and 151.2% for subjects with severe, moderate, or mild hepatic impairment, respectively, versus healthy subjects. All TEAEs were mild in severity except for 1 subject in the moderate hepatic impairment group with the moderate TEAE of bronchitis. Overall, 3 subjects (9.4%) had TEAEs of diarrhea, nausea, headache, and flushing that were suspected of being related to investigational product. All TEAEs resolved by the end of the study. There were no deaths and no subject discontinued due to a TEAE. Mean alanine aminotransferase, aspartate aminotransferase, bilirubin, and glucose values were elevated in subjects with hepatic impairment but were not considered clinically significant. No subject had a clinical laboratory, vital sign, or ECG result that was considered clinically significant or reported as a TEAE. There were no apparent group-related trends in clinical laboratory results, vital sign measurements, or 12-lead ECG results.

Disclosures

Yan Li, Xiaomin Wang, Liangang Liu, Chengyue Zhang, Josephine Reyes, Maria Palmisano, and Simon Zhou are employees of and hold equity ownership in Celgene Corporation.

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