Modeling and Simulation to Probe the Pharmacokinetic Disposition of Pomalidomide R- and S-Enantiomers

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ABSTRACT

Pomalidomide, a potent novel immunomodulatory agent, has been developed as a racemic mixture of its R- and S-isomers. Pharmacokinetic (PK) analyses were conducted to determine the PK disposition of the isomers from their PK profiles in humans and monkeys. Modeling and simulation were performed to describe the observed PK profiles and explore potential differences in isomer disposition and exposure. PK profiles of S- and R-isomers were measured in a human absorption, distribution, metabolism, and excretion study after oral administration of pomalidomide; PK profiles of S- and R-isomers were measured in a human absorption, distribution, metabolism, and excretion study after oral administration of pomalidomide; PK profiles of S- and R-isomers were measured in monkeys after intravenous and oral administration of S- or R-isomers and pomalidomide racemate. Modeling and simulation were performed using NONMEM 7.2 (Globomax, Ellicott City, MD) to describe the observed PK profiles of S- and R-isomers in humans and monkeys. The results showed that in humans, the in vivo elimination rate of pomalidomide isomers was lower than the R-/S-interconversion rate, resulting in no clinically relevant difference in overall exposure to the two isomers. However, in monkeys, the in vivo elimination rate was higher than the R-/S-interconversion rate, resulting in 1.72- and 1.55-fold differences in R- versus S-isomer exposures. Monte Carlo simulation indicated that exposure to R- and S-enantiomers in humans should be comparable even if single isomers are administered. Thus, in humans, rapid isomeric interconversion of pomalidomide isomers results in comparable exposure to R- and S-enantiomers regardless of whether pomalidomide is administered as a single enantiomer or as a racemate, therefore justifying the clinical development of pomalidomide as a racemate.

Introduction

Pomalidomide (CC-4047; Fig. 1) is a novel immunomodulatory agent with pleiotropic cytotoxic effects against multiple myeloma cells (Mitsiades et al., 2002; Zhu et al., 2008), as well as antiproliferative (Hideshima et al., 2000; Verhelle et al., 2007), antiangiogenic (Gupta et al., 2001; Reddy et al., 2008; Lu et al., 2009), and immunomodulatory actions (Corral et al., 1999; Hayashi et al., 2005; Reddy et al., 2008). It has potent effects on key cytokines, including tumor necrosis factor-α (TNF-α), interleukin-10, and interferon-γ (Teo et al., 2003). Potential therapeutic benefits have been shown in the treatment of various hematologic and nonneoplastic hematologic disorders. Pomalidomide is currently approved in the United States (Pomalyst; Celgene Corporation, Summit, NJ), and Europe (Imnovid; Celgene Corporation) for the treatment of relapsed/refractory multiple myeloma in patients who have received at least two prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy. It is also undergoing clinical evaluation for the treatment of myelofibrosis and systemic sclerosis.

Pomalidomide is a chiral compound with an asymmetric carbon center and can therefore exist as the optically active forms of S (-) and R (+). The S-isomer is termed CC-5083, and the R-isomer is termed CC-6016. The R- and S-isomers exist in a 50:50 ratio and interconvert in plasma via enzymatic and nonenzymatic pathways (Hoffmann et al., 2013). Pomalidomide has been developed as a racemic mixture of its R- and S-isomers, even though the S-isomer of pomalidomide has been reported to be the more potent enantiomer of the racemate (Teo et al., 2003), and in vitro studies have shown that the anti-TNF-α and immunomodulatory activities are primarily due to the S-isomer (Corral et al., 1996; Muller et al., 1999; Davies et al., 2001).

Although the R- and S-isomers of pomalidomide are identical in terms of their molecular formula, atomic bonds, and bond distances, they have different three-dimensional structures and are nonsuperimposable (Teo et al., 2003). Biologic systems are themselves chiral environments (e.g., right-handed B-DNA and left-handed Z-DNA, D-carbohydrate forms, and L-amino acid structures), and within the biochemical environment of living systems, specific tertiary structural forms are often required for biologic activity to occur (e.g., enzyme catalysis, receptor bonding, molecular transport, etc.). Therefore,
in biochemical systems, racemic mixtures (or individual enantiomers) can exhibit distinctive absorption, transport, protein-binding, metabolism, and elimination, leading to different pharmacokinetic (PK), pharmacodynamic, and toxicity profiles, depending on the composition of the enantiomers and the rate of interconversion between the stereoisomeric forms. Stereo-specific variations have been reported for many classes of pharmaceuticals, including antibiotics, cardiovascular drugs, chemotherapy agents, and antirheumatics (Smith, 2009). Thus, it is important that clinical pharmacologic evaluations during the development of chiral compounds take into account the potential differences in enantiomer disposition, exposure, and dose-response relationships.

The aim of this analysis was to determine the potential differences in PK disposition of the R- and S-pomalidomide isomers from the PK profile of the R- and S-pomalidomide isomers after oral administration of pomalidomide racemate in humans, and from R- and S-isomer PK profiles in a monkey study after intravenous and oral administration of S- or R-isomers and pomalidomide racemate. In addition, modeling and simulations were performed to probe the interplay of isomer interconversion versus elimination on plasma exposure of isomers. Simulations were also conducted to evaluate potential differences in plasma exposure of R- and S-isomers when R- or S-isomers or racemate are administered.

**Materials and Methods**

**Pharmacokinetic Study of Pomalidomide and Its Two Enantiomers in Monkeys.** The plasma concentration–time profiles of CC-4047 and its two enantiomers (CC-5083 and CC-6016) were measured after intravenous and oral administration to monkeys. These experiments were performed according to the Care and Use of Laboratory Animals guidelines, as adopted and promulgated by the US National Institutes of Health. CC-4047, CC-5083, and CC-6016 were formulated in aqueous 1.0% (weight per volume) carboxymethyl cellulose for oral dosing, and 5% dimethylacetamide, 45% polyethylene glycol 400, and 50% saline for intravenous dosing. CC-4047, CC-5083, and CC-6016 were administered to three groups of male cynomolgus monkeys (total of nine monkeys). The doses were 1 mg/kg (i.v.) and 2 mg/kg (oral) for CC-4047 and 0.5 mg/kg (i.v.) and 1.0 mg/kg (oral) for the individual enantiomers. Serial blood samples (approximately 1 ml) were collected from each animal at the following time points: predose, and at 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose for the intravenous cohort, and predose, and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose for the oral cohort. Plasma samples were prepared by centrifugation, then diluted into an equal volume of Sorenson’s citrate buffer, pH 2.5, to stabilize the analytes.

**Pharmacokinetic Study of Pomalidomide in Healthy Human Subjects.** This phase 1 study was an open-label, single-center, single-dose study. Eight healthy male subjects were enrolled and all completed the study. The study consisted of a 21-day screening period, a baseline period (day 1), a single oral dose treatment on day 1, sample collection up to day 15 (336 hours postdose), a study completion evaluation on day 15 (or day of discharge), and a follow-up visit 7 to 10 days from day of discharge.

Prior to study initiation, the study protocol, investigator’s brochure, and informed consent form were reviewed and approved by the Independent Investigational Review Board, Inc. (Plantation, FL). All eight subjects consented to the study prior to dosing.

On day 1, each subject received a single 2-mg oral dose of pomalidomide that contained approximately 100 μCi of [14C]-CC-4047, after at least an 8-hour fast. Blood samples were collected at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 48, 72, 120, and 168 hours postdose. Plasma samples were prepared by centrifugation, then transferred to a tube containing citric acid to stabilize the analytes. Samples were used for radioactivity counting; metabolite profiling; and determination of concentration of the parent drug, its enantiomers, and its metabolites, as applicable.

**Bioassay.** Plasma concentrations of pomalidomide and the enantiomers CC-5083 and CC-6016 were measured using chiral liquid chromatography–tandem mass spectrometry. The analytical range of the assay was 1–200 ng/ml.

**Pharmacokinetic Analysis.** Based on visual inspection of the log concentration–time profile, a one-compartment model with first-order absorption and elimination was selected to characterize the PK disposition of CC-4047 and the isomers CC-5083 and CC-6016 in monkeys and humans. A pictorial presentation of the PK model is shown in Fig. 2. The PK model was parameterized in microconstants of the first-order absorption rate constant (kaS for CC-5083 and kaR for CC-6016), the volume of distribution of the central compartment (V/F for humans and V for monkeys), the apparent clearance (CLs for CC-5083 and CLR for CC-6016), and the in vivo interconversion rate constant between R- and S- enantiomers (kinter). Assuming a log-normal distribution for interindividual variability in PK parameters, the interindividual variability was modeled as:

\[
P_i = P_i \cdot e^{\eta_i}
\]

where \(P_i\) was the typical value of the parameter in the population, \(P_i\) was the value of the parameter for the \(i\)th individual, and \(\eta_i\) was a random interindividual effect in the parameter for the \(i\)th subject with a mean of zero and variance \(\sigma^2\) (i.e., \(\eta_i \sim N(0, \sigma^2)\)).

Intraindividual or residual variability was modeled as follows:

\[
\ln(C_{ij}) = \ln(C_{mi}) + \epsilon_{ij}
\]

where \(C_{mi}\) was the model-predicted \(j\)th concentration in the \(i\)th subject, \(C_{ij}\) was the observed \(j\)th concentration in the \(i\)th subject, and \(\epsilon_{ij}\) was the random residual effect for the \(j\)th concentration in the \(i\)th subject with a mean of zero and variance \(\sigma^2\).
PK analysis of the concentration-time data of pomalidomide (CC-4047, CC-5083, and CC-6016) in monkeys and humans was conducted using the nonlinear mixed-effect modeling program (NONMEM, version 7.2 or higher; Globomax, Ellicott City, MD). All fitting procedures were performed under Windows XP with the Intel Visual Fortran Compiler (version 9.1; Intel, Santa Clara, CA). Selection criteria during the model development process were based on the goodness-of-fit plots, changes in the objective function value, residual distributions, and parameter estimates and their relative standard error values.

Simulations to explore key attributes of kinetic properties of interconversion and elimination driving potential exposure difference to individual isomers were performed using Berkeley Madonna (version 8.3.18; University of California at Berkeley, CA). Since the V/F of the R- and S-enantiomer was similar, a simpler model was employed. While multiple values of full permutation of interconversion rate constants and elimination rate constants were tested, the exercise aimed to compare the exposure difference to the two enantiomers and settled on a dimensionless factor of the relative ratio of the elimination rate versus the interconversion rate constant. Different relative ratios of elimination rate constant ($k_{elim}$) versus interconversion rate constant ($k_{inter}$) were simulated to check the difference in isomer exposures under different scenarios.

**Monte Carlo Simulation.** A Monte Carlo simulation was performed using NONMEM to probe whether the anticipated exposures of two enantiomers were comparable after dosing of each individual R- or S-isomer in humans. The dose of each individual isomer of 2 mg was simulated at steady state. The PK profiles and exposure for two individuals under each scenario were compared.

**Results**

**Pharmacokinetics in Monkeys.** The plasma concentration–time profiles of CC-5083 and CC-6016 after intravenous and oral administration of pomalidomide racemate (CC-4047), the S-isomer (CC-5083), or R-isomer (CC-6016) in monkeys are shown in Figs. 3 and 4.

After a single intravenous or oral dose of either R- or S-isomer in monkeys, both isomers were eliminated rapidly with a relatively short half-life, and the extent of in vivo conversion to S- or R-isomer was small by visual inspection, suggesting that the in vivo elimination of the individual R- or S-isomer is relatively faster than their in vivo interconversion. After a single intravenous or oral administration of racemate (CC-4047), the plasma concentration profiles showed comparable plasma exposure to both the R- and S-isomers, with slightly higher concentrations of R-isomer. Plasma exposure (area under the curve [AUC]) to CC-6016 (R-isomer) was approximately 1.5× as compared with that of CC-5083 (S-isomer) after intravenous or oral administration of pomalidomide (1.72× and 1.55× respectively). After intravenous or oral administration of CC-5083, plasma exposure to CC-6016 was smaller than that of CC-5083 (47 and 32%, respectively), and after intravenous or oral administration of CC-6016, plasma exposure to CC-5083 was smaller than that of CC-6016 (22 and 21%, respectively).

**Fig. 3.** Plasma concentration–time profiles of CC-5083 and CC-6016 after intravenous administration of CC-4047, CC-5083, and CC-6016 in monkeys. Concentration profiles shown reflect (A) CC-5083 after intravenous administration of CC-4047 (1 mg/kg), (B) CC-6016 after intravenous administration of CC-4047 (1 mg/kg), (C) CC-5083 after intravenous administration of CC-4047, (0.5 mg/kg), (D) CC-6016 after intravenous administration of CC-5083 (0.5 mg/kg), (E) CC-5083 after intravenous administration of CC-6016 (0.5 mg/kg), and (F) CC-6016 after intravenous administration of CC-6016 (0.5 mg/kg).

**Fig. 4.** Plasma concentration–time profiles of CC-5083 and CC-6016 after oral administration of CC-4047, CC-5083, and CC-6016 in monkeys. Concentration profiles shown reflect (A) CC-5083 after oral administration of CC-4047 (2 mg/kg), (B) CC-6016 after oral administration of CC-4047 (2 mg/kg), (C) CC-5083 after oral administration of CC-4047 (1 mg/kg), (D) CC-6016 after oral administration of CC-5083 (1 mg/kg), (E) CC-5083 after oral administration of CC-6016 (1 mg/kg), and (F) CC-6016 after oral administration of CC-6016 (1 mg/kg).
suggesting only limited to mild interconversion between \(R\)- and \(S\)-isomers.

The PK parameter estimates after intravenous or oral administration in monkeys are presented in Table 1. The structure model parameters were estimated precisely as indicated by small S.E. values (±5–10%) as compared with the population estimates. The diagnostic plots showed good agreement between population-predicted and individual observed values, and no systematic bias could be identified in the visual prediction check plot (Fig. 5), suggesting that the proposed model characterized well the PK central trend and the associated inter-subject variabilities for both the \(R\)- and \(S\)-isomers in monkeys.

Based on the PK modeling analysis, the in vivo interconversion rate between \(R\)- and \(S\)-isomers in monkeys was characterized by a value of 0.223 (1/h), which is comparable to the value characterized in vitro (0.41/h). In addition, the apparent in vivo elimination rates (Table 2) were comparable or higher than the interconversion rate (0.223 1/h).

**Pharmacokinetics in Humans.** The plasma concentration-time profiles of CC-5083 and CC-6016 after oral administration of pomalidomide are shown in Fig. 6. Both CC-6016 and CC-5083 were rapidly absorbed, with \(C_{max}\) observed at a \(T_{max}\) of approximately 3 hours for both isomers. Visual inspection of the PK profiles showed that the \(C_{max}\) and values for CC-5083 and CC-6016 were comparable, indicating that the two enantiomers were present in approximately equal amounts.

In humans, after a single 2-mg oral dose of CC-4047, the \(R\)- and \(S\)-enantiomers were present in approximately equal amounts. For CC-6016, the mean \(C_{max}\) and AUC\(_{0-t}\) values were approximately 49 and 50% of those observed for pomalidomide, and for CC-5083, the mean \(C_{max}\) and AUC\(_{0-t}\) values were approximately 52 and 49% of those observed for pomalidomide.

Different PK models and approaches were tested to identify the most stable and robust PK model to describe the observed PK profiles from \(R\)- and \(S\)-isomers. Initially, the observed PK differences between \(R\)- and \(S\)-enantiomers were forced to a single PK parameter (\(k_a\), V/F, or clearance [CL/F]) in the tested model. It was shown that the relaxed model (different \(k_a\), V/F, and CL/F PK parameters for \(R\)- and \(S\)-enantiomers) best described the PK profiles for both \(R\)- and \(S\)-enantiomers. The PK parameter estimates in humans are presented in Table 3. The structure parameters were estimated precisely as indicated by relatively small S.E. values (~20%) compared with the population estimates. The diagnostic plots showed good agreement between population-predicted and individual observed values, and no systematic bias could be identified in the visual prediction check plot (Fig. 5), suggesting the proposed model characterized well the PK central trend and the associated intersubject variabilities for both \(R\)- and \(S\)-isomers in humans.

The model-identified in vivo interconversion rate between \(R\)- and \(S\)-isomers in humans was 0.353 (1/h), which is comparable to the value of 0.223 (1/h) in monkeys. In addition, the in vivo elimination rates (0.056 and 0.091 1/h for \(S\)- and \(R\)-isomers, respectively) were slower than the interconversion rate (0.353 1/h).

**Simulation Exploring Interconversion and Elimination Rates.** Simulation results for the impact of different ratios of the elimination rate constant (\(k_{elim}\) versus the interconversion rate constant (\(k_{inter}\)) on the drug exposures of \(R\)- and \(S\)-isomers after dosing the \(S\)-isomer are presented in Fig. 7. As expected, the higher the ratio of \(k_{elim}\) versus \(k_{inter}\), the larger the differences of drug exposures between \(R\)- and \(S\)-isomers. In monkeys, the elimination rate constant is higher/ comparable to the interconversion rate constant in vivo (\(k_{elim}/k_{inter}\) is ~2.5), and significantly higher drug exposure for the isomer dosed is expected. The model-predicted ratio of \(R\)- to \(S\)-enantiomers is approximately 30%, comparable to the observed ratio of a range from 20 to 40% after intravenous and oral administration. In humans, the elimination rate constant is slower than the interconversion rate constant in vivo (\(k_{elim}/k_{inter}\) is ~0.25), and therefore, comparable drug exposure for \(R\)- and \(S\)-isomers is expected. The model-predicted ratio of \(R\)- to \(S\)-enantiomers is approximately 95%, comparable to the observed ratio of 94% after oral administration.

**Monte Carlo Simulation.** Based on the final model derived from human data, Monte Carlo simulations were performed to assess the difference in plasma exposures of the two enantiomers after oral dosing of each individual \(R\)- or \(S\)-isomer in humans. The results are shown in Fig. 8.

After administration of 2 mg of \(S\)-isomer (CC-5083) or \(R\)-isomer (CC-6016), comparable PK profiles between \(R\)- and \(S\)-isomers were observed. Monte Carlo simulation showed that after administration of 2 mg of \(S\)-isomer (CC-5083), the drug exposures (AUC\(_{inf}\)) were 105.7 and 92.7 ng/ml after administration of 2 mg of \(R\)-isomer (CC-6016), comparable PK profiles between \(R\)- and \(S\)-isomers were observed. Monte Carlo simulation showed that after administration of 2 mg of \(S\)-isomer (CC-5083), the drug exposures (AUC\(_{inf}\)) were 105.7 and 92.7 ng/ml-hour for \(S\)-isomer (CC-5083) and \(R\)-isomer (CC-6016), respectively, and after administration of 2 mg of \(R\)-isomer (CC-6016), the drug exposures (AUC\(_{inf}\)) were 90.0 and 104.9 ng/ml-hour for \(S\)-isomer (CC-5083) and \(R\)-isomer (CC-6016), respectively, indicating comparable drug exposure between \(R\)- and \(S\)-isomers after dosing of each individual \(R\)- or \(S\)-isomer in humans.

**Discussion**

Pomalidomide exists as a racemic mixture of \(R\)- and \(S\)-isomers (50:50). The \(S\)-isomer of pomalidomide has been reported to be

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**TABLE 1**
Population pharmacokinetic parameter estimates for pomalidomide in monkeys

<table>
<thead>
<tr>
<th>Structure Model</th>
<th>Population Estimate</th>
<th>Relative S.E.</th>
<th>Interindividual Variability</th>
<th>Relative S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(V (l))</td>
<td>2.9</td>
<td>4.0</td>
<td>0.00747</td>
</tr>
<tr>
<td></td>
<td>(CL_{a} \ (l/h))</td>
<td>1.61</td>
<td>11.0</td>
<td>0.0954</td>
</tr>
<tr>
<td></td>
<td>(CL_{m} \ (l/h))</td>
<td>0.228</td>
<td>8.7</td>
<td>0.0625</td>
</tr>
<tr>
<td></td>
<td>(k_{inter} \ (1/h))</td>
<td>0.223</td>
<td>5.8</td>
<td>0.0388</td>
</tr>
<tr>
<td>Residual error (\sigma^2)</td>
<td>0.123</td>
<td>16.8</td>
<td></td>
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\(CL_{a}\), total body clearance of \(S\)-isomer; \(CL_{m}\), total body clearance of \(R\)-isomer.
the more potent enantiomer of the racemate (Teo et al., 2003), and in vitro studies have shown that the anti–TNF-α and immunomodulatory activities are primarily due to the S-isomer (Corral et al., 1996; Muller et al., 1999; Davies et al., 2001). In the present study, we analyzed in vivo PK data and identified interesting disposition differences between the two enantiomers CC-5083 and CC-6016 in monkeys and humans. A PK model was developed to describe the difference in

\[ \text{Pharmacokinetics of } R- \text{ and } S-\text{Enantiomers of Pomalidomide} \]

\[ \text{Fig. 5. Visual prediction check (VPC) plots of the model fittings for the time profiles of CC-5083 and CC-6016. VPC plots shown above correspond to the following time profiles: (A) CC-5083 after oral administration of CC-4047 in humans (2 mg), (B) CC-6016 after oral administration of CC-4047 in humans (2 mg), (C) CC-5083 after intravenous administration of CC-4047 in monkeys (1 mg/kg), (D) CC-6016 after intravenous administration of CC-4047 in monkeys (1 mg/kg), (E) CC-5083 after intravenous administration of CC-5083 in monkeys (0.5 mg/kg), (F) CC-6016 after intravenous administration of CC-5083 in monkeys (0.5 mg/kg), (G) CC-5083 after intravenous administration of CC-6016 in monkeys (0.5 mg/kg), and (H) CC-6016 after intravenous administration of CC-6016 in monkeys (0.5 mg/kg). Blue circles represent observed data. Red solid lines represent the 50th percentiles of the observed data. Pink shaded areas represent nonparametric 95% confidence intervals about the 50th percentiles for the corresponding model predicted percentiles.} \]
kinetics of $S$- and $R$-isomer (CC-5083 and CC-6016) disposition in monkeys and humans, and it derived a dimensionless factor of the relative ratio of the elimination rate constant versus the interconversion rate constant that drives the PK exposure difference between the two enantiomers in vivo.

Evaluation of stability and interconversion of CC-6016 ($R$-isomer) and CC-5083 ($S$-isomer) in humans and monkeys in vitro and ex vivo showed gradual degradation (approximate half-life of 24 hours) and interconversion of the enantiomers (Teo et al., 2003). Both degradation (approximate half-lives of 3–4 hours) and interconversion (1:1 ratio achieved by approximately 4 hours) occurred rapidly, suggesting that both processes may occur via enzymatic and nonenzymatic pathways (Teo et al., 2003). The model identified in vivo interconversion rate constants between $R$- and $S$-isomers of 0.223 1/h in monkeys and 0.353 1/h in humans, which are comparable to that identified in vitro (0.4 1/h); however, the model identified different elimination rate constants in monkeys and humans in vivo.

For pomalidomide, in monkeys, the in vivo elimination rate constants of $R$- and $S$-isomers are comparable or higher than the interconversion rate constant (Table 2), resulting in differences in isomer exposure after dosing individual isomers or racemate (Figs. 3 and 4). However, in humans, the in vivo elimination rate constants are lower than the interconversion rate constant between $R$- and $S$-isomers, which allows the racemization between $R$- and $S$-isomers in a clinically meaningful time frame, resulting in a small difference in isomer exposures after dosing the racemate (Fig. 6). In addition, the Monte Carlo simulation of human data in this study showed the comparable PK profiles and comparable drug exposures between $R$- and $S$-isomers after administration of a single dose of either $S$- or $R$-isomer provided the scientific basis for the development of racemate pomalidomide (Fig. 8). Therefore, the development of a single pomalidomide enantiomer will not confer a clinical/therapeutic advantage over the racemate.

A chiral center confers different spatial orientation of the enantiomers, and thus often results in differing pharmacologic effects. It has been long accepted that most of the biologic activity observed for a racemate often likely resides within

<table>
<thead>
<tr>
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<th>Monkeys</th>
<th>Humans</th>
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<tbody>
<tr>
<td>$k_{\text{inter}}$ (1/h)</td>
<td>0.22</td>
<td>0.35</td>
</tr>
<tr>
<td>$k_{\text{elim}}$ (1/h) ($S$-isomer)</td>
<td>0.56</td>
<td>0.056</td>
</tr>
<tr>
<td>$k_{\text{elim}}$ (1/h) ($R$-isomer)</td>
<td>0.08</td>
<td>0.091</td>
</tr>
<tr>
<td>$k_{\text{elim}}/k_{\text{inter}}$</td>
<td>2.49</td>
<td>0.258</td>
</tr>
</tbody>
</table>

*Faster $k_{\text{elim}}$ constants from $S$- and $R$-isomers were used.

Fig. 6. Plasma concentration–time profiles of CC-5083 (blue solid lines) and CC-6016 (red solid lines) after oral administration of CC-4047 in humans. Different panels represent data from different subjects.
a single enantiomer. It was estimated that, before the 1990s, nearly 50% of all drugs used were racemate (Walther and Netscher, 1996). However, regulatory agencies’ interest in evaluating each enantiomer in a racemate spurred development of single enantiomers, which now account for 55% of the new molecular entities approved by the US Food and Drug Administration (Agranat et al., 2012).

Although the decision to develop a single-enantiomer product should include both scientific and economic rationales (Blake and Raissy, 2013), poor understanding of the kinetics of each individual enantiomer, especially the interplay between enantiomer racemization and difference in enantiomer elimination, can still lead to redundant investment in developing an enantiomer over the racemate. Levalbuterol, the \( R \)-enantiomer of albuterol, was introduced in the US market in 1999 based on the fact that the \( R \)-enantiomer is stereoselective at the target receptor with a 68-fold greater potency than the \( S \)-enantiomer (Brittain et al., 1973). However, a randomized crossover study in which the racemate and the \( R \)- and \( S \)-enantiomers were administered demonstrated that the therapeutic ratio of the \( R \)-enantiomer was comparable with that of the racemate in asthma patients (Lotvall et al., 2001), which might be due to the limited understanding of the interplay between enantiomer racemization and enantiomer elimination in vivo. Similarly, arformoterol, the \((R,R)\)-enantiomer of formoterol, having a 1000-fold greater potency than the \((S,S)\)-enantiomer, was approved by the US Food and Drug Administration in 2006 (Blake and Raissy, 2013). Available data indicate that there is no evidence to suggest an advantage of the \((R,R)\)-enantiomer, which might be due to the different kinetic profiles. Another example is thalidomide. The \( R \)-enantiomer of thalidomide is...
effective against morning sickness, while the S-enantiomer is teratogenic, causing birth defects (Trapnell, 1998). However, there is no rationale for developing a single enantiomer drug of thalidomide, since the single enantiomer is converted into a racemate within a clinically meaningful time frame in vivo (Eriksson et al., 2001). All these cases indicate that kinetic properties, including racemization and elimination of enantiomers, play a critical role in the decision whether to develop an enantiomer or a racemate in addition to using only data on in vitro stereoselectivity at the target receptor. However, the development of single-enantiomer drugs from established or previously marketed racemates may still have the potential benefits of less complex, more selective pharmacodynamic profiles, and potential for an improved therapeutic index, less toxicity, and reduced potential for complex drug interactions (Hutt and Valentova, 2003; Mansfield et al., 2004). This was successfully demonstrated by the nonsteroidal anti-inflammatory drugs dextroketoprofen and dexibuprofen, the proton pump inhibitor esomeprazole, the antimicrobial levofloxacin, the selective serotoni

en uptake inhibitor escitalopram, the anesthetic ketamine, the histamine H1-receptor antagonist levocetirizine, etc. (Hutt and Valentova, 2003). The decision of whether to develop the racemate or its enantiomers requires scientific justification based on quality, safety, and efficacy, together with the risk-benefit ratio.

The decision tree is to invest in the development of an active enantiomer from a racemate begins with confirmation of stereoselectivity in receptor recognition and includes in vivo efficacy (Blake and Raissy, 2013). Importantly, the active enantiomer must not racemize (interconvert between enan
tiomers) in any clinically meaningful time frame and extent, have no pharmacodynamic or PK interaction with the inactive enantiomer, and have no adverse effects not already known for the racemate. Moreover, the enantiomer must represent a therapeutically advantageous for the patient by having a more selective pharmacodynamic profile; improved therapeutic index; a less complex PK profile, such as a more direct toxicokinetics; and a less complex PK profile, such as a more direct therapeutic index; a less complex PK profile, such as a more direct therapeutic advantage for the patient by having a more selective pharmacodynamic profile; improved therapeutic index; a less complex PK profile, such as a more direct relationship between concentration and effect; and reduced potential for drug interactions (Blake and Raissy, 2013).

To explore the sensitivity of the drug exposure of the R- and S-isomers in relation to the elimination rate constant and the interconversion rate constant, a dimensionless factor for the relative ratio of elimination/interconversion rate was proposed. The PK exposure ratios between the R- and S-isomers were simulated after different scenarios of dimensionless factors. The simulation showed that the higher the ratio of the elimination rate constant over the interconversion rate constant, the larger the differences in PK exposures between the R- and S-isomers. Therefore, the potential difference to isomer exposure is primarily determined by the ratio of the rate of elimination over the rate of the interconversion, and secondarily to potential differences in isomer PK disposition. This quantitative measure can aid in determining if a new single enantiomer product might or might not confer any clinical advantages over the racemate.

In conclusion, a population PK model was successfully developed to describe the PK disposition of R- and S-isomers in monkeys and in humans in vivo. The model was able to predict the comparable PK profiles and comparable drug exposures of R- and S-isomers after dosing of a single isomer. The relatively slower elimination rate constant as compared with the interconversion rate constant in humans may result in fast racemization between R- and S-isomers, indicating no clinical/therapeutic advantage of developing single-enantiomer pomalidomide versus developing racemate pomalidomide.

Authorship Contributions

Participated in research design: Hoffman.

Performed data analysis: Li, Zhou, Hoffman.

Wrote or contributed to the writing of the manuscript: Li, Zhou, Hoffman, Kumar, Palmisano.

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