Model-Based Meta-analysis for the Population Pharmacokinetics of Iberdomide and Its Major Active Metabolite in Healthy Subjects and Subjects with Relapse and Refractory Multiple Myeloma

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Abstract

Aim A parent-metabolite population pharmacokinetic (popPK) model of iberdomide was developed and the influence of demographic and disease-related covariates on popPK parameters was assessed based on data from three clinical studies of iberdomide (dose range, 0.1 to 6 mg) in healthy subjects (N=81) and subjects with relapsed and refractory multiple myeloma (N=245). Methods Nonlinear mixed effects modeling was used to develop the popPK model based on data from 326 subjects across 3 clinical studies. Results The pharmacokinetics (PK) of iberdomide were adequately described with a two-compartment model with first-order absorption and elimination. A first order conversion rate was used to link the one-compartment linear elimination metabolite model with the parent model. Subject type (multiple myeloma subjects vs. healthy subject) was a statistically significant covariate on apparent clearance (CL/F) and apparent volume of distribution for the central compartment (V1/F), suggesting different PK between subjects with multiple myeloma and healthy subjects. Aspartate aminotransferase (AST), alkaline phosphatase (ALP) and sex were statistically but not clinically relevant covariates on CL/F. Metabolite (M12) PK tracked the PK of iberdomide. The metabolite to parent ratio was consistent across doses and combinations. Conclusion In conclusion, the parent-metabolite population pharmacokinetic model adequately described the time course PK data of iberdomide and M12. Iberdomide and M12 show robust PK exposure, not complicated by demographic factors, combination, hepatic or (mild and moderate) renal impairments. The model can be used to guide the dosing strategy for special patient population and inform future iberdomide study design.

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What is already known about this subject

Iberdomide is a potent and orally available cereblon E3 ligase modulator, which is being investigated for the treatment of inflammatory and autoimmune-mediated diseases and hematological malignancies including multiple myeloma.

What this study adds

- Iberdomide and major metabolite (M12) show robust PK exposure, not complicated by demographic factors, combination, hepatic or (mild and moderate) renal impairments
- M12 PK tracked the PK of iberdomide. The metabolite to parent ratio was consistent across doses and combinations
- Results should inform iberdomide dosing strategy and study design

Aim

A parent-metabolite population pharmacokinetic (popPK) model of iberdomide was developed and the influence of demographic and disease-related covariates on popPK parameters was assessed based on data from three clinical studies of iberdomide (dose range, 0.1 to 6 mg) in healthy subjects (N=81) and subjects with relapsed and refractory multiple myeloma (N=245).

Methods

Nonlinear mixed effects modeling was used to develop the popPK model based on data from 326 subjects across 3 clinical studies.

Results

The pharmacokinetics (PK) of iberdomide were adequately described with a two-compartment model with first-order absorption and elimination. A first order conversion rate was used to link the one-compartment linear elimination metabolite model with the parent model. Subject type (multiple myeloma subjects vs. healthy subject) was a statistically significant covariate on apparent clearance (CL/F) and apparent volume of distribution for the central compartment (V1/F), suggesting different PK between subjects with multiple myeloma and healthy subjects. Aspartate aminotransferase (AST), alkaline phosphatase (ALP) and sex were statistically but not clinically relevant covariates on CL/F. Metabolite (M12) PK tracked the PK of iberdomide. The metabolite to parent ratio was consistent across doses and combinations.

Conclusion

In conclusion, the parent-metabolite population pharmacokinetic model adequately described the time course PK data of iberdomide and M12. Iberdomide and M12 show robust PK exposure, not complicated by demographic factors, combination, hepatic or (mild and moderate) renal impairments. The model can be used to guide the dosing strategy for special patient population and inform future iberdomide study design.

Keyword

iberdomide, metabolite, multiple myeloma, population pharmacokinetics

1. Introduction

Iberdomide (CC-220) is an orally available agent which binds to the cereblon E3 ubiquitin ligase complex, resulting in proteasomal degradation of Ikaros and Aiolos, which are key transcriptional regulators in hematopoietic cell differentiation of the immune system, including B cells, T cells, monocytes, and plasmacytoid dendritic cells. Iberdomide is a potent antiproliferative agent in B cell-derived tumors, including multiple myeloma (MM) and lymphoma tumor cell lines[1-3]. Based on these pharmacological activities, iberdomide is being investigated for the treatment of inflammatory and autoimmune-mediated diseases and hematological malignancies including multiple myeloma [4-7].

The pharmacokinetics (PK) of iberdomide have been characterized in several clinical studies. Reports from single-ascending-dose (SAD) and multiple-ascending dose (MAD) studies conducted in healthy subjects showed that the iberdomide PK exposure (e.g., maximum (peak) plasma concentration (Cmax) and area under the plasma concentration time-curve (AUC)) increased in a dose-proportional manner over the tested dose range (0.1 to 6 mg). Following multiple daily oral doses, iberdomide steady state was attained after approximately 7 days, with an accumulation ratio of 2-fold. The median time of maximum observed concentration (Tmax) was observed between 2.5-4 hours postdose. The half-life of iberdomide was estimated to be approximately 9 to 13 hours after single oral dose. Coadministration with food did not affect the oral bioavailability of iberdomide. The systemic exposure of the R-enantiomer of iberdomide (CC-17195) was <9% of iberdomide in the SAD study across all doses and <8% in the MAD study (1 mg) based on AUC [8]. Additionally, Gaudy et al. evaluated the iberdomide drug-drug interaction potential with cytochrome P450 (CYP) 3A4/5 enzymes in a clinical study. Results showed that co-administration with itraconazole (a strong CYP3A inhibitor) increased the AUC for plasma iberdomide by approximately 136%; and co-administration with rifampin (CYP3A inducer) substantially decreased the overall exposure (AUC) and Cmax by approximately 82% and 70%, respectively [9].

Based on results from a radiolabeled human mass balance study (data on file, Bristol Myers Squibb), from which 1 mg ^{14}[C] labelled iberdomide was administered in healthy subjects, intact parent molecule in urine and feces constitute 16% and 11% respectively, indicating the absorbed drug is extensively metabolized and excreted mostly as metabolites, with nearly equal contribution from urinary and fecal elimination route. In systemic circulation, iberdomide was the predominant component in human plasma, with M12 being the most prominent circulating metabolite. Based on exposure (AUC), iberdomide and M12 accounted for approximately 59% and 14% of circulating total radioactivity (TRA) exposure, respectively.

CC-220-MM-001 study (herein as MM-001) is an on-going phase 1b/2a, multicenter, open-label, dose-escalation study to determine the maximum tolerated dose, assess the safety, tolerability, pharmacokinetics and efficacy of CC-220 as monotherapy and in combination with other treatments in subjects with multiple myeloma (MM). Iberdomide in combination with dexamethasone (DEX), in combination with DEX and daratumumab (DARA) or bortezomib (BORT), are being investigated in CC-220-MM-001 as treatment regimens and showed encouraging clinical outcome in subjects with heavily pre-treated relapsed and refractory (RR) MM [6,10].

To support the clinical development of iberdomide in RRMM, a parent-metabolite population pharmacokinetic (popPK) model was developed to: 1) characterize the PK of iberdomide and M12 in subjects with RRMM given both molecules were prominent in systemic circulation and pharmacologically active; and 2) assess the influence of covariates on the PK of iberdomide and M12 to inform the dosing strategy in special populations.

2. Method

2.1 Study Description

Three clinical studies were pooled together for popPK analysis, including CC-220-CP-001(single ascending dose study in healthy subjects; herein as CP-001; NCT01733875), CC-220-CP-002 (multiple ascending dose

study in healthy subjects; herein as CP-002; NCT02034773) and CC-220-MM-001 studies (subjects with RRMM; NCT02773030). Study description was presented in Table 1.

The studies were conducted in accordance with the ethical principles of Good Clinical Practice. All subjects gave written informed consent prior to enrollment. The studies were approved by the institutional review boards of the participating center and were conducted according to the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice.

2.2 Pharmacokinetic Schedule

Iberdomide PK data was collected for all three studies. All available PK data from CP-001, Part 1(multiple ascending dose; Table 1) and 3 (relative bioavailability; Table 1) from CP-002 and cohorts A (iberdomide monotherapy dose escalation; Table 1), B (iberdomide in combination with DEX dose escalation; Table 1), D (iberdomide in combination with DEX dose expansion; Table 1), E (iberdomide in combination with DARA and DEX dose escalation; Table 1),) and I (iberdomide in combination with DEX dose expansion; Table 1) from MM-001 studies were included in the popPK analysis, based upon the relevance to this analysis. M12 PK data was only collected in CC-220-MM-001 Cohorts A, B and E. The sampling schedule of M12 is similar as iberdomide.

The PK sampling schedule was detailed in Table 1.

2.3 Bioanalytical Method

Human whole blood was collected and centrifuged to obtain plasma. The harvested plasma was transferred to precharged citric acid tubes to obtain acidified plasma (40 mM) for measurement of iberdomide and M12, with two validated human plasma liquid chromatography-tandem mass spectrometry assays (LC-MS/MS): 1) solid phase extraction (SPE, Waters Oasis Elution HLB cartridges) for iberdomide or M12 sample cleanup; 2) chiral LC (Chiral Tech, CHIRALPAK CBH, 100 x 3 mm, 5 μm column) for iberdomide separation (from its R-enantiomer), or achiral LC (Phenomenex Synergi Polar-RP, 2.0 x 50 mm, 4 μm column) for M12 separation; and 3) Turbo IonSpray® with MS/MS detection for iberdomide (SCIEX API 4000, Framingham, MA) or M12 (SCIEX API 5500). The calibration curves for iberdomide and M12 ranged from 0.1 to 100 ng/mL and 0.1 to 50 ng/mL in acidified human plasma respectively, with the lower limit of quantification (LLOQ) being 0.1 ng/mL for both assays. In both method validation and study sample analysis, the precision and accuracy data for standard/quality control samples were well within acceptance criteria for both iberdomide and M12.

2.4 Software

The software applications used in the data analyses and data presentation include:

- NONMEM (version 7.4, ICON Development Solution, MD, US)
- R (version 3.5.3 or higher, The R Foundation for Statistical Computing, US)
- SAS (version 9.4, SAS Institute, Inc., Cary, NC, US)
- Monolix (Version 2020R1, Lixoft, Antony, France)

The analyses were performed on Intel Xeon-based multi-core Central Processing Unit servers running Ubuntu 18.04 in Amazon Web Services (AWS).

2.5 Population Pharmacokinetic Model Building

Based on previous experience and visual inspection, a 2-compartment structure PK model was selected based on the objective function value (OFV) using the log-likelihood ratio test, Bayesian information criterion (BIC), the goodness-of-fit criteria and visual predictive check.

Unexplained interindividual variability (IIV) in a PK parameter was assumed to be log-normally distributed. The relationship was shown in equation 1.

Equation 1:$\text{Log (Pi)} = Log\ (P_{\text{pop}}) + \eta_i$

where Pi is the individual parameter; Ppop represents the typical parameter (fixed effect); η_i denotes the random effect.

Intra-individual or residual variability (RV) was modeled according to the Monolix library. Proportional error model was chosen based on the model fitting (Equation 2).

2.6 Covariates Model

The following variables were explored as covariates for their potential to influence iberdomide PK parameters:

- Demographic factors: age, body weight, body surface area (BSA), body mass index (BMI), sex, and race;
- Baseline laboratory test: total bilirubin (BILI), aspartate aminotransferase (AST), alanine aminotransferase (ALT), Alkaline Phosphatase (ALP) and Albumin (ALB);
- Renal function marker: creatinine clearance estimated by Cockcroft-Gault formula, Estimated Glomerular Filtration Rate (eGFR) by CKD EPI equation;
- Disease status: healthy subjects versus MM patients;
- Baseline disease: ECOG, ISS stage at study entry;
- Iberdomide combinations: monotherapy versus Iberdomide in combination with DEX versus Iberdomide in combination with DEX and DARA

Data visualization was used to examine the relationship between intrinsic or extrinsic factors and subject-level PK parameters. Initial selection of covariates was guided by graphic inspection and biological plausibility. Potential covariates were tested further in Monolix.

COSSAC (conditional sampling use for stepwise approach based on correlation tests) was used for covariate search based on a previous publication [11]. The iterations of COSSAC alternated between a forward selection and a backward selection, depending on the results of the correlation tests. In brief, during the forward selection step, covariate with the smallest correlation p-value (among the remaining parameter-covariate relationships) was added to the model, or the next smallest if the smallest has already been tried, and so until no correlation p-values above a threshold remain. Acceptance/rejection of the relationship was based BIC: The covariate was not retained if the criteria (0.3) did not improve (with a threshold for the likelihood ratio test). During the backward selection, among the covariates presented in the model, covariate with the highest (less significant) correlation p-value, or the next highest if the highest has already been tried, was removed, until no correlation p-values below a threshold remain. Acceptance/rejection of the relationship removal was based on BIC: The covariate was not retained if the criteria (0.01) did not improve (with a threshold for the likelihood ratio test). The algorithm continued until no forward or backward selection was possible.

2.7 Model Performance

Model evaluation was performed using visual predictive check (VPC) that provided an evaluation of model assumptions and population parameter estimates by comparing model predictions with observations. The ability of the final popPK model to describe the observed concentration data was evaluated by simulating 500 datasets having the same doses, dosing schedules and sampling times as the original dataset and by performing VPCs. Binning of observations around logical post dose time points of interest was done to ensure sufficient density of observations.

3. Results

3.1 Demographic

The iberdomide popPK analysis dataset included 326 subjects. Table 2 summarized the demographic and baseline disease characteristics of the subjects. There were more male subjects (63.2%) than female (36.8%). Most of the subject were white with a median age of 61 years and median body weight of 76.8 kg. Of note, based on creatinine clearance (CLcr), 45.1% subjects were with normal renal function (CLcr [?] 90 mL/min), 37.1% subjects were with mild (CLcr 60 to 89 mL/min) and 17.8% moderate (CLcr 30 to 59 mL/min) renal

impairment, respectively. Most subjects were with normal hepatic function (93.9%) as per National Cancer Institute organ dysfunction working group criteria.

3.2 Population Pharmacokinetic Base Model

All iberdomide and M12 concentrations were converted to molar concentrations for modeling purpose. The starting structural model of iberdomide was a two-compartment model with first order absorption and elimination based on the observed concentration-time profile (Figure 1). Incorporating a lag time improved the model fitting by significantly decreasing OFV (-576). A first order conversion rate (Kpm) was used to account for the transformation of iberdomide to M12. M12 PK was described by a one-compartment model with first order elimination. Of note, to rule out the occurrence of parameter identifiability issues existing in typical parent-metabolite popPK models which has been discussed in previous publication [12], the volume of distribution of M12 was assumed to be similar as that of iberdomide (V1/F). The model structure was shown in Figure 2. During the modelling process, iberdomide and M12 PK data were fitted simultaneously into the model.

In addition, the inter-individual variability (IIV) associated with the PK parameters in the model were estimated as log-normally distributed with a non-zero covariance, as described in the method section. Based on modeling fitting, proportional error model was selected for both iberdomide and M12 PK. Equation 2 described the error model, where y1 and y2 denoted observed concentration of iberdomide and M12, respectively; Cp and Cm represented the model predicted concentration of iberdomide and M12; b1 and b2 were proportional parameters; e was the base of the natural logarithm.

Equation 2: $y1 = Cp + b1 * Cp * e$

$y2 = Cm + b2 * Cm * e$

In conclusion, a two-compartment model with first order absorption rate constant incorporating a lag time for iberdomide and a first order conversion rate linking the one-compartment metabolite model was selected as the base model.

3.3 Covariate Analysis

Covariates of interest which were presented in Table 1 were included in the covariate model development using the COSSAC algorithm. The covariate search results showed that inclusion of ALP, AST, Sex, Subject Type (MM vs. Healthy Subjects) on CL/F and Subject Type (MM vs. Healthy Subjects) on V1/F significantly improved the model fitting. The output of the final model was summarized in Table 3.

Most of the PK parameters for the final model were estimated with good precision (i.e., small % relative standard error (RSE)), suggesting adequate reliability. However, the covariates (ALP, AST and sex) on CL/F were estimated with relatively low confidence (%RSE > 30). This was likely attributed to the marginal effects of such covariates on PK parameters. To validate this point, a forest plot (Figure 3) was generated which showed that the influence of ALP (1st tertile and 3rd tertile vs. 2nd tertile [reference]), AST (1st tertile and 3rd tertile vs. 2nd tertile [reference]) and sex (female vs. male [reference]) was in small magnitude ([?] 80% and [?] 125%), and therefore, was unlikely to be clinically meaningful.

Subject type was a significant covariate on CL/F and V1/F. Based on the forest plot, MM patients showed 238% higher CL/F and 84% lower V1/F as compared to healthy subjects (Figure 3). It should be noted that the CL/F only constituted part of total iberdomide clearance. The metabolism clearance, which can be calculated as Kpm*V1, was believed to largely contribute to the iberdomide clearance. In fact, the total iberdomide clearance for typical MM subjects (9.48 L/hr) was even lower than that of healthy subjects (20.41 L/hr) (Table 4). Notably, the model estimated clearance for healthy subjects were in line with the published results based on non-compartmental analysis[8], indicating good model performance.

Renal function was examined on the PK of iberdomide and M12. The impact of CLcr, eGFR and renal function category on PK parameters, including CL/F, V1/F, CLm and Kpm were assessed. Figure 4 showed that no correlation was observed between CLcr and eGFR versus PK parameters and the PK parameters were

comparable among renal function groups. These results suggested that moderate and mild renal impairment (CLcr [?] 30 mL/min) was unlike to change the PK exposure of iberdomide and M12.

Combinations (DEX and/or DARA) were assessed as a covariate. Figure 5 showed comparable PK among different combos, suggesting that combination had no impact on the PK of iberdomide and M12.

Other covariates, including age, body weight, BMI, BSA and baseline disease factors (e.g., ECOG) were not significant in the model and therefore, were not retained in the final model.

3.4 Model Evaluation

The model was validated by visual predictive check (VPC). The results of the VPC evaluation were presented in Figure 6. The 5th, 50th and 95th percentiles of the observed concentration data at each time point were generally contained within the respective 90% CI (shaded area, pink for the 50th percentile and blue for 5th and 95th percentiles) of the simulated data (Figure 5). There was a good agreement in the time course and central tendency between distributions of observed and simulated data, with no obvious bias. Overall, the estimated IIV adequately described the observed variability in iberdomide and M12 concentrations.

Taken together, iberdomide and M12 concentrations were well characterized by the final popPK model. This enabled the proper use of the model for subsequent simulations.

3.5 Metabolite (M12) PK Exposure Relative to Parent (iberdomide)

Based on the model, AUC and Cmax for each individual patient who had both iberdomide and M12 PK data (Cohorts A, B and E from MM-001 study) were simulated. Metabolite to parent ratio was calculated and stratified by dose and cohort (Figure 7 and Table 5). The goal was to assess the influence of dose and combination on the extent of metabolite exposure. Results showed that the metabolite to parent ratio (both in terms of Cmax and AUC) was consistent, irrespective of dose and cohorts. In addition, iberdomide and M12 PK profile were simulated for a typical MM patient on 1.6 mg 21/28 schedule and were overlaid in Figure 8. The plot showed that M12 PK profile generally tracked the PK of iberdomide, as demonstrated by the two parallel curves.

In conclusion, the totality of data suggested that iberdomide PK was adequate to represent the pharmacological active exposures in systemic circulation, regardless of time, dose and combinations.

4. Discussions and Conclusions

Herein, we reported the first population pharmacokinetic analysis for iberdomide and its major active metabolite, M12 in both healthy and RRMM subjects and assessed the effect of covariates of interest on iberdomide and M12 PK. Over the tested dose range (0.1 mg to 6 mg), iberdomide and M12 (where applicable) showed linear, time-independent PK. Subject type (MM vs. healthy subject) was a statistically significant covariate on CL/F and V1/F. Sex, AST, ALP was statistically but not clinically relevant on CL/F. Metabolite (M12) PK was consistent across doses and combinations, as demonstrated by the comparable metabolite to parent ratio. Overall, the model was robust and adequate to describe the central tendency and variabilities of the data.

Given the lack of actual input information (e.g., amount) of metabolite, mathematically the metabolite model parameters were unidentifiable. Evans et al. discussed this and suggested taking prior knowledge of metabolite volume of distribution in the model to avoid the issue[12]. In line with this, Bertrand et al. assumed similar volume of distribution for parent and metabolite, which enabled all the parameters to be identifiable [13]. Alternatively, a more mechanistical solution was to fix the metabolite conversion ratio (e.g., fm) based on the understanding of the drug's PK properties[14]. Herein, we took the former approach to develop the model for the following reasons: 1). the parsimonious structural model can adequately fit the purpose of the analysis; 2). biological evidence showed that the plasma protein binding of iberdomide and M12 was roughly comparable (78.4% vs. 67.4%; data on file, Bristol Myers Squibb), with no saturation of plasma protein binding for both molecules.

In the covariate analysis, the most influential covariates on the disposition of iberdomide were subject type (MM vs. healthy subjects), AST, ALP and sex on CL/F and subject type (MM vs. healthy subjects) on V1/F. However, the forest plot suggested that except for subject type on CL/F and V1/F, the effects of AST, ALP and sex on CL/F were marginal and unlikely to be clinically relevant.

The iberdomide PK difference between healthy subjects and those with MM was noticeable. The model estimated total clearance of iberdomide and V1/F were lower in subjects with MM as compared to healthy subjects. Based on the model, subjects with MM were expected to have higher exposure than healthy subjects for the same dose (Figure 9). However, this difference was not taken into consideration on iberdomide dosing, given the iberdomide therapeutic doses were selected solely based on data from clinical trials in RRMM. Of note, similar observation was seen with lenalidomide [15], in which higher exposure was observed in MM patients than healthy subjects. Other compounds, including pomalidomide, enasidenibCC-122 also exhibited disease specific PK [16-18].

Due to the lack of M12 data in healthy subjects in this analysis, the influence of subject type on metabolite PK (Kpm and CLm) was not assessed.

Based on the mass balance study, only 16% of the iberdomide dose was excreted as unchanged in urine, suggesting limited contribution of renal route on drug elimination. In line with this, the popPK analysis showed that renal functions (CLcr, eGFR and renal function category) had no impact on the PK parameters. It should be noted that in the current dataset, there were no subjects with severe or end-stage renal deficiency (CLcr $<$ 30 mL/min). Therefore, the interpretation should be only focused on moderate and mild renal impairment population only.

DEX in combination with iberdomide was one of the dosing regimens in the MM-001 study. DEX is known as a CYP3A4 inducer [19,20]. The popPK analysis assessed the influence of iberdomide in combination with DEX given iberdomide was a substrate for CYP3A. Post hoc analysis showed similar PK between DEX and/or DARA combo vs. iberdomide monotherapy, suggesting that the presence of DEX and/or DARA was unlikely to change iberdomide and M12 PK.

Although the hepatic function covariates were not considered as clinically relevant, it should be noted that in the current dataset, most of the subjects (93.9%) had liver tests within the limits of normal. Therefore, the dedicated hepatic impairment study (data on file, Bristol Myers Squibb) was more informative to guide dose adjustment for patients with hepatic deficiency.

Body weight (range: 41 to 172 kg), BSA (range: 1.4 to 2.7 m2), BMI (16.4 to 59.3 kg/m2) and age (19 to 82 years) were statistically non-significant. Race was found not to have any effects on iberdomide and M12 PK. The popPK dataset contained majority of Whites (73.3%), and only 2 Asians, 1 American Indian/Alaska Native and 44 Black/African Americans. Thus, the effects of race should be interpreted with cautions. Baseline disease characteristics, including ISS and ECOG had no statistically significant effects and therefore was not retained in the final model.

Given the level of exposure and the pharmacological activities, M12 PK was characterized during the clinical development of iberdomide. In the popPK analysis, M12 PK data from MM-001 cohorts A, B and E were incorporated. The objective was to assess the M12 exposure relative to the parent drug across doses and combinations. Results suggested consistent metabolite to parent ratio among the tested doses and cohorts. Additionally, the parallel PK profiles indicated that M12 PK tracked iberdomide, irrespective of time. Moreover, based on the human mass balance study in healthy subject, the metabolite to parent ratio was 0.24, which was in general comparable with that in subjects with MM (0.25 and 0.28 for Cmax and AUC, respectively) taking into account the observed variability (%CV: 29.8 to 33.1). Taken together, given the stable and time-insensitive M12 PK in relative to parent drug, the PK of iberdomide was adequate to represent the major pharmacological active exposure in the systemic circulation in the context of extent and time course.

In conclusion, the iberdomide parent-metabolite popPK model described herein was adequate to describe the

PK of iberdomide and M12. Covariate analysis suggested that MM patients had lower clearance (iberdomide) and volume of distribution than healthy volunteers. Other covariates, including demographic, combination, renal and hepatic function tests had no clinically relevant impact. M12 PK in relative to iberdomide was consistent across doses and combinations.

Consent for publication

All the authors have reviewed and concurred with the manuscript.

Data Sharing Statement

The datasets are available from the corresponding author upon request.

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Disclosures

Y.C., Y.X., L.C, M.M, P.M., T.P., S.Z. and Y.L. are employees and hold equity ownership in Bristol Myers Squibb.

Authors' contributions

Y.C., Y.X., M.M., P.M. and T.P. contributed to conception and design; Y.C., Y.X. and M.M. contributed to acquisition of data; Y.C., L.C., S.Z. and Y.L. contributed to analysis; P.M. and T.P. conducted the clinical trial; Y.C., S.Z. and Y.L. drafted and revised the article. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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Figure Legend:

Figure 1. Concentration - time profiles of iberdomide and M12 by study. [A]. Iberdomide; [B]. M12. Solid circles represent observed concentrations, which were grouped by dose level.

Figure 2. The joint population pharmacokinetic model of iberdomide and M12. The model comprises two parts: parent (iberdomide) and metabolite (M12). The parent model is a two-compartment with first-order absorption incorporating a lag time and first-order elimination. The metabolite model is a one compartment model with first order elimination. A first order conversion rate described the transformation from parent to metabolite.

Figure 3. Forest plot of significant covariates on apparent clearance (CL/F, A) and apparent volume of distribution of the central compartment (V1/F, B). Data are shown as median (90% confidence interval). (A) References are 2nd tertile of AST (17 to 23 U/L), healthy subject, 2nd tertile of ALP (55.0 to 72.5 U/L) and male subjects, respectively. (B). Reference is healthy subject.

Figure 4. Correlation between renal function and population PK parameters. Solid circles are individual PK parameters generated from the model. Blue line represented the locally weighted smoothing line. CLcr = creatinine clearance; EGFR = estimate glomerular filtration rate.

Figure 5. Correlation between combinations and population PK parameters. Solid circles are individual PK parameters generated from the model. dex = dexamethasone; dara = daratumumab.

Figure 6. Visual predictive check plots of iberdomide and M12. [A]. iberdomide concentration; unit: umol/L; [B]. M12 concentration; unit: umol/L. The blue dots show the observed concentration data. The solid blue lines show the empirical 10th, 50th, and 90th percentiles calculated directly from the population

data. The blue-shaded areas denote the confidence intervals of the 10th and 90th percentiles from the model; and the pink shaded area shows the 50th percentile.

Figure 7. Metabolite to parent ratio by cohort and dose from CC-220-MM-001 study. [A and B]: Cmax ratio; [C and D]: AUC ratio. Cmax = maximum concentration; AUC = area under the concentration - time profile over one dosing interval (24 hours).

Figure 8. Simulated concentration - time profile of iberdomide (red) and M12 (blue) for a typical subject from CC-220-MM-001 study on 1.6 mg, 21/28 day schedule.

Figure 9. Simulated iberdomide concentration - time profile for a typical healthy subject (red) and multiple myeloma patients (blue) on 1.6 mg, 21/28 day schedule.

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